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李玉林, 贺蕊莹, 黄玉, 李梦, 武艳, 高洁 （湖北大学化学与化工学院；华东理工大学材料科学与工程学院超细材料教育部重点实验室；牡丹江医科大学生命科学学院；中国人民解放军海军军医大学第一附属医院临床研究中心；上海交通大学附属第九人民医院皮肤科）

Engineering mitochondrial uncoupler synergistic photodynamic nanoplatform to harness immunostimulatory pro-death autophagy/mitophagy

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Abstract: In view of autophagy/mitophagy commonly plays a pro-survival role to prevent themselves from cell death by increasing the adaptation of cells to metabolic stresses and cancer therapies, autophagy inhibitors have been widely used to improve the therapeutic effects of PDT, including our previous study. Nevertheless, using autophagy inhibitors to either interdict autophagosome formation or increase lysosomal pH will dramatically attenuate the ATP secretion and antigen presentation, subsequently compromise the immunogenicity of dying tumor cells and anti-tumor immune response. Therefore, a more effective and well-designed autophagy/mitophagy controlling strategy is required for optimized cancer PDT. Mitochondrial uncoupler, such as carbonyl cyanide 3-chlorophenylhydrazone (CCCP), has been reported to induce mitochondrial depolarization and promote cellular respiration, mainly for in vitro studies. Nevertheless, using CCCP to improve autophagic cell death and immunogenicity of tumor cells has never been studied. In this research, we have constructed a CCCP loaded and MnO_2 coated multifunctional porphyrinic PCN-224 nanoparticles for mutually reinforced cancer PDT via harnessing the pro-death role and immunomodulating effect of autophagy/mitophagy. To the best of our knowledge, the immunomodulating effect of excessively activated pro-death autophagy/mitophagy of tumor cells has been rarely evaluated in cancer PDT. Hence, we believe that this research might underline the pro-death role of autophagy/mitophagy in malignant cells and thus provides a novel target for designs of nanoplatforms or biomaterials for cancer therapy.

Keywords: photodynamic immunotherapy; in situ self-assembly, chromatin decompaction, nuclear DNA damage

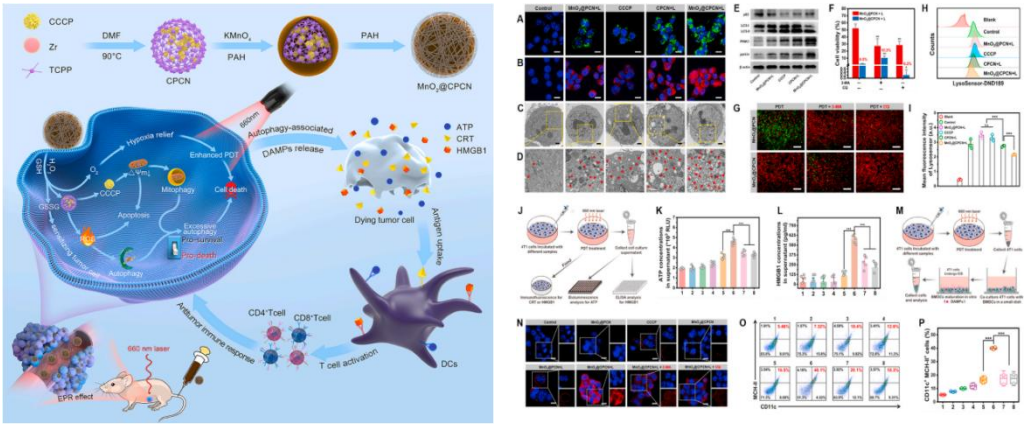

Figure. 1 Schematic illustration of the synthesis and the simplified antitumor mechanism of mitochondrial uncoupler encapsulated and MnO2 wrapped PCN nanoparticles for mutually reinforced photodynamic therapy. Activating excessive autophagy/mitophagy has shown aggravated tumor cell death and “ self-vaccine ” of tumor cells, leading to long-lasting tumor inhibition (Left); and Excessive autophagy/mitophagy induced by MnO2@CPCN þ L leads to autophagic and immunogenic cell death. (Right).

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Design of bionic cell membrane coated liposomes for diagnosis and treatment of inflammatory bowel disease

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Objectives: Inflammatory bowel disease (IBD) is a refractory chronic intestinal inflammatory disease caused by a malfunction of immune system. Due to the recurrence of inflammation, IBD treatment prone to incurable that is a huge challenge in clinic and results in obvious decline of life quality and long-term treatment with higher financial burden. Current approved drugs including aminosalicylates, corticosteroids and immunomodulators exist insufficient anti-inflammatory effect and systemic side effect. Due to the critical role of macrophage function for IBD progress, a novel bionic liposome nanoparticle is designed for macrophage targeting to improve IBD treatment efficiency.

Methods: To find a more effective drug delivery system, bionic liposome is prepared for precise macrophage targeting. Firstly, red blood cells (RBC) are collected from C57BL/6 mice, and then induce RBC apoptosis. Phosphatidylserine is exposed on the RBC membrane, that is the natural signal for macrophage recognition and phagocytosis. Rosiglitazone (ROSI) is an agonist of PPAR-γ that induce macrophage polarized as M2 phenotype to exert anti-inflammatory effects. Meanwhile DPP is the synthesized molecules that can react with NO and show the NIR-II imaging feature. DPP and ROSI are co-coated into liposomes as model drug and then co-extruded with apoptotic RBC membrane to prepare bionic macrophage targeting liposomes.

Results: Compared with normal liposome particles, apoptotic membrane coated liposome (A-LP) show the better uptake by RAW264.7 cell. More dye labeled A-LPs are accumulated into colon site of IBD mouse with higher fluorescence, which indicate A-LP could target for macrophage and further accumulate in inflammatory site. In-vivo animal study has confirmed that A-LP show the best therapeutic effect on IBD mouse model. Except therapeutic effect, DPP exhibit NIR-II signal in inflammatory colon sites *in-vivo* that achieve integration of diagnosis and treatment for IBD.

Conclusion: This work provides a novel macrophage targeting way by induced RBC membrane coating liposome particles. The bionic nanoparticles with high biocompatibility achieve the better therapeutic effect and diagnosis by NIR-II imaging for IBD.

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Investigation on probiotic spores based intestinal in-situ reassembled nanomedicines for treatment of inflammatory bowel disease

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Abstract: Studies have shown that intestinal microbiota imbalance, intestinal mucosal damage, and immune dysfunction are closely related to the development of IBD. It is a new idea to improve the efficacy of treating IBD through the multiple effects of regulating flora, repairing damaged intestinal mucosa, and maintaining immune homeostasis. This project constructed an intestinal in situ reassembly nanomedicine based on probiotic spores. Not only can it successfully overcome the oral physiological barrier through gastric acid environment, enhance bioadhesion and permeability, and promote trans-intestinal epithelial cell transport, but also effectively treat IBD through the multiple effects of intestinal flora regulation, intestinal mucosa repair, and immune regulation.First, the Aryl hydrocarbon receptor (AHR) agonist ITE was loaded into poly-N-vinyl caprolactam nanoparticles (PVCL NPs), and ITE/PVCL was chemically modified on the surface of Clostridium butyricum spores (CBs) to construct ITE/PVCL@ CBs preparations. The nanomedicines constructed in this paper based on the intestinal in situ reassembly of probiotic spores have multiple functions of intestinal flora regulation, intestinal mucosa repair, and immune regulation, which are of great significance for the treatment of IBD.In conclusion, the constructed ITE/PVCL@CBs can be reassembled in situ into ITE/PVCL@SP nanosystems in the gut, Overcome the oral absorption barrier, effectively treat IBD through the triple regulation effect of regulating the flora, repairing the damaged intestinal mucosa, and maintaining immune homeostasis, and solving the limitations of monotherapy in the treatment of IBD. In addition, the colonic targeting of CBs will alleviate the toxic side effects of long-term drug treatment.

Keywords: probiotics; immunotherapy; microbiota regulation; mucosal barrie

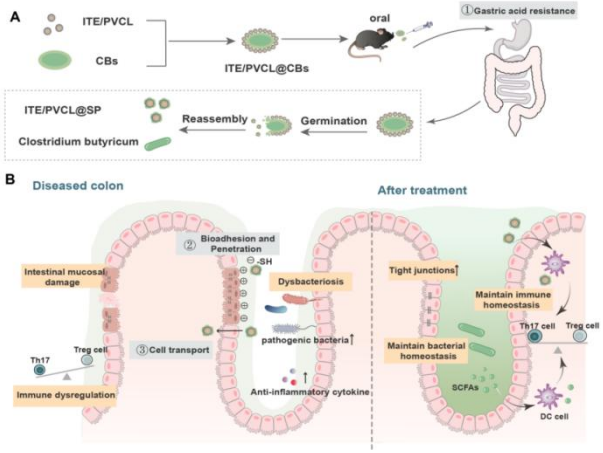

Figure. 1 Schematic diagram of in-situ recombinant nanoparticle based on probiotic spores for IBD treatment.

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Framework Nucleic Acids Loading siTNF-α for Topical Psoriasis Treatment

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Abstract: Psoriasis, as an autoimmune disease, plagues more than 1.25 million worldwide. TNF-α, as one of the major inflammatory cytokines, play an important role in pathogenetic process. TNF-α therapy has showed great success in better management for psoriasis. So far, TNF-α therapy mainly relied on antibody injection, which lacked of compliance and convenience. Our work provided a novel topical TNF-α therapy by applying tetrahedral framework nucleic acid to deliver siTNF-α for psoriasis treatment. By complementary base pairing, siRNA with sticky end was successfully integrated into framework nucleic acid (FNA). To exam the ability of FNA to deliver siRNA, GAPDH as a model siRNA was applied. On both cellular level and mice model, FNA-siGAPDH showed higher GAPDH mRNA downregulation efficiency as well as transdermal efficiency than free siGAPDH. Further in LPS-induced Raw 264.7 cell line, FNA-siTNF-α showed the advantage in lowering the mRNA level of siTNF-α compared to free siTNF-α. In psoriasis-like mice model, after five-day FNA-siTNF-α cream topical administration, the symptoms of psoriasis were relief from both desquamation and erythema aspects. The level of TNF-α, tested by qPCR and Elisa, was significantly reduced which indicated the successful delivery of siTNF-α. Therefore, FNA-siTNF-α showed the possibility in psoriasis treatment.

Keywords: topical drug delivery; framework nucleic acid; siRNA; psoriasis

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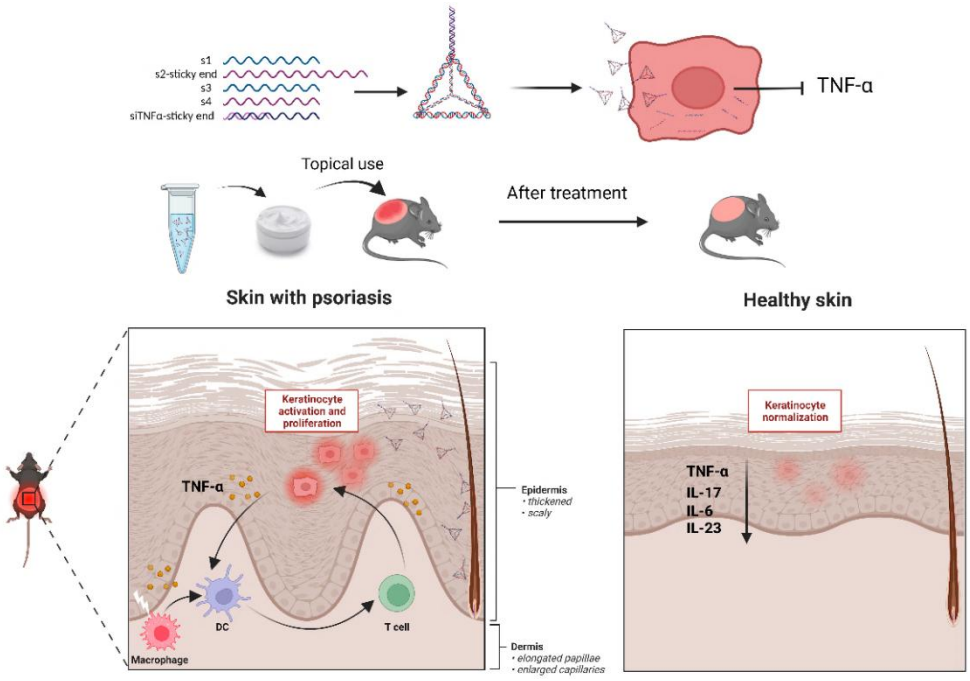

A Metabolic Intervention Strategy to Break Evolutionary Adaptability of Tumor for Reinforced Immunotherapy

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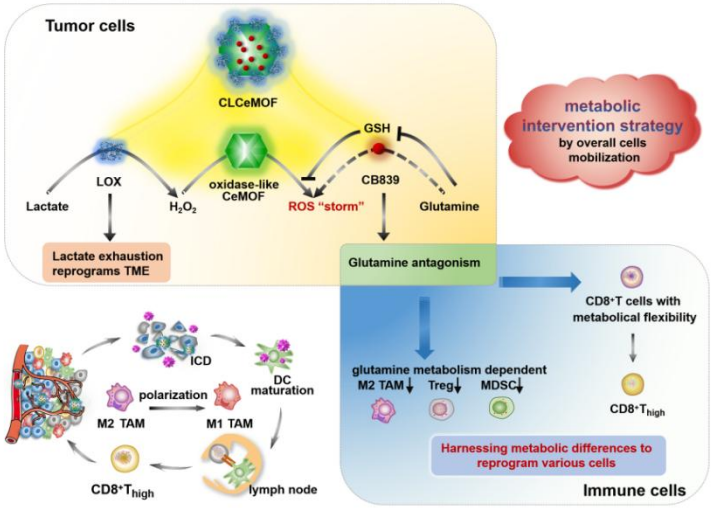
Abstract: The typical hallmark of tumor evolution is metabolic dysregulation. In addition to secreting immunoregulatory metabolites, tumor cells and various immune cells display different metabolic pathways and plasticity. Harnessing the metabolic differences to reduce tumor and immunosuppressive cells while enhance the activity of positive immunoregulatory cells is a promising strategy. We develop a nanoplatform (CLCeMOF) based on cerium metal-organic framework (CeMOF) by lactate oxidase (LOX) modification and glutaminase inhibitor (CB839) loading. The cascade catalytic reactions induced by CLCeMOF generate reactive oxygen species “storm” to elicit immune responses. Meanwhile, LOX mediated metabolite lactate exhaustion relieves the immunosuppressive tumor microenvironment, preparing the ground for intracellular regulation. Most noticeably, the immunometabolic checkpoint blockade therapy as a result of glutamine antagonism is exploited for overall cells mobilization. It is found that CLCeMOF inhibits glutamine metabolism dependent tumor cells and immunosuppressive cells, increases infiltration of dendritic cells, and especially, reprograms CD8+ T lymphocytes with considerable metabolic flexibility toward a highly activated, long lived and memory-like phenotype. Such idea intervenes both metabolite (lactate) and cellular metabolic pathway, which essentially alters overall cell fates toward the desired situation. Collectively, the metabolic intervention strategy is bound to break evolutionary adaptability of tumor for reinforced immunotherapy.

Keywords:metabolic intervention, immunotherapy, glutamine metabolism, lactate, reactive oxygen species



Scheme 1. Schematic mechanism of CLCeMOF to break evolutionary adaptability of tumor. Metabolically intervention strategy hererin reinforced immunotherapy by overall tumoral cells mobilization.

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Hollow manganese dioxide based on host-guest interactions Nanoplatform for anti-tumor immunotherapy research

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Abstract: Tumor immunotherapy is limited by the low immunogenicity and immunosuppressive microenvironment at the tumor site. In this study, we constructed a dual nanodrug delivery platform HM@Oxp/CB[7]-CBX that can effectively induce tumor immunogenic cell death (ICD), which is used to reversing of the immunosuppressive microenvironment for the purpose of effective immunotherapy. Based on the pH-responsive material hollow mesoporous manganese dioxide (HM), the chemotherapeutic agent Oxaliplatin (Oxp), which can cause ICD production in tumors, is loaded inside. The presence of large amounts of polyamines that promote the proliferation and development of colorectal cancer (CRC) at the tumor site, and the non-steroidal anti-inflammatory drug Celecoxib (CBX) was shown to promote the catabolism of polyamines and reduce their effects on the immunosuppressive microenvironment. CBX was encapsulated in Cucurbit[7]uril (CB[7]) cavities by host-guest interactions and CB[7] was modified on the HM surface by electrostatic interactions. After this nano-platform reaches the tumor site, on the one hand, Mn^{2+} is released in response to HM proton in the naturally occurring acidic microenvironment at the tumor site. Subsequently, the H_2O_2 in situ at the tumor is converted to ·OH by Mn^{2+} through Fenton-like reaction, thus synergizing inducing ICD in the tumor with Oxp; on the other hand, excessive polyamines at the tumor site, as natural object clues, can not only attract HM@Oxp/CB[7]-CBX to the tumor site, moreover, spermine competitively binds within the CB[7] lumen and the depletion of polyamines reverses the immunosuppressive microenvironment while CBX is released, which is synergistic with Oxp in the treatment of CRC.

Keywords: Hollow mesoporous manganese dioxide; Polyamines; Immunogenic cell death; Two-drug combination

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Self-Amplified ROS Production from Fatty Acid Oxidation Enhanced Tumor Immunotherapy by Atorvastatin/PD-L1 siRNA Lipopeptide Nanoplexes

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Abstract: Despite the important role of reactive oxygen species (ROS) in battling cancer, ROS production with current approaches has been severely limited by the deficiency of oxy-substrates in tumor microenvironment. Herein, an atorvastatin (Ato)-catalytic self-amplified approach was utilized for sustainable ROS production and enhancing anti-tumor efficacy of PD-L1 silencing. A C_{18}-pArg_8-ss-pHis_{10} lipopeptide based self-assembled nanoplexes (SLNP) was developed to co-encapsulate AMP-activated protein kinase (AMPK) activator of Ato and PD-L1 siRNA. Efficient delivery of payloads was achieved because of the acidic pH triggered the protonation of pHis_{10}, disulfide-bond exposure for cleavage and subsequent endo-lysosome escape/cytosolic translocation. Ato was found to activate AMPK, boosting the highly restrained mitochondrial fatty acid oxidation (FAO) in cancer cells for ROS production. The ROS derived from FAO further activated AMPK, creating a positive-feedback mechanism of sustainable ROS production. The self-amplified ROS production from cellular mitochondrial FAO was maintained by the sufficient intracellular fatty acid substrates arising from the dysregulated lipid metabolism and Ato inhibited triglyceride synthesis in cancer cells. The excessive ROS level was found to successfully induce immunogenic cell death effect, boosting the anti-tumor efficacy of PD-L1 silencing. Overall, the Ato catalyzed self-amplified ROS production has been demonstrated as a promising alternative for cancer therapy.

Keywords: reactive oxygen species, fatty acid oxidation, self-amplified, lipopeptide amphiphile, PD-L1 silencing, endo-lysosome escape

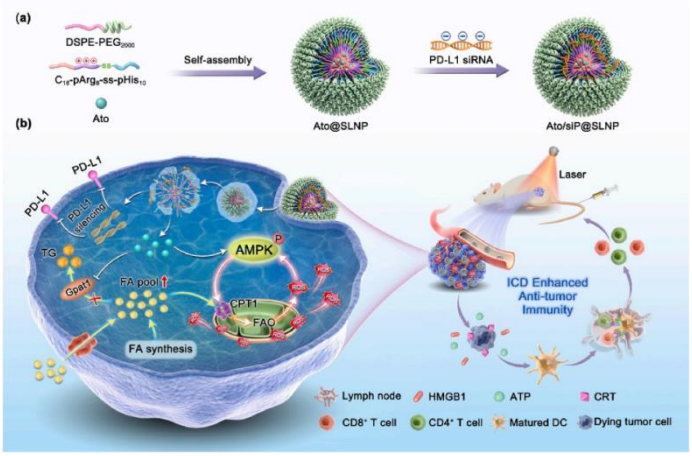

Figure. 1 Schematic illustration for the design of Ato/siP@SLNP (a), and the self-amplified ROS production by Ato catalyzed AMPK/FAO/ROS positive-feedback loop, which was maintained by the sufficient intracellular fatty acid substrates arising from Ato inhibited triglyceride synthesis and dysregulated lipid metabolism in cancer cells, the elevated ROS level produced ICD effect boosting the anti-tumor efficacy of PD-L1 silencing (b).

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$ATB^{0,+}$-targeted nanoparticles initiate autophagy suppression to overcome chemoresistance for enhanced colorectal cancer therapy

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Abstract: Oxaliplatin (OXA) resistance remains the major obstacle to the successful chemotherapy of colorectal cancer (CRC). As a self-protection mechanism, autophagy may contribute to tumor drug resistance, therefore autophagy suppression could be regarded as a possible treatment option in chemotherapy. Cancer cells, especially drug-resistant tumor cells, increase their demand for specific amino acids by expanding exogenous supply and up-regulating de novo synthesis, to meet the needs for excessive proliferation. Therefore, it is possible to inhibit cancer cell proliferation through pharmacologically blocking the entry of amino acid into cancer cells. SLC6A14 ($ATB^{0,+}$) is an essential amino acid transporter, that is often abnormally up-regulated in most cancer cells. Herein, in this study, we designed oxaliplatin/berbamine-coloaded, $ATB^{0,+}$-targeted nanoparticles ((O+B)@Trp-NPs) to therapeutically target SLC6A14 ($ATB^{0,+}$) and inhibit cancer proliferation. The (O+B)@Trp-NPs utilize the surface-modified tryptophan to achieve SLC6A14-targeted delivery of Berbamine (BBM), a compound from Chinese medicine, which could suppress autolysosome formation though impairing autophagosome-lysosome fusion. We verified the feasibility of this strategy to overcome the OXA resistance during colorectal cancer treatment. The (O+B)@Trp-NPs significantly inhibited the proliferation and decreased the drug resistance of resistant colorectal cancer cells. In vivo, (O+B)@Trp-NPs greatly suppressed the tumor growth in tumor-bearing mice, which is consistent with the in vitro data. This research offers a unique and promising chemotherapeutic treatment for colorectal cancer.

Keywords: $ATB^{0,+}$, Berbamine, Oxaliplatin, Chemoresistance, Autophagy

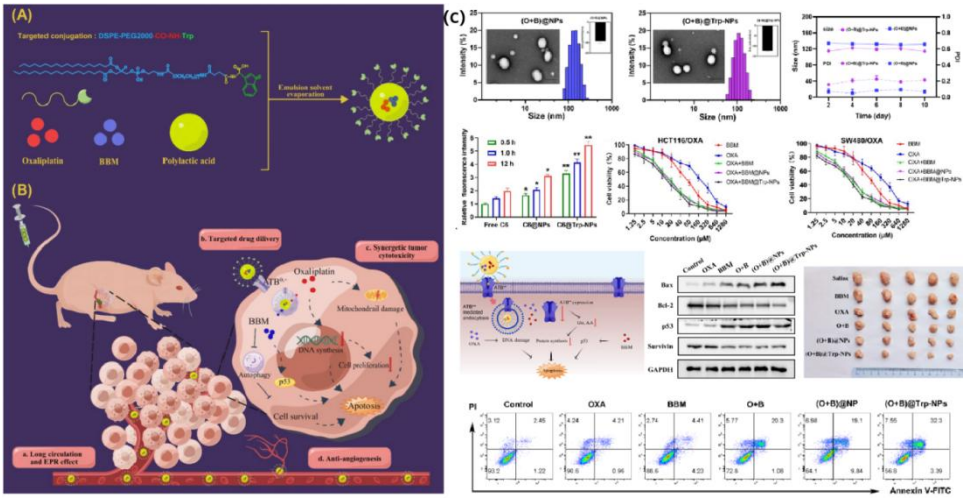

Fig.1 (A) The design and development of oxaliplatin/berbamine-coloaded amino acid-conjugated nanoparticles (O+B)@Trp-NPs. (B) The delivery characteristics and antitumor mechanism of (O+B)@Trp-NPs. (C) Characterization and therapeutic effect of (O+B)@Trp-NPs .

Remodeling immune microenvironment in rheumatoid arthritis by bioinspired gas generator for combined H2 delivery and immune modulation

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Abstract: Oxidative stress induced reactive oxygen sepsis (ROS) overproduction plays a vital role for rheumatoid arthritis (RA) progression as it can cause immune cells infiltration/activation in combination with pro-inflammatory cytokines secretion and produce an inflammatory environment in RA joint. Hydrogen therapy is an emerging strategy for inflammation-related disease as it can react with highly toxic hydroxyl radical (·OH) for ROS scavenging, while efficient and continuous *in situ* H_2 delivery is still challenging. To overcome these drawbacks, a M1 macrophages membrane coated biomimic H_2 generator (RADP@M1) was fabricated for targeted delivery ammonia borane (AB) and rapamycin (RAP) into RA joints. AB could release H_2 under acidic RA pathological environment for efficient ·OH scavenging and downregulate ROS level. By the virtue of M1 macrophage during progression of RA, M1 macrophage membrane from RADP@M1 could efficiently absorb board spectrum pro-inflammatory cytokines. Together with RAP, the as-prepared RADP@M1 could efficiently produce a non-inflammatory environment and induce dendritic cells (DCs) tolerance, M2 macrophages transition and regulatory T cells (T_{regs}) proliferation, thereby providing an immunosuppressive microenvironment. Overall, this work provided a novel approach for *in situ* hydrogen therapy in combination with synergistic immunoregulatory effect for RA immunotherapy.

Keywords: rheumatoid arthritis; immune microenvironment; hydrogen therapy; rapamycin; M1 macrophages membrane; ROS-responsive.

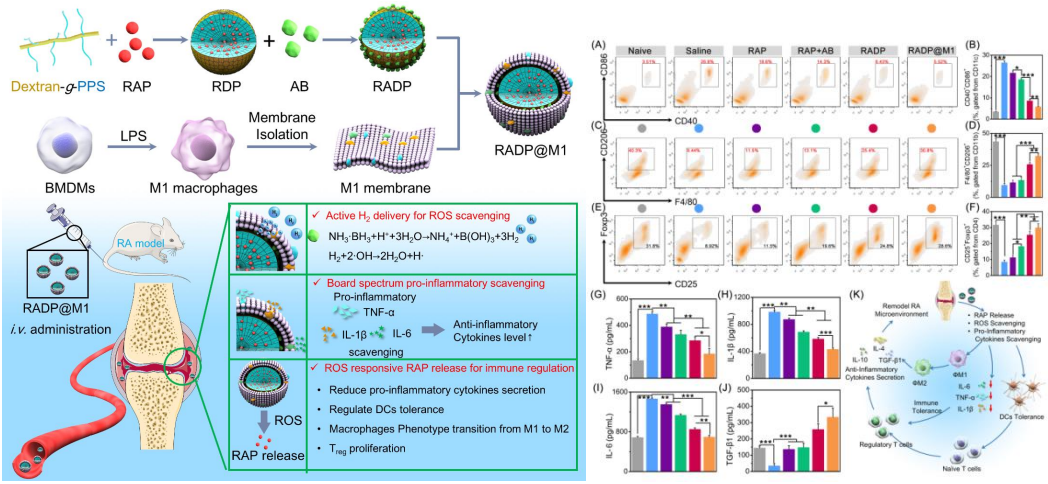

Figure. 1 schematic illustration of RADP@M1 preparation and its potential mechanism for anti-inflammatory therapy. (Left); and RADP@M1-mediated immune microenvironment modulation (Right).

Reference:

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Microenvironment-responsive liposomes with immune regulation function for Alzheimer's disease therapy

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Abstract: Alzheimer's disease (AD) is a complex neurodegenerative disease characterized by amyloid plaques formed by misfolded amyloid beta (Aβ). Microglia can degrade misfolded Aβ protein through autophagy, but under AD pathological conditions, microglia phagocytosis is impaired, and pro-inflammatory factors are released to accelerate AD progression, thereby inhibiting Aβ misfolding and increasing microglia Cellular clearance of aggregated Aβ is the key to the treatment of AD.Based on the above, this paper proposes a nano-drug delivery system RCLs@CNPs with dual effects of inhibiting Aβ aggregation and accelerating clearance. In this study, curcumin (Cur) was used as a drug to synthesize CNPs nanoparticles, and cardiolipin, DSPC, DOPC, etc. were used as raw materials to synthesize CNPs nanoparticles. The final formulation, RCLs@CNPs, escaped the blood-brain barrier through the trigeminal nerve pathway and reached the lesions in the brain after nasal administration. Under the influence of high reactive oxygen species in AD lesions, RCLs@CNPs disintegrated in response to reactive oxygen species. The CNPs nanoparticles encapsulated inside are released, and play the following roles: 1) Combine with Aβ through van der Waals force, hydrogen bond, electrostatic force and other forces, destroy the binding force between the misfolding of Aβ protein itself, thereby effectively inhibiting Aβ Protein misfolding. 2) Improve the autophagy function of microglia， and the ability of microglia to clear Aβ through the autophagy-lysosome pathway. 3) Polarized microglia phenotype, polarizing microglia from pro-inflammatory type (M1 type) to anti-inflammatory type (M2 type), and improve inflammation at AD lesions microenvironment, repair damaged neurons.

Keywords: Alzheimer’s disease; amyloid-β; microglia

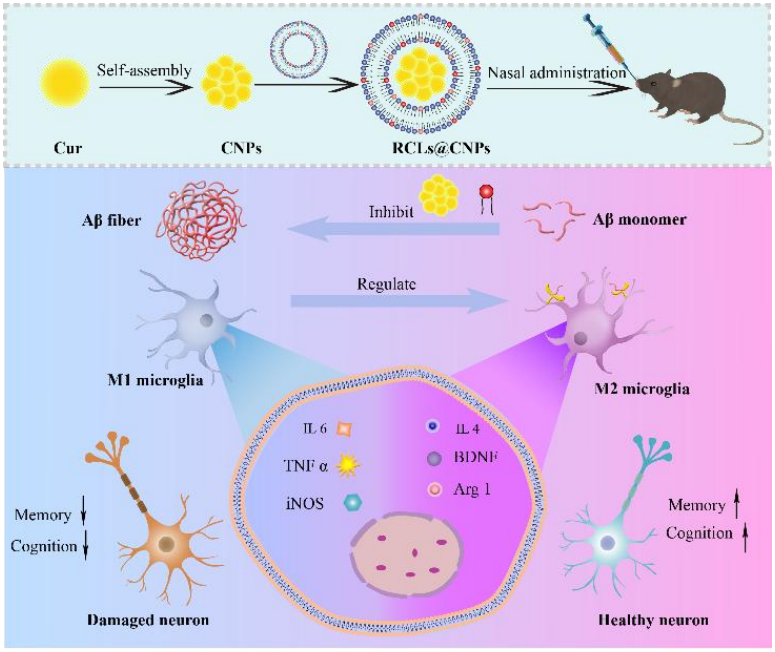

Figure. 1 Schematic showing the preparation and therapeutic effect of nanosystem.

Reference:

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Bromocriptine mesylate-loaded nanoparticles co-modified with low molecular weight protamine and lactoferrin for the treatment of Parkinson's disease

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Abstract: Parkinson's disease (PD) is a spontaneous nervous system disease, the existence of blood-brain barrier greatly reduces the amount of drugs entering the central nervous system. The aim of this study is to prepare Bromocriptine mesylate-loaded, low molecular weight protamine (LMWP) and lactoferrin (Lf) co-modified PLGA nanoparticles (LMWP/Lf-BCM-NPs) for targeted treatment of Parkinson's disease through intranasal administration. The solid spheres with modified surfaces could be observed under the transmission electron microscope. The optimized formulation prepared by emulsified solvent evaporation method exhibited a size of 248.53 ± 16.25 nm, and zeta potential of -2.63 ± 0.74 mV. Fourier transform infrared spectroscopy confirmed that LMWP and Lf were successfully attached to the nanoparticle surface. Using 16HBE14o- cells and BCECs cells as the cell model, flow cytometry analysed that the optimal ratio of LMWP and Lf was 3:1. The LMWP/Lf-NPs was found to exhibit significantly enhanced cellular accumulation than that of single-functionalized ligand-modified particles without causing observable cytotoxic effects. The cellular uptake demonstrated that LMWP was good as a first stage targeting ligand and Lf was good for the second stage. Following in vivo studies will be conducted to evaluate the therapeutic effects, biological safety and brain-targeting. We hope to develop a new non-invasive local brain-targeted drug delivery system through this study, which will provide a feasible scheme for the subsequent clinical treatment of PD.

Keywords: Parkinson's disease, nose-to-brain delivery, low molecular weight protamine, lactoferrin, nanoparticles

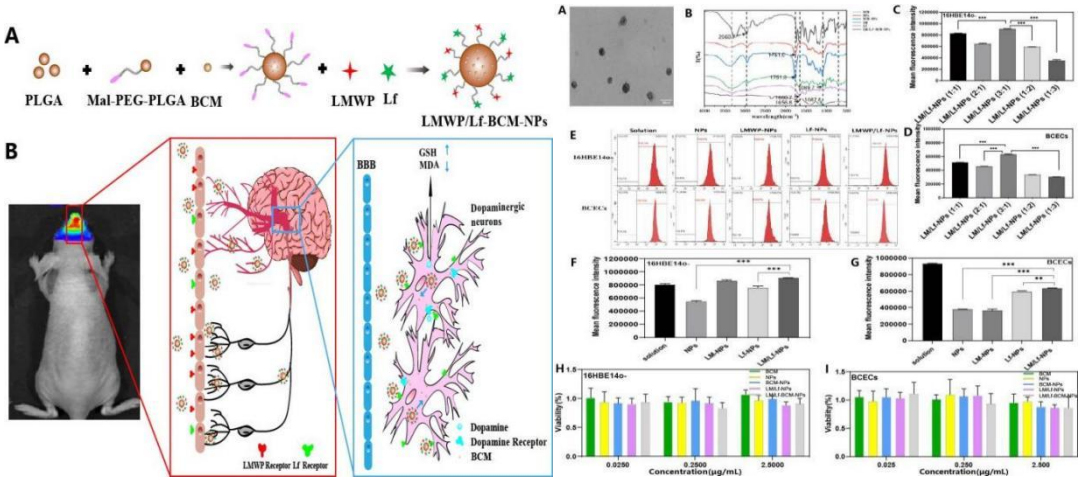

Figure. 1 Schematic illustration of the synthesis process and the nose-to-brain targeting mechanism of the LMWP/Lf-BCM-NPs (Left); Characterization and in vitro studies of the LMWP/Lf-BCM-NPs (Right)

Reference:

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Nanodelivery of juglone modulates intratumoral microbiota to reverse immunosuppressive tumor microenvironment of colorectal cancer

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Abstract: The increase in the relative abundance of carcinogenic microbiota within the tumor is correlated with colorectal carcinogenesis [1]. The modulation of intratumoral microbiome demonstrates great potential for treating colorectal cancer (CRC) [2]. Juglone (JUG, a naturally occurring quinone found in walnuts) exhibits pro-apoptotic and anti-bacterial effects. In this study, a poly(lactic-co-glycolic acid) (PLGA)-based nanoparticle modified with PEGylated aminoethyl anisamide (AEAA, a targeting ligand for Sigma-1 receptor on CRC) was developed for delivery of JUG to modulate intratumoral microbiota of CRC. The nanoformulation (PLGA.JUG.PEG-AEAA) demonstrated particle size (~ 114 nm), surface charge (~ -16 mV), and loading capacity (~ 6 wt%). PLGA.JUG.PEG-AEAA significantly promoted cellular uptake and cytotoxicity in CT26 cells. Tumor growth in CT26-luc-derived orthotopic CRC mice was significantly inhibited by PLGA.JUG.PEG-AEAA compared to other controls. PLGA.JUG.PEG-AEAA also significantly altered the microbial species diversity in the tumor, and the relative abundance of protective genera (e.g., Lachnospiraceae, Roseburia, Faecalibacterium and Bifidobacterium) was significantly increased. The change of intratumoral microbiota resulted in the reversal of immunosuppressive tumor microenvironment, which was evident by the increase of $CD8^+$ T cells and the reduction of regulatory T (Treg) cells within the tumor. These preliminary results indicate the potential of our nanoformulation in the treatment of CRC.

Keywords: intratumoral microbiota, nanoparticle, drug delivery, colorectal cancer, immunotherapy

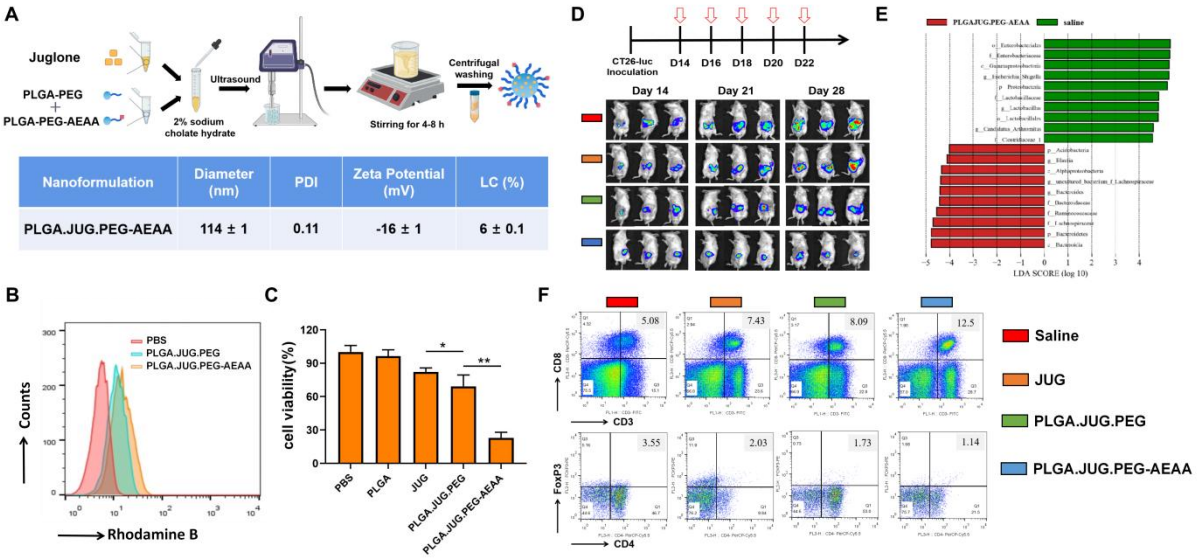

Figure. 1 The PLGA.JUG.PEG-AEAA modulates intratumoral microbiota and reverses immunosuppressive tumor microenvironment of CRC.

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Immunosuppressive triangle depletion through the combination punches strategy for enhanced immunotherapy

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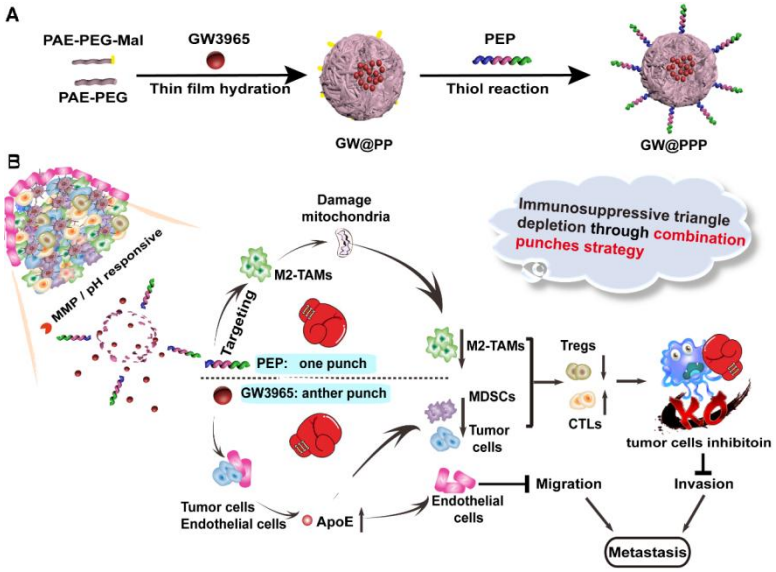
Abstract: Tumor immunotherapy non-responders often have high levels of tumor-associated macrophages (TAMs), circulating myeloid-derived suppressor cells (MDSCs), and regulatory T cells (Tregs), which forms a vicious “immunosuppressive triangle” to promote tumor growth and metastasis. Rather than single immunosuppressive cell modulation in some reports, it is more meaningful to precisely target as well as overall deplete the immunosuppressive triangle for enhanced immunotherapy. To achieve this, a pH/matrix metalloproteinase-2 (MMP2) dual responsive nanoplatform was constructed. The acidic sensitive poly β-amino esters-polyethylene glycol nanoparticles (PAE-PEG NPs) loaded with liver-X-receptor agonist GW3965 were prepared, and then were decorated with MMP2 sensitive M2-TAMs targeted apoptotic peptides (PEP) to obtain GW3965@PAE-PEG-PEP (GW@PPP). After reaching tumor microenvironment, the combination punches strategy based on this nanoplatform was implemented. As one punch, the MMP2 cleaved PEP segments induced M2-TAMs apoptosis specifically. As another punch, the acidic responsive GW3965 release promoted immunoregulatory apolipoprotein E (ApoE) transcription, further inhibiting the survival of MDSCs, tumor cells and endothelial recruitment. In addition, Tregs, the formation and recruitment of which was related to MDSC and TAMs, were suppressed subsequently. Overall, the GW@PPP directly drove immunosuppressive triangle depletion and further immune response, which effectively prevented tumor growth and metastasis for enhanced immunotherapy in an all-round way.

Keywords: Liver-X-receptor agonist; apolipoprotein E; immunosuppressive triangle; immunotherapy



Scheme 1. A) Formulation of GW@PPP. B) GW@PPP depleted immunosuppressive triangle completely and directly based on combination punches strategy, thereby driving immune response and prevent tumor growth and metastasis.

References:

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A Supramolecular Hydrogel for Alleviating Renal Interstitial Fibrosis via Extended-Release of miR-29b

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Abstract: Micro RNAs (miRNAs)-based therapies targeting activated fibroblasts have shown great therapeutics potential for alleviating fibrosis. Previous studies showed miR-29 family has been involved in the development of multiple organ fibrosis by regulating the extracellular matrix synthesis. miR-29b is shown to be down-regulated in various animal models of renal fibrosis. Thereby, we hypothesize that miR-29b replacement represents a promising treatment option against renal fibrosis. However, an efficient method of kidney-targeted miRNA delivery has yet to be established. For kidney-targeted gene delivery, cationic bovine serum albumin (cBSA) has great potential for clinical application. Here, we report the development of a localized and sustained delivery of cBSA/miR-29b nanocomplex via a host-guest supramolecular hydrogel to the kidney. Specifically, cationic bovine serum albumin is used to complex with miR-29b to afford nanocomplexes (cBSA/miR-29b), which is proven to specifically inhibit fibroblast activation in a dose-dependent manner in vitro. Following unilateral ureteral obstruction in mice, a single injection of the hydrogel loaded with cBSA/miR-29b in vivo, significantly downregulated proteins and genes related to fibrosis for up to 21 days without affecting the normal liver or kidney functions. Overall, the localized delivery of cBSA/miR-29b via a host-guest supramolecular hydrogel represents a safe and effective intervention strategy to delay and reverse the progression of interstitial renal fibrosis.

Keywords: Supramolecular hydrogel; Host-guest interaction; Renal fibrosis; Cationic albumin; miR-29b

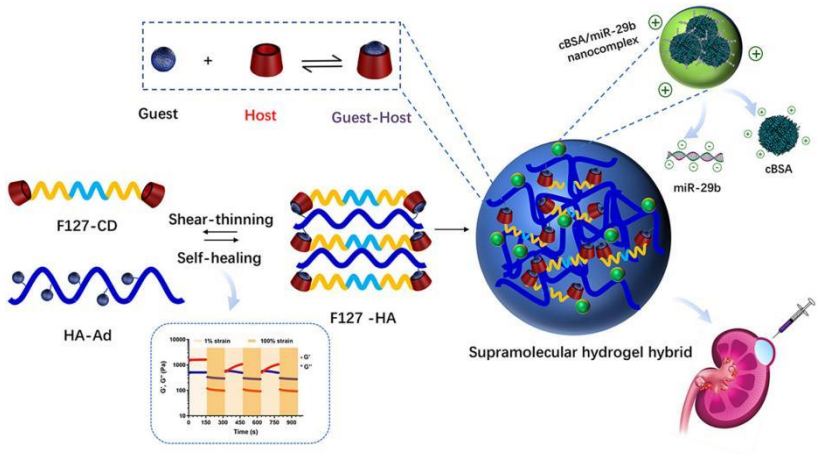

Figure. 1 Schematic illustration of host-guest supramolecular hydrogel (F127-HA) loaded cationic albumin miRNA nanocomplexes (cBSA/miR-29 b) for renal fibrosis therapy.

The Dissolution, Reassembly and Further Clearance of Amyloid-β Fibrils by Tailor-designed Dissociable Nanosystem for Alzheimer's Disease Therapy

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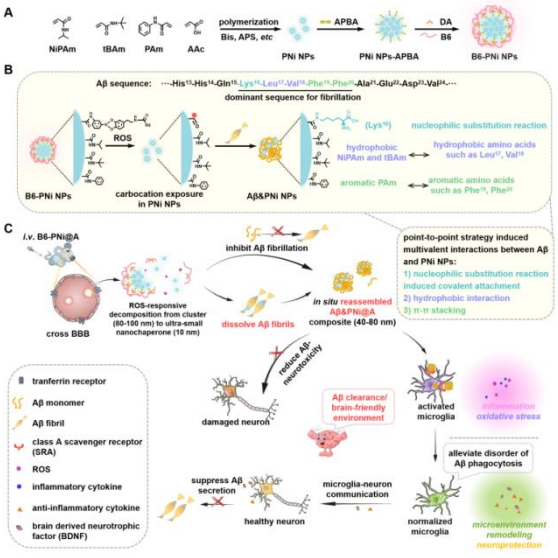
Abstract: The fibrillation of amyloid-β (Aβ) is the critical causal factor in Alzheimer's disease (AD), the dissolution and clearance of which are promising for AD therapy. Inspired by molecular chaperone that disassembles Aβ fibrils, artificial chaperone is an attractive alternative, however, its design is challenging due to the demand for high Aβ-binding selectivity/affinity. Here, clustered nanochaperone is tailor-designed with controllable size and surface chemistry. In response to AD microenviroment, clustered nanochaperone decomposes into ultra-small nanochaperones, exposing more binding sites available for interaction with Aβ. Based on point-to-point matching with Aβ strategy, nanochaperone captures Aβ with multiple interactions, including convelent linkage formed by nucleophilic substitution reaction. Such high Aβ-binding selectivity/affinity allows the reduction of Aβ-Aβ interactions to disassemble Aβ fibrils. More than that, monomeric Aβ after fibrils dissolution and nanochaperones reassemble into Aβ&nanochaperone composite. The *in situ* reassembly pattern achieves Aβ receptor-mediated drug delivery into microglia, and further Aβ clearance by normalizing microglial dysfunction. Overall, clustered nanochaperone realizes cascaded targeted Aβ and microglia for dissolution/reassembly/clearance of Aβ fibrils. After treatment, the Aβ burden, neuroinflammation, and cognitive impairments are relieved in mice. The point-to-point matching strategy provides a clue to nanochaperone design in amyloid diseases, showing meaningful insight in biomedicine.

Keywords: Alzheimer's disease; amyloid-β; dissociable nanosystem; neuroinflammation



Scheme 1. Schematic showing the preparation and therapeutic effect of tailor-designed dissociable nanosystem.

Reference:

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Cell penetrating peptide modified liposomes prepared by HA post-crosslinking or electrostatic absorption for trans-endothelial delivery and tumor retention

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Abstract: Nano-drug delivery systems that rely on the enhanced penetration and retention (EPR) effects suffer from limited extravasation into the tumor. Therefore, some researchers have proposed active transcytosis pathway to improve the extravasation and penetration efficiency of nano-drugs. However, transcytosis between tumor cells may lead to drugs efflux from tumor cells, similar to drug resistance, resulting in poor anti-tumor effects. To address the paradox between endothelial transcytosis and tumor retention, this study developed two drug delivery systems modified with a cell penetrating peptide (CPP)-low molecular weight protamine (LMWP), then crosslinked (HA-P-L) or electrostatically (HA/P-L) modified with hyaluronic acid (HA). *In vitro* studies demonstrated that HA-P-L could be uptaken by endothelial cells (bEnd.3) via an active, caveolin and heparin sulfate proteoglycan (HSPG)-mediated endocytosis and achieved trans-endothelial delivery. Moreover, HA-P-L could maintain higher integrity after transcytosis for further tumor targeting, compared to HA/P-L. More importantly, more HA-P-L could be retained in tumor cells (4T1) compared to HA/P-L, HA-L or P-L, leading to more potent efficacy. This may be attributed to the aggregation of HA-P-L after HA degradation inside 4T1 cells in response to intracellular hyaluronidase (HAase), which was consistent with the aggregation of liposomes after incubation with HAase in TEM images. In small tumor-bearing mice with little EPR effect, HA-P-L_{BAY} exhibited enhanced tumor targeting and extravasation, as well as optimal suppression of tumor growth due to the retention compared with other BAY formulations. Overall, the HA post-crosslinked CPP-modified liposomes can actively transport across endothelial cells with higher integrity, which could help them retain within cancer cells and exhibit effective anti-tumor activity.

Keywords: Active transport; trans-endothelial; post-crosslinking liposomes; tumor retention

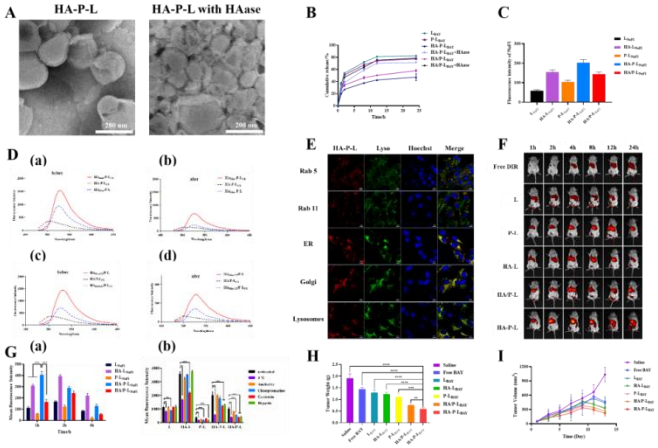

Figure. 1 HA-P-L for trans-endothelial delivery and tumor retention.

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Study on the treatment of ulcerative colitis with a probiotic spore drug complex

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Abstract: UC has become a global human disease and is classified by the WTO as one of the common intractable diseases. Sulfasalazine (SSZ) is a clinically approved drug of choice for the treatment of ulcerative colitis. Azo reductase (AR) secreted by microorganisms decomposes SSZ into 5-aminosalicylic acid (5-ASA) and sulfasalazine (SP), which exert anti-inflammatory effects, while SP often triggers a series of adverse reactions. Long term use of SSZ can also lead to a sustained decrease in AR secretion in the colon due to the antibacterial effect of SP. In addition, UC patients have a very limited and low diversity of gut microbiota, which will further inhibit the secretion of AR. However, the content of AR is crucial for SSZ to exert anti-inflammatory effects. Therefore, we constructed a "probiotic spore drug" complex (CBs/SSZ/CS/EudS-100), which has the following advantages: (1) CBs successfully loaded hydrophobic drug SSZ in a simple way, improving the dispersibility of hydrophobic drug SSZ and the loaded SSZ did not affect the germination of CBs or inhibit the activity of CB. (2) CBs germinate into CB and secrete AR, which in turn regulates the intestinal microbiota to secrete AR, thereby double enhancing the efficiency of SSZ conversion into anti-inflammatory drugs 5-ASA. (3) Under the protection of colon responsive materials CS and EudS-100, SSZ can smoothly reach the colon through the stomach and small intestine, achieving precise controlled release. (4) By repairing the intestinal epithelial barrier, SP can be inhibited from entering the bloodstream, thereby reducing the toxic and side effects caused by SP. This strategy cleverly combines intestinal microbiota regulation with SSZ anti-inflammatory therapy to maximize the efficacy of SSZ, reduce oral dose, and toxic side effects.

Keywords: ulcerative colitis, clostridium butyricum spores, salazosulfapyridine, azo reductase, intestinal flora

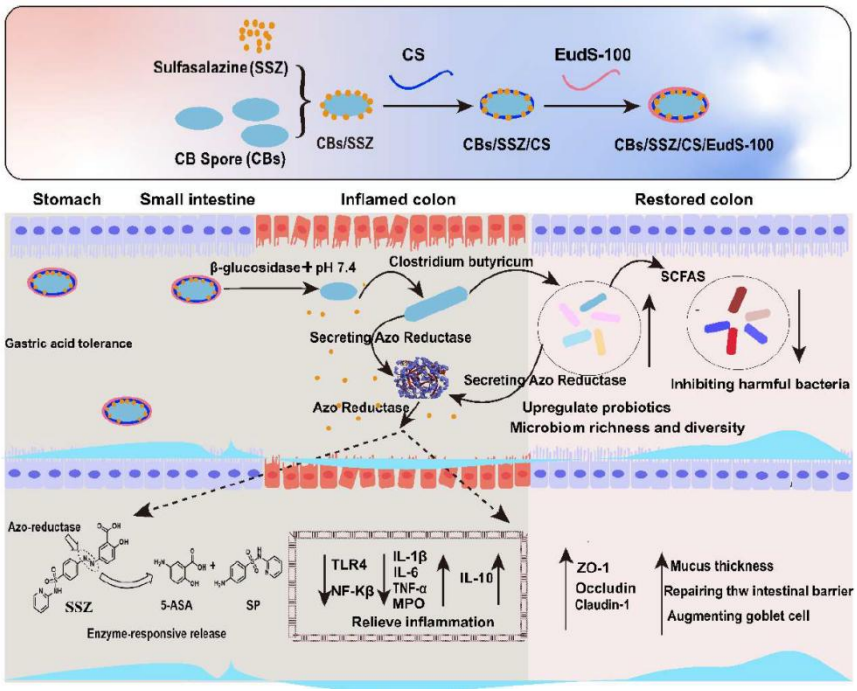

Figure. 1 Schematic illustration of the synthetic procedure of CBs/SSZ/CS/EudS-100 and the proposed mechanism of CBs/SSZ/CS/EudS-100-mediated treatment of ulcerative colitis.

Nanoparticle cluster depolymerizes and removes amyloid fibrils for Alzheimer’s disease treatment

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Abstract: Aberrant amyloid-β (Aβ) fibrillation is the key event in Alzheimer's disease (AD), the depolymerization and removal of which are being pursued with enthusiasm. Herein, a nanoparticle cluster is designed for amyloid-matching based on point-to-point strategy to prevent amyloid fibrillation. After reaching AD nidus, this cluster decomposes into ultra-small nanoparticles, and exposes more binding sites in different types to match with Aβ sequence via multivalent binding. Notably, AD microenvironment sensitive nucleophilic substitution reaction generates strong covalent linkage between nanoparticle and amyloid, which ensures high binding specificity/affinity. The strong binding event competitively reduces amyloid-amyloid interactions thereby disintegrating amyloid fibrils. Not only that, monomeric Aβ after fibrils depolymerization and nanoparticles reassemble into nanoparticle&Aβ composite. Such composite realizes Aβ receptor mediated precise rapamycin delivery into microglia, further normalizing microglial immunologic dysfunction for Aβ removal and brain-friendly environment. This system interferes with amyloid fate, rescues memory deficits in AD.

Keywords: Alzheimer's disease; amyloid fibrils; microglia; reassembly

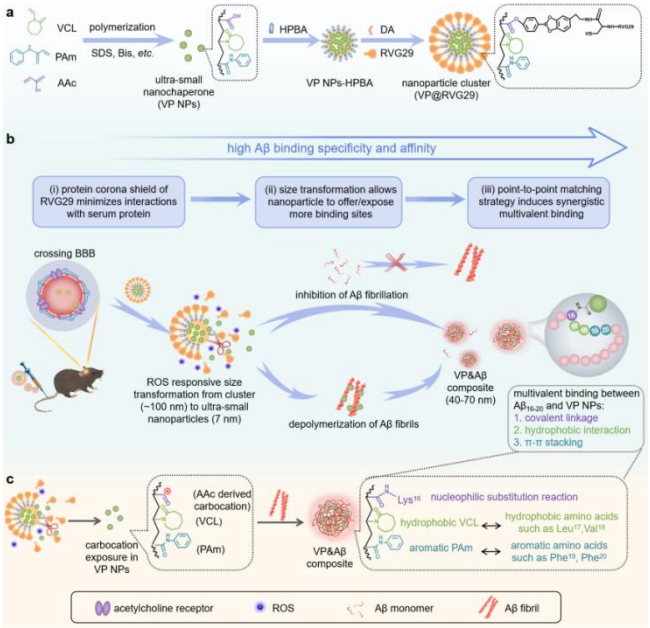

Figure. 1 Design and mechanism of nanoparticle cluster (VP@RVG29). A) Construction of VP@RVG29. The surface conjugation with HPBA induces nanoparticle (VP NPs) to aggregate into nanocluster, and then facilitates DA and RVG29 modification to form nanoparticle cluster (VP@RVG29). B) Schematic showing that VP@RVG29 depolymerizes Aβ fibrils with high Aβ binding specificity and affinity.

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Mechanism of downregulation of miR-1343-3p-map3k6 / mmp24 protein expression by salidroside inhibits gastric cancer cell proliferation and migration

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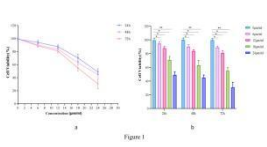
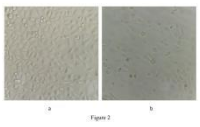
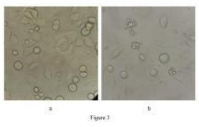
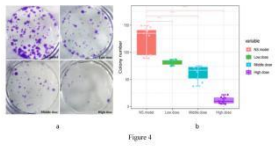
Abstract: Objective: To investigate the effects of salidroside on the proliferation and migration of human gastric cancer MGC-803 cells, and to explain the molecular mechanism and provide new ideas for the clinical treatment of gastric cancer. Methods: the anti proliferative effects of salidroside on human gastric cancer cells were evaluated by CCK-8 assay; Clonogenic assay to examine the effects of salidroside drugs on the clonogenic ability of human gastric cancer cells; Transwell assay was performed to detect the effect of salidroside on the invasive ability of human gastric cancer cells; Cell scratch assay was performed to detect the effect of salidroside on the migration ability of human gastric cancer cells; The effects of salidroside on the protein expression of map3k6 and mmp24 in human gastric cancer cells were determined by immunofluorescence. The miRNA expression of miR-1343-3p gene and the mRNA expression of MAP3K6 and MMP24 gene were detected by qRT-PCR. Results: CCK-8 cytotoxicity assay showed that salidroside significantly inhibited the proliferation of human gastric cancer MGC-803 cells,and the inhibitory effects of salidroside exhibited a concentration time effect dependence. Cell clonogenic assay showed that salidroside decreased cell clonogenic capacity. Cell invasion assay showed that after salidroside was applied to human gastric cancer MGC-803 cells, the invasive ability of the cells was significantly decreased with the administration of increasing concentrations. Scratch assay showed that salidroside decreased the wound healing ability of gastric cancer cells, and the effect of high concentration was significant.Immunofluorescence analysis and QRT PCR showed that mRNA and protein expression of map3k6 and mmp24 genes were downregulated and miRNA expression of mir-1343-3p gene was upregulated after salidroside treatment on human gastric cancer MGC-803.Conclusions: Salidroside can significantly inhibit the proliferation and migration abilities of human gastric cancer MGC-803 cells.

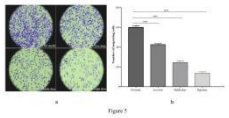
Key words : Salidroside; Stomach; miR-1343-3p; MAP3K6;MMP24;

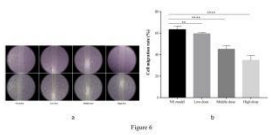


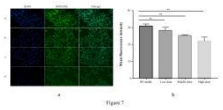


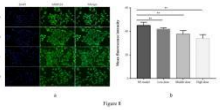


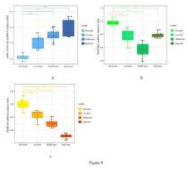












Polyamine metabolism-based regulation of “vesicles”for antitumor immunotherapy

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Abstract: In the hypoxic tumor microenvironment (TME), the upregulation of polyamine metabolism is a crucial mechanism for cancer cells to maintain a consistent and heightened level of intracellular polyamines necessary for sustaining their proliferation efforts. The polyamine pathway is a crucial metabolic pathway linked to the progression and development of cancer. Ornithine decarboxylase (ODC), the rate-limiting enzyme in polyamine biosynthesis, is a direct transcriptional target of the oncogene MYCN. Furthermore, glutathione (GSH) plays a significant role in ensuring high levels of redox homeostasis in tumors. However, elevated levels of GSH in tumors can undermine the immune response against cancer. Therefore, in this paper, The present study describes the synthesis of novel vesicles, termed DCs, composed of lipid-like materials derived from the ODC inhibitor difluoromethyl ornithine (DFMO) and cinnamaldehyde (Cin). These vesicles possess the unique capability of inhibiting polyamine synthesis and depleting intracellular GSH, which is achieved through the precipitation of Cin in a Michael addition reaction with GSH. Furthermore, encapsulation of the first-line chemotherapeutic agent oxaliplatin (OXP) within the DCs promotes immunotherapy of colorectal cancer by inducing immunogenic cell death and stimulating dendritic cell maturation and CD8+ T cell infiltration. Upon reaching the tumor, the DCs dissociate in response to the acidic tumor microenvironment, triggering the release of DFMO and leading to intracellular depletion of GSH. Altogether, the synthesized DC@OXP formulation offers a simple and effective approach for targeting the immunosuppressive microenvironment of colorectal cancer and inducing robust antitumor immune responses.

Keywords: Polyamines;tumor metabolism;drug delivery

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Redox-Responsive Nanomedicine of Doxorubicin-Conjugated Poly-L-Glutathione Oxidized for Cancer Therapy

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[#] These authors contributed equally to this work.

Abstract: Abstract: Nanomedicines with unapproved materials could not be applied in clinic. Herein, we fabricated a redox-responsive nanomedicine with clinical-applied anticancer of doxorubicin (Dox) and endogenous molecule of L-glutathione oxidized (GSSG) for cancer therapy. The carboxyl and amino groups in L-glutathione oxidized can be reacted itself to form the poly-L-glutathione oxidized peptide-like polymer. Meanwhile, the Dox were conjugated in poly-L-glutathione oxidized polymer by amnio group in Dox and the structure of Dox-conjugated poly-L-glutathione oxidized polymer (Dox-Poly GSSG) was confirmed by FT-IR, NMR and MALDIT-TOF. Afterward, the drug loading of Dox (22%) in poly-GSSG was measured by UV-vis and the accumulative Dox release rate of Dox-Poly GSSG is 46% in 5 mg/mL reduced glutathione (GSH) environment at 72 h. The size stability of Dox-Poly GSSG in PBS and PBS with GSH was evaluated by dynamic laser scatter (DLS) and transmit emission microscopy (TEM). Furthermore, cell viabilities of Dox-Poly GSSG were similar with free Dox evaluated by CCK-8 assay and flow cytometry experiment, respectively. The Dox-Poly GSSG could distribute into nuclei at 8 h in Hela cells and tumor tissues in 48 h in H22-bearing mice. The tumor inhibition experiments showed that the Dox-Poly GSSG group can significantly inhibit the tumor growth compared to saline group and avoid major side effects to normal tissues compared to free Dox. Based on these results, we can make a conclusion that this redox-responsive nanomedicine with clinical-applied anticancer of Dox and endogenous molecule of GSSG is a potential candidate for clinical application.

Keywords: Redox-responsiveness, Doxorubicin, L-Glutathione oxidized, nanomedicine

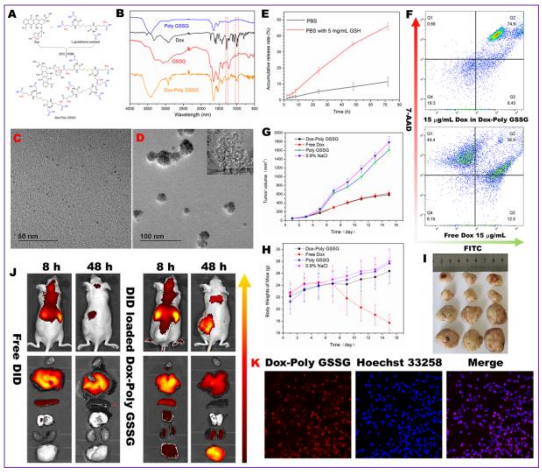

Figure 1 (A)The synthesis route of Dox-Poly GSSG; (B) FT-IR spectra of Dox, GSSG, Poly GSSG and Dox-Poly GSSG; The nanoparticles of (C) Dox-Poly GSSG in water and (D) in GSH environment measured by TEM; (E) The accumulative Dox release rate from Dox-Poly GSSG in 5 mg/mL GSH environment in 72 h; (F) H22 cell apoptosis results of free Dox and Dox-Poly GSSG at 24 h; (G) Tumor volumes and (H) body weights evaluated by H22-bearing nude mice of 0.9% NaCl, Poly GSSG, free Dox and Dox-Poly GSSG groups in 15 days; (I) The final tumor

Cascade-responsive "oxidative stress amplifiers"simultaneously destroy lysosomes and co-deliver CRISPR/Cas9 to enhance oxidative damage in tumor

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Abstract: Amplifying intracellular oxidative stress by organelle-targeting ROS production combined with tumor cell-specific gene silencing is a promising strategy for tumor treatment. However, due to the vulnerability of CRISPR/Cas9 ribonucleoproteins (RNPs) to ROS, co-delivery of CRISPR/Cas9 RNPs and ROS generators to enhance the sensitivity of tumor cells to oxidative stress remains challenging. Here, we propose a cascade-responsive "oxidative stress amplifier" (named DR-TAF-pHT/FA), which can successively respond to cathepsin B, localized laser irradiation and ATP to generate ROS on tumor cell lysosomal membranes and release Cas9/sg*Nrf2* RNPs for efficient gene silencing. We demonstrate that, under NIR irradiation, DR-TAF-pHT/FA achieves targeted rupture of lysosomal membranes, inducing significant intracellular oxidative stress. Meanwhile, due to the protective function of TAF coating (TA-Fe^{3+} coordination self-assembled networks), Cas9/sg*Nrf2* RNPs can safely escape into the cytoplasm and be released in response to ATP, further amplifying oxidative stress through efficient *Nrf2* gene silencing and promoting tumor cell apoptosis. Furthermore, treatment with DR-TAF-pHT/FA+NIR significantly improves tumor ablation efficiency and extend median survival time (over 70 days) in Hela xenograft models. We think this "oxidative stress amplifier" provides a new paradigm for multimodal and synergistic tumor therapy through precise lysosomal membrane bursting together with efficient *Nrf2* gene silencing.

Keywords: intracellular oxidative stress, synergistic tumor therapy, lysosomal membranes rupture, CRISPR/Cas9 delivery, gene editing

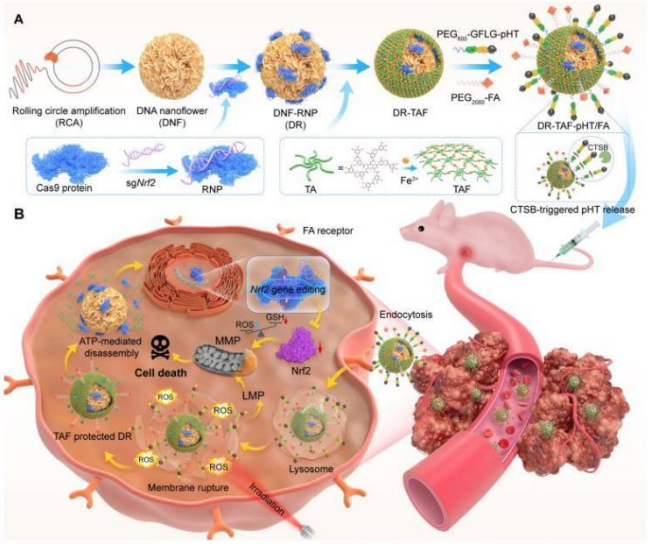

Figure 1. Schematic illustration of the preparation and intracellular fate of the cascade-responsive uncloaking nanoplatform (DR-TAF-pHT/FA) for amplifying oxidative stress in tumor cells.

A probiotic delivery system based on calcium tungstate hydrogel for precise regulation of intestinal microbiota in the treatment of colitis

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Abstract: The gut microbiome is closely associated with the occurrence and development of inflammatory bowel disease (IBD). Gut microbial dysbiosis is a key cause of IBD. Modulation of gut microbiome homeostasis is a promising strategy for the prevention and treatment of IBD. Delivery and colonization of the gut microbiome with probiotics can modulate intestinal flora homeostasis. However, oral delivery of probiotics is not only attacked by the harsh physiological environment of the gastrointestinal tract, but also the abnormal expansion of Enterobacteriaceae in the pathological environment of IBD can make it difficult for the delivered probiotics to survive and colonize.Based on this, in order to selectively inhibit Enterobacteriaceae to provide ecological niches for probiotics colonization, a novel oral probiotic delivery system (BC@CTM) was successfully constructed by encapsulating the probiotic Bacillus coagulans (BC) with calcium tungstate microgel (CTM). BC@CTM not only protects probiotics against the harsh physiological environment of the gastrointestinal tract and enhances their intestinal adhesion, but also responds to the over-expression of calprotectin (CP) in pathological conditions of enteritis by releasing tungsten, and tungsten selectively inhibits Enterobacteriaceae by replacing molybdenum in the molybdenum cofactor in the respiratory-dependent nitrate reductase of Enterobacteriaceae, breaks the ecological niche occupied by harmful bacteria, enhances the colonization of delivered probiotics, and ultimately improves the therapeutic effect of probiotics on IBD.

Keywords: colitis; intestinal flora; probiotic delivery system; calmodulin response; ecological niche competition

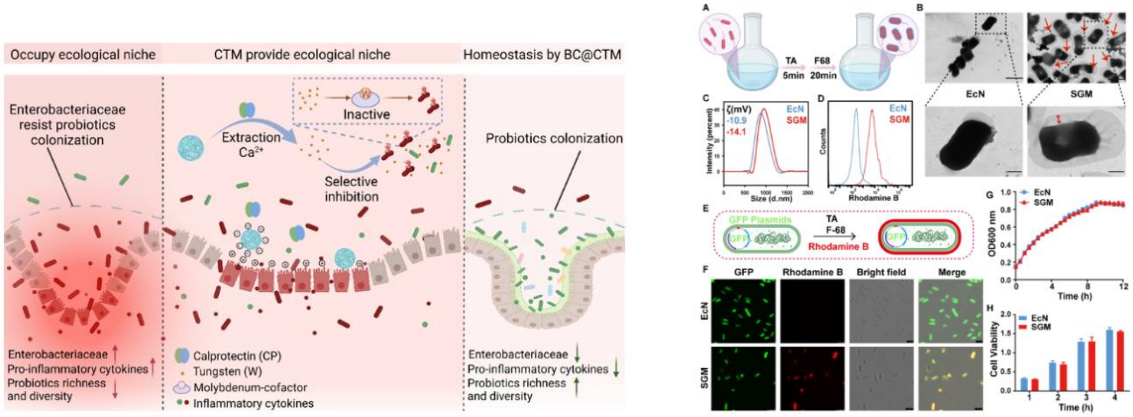

Figure. 1 BC@CTM provides a strategy that protects probiotics while providing additional ecological niches for probiotic colonization during colitis. Preparation and characterization of CTM and selective inhibition of Enterobacteriaceae

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“Y-type” PEG modified liposomes could eliminate the accelerated blood clearance (ABC) phenomenon and improved tumor therapy

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Abstract: Poly(ethylene glycol) (PEG) is widely applied to decorate nanocarriers due to its “long circulation” characteristics. However, the applications of linear PEG-modified nanocarriers have been hindered by severe adverse effects due to the accelerated blood clearance (ABC) phenomenon. It was universally known that anti-PEG antibodies (APAs) were main culprits in ABC phenomenon which induced the significant change in pharmacokinetics, biological distributions of the second injection and triggered complement activation-related pseudoallergies (CARPA). Recent studies have illustrated that APAs triggered the ABC phenomenon of PEGylated protein drug and even related to the CARPA of COVID-19 vaccine. Therefore, it is urgent to inhibit the generation of APAs and eliminate the ABC phenomenon. Here, “Y-type” PEG was chosen to replace linear PEG due to its weak immunogenicity. “Y-type” PEG-lipid derivatives [DSPE-mPEG$_{2,n}$ (n = 2, 10, and 20 kDa)]-modified doxorubicin liposomes (DOX-PL$_{2,n}$) and topotecan liposomes (TP-PL$_{2,n}$) induced lower levels of APAs and could avoid activating complement system. In further research, we found that liposomes decorated with DSPE-mPEG$_{2,n}$ could avoid the ABC phenomenon after duplicate injections. Furthermore, pharmacodynamic tests indicated that DOX-PL$_{2,n}$ and TP-PL$_{2,n}$ improved the curative effect of S180 tumor than DOX-PL$_{2k}$ and TP-PL$_{2k}$ (linear PEGylated liposomes). For the first time, DOX-PL$_{2,n}$ and TP-PL$_{2,n}$ were used for *in vivo* pharmacokinetic and pharmacodynamic experiments. Liposomes ornamented with “Y-type” PEG may provide new approaches to maintaining long blood circulation time, eliminating the ABC phenomenon of encapsulated active compounds, and also could weaken CARPA and improve tumor therapeutic effect. Our research aims to promote the research and development of “Y-type” PEG-decorated nanocarriers and provide a substantial academic basis for its clinical application.

Keywords: “Y-type” PEG derivatives; Accelerated blood clearance; Liposomes; Anti-PEG antibody; Tumor treatment

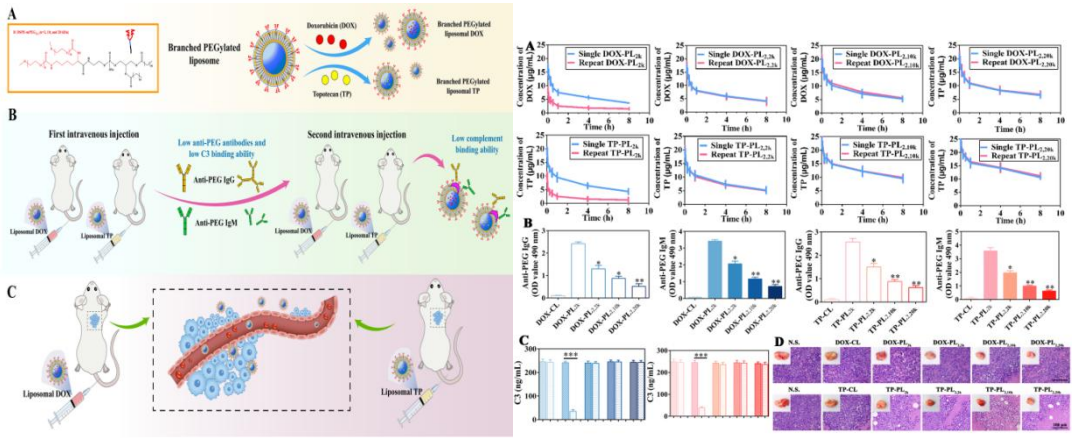

Figure. 1 Schematic illustration of the preparation of “Y-type” PEGylated liposomal DOX and liposomal TP, which could avoid the ABC phenomenon and improve anti-tumor effect (Left); “Y-type” PEGylated liposomal DOX and liposomal TP eliminated the ABC phenomenon by inducing lower levels of APAs and inactivating complement system, and imrproved tumor therapeutic effect. (Right).

Reference:

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Probing the Superiority of Diselenium Bond on Docetaxel Dimeric Prodrug Nanoassemblies: Small Roles Taking Big Responsibilities

Shiyi Zuo, Bingjun Sun, Yinxian Yang, Shuang Zhou, Yu Zhang, Mengran Guo, Mengchi Sun, Cong Luo, Zhonggui He and Jin Sun*

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Keywords: diselenide bond, dimeric prodrug, self-assembly, redox-responsive, chemotherapy

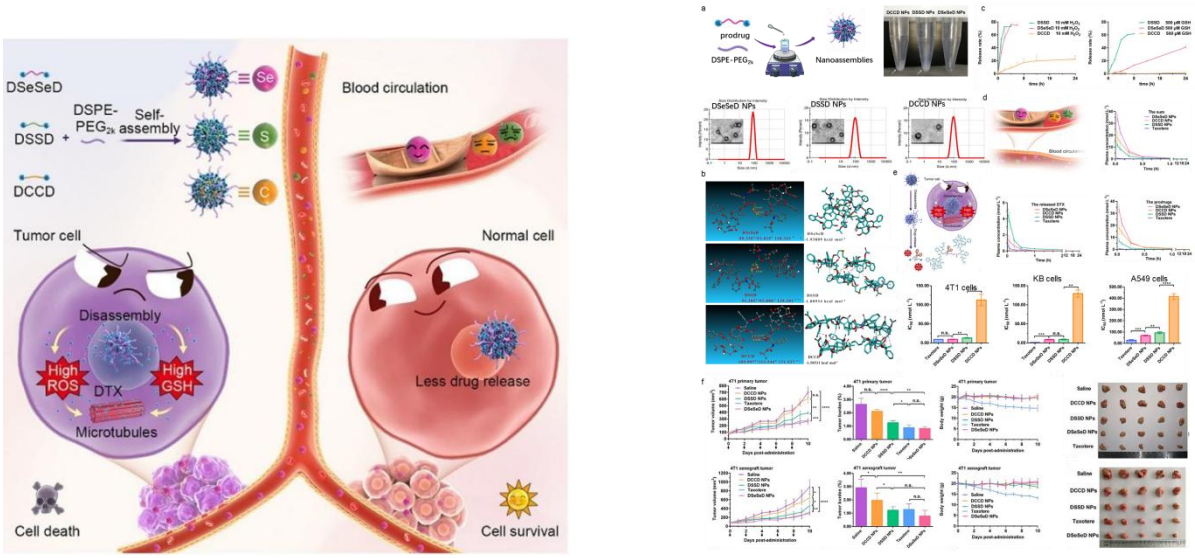

Figure. 1 Schematic illustration (Left); and the Superiority of Diselenium Bond on Docetaxel Dimeric Prodrug Nanoassemblies for cancer therapy (Right).

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A Probiotic Spore-Based Oral Autonomous Nanoparticles Generator for Cancer Therapy

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Abstract: Recently, oral drug-delivery systems based on probiotics have attracted wide attention, especially for colon cancer therapy due to the exceptional tumor colonizing and targeting abilities of probiotics.Interestingly, dormant spores of BC encased in a thick hydrophobic protein coat are one of the most durable static biological structures, which could resist the harsh acidic environment, toxic chemicals, and extreme temperature.Spores, the dormant life forms of probiotics, can germinate to metabolically active vegetative cells with the disintegration of their hydrophobic protein coat in the intestinal microenvironment, which provides the possibility for the formation of nanoparticles (NPs) in vivo. Inspired by the natural physiological process of spores, herein, an oral autonomous NPs generator is developed to overcome the spatially variable gastrointestinal tract environment and multibiological barriers. Spores modified with deoxycholic acid (DA) and loaded with chemotherapeutic drugs (doxorubicin and sorafenib, DOX/SOR) serve as an autonomous production line of NPs, which can efficaciously protect the drugs passing through the rugged environment of the stomach and furthermore can be transported to the intestinal environment and colonized rapidly.Subsequently, the DOX/SOR/Spore-DA NPs are produced by the autonomous NPs generator in the intestinal regions based on the disintegrated hydrophobic protein and the hydrophilic DA, and they can efficiently penetrate the epithelial cells via the bile acid pathway, increasing basolateral drug release. In vitro and in vivo studies confirm that this biological nanogenerator can autonomously produce substantial NPs in the intestine, providing a promising strategy for cancer therapy.

Keywords: probiotic;spore;nanoparticle;CRC

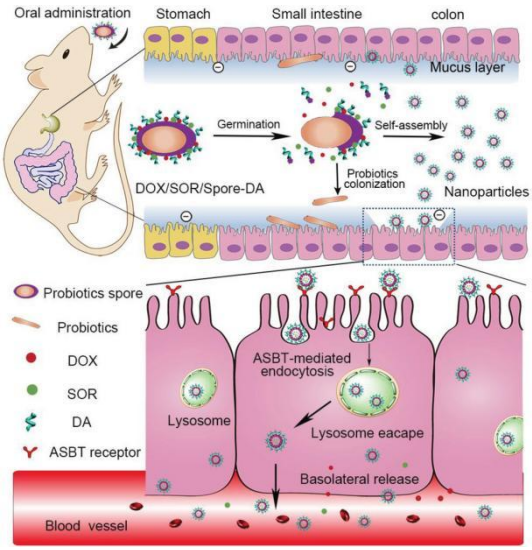

Figure.1 Schematic illustration of the autonomous nanoparticles generator based on intestinal microenvironment control fabrication and transepithelial transport mechanism of DOX/SOR/Spore-DA

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Supramolecular Macrocycle as an Efficient Joint Lubricant and Drug Delivery System for Synergistic Osteoarthritis Therapy

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Abstract: The complexity and progressive nature of diseases require multifunctional materials for combination therapy to enhance treatment efficacy. Multifunctional materials are an effective way to achieve drug synergism and desired therapeutic effects. However, multifunctional materials face the problem of having a complex composition. Herein, in view of the complex nature of diseases, based on the concept of supramolecular chemistry, we constructed a three-in-one combination therapy platform between zwitterionic-modified cavitand (CV-2) and drugs. The well-designed CV-2 forms the chemical basis for multifunctional biomaterials, which can not only be used as a carrier to accurately load various drugs but also as a therapeutic agent with lubricating function for the treatment of diseases. Based on the disease characteristics of osteoarthritis (OA), we delivered kartogenin (KGN, cartilage regeneration) and flurbiprofen (FP, anti-inflammatory) in combined treatment. Through self-assembly and molecular recognition, the CV-2 can load KGN and FP via host-guest interactions in a single system, and the KGN/FP@CV-2 nanoassembly provides synergistic therapeutic benefits in the long term by sustained drug release and intrinsic lubrication function. Thus, the functional integration of macrocyclic delivery and therapeutics provides a simple, flexible and universal platform for the synergistic treatment of diseases involving multiple drugs.

Keywords: supramolecular macrocycle; hydration lubrication; drug delivery; combination therapy; osteoarthritis

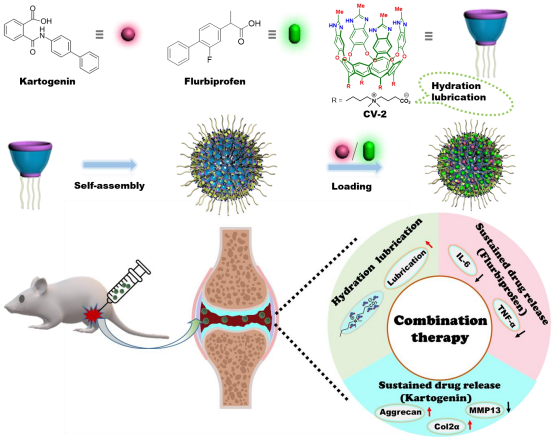

Figure. 1 Schematic illustration of the design principle of KGN/FP@CV-2 and its combination therapy for OA.

Reference:

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Renal tubule targeting host-guest drug delivery system based on chiral serine-modified azocalix[4]arene for acute kidney injury

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Abstract: High incidence of acute kidney injury (AKI) and systemic side effects associated with high-dose administration necessitate the development of renal tubule-targeted drug delivery vehicles to enhance the therapeutic effect. Host-guest drug delivery systems have significant advantages of simplicity, molecular-level control of composition, and enabling quantitative drug loading, offering new opportunities for refined applications. The chirality of carriers directly influences their interaction with biological systems and cells, thereby influencing drug circulation, accumulation, targeting, and bioavailability, ultimately affecting therapeutic consequences. Therefore, developing chiral macrocyclic carriers that can target the injured kidney may offer new opportunities for the treatment of AKI. Accordingly, taking the serine, which has been found to exhibit specific interactions with kidney injury molecule-1 (KIM-1), as a targeting molecule, we designed the novel drug carrier, serine-modified azocalixarene (SerAC4A). The SerAC4A is able to selectively target renal tubules and exhibits strong binding affinity to the anti-inflammatory drug Ginsenoside Rb1 (10^7 M^{-1}). The high affinity is prerequisite to avoid unwarranted off-target leaking during blood circulation. At the site of the lesion, reduced blood perfusion can lead to renal hypoxia, and SerAC4A can respond to hypoxia, accompanied by the release of loaded drugs. Furthermore, we investigated the effect of chirality on drug delivery efficacy, compared with the L-SerAC4A, D-SerAC4A has higher binding affinity with the renal tubule cell membrane and is better internalized by renal tubular epithelial cells. The utilization of D-SerAC4A enabled high-sensitivity imaging of the injured kidney and effective treatment of renal injury.

Keywords: acute kidney injury; drug delivery; chiral; host-guest chemistry; calixarene

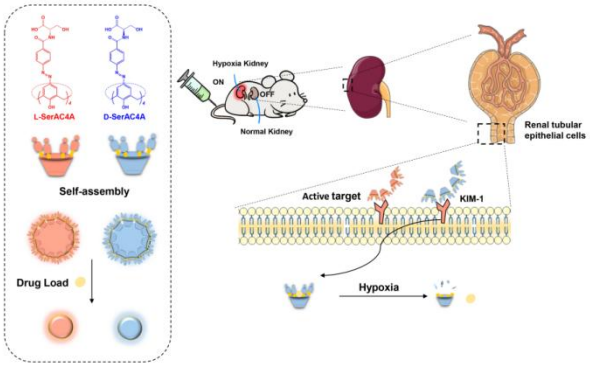

Figure. 1 Chemical structures of L-SerAC4A and D-SerAC4A, and the schematic illustration showing injured kidney targeted drug delivery and controlled release.

Reference:

[1] Zhang Z.-Z., Yue Y.-X., Xu L., Wang Y., Geng W.-C., Li J.-J., Kong X.-L., Zhao X., Zheng Y., Zhao Y., Shi L.-Q., Guo D.-S., Liu Y., Advanced Materials[J], 2021, 33(12), e2007719.

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Study of the Chiral Effects in Drug Delivery Using Chiral Macrocyclic Carriers

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Abstract: Chirality greatly affects the pharmacokinetics and therapeutic effects of drugs, so it plays an important role in drug design. Similarly, the chirality of drug carriers also shows great differences in circulation, accumulation, and cell internalization. Studying the chiral effect is helpful to develop carriers with high drug delivery efficiency, so as to achieve effective treatment of diseases. However, unlike the small molecule drugs, which have precise chiral structures, drug carriers are often designed to be more complex, making most of them do not have a definite structure. Moreover, additional variables may be introduced in the process of drug loading, such as drug loading efficiency and encapsulation percentage. These variables make it difficult to attribute the differences in therapeutic effect to the chiral effect of the carrier. Here, we designed lysine-modified azocalix[4]arenes (KAC4A) with precise enantiomeric structures as a tool for accurately studying the chiral effects of drug carriers. As enantiomers, L-KAC4A and D-KAC4A have clear mirror symmetry structures and opposite chiral signals, similar binding constants with drugs to achieve the same drug loading efficiency, and similar stimuli-responsive drug release kinetics. Therefore, it allows us to exclude other interfering factors to study the effect of chirality of the carrier on its drug delivery efficiency. *In vitro* and *in vivo* experiments showed that D-KAC4A had significantly higher cellular internalization and intratumoral accumulation ability than L-KAC4A. The tumor inhibition rate of D-KAC4A@taxol group (80.6%) was higher than that of L-KAC4A@taxol group (53.4%) and that of LD-KAC4A@taxol group (chiral mixed group; 63.7%). Our work provides new materials and ideas for further study of the chiral effect of drug carriers.

Keywords: chirality; drug delivery; supramolecule; macrocycle carrier; tumor

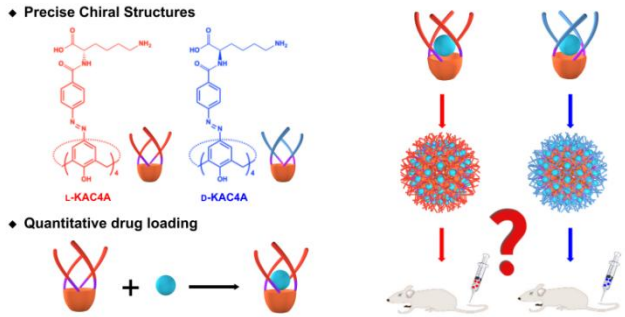

Figure. 1 Molecular design of drug carriers with precise chiral structures and quantitative drug loading ability.

Reference:

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One Family of Supramolecular Excipients with High Binding Affinity, Universality and Hypoxia-Responsiveness

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Abstract: Excipient, which is the inactive substance that mixed with active pharmaceutical ingredients (APIs) to increase the solubility, stability, bioavailability, safety and accessibility of APIs, is important component that affect the quality, safety and effectiveness of drugs. Macrocycles are one kind of widely focused excipient and have advantages of accurate molecular structure and well-defined interaction modes with APIs. As an outstanding example, sulfobutylether-β-cyclodextrin, which is famous as Captisol®, has successfully formulated and marketed multiple pharmaceutical products, such as Geodon® and Vfend®. Recent years, the development of precision medicine has put forward new requirements for excipients, such as, the multifunctional integrated, controlled payload release, and high modification efficiency. Therefore, the macrocycles with high binding affinity to APIs to improve the modification efficiency, and disease microenvironment responsiveness to achieve the targeted release are on highly demand. Calixarenes (CAs) are the macrocycles with (almost) unlimited possibilities due to their truncated conical structure and ease of modification, making them possible to develop new desired excipients. Herein, we reported the azocalixarenes (AzoCAs) as one family of broad-spectrum excipients for around 30 APIs and effectively regulated their physicochemical properties, including the solubility, stability, bioavailability, and safety. Moreover, AzoCAs can be reduced by azoreductases overexpressed under hypoxic environments leading to a controlled release of APIs. AzoCAs have good bench-to-bedside translation prospect and provide a new avenue for the development of novel excipients.

Keywords: excipients; macrocycles; azocalixarenes; host-guest recognition; hypoxia-response

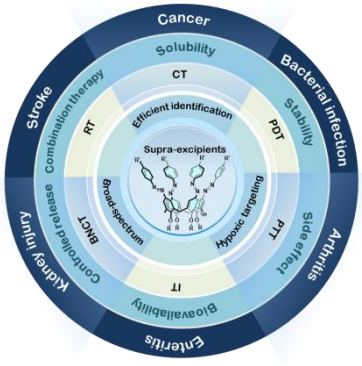

Figure. 1 Schematic illustration of the supramolecular excipients with high binding affinity, universality and hypoxia-responsiveness and their functions and applications.

Reference:

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Janus Structured Nanoparticles For Multi-Mode Imaging Guided Chemo-Photothermal Synergistic Therapy

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Abstract: The emergence of novel multifunctional nanomaterials brings new hope for obtaining more advanced drug delivery systems to realize early diagnosis and combined treatment of tumors. Multifunctional polymer-inorganic Janus nanoparticles (JNPs) that simultaneously have therapeutic and imaging functions are highly desired in biomedical applications. Here, we prepared spherical dopamine/mesoporous zinc phosphate hollow JNPs (PDA/mZnP H-JNPs) using a novel and convenient method. The obtained PDA/mZnP H-JNPs are further selectively functionalized by methoxy polyethylene glycol mercaptan (PEG-SH), resulting in good biocompatibility and prolonged blood circulation time in vivo. The mesoporous structure of mZnP serves as a storage space and pathway for the anticancer drug doxorubicin (DOX). The obtained PEG-PDA/mZnP H-JNPs have high drug loading capacity, good photothermal conversion efficiency, strong near-infrared (NIR) absorption, and pH/NIR dual response characteristics, making them suitable for PA imaging guided in vitro and in vivo synergistic tumor photo-chemotherapy. In addition, this synthesis method can also be extended to the preparation of PDA/various spherical mesoporous inorganic H-JNPs.

Keywords: polydopamine; photothermal therapy; breast cancer

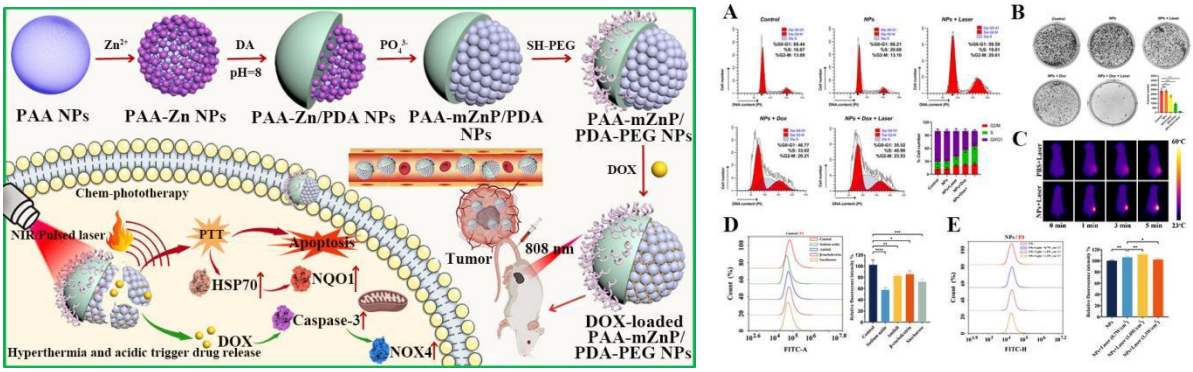

Figure. 1 A facile formation route for pH/NIR dual-responsive biodegradable nanospheres for cancer theranostic applications (Left), and the mechanism of action on cancer cells (Right).

Reference:

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A biomimetic spore nanoplatform for boosting chemodynamic therapy and antitumor immunity for synergistic cancer treatment

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Abstract: Bacterial based antitumor immunity has become a promising strategy to activate the immune system for fighting cancer. But single therapy is typically unable to eradicate this multifactorial disease. Moreover, stability and infections of bacteria or its spore limit the future application of bacterial therapy. In this study, based on our discovery that spore shell (SS) of bacillus coagulans exhibit excellent tumor targeting ability and adjuvant activity, we develop a biomimetic spore nanoplatform to boost bacteria-mediated antitumor therapy (BMAT), chemodynamic therapy and antitumor immunity for synergistic cancer treatment. In detail, SS is separated from probiotic spore and then coated on the surface of liposome (Lipo) that loaded with hemoglobin (Hb), glucose oxidase (GOx) and JQ1 to construct SS@Lipo/Hb/GOx/JQ1. In tumor tissue, highly toxic hydroxyl radicals (•OH) are generated through sequential catalytic reactions: GOx catalyzing glucose into H_2O_2 and Fe^{2+} in Hb decomposing H_2O_2 into •OH. The combination of •OH and SS adjuvant can facilitate tumor immunogenicity and activate immune system through antigen processing and presentation pathway. Meanwhile, JQ1 mediated down-regulation of PD-L1 and Hb induced hypoxia alleviation synergistically reshape immunosuppressive tumor microenvironment and potentiate immune responses. In this manner, SS@Lipo/Hb/GOx/JQ1 significantly suppresses tumor growth and metastasis. Collectively, the nanoplatform represents an optimum strategy to potentiate immune activation for caner immunotherapy.

Keywords: biomimetic spore, bacteria-mediated antitumor therapy, chemodynamic therapy, tumor immunogenicity, tumor microenvironment

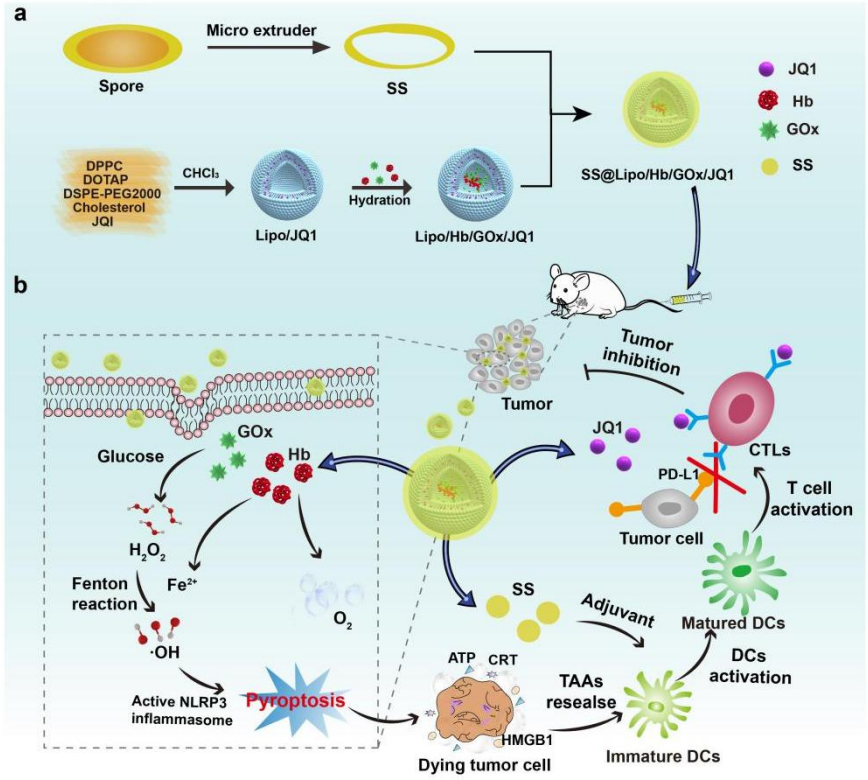

Figure. 1 Schematic illustration of the preparation and anti-tumor mechanism of SS@Lipo/Hb/GOx/JQ1.

An oral drug delivery system with programmed drug release and imaging properties for orthotopic colon cancer therapy

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Abstract: Oral drug delivery systems (ODDSs) have attracted considerable attention in relation to orthotopic colon cancer therapy due to certain popular advantages. Unfortunately, their clinical applications are generally limited by the side-effects caused by systemic drug exposure and poor real-time monitoring capabilities. Inspired by the characteristics of pH changes of the gastrointestinal tract (GIT) and specific enzymes secreted by the colonic microflora, we anchored polyacrylic acid (PAA) and chitosan (CS) on Gd3+-doped mesoporous hydroxyapatite nanoparticles (Gd-MHAp NPs) to realize programmed drug release and magnetic resonance imaging (MRI) at the tumor sites. In particular, the grafted PAA, as a pH-responsive switch, could effect controlled drug release in the colon. Further, CS is functionalized as the enzyme-sensitive moiety, which could be degraded by β-glycosidase in the colon. Gadolinium is a paramagnetic lanthanide element used in chelates, working as a contrast medium agent for an MRI system. Interestingly, after oral administration, CS and PAA could protect the drug-loaded nanoparticles (NPs) against variable physiological conditions in the GIT, allowing the drug to reach the colon tumor sites, preventing premature drug release. Enhanced drug concentrations at the colon tumor sites were achieved via this programmed drug release, which subsequently ameliorated the therapeutic effect. In addition, encapsulating both chemotherapeutic (5-fluorouracil, 5-FU) and targeted therapy drug (gefitinib, Gef) within Gd-MHAp NPs produced a synergistic therapeutic effect. In summary, this study demonstrated that such a novel drug system (Gd-MHAp/5-FU/Gef/CS/PAA NPs) could protect, transport, and program drug release locally within the colonic environment; further, this system exhibited a worthwhile therapeutic effect, providing a promising novel treatment strategy for orthotopic colon cancer.

Keywords; oral drug delivery system, colon cancer, target

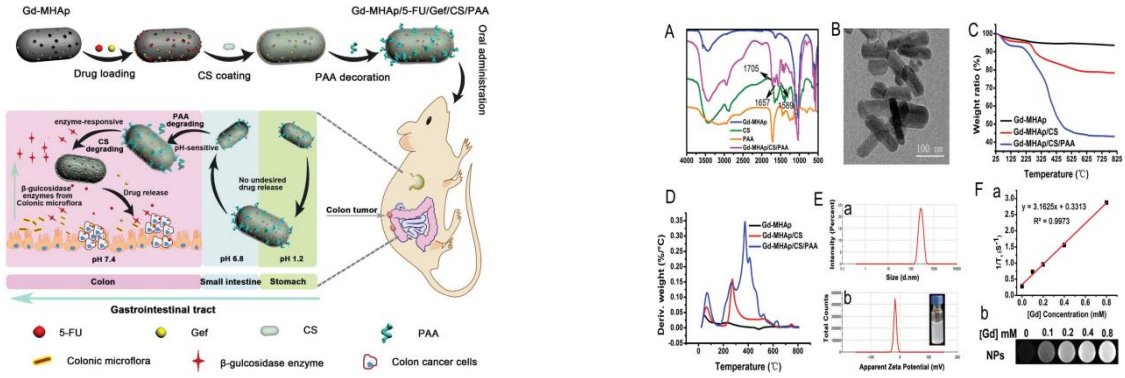

Figure. 1 Schematic illustration of the preparation of Gd-MHAp/5-FU/Gef/CS/PAA NPs and the mechanism of drug release in different physiological environments in the GIT (Left); and Characterization of Gd-MHAp/5-FU/Gef/CS/PAA NPs (Right).

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Crosslinked Cyclodextrin Metal-Organic Framework as a Nanocarrier of Minoxidil and Cedrol to Synergistically Reverse Androgenetic Alopecia: a Potential System for Follicular Drug Delivery

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Abstract: Minoxidil (MXD) is widely applied in clinics for topical treatment of androgenetic alopecia, however, MXD has dose-dependent adverse reactions and its conventional dosage forms encountered hurdles in the selective targeted delivery to hair follicles. Thus, more safe and effective therapeutic options are needed. In this study, we found minoxidil and cedrol (CED) showed synergistic effect on androgenetic alopecia, and developed a therapeutic strategy by constructing a follicular delivery system with cross-linked cyclodextrin metal-organic framework (CDF) as a carrier for co-loading MXD and CED. The CDF improved drug release performance and enhanced follicular drug delivery via ratchet effect, and increased proliferation of the human dermal papilla cells. The therapeutic effect on androgenetic alopecia in mice was synergistically risen by regulating the expression of VEGF, IGF-1, KGF and TGF-β, activating Wnt/β-catenin, AKT/ERK and Shh/Gli signaling pathway.

Keywords: androgenetic alopecia; hair follicle; minoxidil; cedrol; cross-linked cyclodextrin metal organic framework

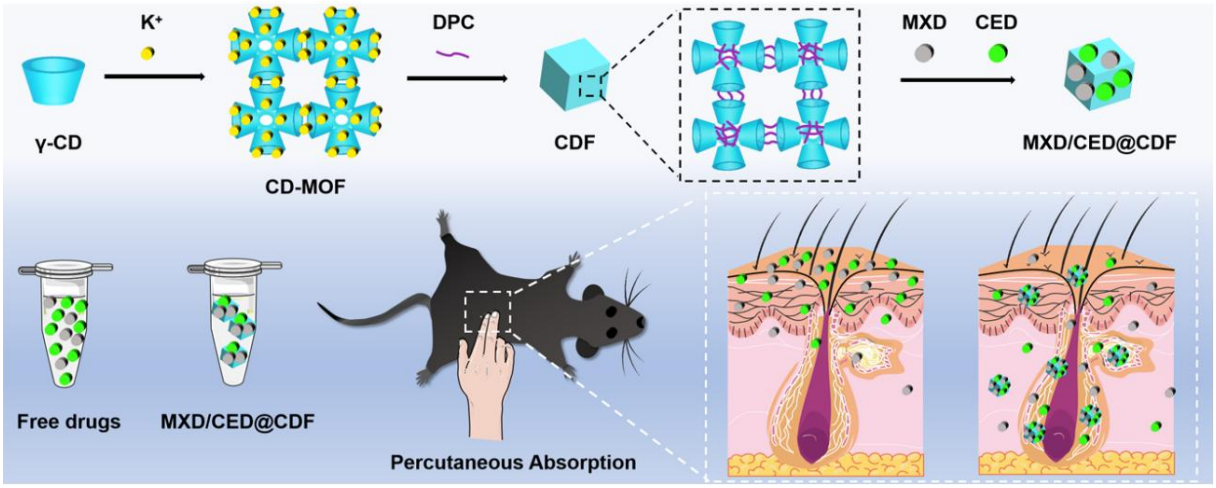

Figure. 1 Schematic illustration of follicular delivery efficiency of MXD-CED@CDF(cross-linked cyclodextrin metal-organic framework loaded with minoxidil and cedrol) and free drugs: CDF achieve a more targeted delivery to the hair follicle than free drugs in solution, and application of massage further amplified this effect.

Photodynamic Therapy of Anti-metastatic Melanoma Based on the Inhibition of Antioxidase Enzymes and Self-supplying Oxygen Properties by Nanodopants

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Abstract: Photodynamic therapy (PDT) with high selectivity and safety has been widely regarded as a promising treatment method in cancer treatment. However, the efficacy of PDT is severely limited due to the antioxidant effects of antioxidant defense enzymes and insufficient oxygen supply. Therefore, in order to enhance the ability of PDT to resist melanoma, we designed a continuous enhanced PDT treatment platform (Au@MTM-HA). Firstly, the treatment platform uses TiO_2 as a photosensitizer and doped with MnO_2 to form a mesoporous nano dopant (MTM). MTM can continuously provide oxygen, thereby increasing the level of reactive oxygen species (ROS) and reducing metastasis effects by alleviating the hypoxic environment of tumors. In addition, the released $Au_{25}Sv_9$ can inhibit the activity of antioxidant defense enzymes, reduce the clearance of ROS, and further enhance the PDT effect. At the same time, surface modified HA can not only recognize CD44 receptors, but also serve as a carrier sealant. The experimental results show that, Au@MTM-HA The ability to explosively generate more than three times the ROS significantly improves the PDT effect. Therefore, this work can provide Au@MTM-HA As a promising PDT candidate, it provides strong evidence for the treatment of metastatic melanoma.

Keywords: Reactive oxygen species; $Au_{25}Sv_9$; TrxR; Melanoma; photodynamics therapy

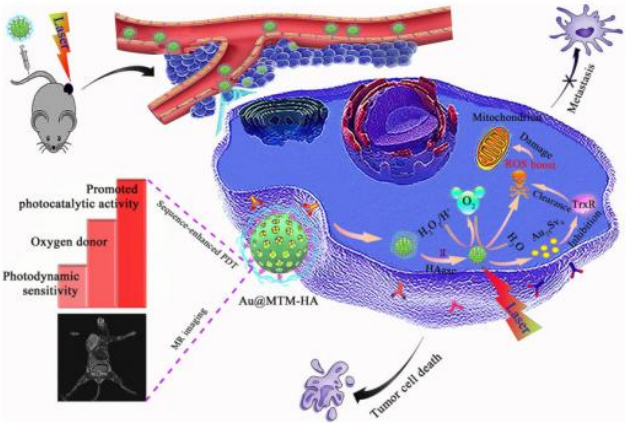

Figure. 1 Schematic diagram of Au@MTM-HA for boosted ROS and sequence-enhanced photodynamic therapy strategy in B16-F10 melanoma cell under 532 nm laser.

Reference:

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Application of pH-senstive Mesoporous Zinc Phosphate Microsphere in Photodynamic Therapy to Treat Psoriasis

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Abstract: This study aims to develop mesoporous zinc phosphate (MZP), which could alleviate psoriasis under bule light irradiation. Xylene has been selected as reducing agent to synthesize MZP2 by hydrothermal method because MZP2 with higher yield, larger specific surface area and pore volume is more sensitve to low pH compared to that of MZP1 synthesized by toluene. Curcumin (Cur) and glycyrrhizic acid (GA) are loaded together into MZP2 as Cur-GA-MZP2, which is confirmed as microspheres with diameter about 1 μm, observed by SEM and dynamic light scattering method. It is verified to be in an amorphous state by XRD, and its saturation solubility is confirmed to be 50 times that of raw curcumin (Cur RDP) by UV. The cumulative release rate of Cur-GA-MZP2 at pH 5.4 is significantly higher than that at pH 7.2, confirming the pH-sensitive property again. By detecting the decrease of the absorbance at 410 nm of DPBF which had been mixed with the preparation irradiated by blue light, it is confirmed that ROS generation ability of Cur-GA-MZP2 at pH 5.4 is higher than that of Cur RDP, physical mixture, as well as Cur-GA-silica which has no pH-sensitve characteristics. MZP2 could also increase ROS along with the irration time. The superiority of both Cur-GA-MZP2 and MZP2 on auricle inflammation induced by xylene as well as on psoriasis-like mice model induced by imiquimoid only exists under bule ligh irradation, with the allievated macroscopic and microscopic appearance of skin lesion area. The mechanism is likely attributed to IL-17A detected by immunohistochemistry and ELISA, NF- ƙB pathway as well as MAPK pathway detected by western blot. In sum, this study achieved mesoporous zinc microspheres based on xylene, which could play a role on psoriasis itself or together with curcumin and glycyrrhizic acid, when in low pH and under blue light irradiation.

Keywords: photodynamic therapy; pH-senstive, mesoporous zinc phosphate, psoriasis

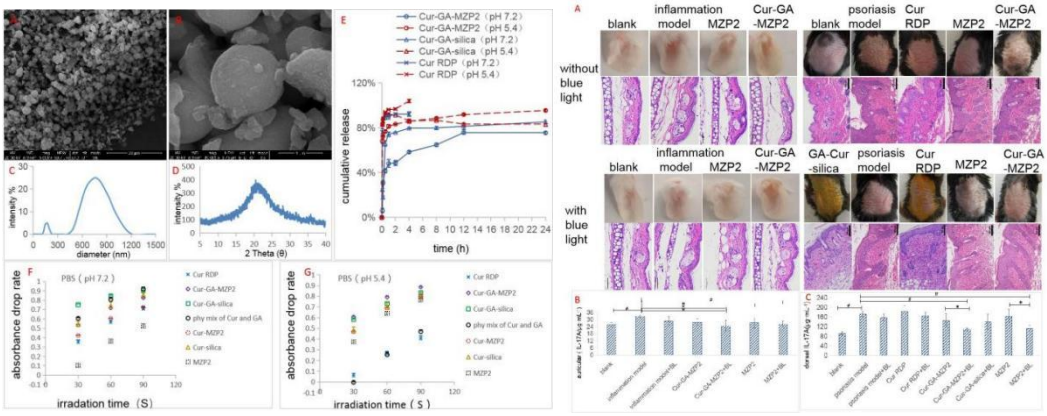

Figure. 1 Physical characteristics of the Cur-GA-MZP2.

Figure. 2 Inhibition effect of Cur-GA-MZP2 and MZP2 under blue light irradiation on inflammation (Left) and on psoriasis (Right).

Reference:

[1] Srivastava, A., Nogoskar, S., Srivastava, A.K., Mahato, P.K., Journal of Pharmaceutical Negative Results[J], 2022, 13(10),1464-1470.

An in situ nanoparticle recombinant strategy for the enhancement of photothermal therapy

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Abstract: Photothermal therapy (PTT)-induced immune response has attracted much attention, however, which cannot work at full capacity. In this study, the simvastatin (SV) adjuvant is loaded into gold nanocages (AuNCs) to develop a simple drug delivery system, which can efficiently utilize the tumor-associated antigens (TAAs) for improving immune responses. AuNCs/SV-mediated PTT treatment enhances tumor cells damage and promotes the release of TAAs which are immediately captured by AuNCs/SV to form AuNCs/SV/TAAs recombinant nanoparticle. Impressively, AuNCs/SV/TAAs can accumulate in lymph nodes effectively due to the suitable size of ~55 nm and hyperthermia-induced vasodilative effect. And the co-delivery of antigen and adjuvant is beneficial to stimulating the maturation of dendritic cells for further activating T cells. In a word, the recombinant strategy could make full use of TAAs to produce an individual powerful immunotherapy.

Keywords: Photothermal therapy; Tumor-associated antigens; Recombinant nanoparticle; T cells activation; Individual immunotherapy

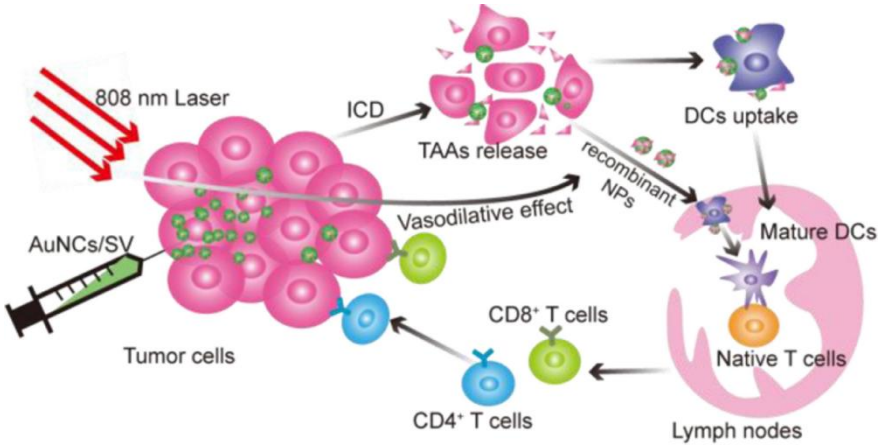

Figure. 1 Schematic overview of the construction of in situ recombinant nanoparticle with lymph node-targeting ability for enhancing PTT-immunotherapy.

A Double-layered Semi-interpenetrating Network-based Microneedle for Local Anesthesia

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Abstract: To improve the mechanical strength of a polyvinylpyrrolidone (PVP K29/32)-derived dissolvable microneedle, a double-layered semi-interpenetrating network is developed using covalently crosslinked methacrylate chondroitin sulfate (CS-MA) in combination with PVP K29/32, which is used to successfully load lidocaine (LD) and applied as a microneedle patch for rapid local anesthesia. Herein, the double-layered microneedles are fabricated using commercially available materials and a simple micro molding preparation method for adrenaline release in the outer layer, and sustained release of LD in the inner layer. CS-MA when mixed with soluble PVP and photoinitiators afforded a covalently cross-linked three-dimensional network (CS-MA/PVP MN) after irradiation at 405 nm for 1 min. CS-MA/PVP MNs demonstrated greatly enhanced mechanical strength and reduced moisture absorption rate as compared to PVP MN. The content of LD in each microneedle array was determined as 802.8 ± 22.8 μg. The obtained CS-MA/PVP MNs displayed sharp needle edges with a uniform appearance under a scanning electron microscope. Penetration studies showed that the prepared microneedles were able to penetrate the skin of experimental animals causing minimum irritation. The biosafety study showed that the trauma to the skin was almost negligible after the application of microneedles. Furthermore, preliminary pharmacodynamic studies in guinea pigs revealed the prepared microneedles achieved a rapid onset of action (< 1 min) compared to the commercially available lidocaine cream (about one hour). Overall, LIDH-loaded semi-interpenetrating network-based microneedles serve as a promising transdermal delivery platform for achieving rapid and efficient local anesthesia.

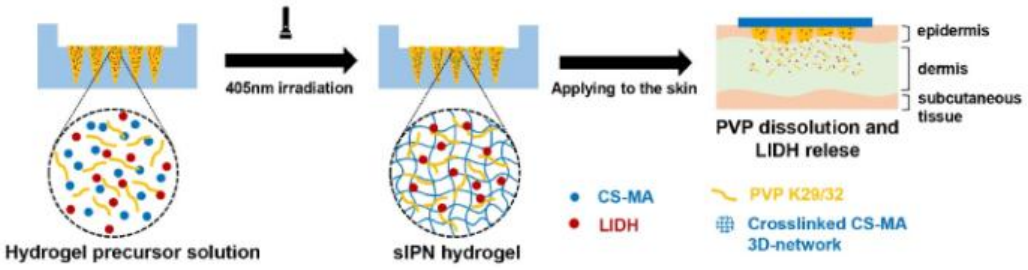

Fig. 1. Schematic illustration of sIPN-based microneedle for achieving dissolution-controlled rapid release.

In situ safe engineering of cancer-associated fibroblasts for enhanced immunotherapy

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Abstract: Immune checkpoint blockade (ICB) has shown potential in the treatment of a variety of tumors, but has a poor clinical response rate, particularly in malignant breast cancers characterized by hyperfibrosis. Accumulating evidence suggests that cancer-associated fibroblasts (CAFs), which are abundant in breast cancer tissues, can directly disable $CD8^+$ cytotoxic T lymphocytes (CTL) and promote infiltration of regulatory T lymphocyte (Treg) cells. Inspired by the similar antigen processing ability of CAFs and professional antigen-presenting cells (APCs), an "enemy to friend" strategy was proposed to convert immunosuppressed CAFs into immune-activated APCs by in situ engineering to improve the response rate of ICBs. To achieve safe and specific engineering of CAFs in vivo, we developed a thermochromic spatiotemporal light-controlled gene expression nanosystem by self-assembly of molten eutectic mixture, chitosan and fusion plasmids. After photoactivated gene expression, CAFs can be engineered into APCs through the expression of co-stimulatory molecules (CD86), effectively inducing activation and proliferation of antigen-specific $CD8^+$ T cells. At the same time, engineered CAFs can also secrete PD-L1 trap proteins in situ, avoiding the potential side effects caused by the "off-target" effect of clinically applied PD-L1 antibodies. It was shown that the designed nanosystem can effectively program CAFs, significantly increase the percentage of $CD8^+$ T cells, and induce long-term immune memory effects and effectively inhibit lung metastasis.

Keywords: In-situ safety engineering; Cancer-associated fibroblasts; Immunotherapy

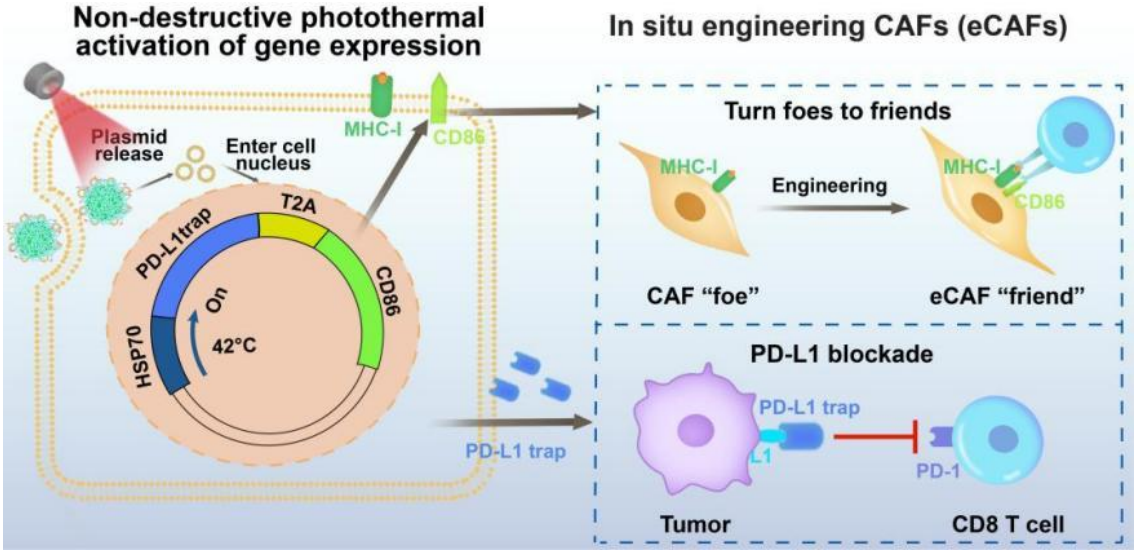

Figure 1. In situ engineered cancer-associated fibroblasts to amplify immunotherapy.

Reference:

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Effectively inhibit the progression of colon cancer in situ and liver metastases by regulating the polarization of tumor-associated macrophages

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Abstract: Immune checkpoint inhibitors (ICIs) exhibit compromised therapeutic efficacy in many patients with advanced cancers, particularly those with liver metastases. Much of this incapability can be ascribed as an irresponsiveness resulting from the hepatic immune desert that acts as T cell “traps” for which there currently lacks countermeasures. Here, we report a novel form of nanomedicine that remodels the hepatic immune microenvironment to an immune oasis by targeting the acquired hepatic macrophage-centric T cell elimination. Using the nanomedicine, composed of KIRA6 (an endothelium reticulum stress inhibitor) α-Tocopherol nanoemulsions and anti-PD-1 monoclonal antibodies, we found its potency in murine models of both orthotopic colorectal tumors and hepatic metastases with restoration of immune responses and significantly enhanced anti-tumor effects. A post-treatment scrutiny of the immune microenvironment landscape in the liver reveals repolarization of immunosuppressive hepatic macrophages, upregulation of Th1-like effector CD4+ T cells, and rejuvenation of dendritic cells along with CD8+ T cells. These findings inspire general adaptations of liver-directed immune milieu modulation strategy to improve therapeutic efficacy of ICIs for a variety of “cold” tumors in progressive stages and their liver metastases.

Keywords: nanomedicine, immunotherapy, liver metastasis, hepatic macrophage, tumor immune microenvironment, cytotoxic T cell

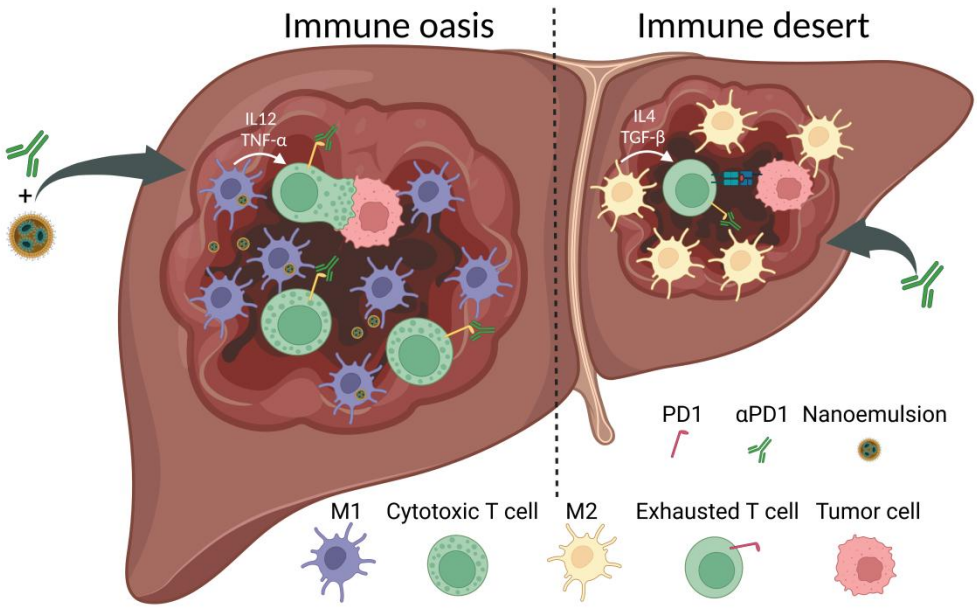

Figure 1. Schematic illustration of effectively inhibition the progression of colon cancer in situ and liver metastases by regulating the polarization of tumor-associated macrophages.

Genotype-specific precision tumor therapy using a mitochondrial DNA mutation-induced drug release system

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Abstract: The precise killing of tumor cells without affecting surrounding normal cells is a challenge. Mitochondrial DNA (mtDNA) mutations, as one of the most common genetic variants in cancer, can directly affect metabolic homeostasis, serving as an ideal regulatory switch for precise tumor therapy. Here, we designed a mtDNA Mutation-Induced Drug Release System (MIDRS), using the single-nucleotide variation (SNVs) recognition ability and trans-cleavage activity of Cas12a to convert tumor-specific mtDNA mutations into a regulatory switch for intracellular drug release, realizing precise tumor cell killing. Using photosensitizer (Ce6) as a model drug, we found that in situ bursts of reactive oxygen species in mitochondria significantly disrupted mitochondrial homeostasis, enabling organelle-level photodynamic therapy. In addition, MIDRS promoted oxidative stress-induced mtDNA efflux, activating the cGAS-STING pathway and leading to the simultaneous activation of innate and adaptive immunity. In vivo evaluation showed that MIDRSMT could identify tumor tissue carrying SNVs in mtDNA in unilateral, bilateral, and heterogeneous tumor models, producing an excellent anti-tumor effect (~82.6%) without affecting surrounding normal cells and thus resulting in a stronger anti-tumor immune response. This is a promising strategy in the expansion of mutation-specific personalized tumor treatment approaches.

Keywords: photodynamic immunotherapy; *in situ* self-assembly, chromatin decompaction, nuclear DNA damage

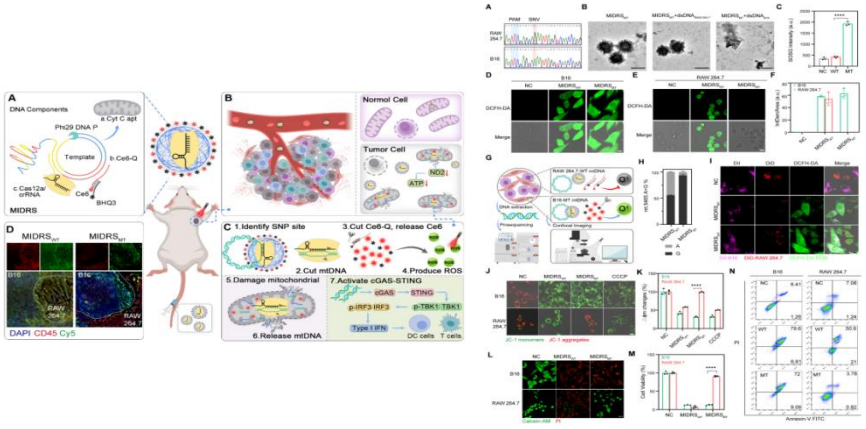

Figure. 1 Schematic diagram of the MIDRS-mediated precision killing of tumor cells through recognition of tumor cell-specific SNVs in mtDNA.

Figure. 2 MIDRS precisely kills tumor cells by recognizing specific SNVs in mtDNA.

Reference:

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A nanosystem with “spear-shield” conversion characteristics for normal tissue protection and tumor repopulation suppression in cancer radiotherapy

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Abstract: Radiotherapy is the first-line treatment for cancer. However, the serious adverse effects and tumor recurrence after radiotherapy remain a huge challenge. Here, we find that Mn_3O_4 nanoparticle can reverse the sensitivity of normal cells and tumor cells to radiotherapy by differentially regulating the levels of intracellular ROS. Specifically, in normal cells with low GSH, Mn_3O_4 exhibits antioxidant enzyme activity that can scavenge excessive reactive oxygen species (ROS), protecting normal tissue from radiation-induced injury; while in cancer cells with high GSH, Mn_3O_4 is rapidly degraded and amplifies ROS production by depleting GSH to enhance radiotherapy efficacy. And then a Mn_3O_4@TA-GSDME (MTG) assembly is fabricated through the diverse supramolecular interactions. The pyroptosis-related Gasdermin E (GSDME) protein can hijack activated caspase 3 and suppress tumor repopulation by reversing apoptosis to pyroptosis. *In vivo* studies demonstrate that the surviving fraction of mice treated with MTG can appreciably increase to 67% when exposed to 6 Gy ionizing radiation. Moreover, compared to the lethally irradiated 4T1 cells, the lethally irradiated 4T1 cells pretreated with MTG markedly decreased the growth of 4T1-luc cells with 88% complete regression of primary tumors, accompanied by the sensitized immunotherapy *via* inflammatory pyroptosis when in combination with anti-PD-L1 therapy. As a catalytic activity tunable agent, MTG can serve as a selective radioprotector for normal tissues and meanwhile holds a great potential for clinical prevention of tumor recurrence.

Keywords: radiotherapy; normal tissue protection, tumor repopulation, Mn_3O_4 nanoparticles

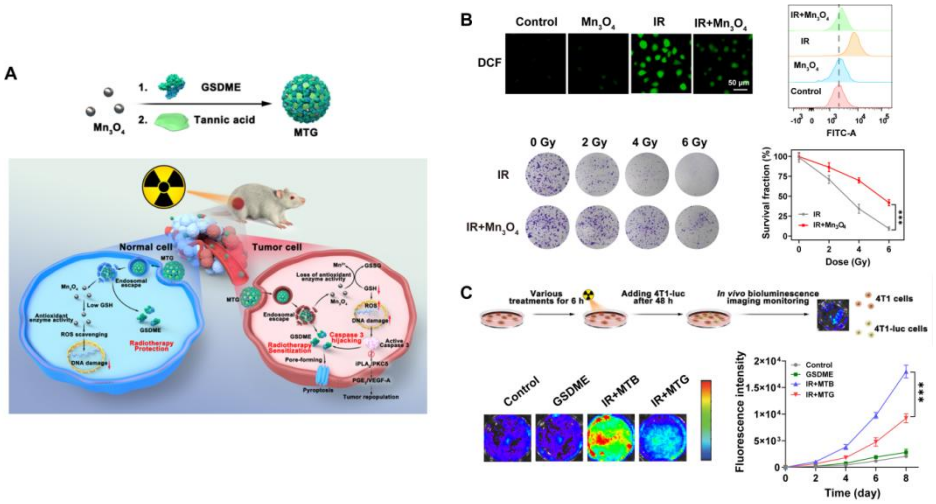

Figure. 1 (A) Schematic illustration of the function tunable MTG-mediated radioprotection of normal cells and tumor repopulation suppression; MTG-mediated (B) normal cell protection and (C) tumor repopulation suppression.

Reference:

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Nanoignitor engineered oncolytic adenovirus for glioblastoma immunotherapy

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Abstract: Glioblastoma (GBM) is one of the most intractable and high-mortality malignancy in central nervous system conferring high resistance to traditional chemo- and radiotherapy. Nowadays, oncolytic viral therapies have been tested in the clinic as a promising therapeutic approach for GBM. However, as one of the most commonly used oncolytic viruses, oncolytic adenovirus (OAds) are facing great hinders in pre-clinical or clinical course since the disappointing efficiency of viral replication and downregulation of coxsackievirus and adenovirus receptor of glioma cells. Herein, we developed a nanoignitor engineered OAds which could both enhance the cellular internalization of adenovirus and accelerate the replication of adenovirus in glioma cells. The enhanced genome transcription of virus was achieved by co-delivered siRNA of nanoignitor, which was designed to downregulate STAT3, a high expression bio-marker of GBM. Results showed that the specific knockdown of STAT3 protein could inhibit the type 1 interferons mediated anti-viral immunity, finally overcome the inhibition of adenovirus replication in GBM. Meanwhile, the nanoignitor also exhibited enhanced function due to the biological process of OAds, showing as higher siRNA internalization, endosomal escape and knockdown efficiency. In murine gl261 glioblastoma models, the nanoignitor successfully improved the viral titer in tumor tissues, which promotes the maturation of dendritic cells and activating of T cells. Notably, a single dose of nanoignitor engineered OAds could significantly inhibit the growth of tumor and prolonged the median survival time of mice without inducing significant toxicity. Collectively, this work may provide an unprecedented opportunity for enhanced oncolytic adenovirus mediated immunotherapy in GBM.

Key words: glioblastoma; oncolytic adenovirus; nanoignitor; STAT3; immunotherapy

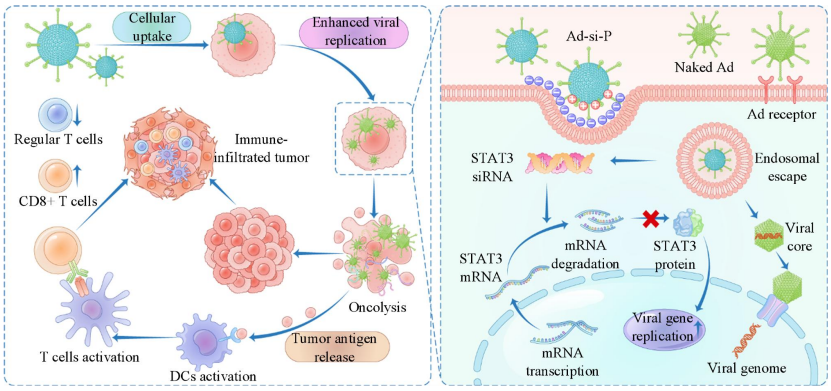

Figure.1 Schematic illustration of nano-ignitor that activates tumoricidal immunity via potentiating proliferation of oncolytic adenovirus.

Reference:

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Ultraviolet B radiation-induced JPH203-loaded keratinocyte extracellular vesicles exerting etiological interventions for psoriasis therapy

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Abstract: Psoriasis is a multifactorial immune-mediated inflammatory skin disease, characterized with keratinocytes hyperproliferation and aberrant immune activation. Although the pathogenesis is complex, the interactions among inflammation, Th17-medicated immune activation, and keratinocyte hyperplasia were considered to play a crucial role in the occurrence and development of psoriasis. Therefore, pharmacological interventions on the "Inflammation-Th17-Keratinocytes" vicious cycle might be potential strategies for psoriasis treatment. In this study, JPH203 (a specific inhibitor of LAT1, which engulfs leucine to activate mTOR signaling)-loaded, ultraviolet B (UVB) radiation induced, keratinocyte-derived extracellular vesicles (J@EV) was prepared for psoriasis therapy. The EV involved increased interleukin 1 receptor antagonist (IL-1RA) content due to UVB irradiation, therefore not only acting as a carrier for JPH203 but also functioning through inhibiting IL-1-mediated inflammation cascades. J@EV effectively restrained the proliferation of inflamed keratinocytes via suppressing mTOR-signaling and NF-κB pathway in in vitro studies. In an imiquimod-induced psoriatic model, J@EV significantly ameliorated the related symptoms as well as suppressed the over-activated immune reaction, evidenced by the decreased keratinocyte hyperplasia, Th17 expansion, and IL17 release. This study showed J@EV exert therapeutic efficacy for psoriasis by suppressing LAT1-mTOR involved keratinocytes hyperproliferation and Th17 expansion, as well as inhibiting IL-1-NF-κB mediated inflammation, representing a novel and promising strategy for psoriasis therapy.

Keywords: Psoriasis; extracellular vesicles; JPH203; m-TOR; IL-1RA

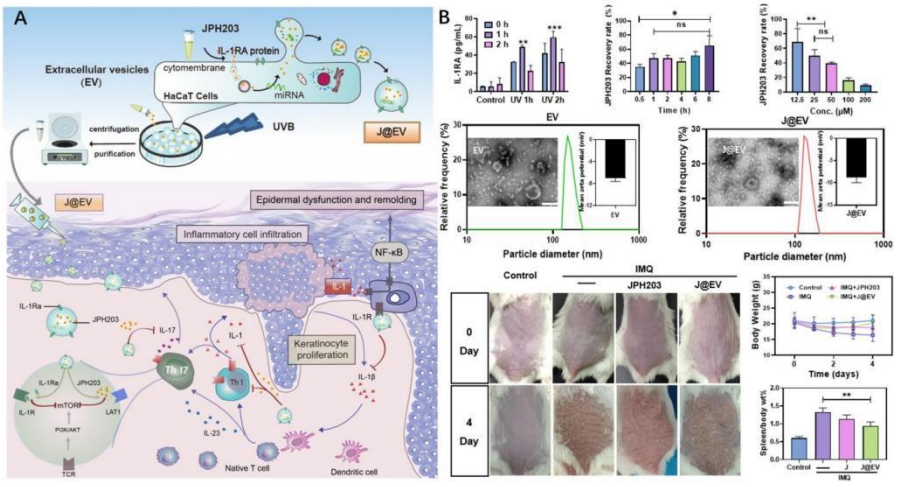

Figure. 1 (A) Schematic illustration for the design and function of J@EV. (B) Characterization and psoriasis therapeutic effect of J@EV by local application.

Neutrophils hitchhiking and reprogramming nanoparticles enhance gene delivery and bacteria-mediated tumor therapy

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Abstract: Bacteria have shown promise as an anti-tumor platform, with an attenuated strain of Salmonella called VNP20009 being used in the first clinical trial. However, VNP20009 has demonstrated low tumor regression and dose-dependent side effects, which has led to unsatisfactory efficiency in tumor treatment. The underlying cause is that Salmonella colonizes the tumor and recruits host neutrophils, which release extracellular DNA traps called neutrophil extracellular traps (NETs) to capture and eliminate bacteria, compromising the effectiveness of bacterial treatment for tumors. In this study, we present an efficient nanoplatform named Sibcl-2/PEI-PDA-SA (SPPS) that hijacks neutrophils from NETosis to apoptosis through an intracellular ROS scavenging-mediated histone glutamate inhibition pathway, thereby enhancing the viability of bacteria in tumors. Furthermore, we find that the gene drug ($siRNA_{bcl-2}$) loaded in SPPS can be re-capsulated in apoptotic bodies, and enable redelivery of drugs to tumor cells, further boosting the antitumor efficacy with synergistic effect. As a result, benefiting from bacterial treatment-mediated enhancement of neutrophil hijacking, primordial NETs producing cutting off and apoptotic bodies mediated sequential gene drug delivery, SPPS exhibites superior antitumor performance with a 90% survival rate compared to bacteria alone, which had a survival rate of 69.7%. Such a nanoplatform represent an efficient strategy for improved bacterial therapy and tumor-targeted drug delivery.

Keywords: Neutrophil Extracellular Traps; Bacteria-mediated Tumor Therapy, apoptotic bodies, Tumor-targeted Drug Delivery

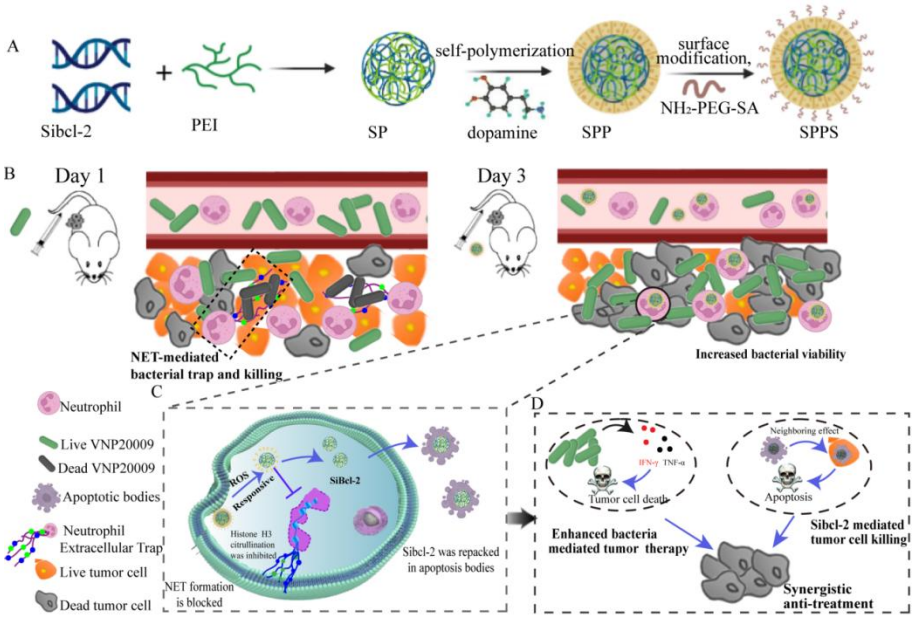

Figure. 1 Schematic illustration showing the neutrophil hijacking and reprogramming nanoparticles for gene drug delivery and enhanced bacteria mediated tumor therapy.

Systematic investigation of endo-lysosomal and autophagic dysfunction in Alzheimer’s disease for novel pharmaceutical measure against Alzheimer’s disease

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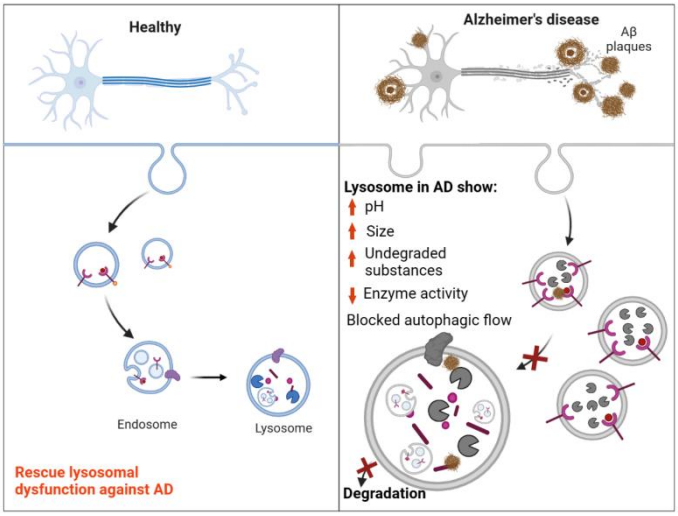
Abstract: Alzheimer's disease (AD), the most common type of dementia, is a chronic, age-related, multifactorial neurodegenerative disease causing progressive cognitive and memory deterioration. AD pathogenesis is believed to be mutually reinforced by multiple complex mechanisms and have been proven extremely difficult to treat due to our limited understanding of their mechanisms. As the major degradative pathway for proteins and organelles, autophagy is essential for survival of mature neurons. Here, we revealed unique Aβ-induced lysosome dysregulation within neurons using different cell lines. In the AD-mimic pathology condition, the dysfunction in neuron lysosomal system including reduced acidity, increased volume, blocked autophagic flow, and diminished degradative capacity were clearly observed. These phenomena become more pronounced with increasing concentrations of Aβ, leading to blunted clearance of excess cellular debris and plaques and contributing to lesion progression. Further, we identified and characterized marked intraneuronal Aβ plaque and lysosomal system pathology in AD transgenic mice mouse model APP/PS1 and FAD^{4T}, similar to our *in vitro* results. These results again indicated that the pathogenesis of AD is not restricted to previous reported protein aggregation and inflammation, but involves strong relationship with lysosomal dysfunction in brain. Extensive autophagic-lysosomal pathology in AD brain contributes to AD pathogenesis. These will drive us to discover deeper mechanisms and, most importantly, to devise novel pharmaceutical measure rescuing neuron lysosomal dysfunction against AD.



Preparation and characterization of a Gemini surfactant-based biomimetic and liver-targeted complex for gene delivery

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Abstract: Gemini Surfactant (GS) was explored as a novel non-viral gene delivery system. To attenuate toxicity and further explore their possibilities in gene delivery, the GS (18-7-18)-based gene delivery systems complexed with red blood cell membranes (RBCM) or liver cell membrane (LCM) were prepared and evaluated in this work. The characteristics of GS were investigated, the pDNA with GS/pDNA were completely retarded at N/P ratio of 4:1.The efficiency of gene transfection was evaluated by delivery of plasmid encoding luciferase via GS-based complexes in liver cells *in vitro* and intravenous application in mice. To evaluate the safety of the GS-based complex, serum biochemical markers, H&E staining, and CCK-8 tests were examined. The results revealed that GS-based complexes were mainly expressed in the liver, and all complexes showed minimal acute toxicity to major organs. In addition, we found that the incorporation of LCM can significantly improve the targeting and cell viability of hepatocytes. To reveal the uptake mechanism of GS-based complexes by liver cells, we investigated the uptake efficiency in the presence with chlorpromazine(CPZ), nystatin(NY), or Cytochalasin D (CD), which showed that the GS delivery system was endocytosed by cells with clathrin mediated endocytosis(CME) pathways. Overall, the results suggested that GS-based complexes possessed great potential as gene delivery vectors *in vivo* and *in vitro* and that LCM may be a promising gene delivery method with homotypic targeting and low toxicity, which can be used to treat liver disease.

Keywords: Gemini surfactant; Red blood cell membrane; Liver cell membrane; Transfection efficiency; Gene delivery

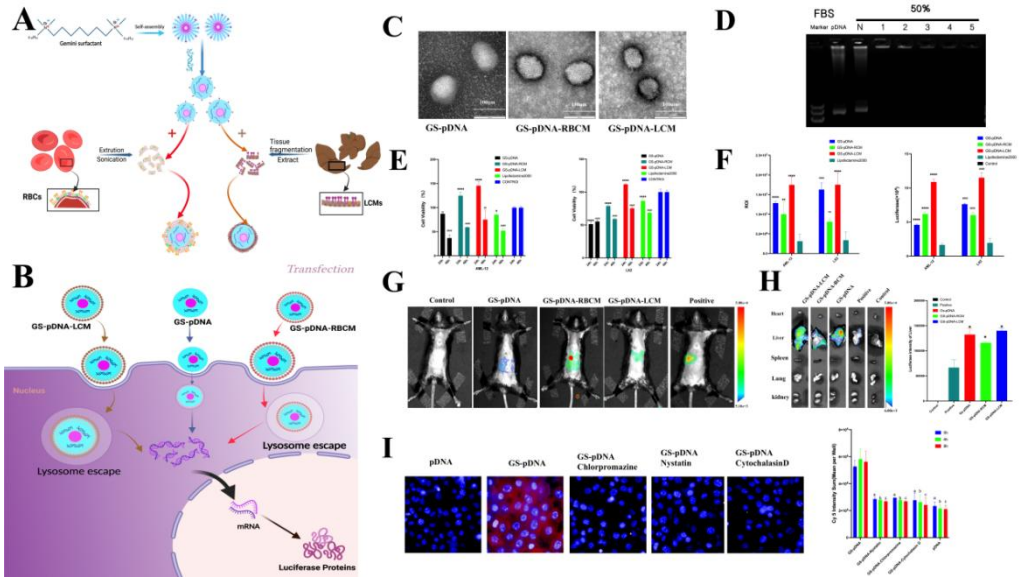

Figure. 1 (A)Schematic of GS-based gene delivery systems complexed with pDNA.(B)The Transfection flow chart.(C)Transmission electron microscope (TEM) of GS-based gene delivery systems.(D)The dissociation effect of sodium heparin on GS is concentration-dependent.(E)*In vitro* safety evaluation of GS system(F)Transfection efficiency of GS system on cells. (G)Transfection of GS-based nanocomplexes *in vivo*.(H)Representative Luciferase expression compared between organs(I)Uptake mechanism of various GS-based nanocomplexes.

Enhanced oral absorption of poorly water-soluble drugs using solid lipid nanoparticle modified with comb-shaped amphiphilic macromolecular materials

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Abstract: Solid lipid nanoparticles (SLNs) have excellent ability to improve the performance of poorly water-soluble drugs. However, the lipid matrix materials in SLNs tend to be degraded by lipase/co-lipase enzymes in the gastrointestinal tract, resulting in rapid release and precipitation of encapsulated poorly water-soluble drugs. Intestinal mucus can also limit the absorption of drugs, reducing the delivery efficacy of SLNs. Herein, comb-shaped amphiphilic macromolecular materials (CAM) with hydrophilic backbone and hydrophobic branches were incorporated into SLNs to minimized their degradation. The hydrophilic tooth-like loops of the CAM on the surface of SLNs might produce the steric hindrance effect and enhance digestion inhibition . In particular, comb-shaped amphiphilic inulin derivatives modified SLNs with hydrophilic, almost electric neutral surface, may exhibit effective mucus penetration. The study of in vitro lipolysis behavior of SLNs showed that CAM modified SLNs, exerted a better digestive tract stability than traditional amphiphilic macromolecular materials (LAM) like PEG. Moreover, when tested on in vitro cell uptake experiments, CAM modified SLNs, especially the Inu18-SLNs, exhibited much enhanced mucus permeability. The in vivo pharmacokinetics results revealed that the oral bioavailability of CAM modified STMC SLNs and Inu18 SLNs were 1.59 times and 1.93 times as compared with free CsA, respectively. We address in this work that CAM modified SLNs have potentials to improve oral drug absorption by significantly reducing gastrointestinal enzymatic degradation and simultaneously enhancing mucus penetration.

Keywords: Solid lipid nanoparticles; Comb-shaped amphiphilic macromolecular materials; Stability in the gastrointestinal tract; Mucus permeability; Oral bioavailability

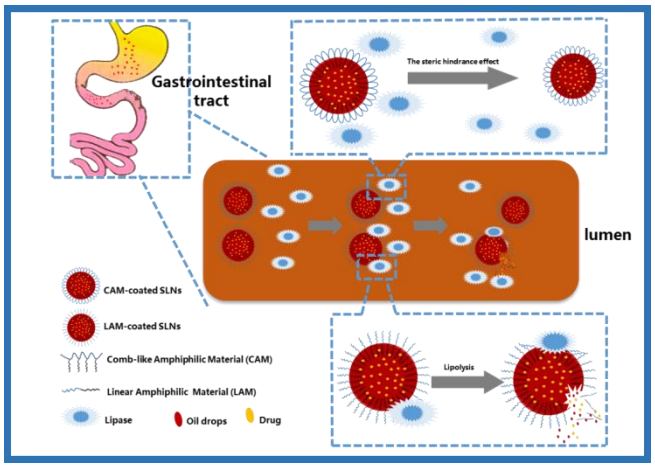

Figure. 1 Schematic illustration of solid lipid nanoparticle modified with comb-shaped amphiphilic macromolecular materials.

“Structure-function relationship” study of novel injectable poly (ortho ester)s as in situ sustained release carriers for small molecule drugs

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Abstract: Poly(ortho esters) (POEs), as a biodegradable material with high biocompatibility and unique surface erosion property, has been widely used in the field of biomedicine and tissue engineering. Previously, we have developed a series of novel POEs functionalized with alkyl groups which demonstrated excellent sustained release and phase transition property. To further investigate the structure-function relationship of the alkylated POEs, herein, we synthesized ten POEs variated in building block ratio of 3,9-Divinyl-2,4,8,10-tetraoxaspiro[5.5]undecane (DETOSU), Triethyleneglycol (TEG) and diglycolate (diGL) with different alkyl side chain lengths. Ropivacaine (ROPI) and Pitavastatin calcium (PITA) were selected as hydrophobic and hydrophilic model drugs to demonstrate the sustained-release property of the novel alkylated POEs. Results showed that the ratio of DETOSU has great influence on the degree of polymerization so as to the molecular weight, with the increase of DETOSU proportion, the viscosity of POEs gradually increased and the sustained-release effect was also enhanced. In addition, TEG ratio has no significant effect on the sustained release effect of ROPI, but it can adjust the viscosity of POE to improve the in situ retention performance. The optimal injection based on POE3 could achieve approximately zero-order release of ROPI within 72 hours.

Keywords: POE, Sustained-release injection, Structure-function relationship

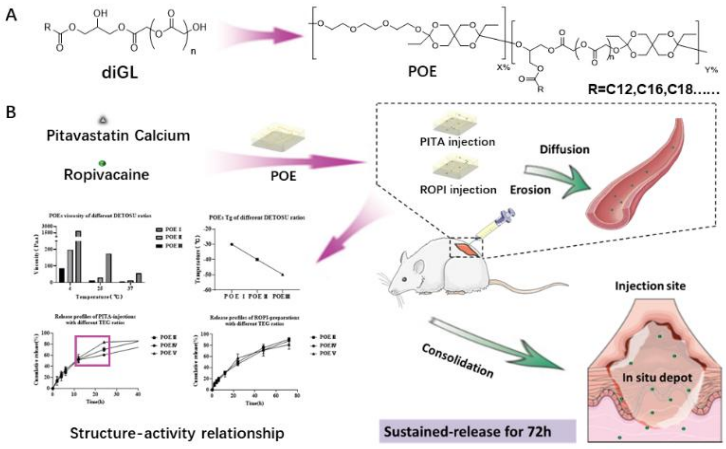

Figure. 1 Scheme illustration of functional study between POE and in vitro drug release behavior and the sustained release effect of injections. (A) Synthesis of the Alkylated POE. (B) Functional study on POE structure and in-vitro drug release and the in-vivo evaluation of sustained release.

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Metformin Delivery System for Androgenetic Alopecia Therapy

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Abstract: Androgenetic alopecia (AGA) is a common hair growth disorder associated with aging, autoimmune action, stress, and other factors. It results in the miniaturization of hair follicle and the apoptosis of dermal papilla cells (DPCs). AGA affects 50% of men and 15-30% of women and creates a significant psychological burden, and its incidence is increasing rapidly. The current drugs approved for AGA treatment are minoxidil and finasteride. However, both have serious adverse effects, including allergic reactions and sexual dysfunction. Hence, novel strategies for treating AGA are warranted. Studies show that metformin, a first-line medication for type 2 diabetes, can induce hair regrowth. However, an effective metformin formulation for AGA treatment is yet to be developed. Black phosphorus (BP), an emerging 2D material, has attracted significant attention in the field of biomedical engineering due to its limited cytotoxicity and superior biocompatibility. However, its instability prevents its use for transdermal drug delivery. Fortunately, this problem can be addressed by modifying BP through complexation. Here, we PEGylated BP to improve its stability and loaded the complex with metformin to generate a transdermal system (BP-PEG-Met) for AGA treatment. Compared with topical minoxidil administration, treatment with BP-PEG-Met significantly improved hair regeneration, producing fewer adverse effects. On a mechanistic level, BP-PEG-Met scavenged excessive reactive oxygen species (ROS) in the skin, alleviating oxidative stress in the hair follicle microenvironment. Moreover, BP-PEG-Met up-regulated the expression of vascular endothelial growth factor (VEGF) and vascular endothelial factor 31 (CD31) in the dermal papilla, which could induce angiogenesis around hair follicles and promote the induction of anagen in the hair follicle cycle. These findings show that BP-PEG-Met was effective in treating AGA. In conclusion, the BP-based transdermal delivery system provides a promising and multifunctional tool for the delivery of drugs to treat alopecia and exhibits significant clinical potential. This work was financially supported through grants from the Key Fields of Biomedicine and Health Foundation of Colleges and Universities in Guangdong Province (2022ZDZX2017), the Guangdong Basic and Applied Basic Research Foundation (2019B1515120043 and 2022A1515012154), the National Natural Science Foundation of China (File no. 82104354), the Science and Technology Development Fund, Macau SAR (File no. 0070/2021/AGJ), and the funding grants from University of Macau (File no. MYRG2022-00198-ICMS).

Keywords: androgenetic alopecia; hair regrowth; metformin; oxidative stress; angiogenesis

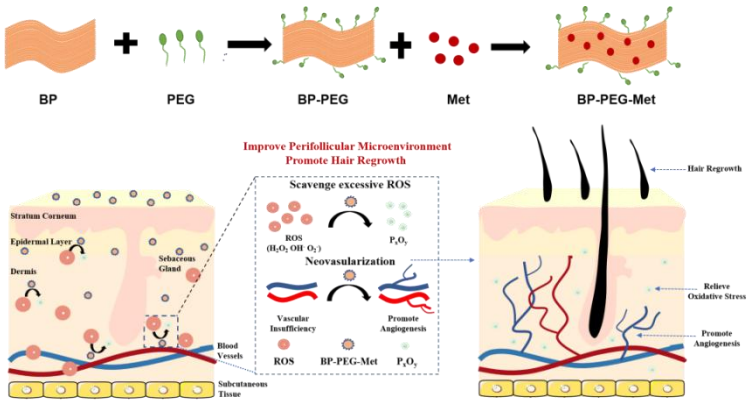

Figure. 1 Schematic illustration showing the synthesis of BP-PEG-Met, and the proposed mechanism of androgenetic alopecia treatment with BP-PEG-Met.

A tetramethylpyrazine-loaded hyaluronic acid-based hydrogel modulates macrophages for promoting diabetic wound healing

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Abstract: The failure of wound healing in diabetic patients causes lower limb disability and amputation. Current strategies for diabetic wound management often fail to achieve the expected outcomes, and emerging alternatives are urgently needed. M1 macrophages release the high level of pro-inflammatory cytokines, forming a chronically sustained inflammatory microenvironment that causes the delayed and impaired wound healing [1]. Accumulating evidence indicates that macrophage polarization from M1 to M2 improves diabetic wound healing [2]. In this study, the pro-healing effects of tetramethylpyrazine (TMP, a natural alkaloid found in *Ligusticum chuanxiong* Hort) for diabetic wounds were demonstrated. The cutaneous healing was mainly achieved by TMP-mediated macrophage polarization from M1 to M2 phenotype. In addition, the hyaluronic acid (HA) hydrogel was developed for the topical administration of TMP to the full-thickness wounds in the experimental diabetic mice. Consequently, TMP-loaded HA hydrogel (TMP-HA) profoundly accelerated the wound closure as compared to TMP-loaded INTRASITE Gel (a commercial hydrogel; TMP-Gel), which was evident with the inflammation mitigation, the angiogenesis enhancement, and the collagen deposition. Our work reveals the macrophage-modulatory function of TMP for diabetic wound healing and demonstrates great potential of TMP-HA for clinical application.

Keywords: natural alkaloid, hyaluronan, hydrogel, drug delivery, regenerative therapeutics

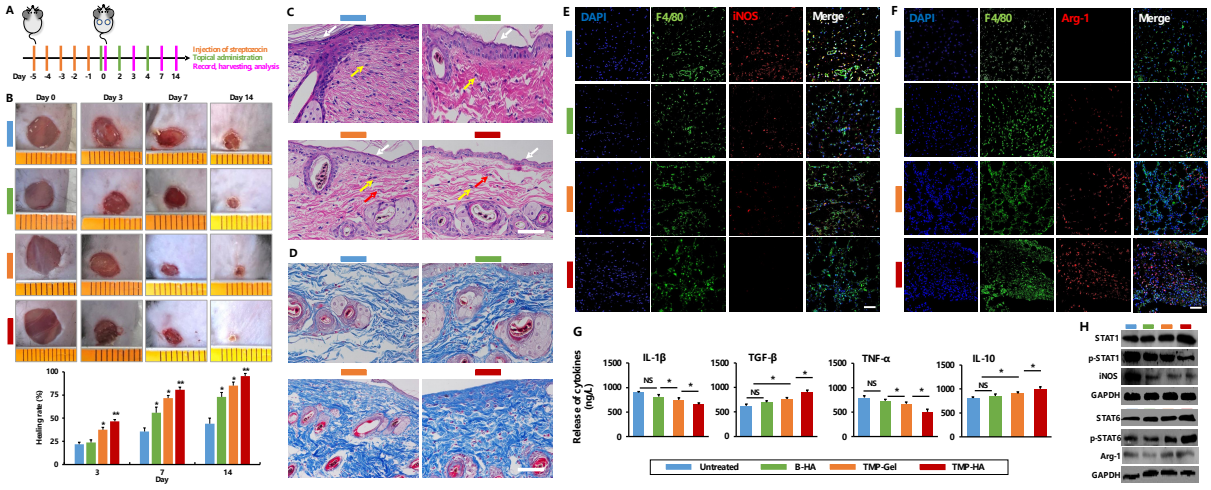

Figure. 1 The TMP-loaded HA hydrogel (TMP-HA) facilitates macrophage polarization for promoting wound recovery in diabetic mice.

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Tumor microenvironment responsive glycogen nanoparticle delivery system for enhancing tumor penetration

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Abstract: Nanotechnology-based chemotherapy is impeded by poor penetration into deep tumor tissues, because the dense tumor extracellular matrix (ECM) in the tumor microenvironment (TME) hinders antitumor drugs penetration. Cross-linked gelatinous hyaluronic acid (HA) is the main component of ECM and supports the 3D structure of ECM. Herein, we reported a TEM responsive glycogen-based nanoparticle delivery system which can release HAase in tumor site and loosen up ECM to accomplish drug deep tumor penetration. Triphenylphosphine with a positively charged core was selected to modify natural glycogen to endow the nanoparticles (Gly-TPP, GT) with the ability to load hyaluronidase through electrostatic interactions, and the chemotherapy drug doxorubicin (DOX) was encapsulated in the cavity of glycogen structure. Furthermore, polyethylene glycol (PEG) containing a MMP-2-cleavable peptide fragment was modified to improve the recycling ability of the nanoparticles and to regulate the release behavior of HAase, obtaining the MMP-2 sensitive glycogen derivative (Gly-TPP-pep-PEG, GTPP). Simultaneously, the MMP-2 insensitive cationic glycogen derivative (Gly-TPP-PEG, GTP) was synthesized as control. DOX/HAase/GTPP can release HAase to degrade HA in the tumor ECM, facilitating the penetration of nanoparticles and antitumor drugs and exhibited enhanced antitumor efficacy. In conclusion, the study provides a new strategy for enhancing drug penetration in solid tumors and improving the efficacy of chemotherapy.

Keywords: glycogen nanoparticles, doxorubicin, hyaluronidase, MMP-2 response, enhanced penetration

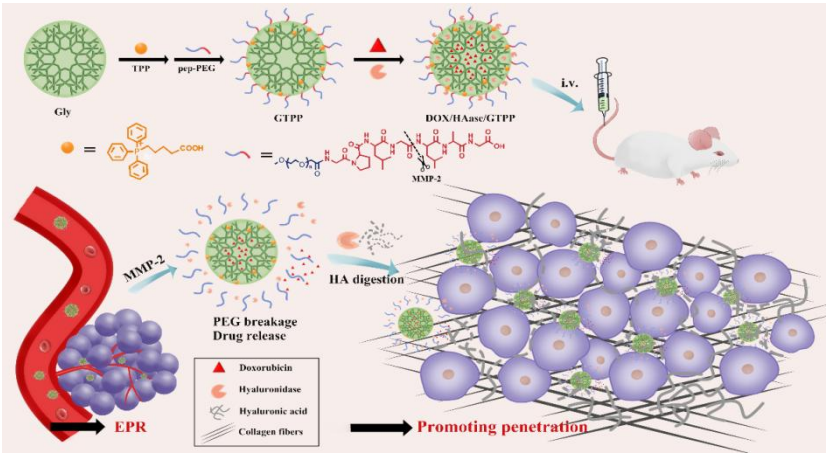

Figure. 1 Schematic diagram of DOX/HAase/GTPP preparation and enhanced tumor penetration.

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Nano-delivery system for in situ nitric oxide generation and its application in precise theranostics of brain diseases

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Abstract: Bioactive signal transmitter gases such as nitric oxide (NO) and hydrogen sulfide (H_2S) can effectively regulate the disease microenvironment, providing new solutions for the precise theranostics of cerebrovascular diseases and brain tumors. However, efficient delivery of these bioactive gases across the blood-brain barrier remains challenging[1]. Herein, a novel NO delivery system based on magnetic field -responsive nanocarriers (NO-MNCs) is reported, which is constructed by encapsulating magnetic nanoparticles and NO prodrugs with biomaterials such as phospholipids [2,3] and cell membranes[4]. Due to the encapsulation of magnetic nanoparticles, NO-MNCs can rapidly target brain lesions and cross the blood-brain barrier under magnetic field guidance. Subsequently, with the accumulation of NO-MNCs at ischemic and tumor sites, the NO prodrug is released, leading to the *in situ* generation of NO gas in the microenvironment of the lesion. It can not only enable the rapid and precise localization of lesions under ultrasound/magnetic resonance dual-mode imaging monitoring, but also exerts biological effects such as inducing vasodilation and promoting tumor cell apoptosis, thereby achieving the integrated and precise diagnosis and treatment of cerebrovascular diseases and brain tumors[5].

Keywords: nitric oxide; *in situ* generation, magnetic nanoparticles, cerebrovascular disease

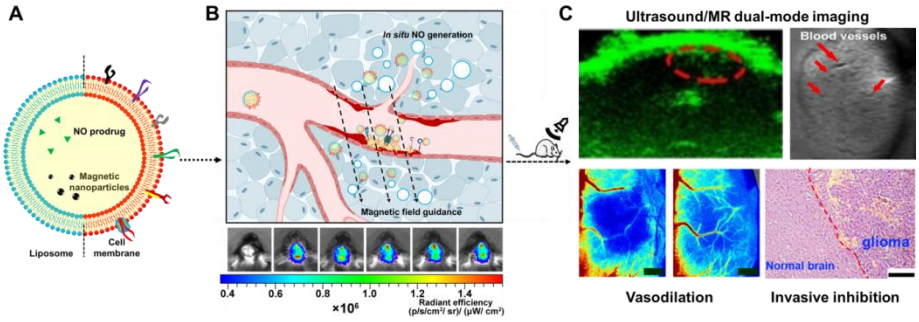

Figure. 1 (A) Schematic diagram of the structure of NO-MNCs. (B) Targeting of NO-MNCs and *in situ* generation of NO under magnetic field guidance. (C) Ultrasound/MRI dual-modal diagnosis of brain lesions after NO-MNCs administration and ischemic stroke (bottom left) and glioma (bottom right) treatment.

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Molecular conjugate drug delivery system

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Abstract: An ideal drug delivery system aims to transport a drug specifically and safely to its designated site of action. However, conventional excipient-based systems like micro- and nano-drug delivery systems often face limitations in achieving precise targeting. To overcome these challenges, the molecular conjugate drug delivery system has emerged as a promising approach, offering numerous advantages over conventional systems. This innovative system enables safer and more specific drug delivery to the desired site of action. The molecular conjugate drug delivery system comprises various types of drug conjugates, including antibody-drug conjugates, polymer-drug conjugates, peptide-drug conjugates, small molecule-drug conjugates, oligonucleotide conjugates, and other types of drug conjugates. These conjugates possess simple formulations yet exhibit remarkable therapeutic effects. Recent advancements in the field of molecular conjugate drug delivery systems have garnered significant attention due to their potential to revolutionize drug delivery. Despite the advancements, there are still challenges to overcome in the development of molecular conjugate drug delivery systems. Looking ahead, the future of molecular conjugate drug delivery systems appears promising. With ongoing research and development, these systems have the potential to reshape the landscape of drug delivery by offering improved therapeutic outcomes, enhanced patient compliance, and reduced side effects. Further innovations in conjugate design, formulation, and manufacturing processes will contribute to the translation of these systems from the laboratory to clinical applications.

Keywords: molecular conjugate drug delivery system; drug conjugates; payload; carrier; linker

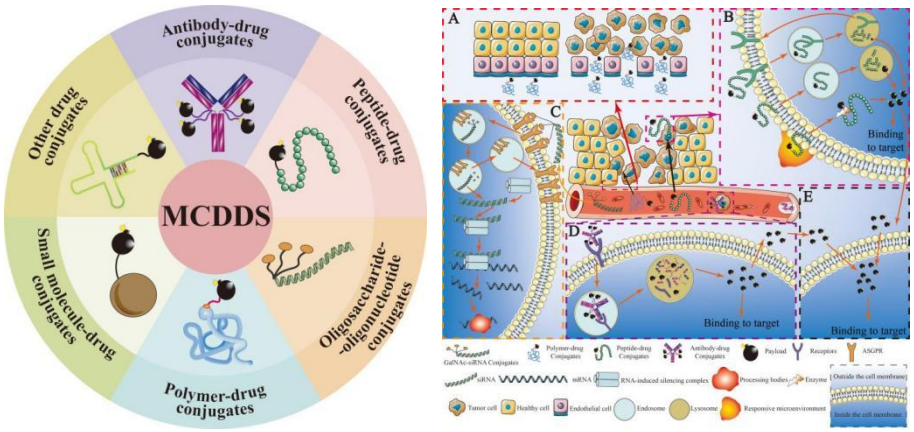

Figure. 1 Schematic illustration of molecular conjugate drug delivery system (MCDDS) (Left); and the mechanisms of molecular conjugate drug delivery system (Right).

Reference:

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Immunotherapeutic Hydrogel for Co-delivery of STAT3 siRNA Liposomes and Lidocaine Hydrochloride for the Postoperative Comprehensive Management of NSCLC

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Abstract: Despite standard treatment for non-small cell lung cancer (NSCLC) is surgical resection, cancer recurrence and complications, such as induction of malignant pleural effusion (MPE) and significant postoperative pain, usually result in treatment failure [1-2]. Herein, an alginate-based hybrid hydrogel (SOG) is developed to control tumor recurrence and comprehensively manage complications, which is injected into the resection surface of the lungs during surgery. In this platform, endoplasmic reticulum-modified liposomes (MSLs) pre-loaded with the signal transducer and activator of transcription 3 (STAT3) small interfering RNA and lidocaine hydrochloride are encapsulated. Once applied, MSLs strongly downregulate STAT3 expression in the tumor microenvironment, resulting in the apoptosis of lung cancer cells and polarization of tumor-associated macrophages towards the M1-like phenotype[3]. Meanwhile, the release of lidocaine hydrochloride is beneficial for pain relief and natural killer cell activation. Our data demonstrated MSL@LID@SOG not only efficiently inhibits tumor growth, but also potently improves the quality of life, including reduced MPE volume and pain in orthotopic NSCLC mouse models even with a single administration. MSL@LID@SOG shows potential for clinical comprehensive management upon tumor resection in NSCLC, and may possibly alter the treatment paradigms for other cancers, such as ovarian carcinoma and mesothelioma.

Keywords: liposome; hydrogel; signal transducer and activator of transcription 3; non-small cell lung cancer; macrophage

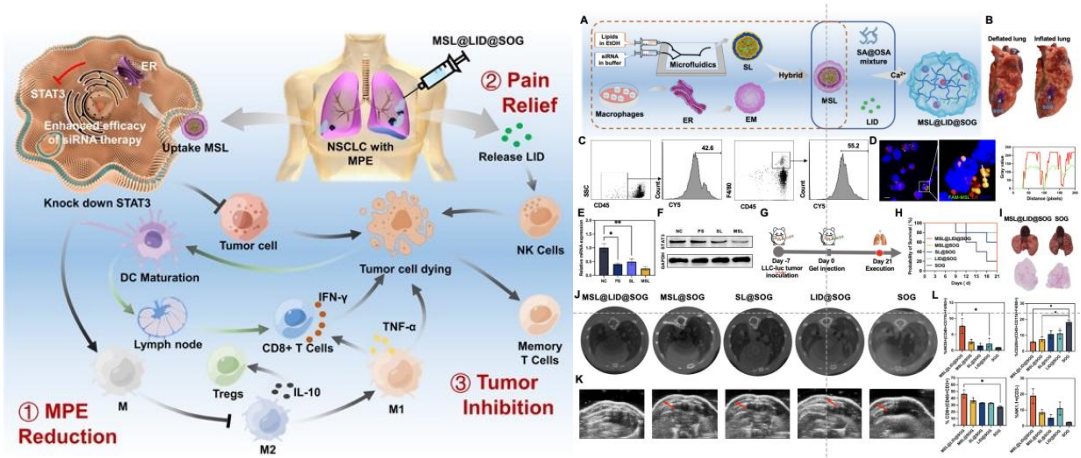

Figure 1 Schematic diagram of the proposed mechanism of MSL@LID@SOG (Left); and SOG-mediated anti-tumor efficacy (Right).

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Preparation and evaluation of brain targeted by dihydroartemisinin/perillyl alcohol co-delivered liposomes for cerebral malaria

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Abstract: Malaria is a serious infectious disease that causes serious harm to human beings, resulting in more than 600,000 deaths every year. It is estimated that about 1 % of children infected with Plasmodium falciparum will develop a more severe brain complication called cerebral malaria (CM). The main problem of drug therapy for CM is how to across blood brain barrier (BBB). Currently, there is a lack of effective means to deliver drugs to the brain tissue. In order to improve the effectiveness of CM treatments, reduce the nervous system damage caused by CM, and deliver more drugs to the brain tissue, liposomes that combine neuroprotective perillyl alcohol (POH) with the dihydroartemisinin (DHA) which is a first-line antimalarial drug are strongly recommended for the treatment of CM, but remains challenging. The brain-targeted DHA/POH co-delivery liposomes (DP@Tyr-Lips) were reported for the treatment of CM. DP@Tyr-Lips was prepared by the physical mixture of TPGS modified with tyrosine which was the substrate of LAT1 transporter, DHA, and POH by the thin film dispersion method. Tyr could target the brain tissue site, so that the drug is effectively concentrated in the brain tissue. It is worth noting that the levels of TNF-α and IFN-γ in the brain tissue could be reduced via the released POH, thus effectively improving the damage of BBB, while the plasmodium isolated in the cerebrovascular could be effectively killed by the released DHA. The synergistic effect of the two drugs could achieve an effective anti-brain malaria effective. Compared with traditional antimalarial drugs, the brain-targeted liposomes co-loaded with DHA and POH not only significantly enhanced the inhibitory effect on the growth of plasmodium and also improved the nervous system damage in mouse CM model, providing a new strategy for the treatment of CM.

Keywords: Dihydroartemisinin; Perillyl alcohol; Co-delivery; Cerebral malaria; *In vivo* pharmacodynamics.

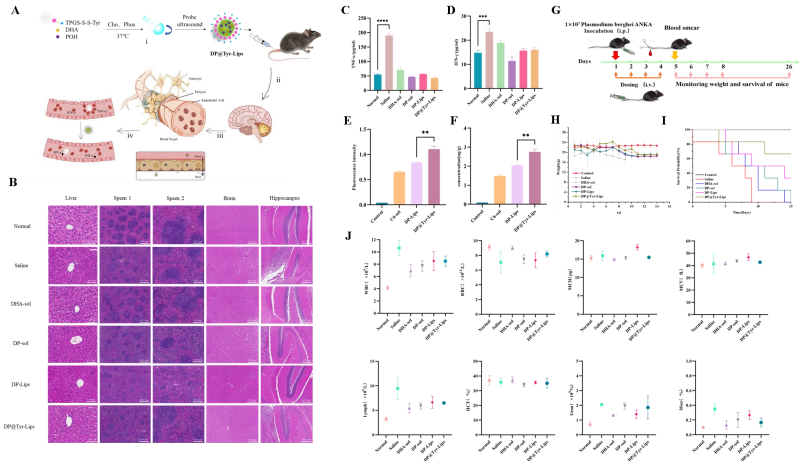

Figure. 1 Schematic diagram of the preparation process of DP@Tyr-Lips and its therapeutic mechanism in a mouse CM model (A); H&E staining results of pathological sections of some organs of experimental mice (B); The concentrations of TNF-α (C) and IFN-γ (D) in brain tissue; The accumulative fluorescence intensity (E) and concentration (F) of C6 of different preparations in brain tissue at different time; The schematic diagram of *in vivo* antimalarial efficacy treatment scheme (G); The changes of weight (H) and survival time (I) of malaria mice in each high-dose administration group; The effects of preparations on blood routine parameters of mice in each experimental group (white blood cells (WBC), red blood cells (RBC), mean red blood cell hemoglobin amount (MCH), mean red blood cell volume (MCV), lymphocytes (Lymph), neutrophils (Gran), and monocytes (Mon) (J).

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Precise Broad Spectrum ROS Scavenging by Stimuli-responsive H2 Generator for Depression Therapy Through Nasal-brain Pathway

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Abstract: Depression is one of the most common mental diseases, which seriously affects patients' physical and mental health. Emerging evidence has indicated that oxidative stress (OS) is a major cause of neurodegeneration and leads to the dysfunction of 5-hydroxytryptamine (5-HT) system to be involved in the pathogenesis of depression. Consequently, targeted reactive oxygen species (ROS) scavenging is regarded as a promising strategy for efficient depression therapy. In addition, insufficient brain drug delivery is a major obstacle to depression therapy owing to the presence of the blood-brain barrier (BBB). To achieve the goals of bypassing the BBB and promoting antioxidant therapy for depression, a broad-spectrum ROS scavenging H2 generator was rationally designed through a nasal-brain pathway developed for combined ROS scavenging and brain drug delivery. A hexa-arginine (R6) modified ROS-responsive dextran derivate was synthesized for antidepressant olanzapine (Olz) and H2 donor amino borane (AB) loading to prepare Olz/RDPA. Subsequently, the nanoparticles were loaded into a thermoresponsive hydrogel system based on poloxamer. *In vitro* and *in vivo* results demonstrated that Olz/RDPA *in situ* thermoresponsive hydrogel system could effectively deliver nanoparticles to the brain *via* the nasal-brain pathway and alleviate depression-like behaviors through combined ROS depletion and inhibition of 5-HT dysfunction of the oxidative stress-induced. The proposed ROS-scavenging nanotherapeutic would open a new window for depression treatment.

Keywords: ROS-responsive nanoparticles; hydrogen; hydrogel; depression; ROS scavenging

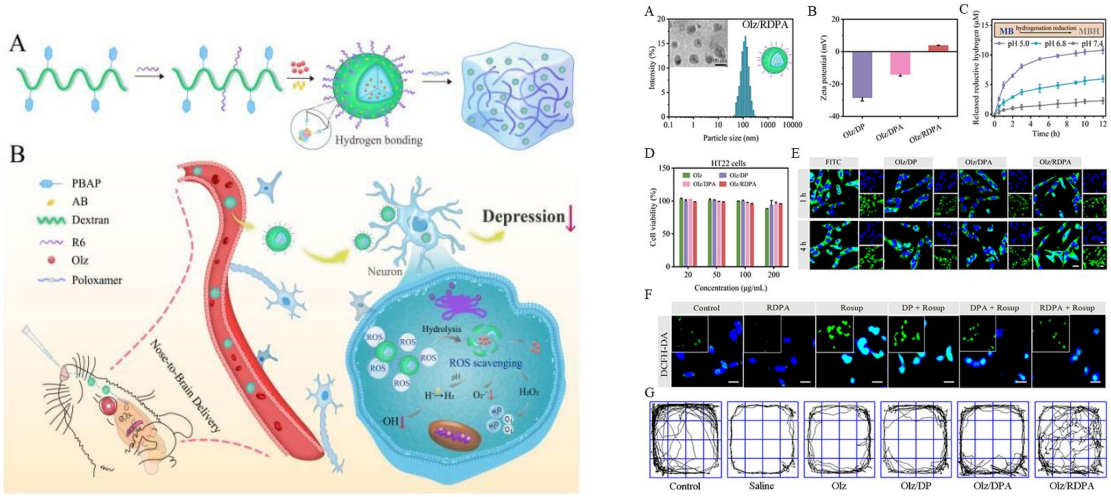

Figure. 1 Schematic illustration of the synthetic procedure of SMTA and the proposed mechanism of Olz/RDPA-mediated antioxidant strategy (Left); and Olz/RDPA-mediated hydrogen release, ROS clearance, and the alleviation of depression-like behavior (Right).

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Mussel-Inspired Caries Management Strategy: Constructing a Tribioactive Tooth Surface with Remineralization, Antibiofilm and Anti-inflammation Activity

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Abstract: Dental caries is a common chronic oral disease in humans resulting from tooth demineralization caused by acid production of bacterial plaque, which leads to the destruction of enamel and dentin and oral inflammation. However, it is still a challenge that the function of natural active ingredients in currently available oral care products is not comprehensive, especially lack of remineralization. Here, inspired by the strong biological adhesion ability of mussels and ancient oral disease plant therapy, a multifunctional strategy is proposed to construct a bioactive tooth surface to treat dental caries. It has been demonstrated that the Turkish gall extract (TGE) can inhibit adhesion of cariogenic bacteria Streptococcus mutans (*S. mutans*) and Actinomyces viscosus (*A. viscosus*), and destroy biofilms on the tooth surface. Meanwhile, TGE can reduce the expression of inflammatory factors. Notably, the TGE coating can induce the growth of hydroxyapatite (HAP) crystals in vivo and in vitro, recovering the enamel mechanical properties under normal oral conditions. MD simulations interpreted the adsorption mechanism by which the hydroxyl groups in TGE bind to phosphate group (PO_4^{3-}) on the tooth surface, attracting calcium ions (Ca^{2+}) as nucleation sites for remineralization. This work underlines the importance of TGE coating in remineralization, anti-biofilm and anti-inflammation activity as a promising strategy for dental caries.

Keywords: dental caries, polyphenols, remineralization, antibiofilm, anti-inflammation

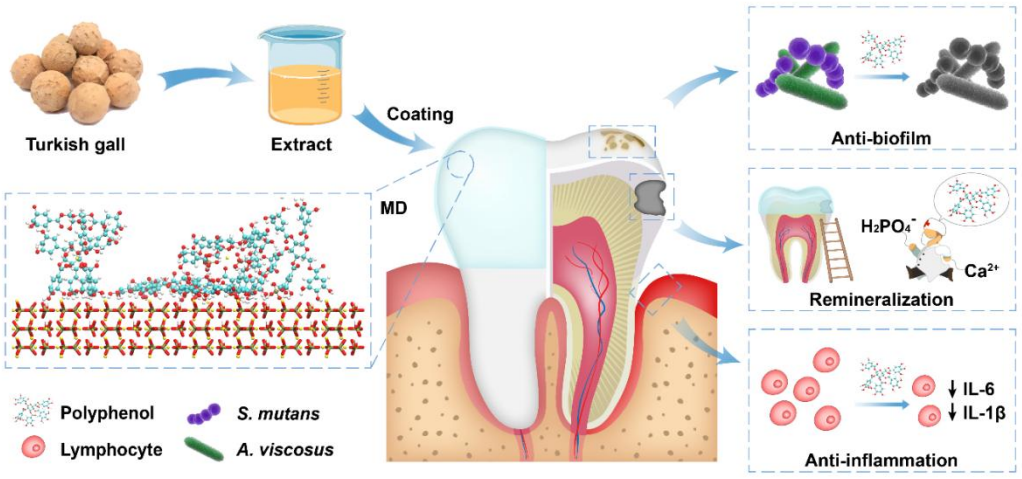

Figure. 1 Schematic illustration of the synthesis and mechanism of action of the TGE coating on tooth and its therapeutic applications.

Reference:

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Cascade Targeting Drug Delivery to Golgi Apparatus for Cancer Metastasis Suppression

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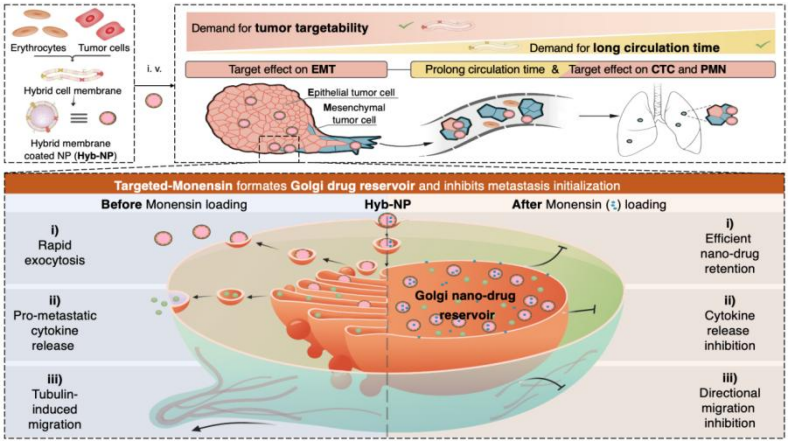
Abstract: As the foremost cause of cancer-related death, metastasis consists of three steps: invasion, circulation, and colonization. Only targeting one single phase of the metastasis cascade may be insufficient since there are many alternative routes for tumor cells to disseminate. Here, to target the whole cascade of metastasis, hybrid erythrocyte and tumor cell membrane-coated nanoparticle (Hyb-NP) is designed with dual functions of increasing circulation time and recognizing primary, circulating, and colonized tumors. After loading with Monensin, a recently reported metastasis inhibitor, the delivery system profoundly reduces spontaneous metastasis in an orthotopic breast cancer model. Our previous researches reported that homologous cancer cell-derived nanoparticles preferentially accumulated in the ER-Golgi network due to the membrane fusion proteins (e.g., SNAREs) existing on the surface of nanoparticles (Nano Today, 2022, 42: 101356). The current mechanism studies further revealed that Hyb-NP can deliver Monensin to its action site in Golgi apparatus, and in return, Monensin can block the exocytosis of Hyb-NP from Golgi apparatus, forming a reservoir-like subcellular structure. Notably, the Golgi apparatus reservoir displays three vital functions for suppressing metastasis initialization, including enhanced subcellular drug retention, metastasis-related cytokine release inhibition, and directional migration inhibition. Collectively, the formation of Golgi nanoparticle reservoir by sequentially targeting Golgi and blocking exocytosis inhibited metastasis initialization in a subcellular level. Meanwhile, hybrid cell membrane camouflaged conferred nanoparticles targetability to metastasis cascade in cell and tissue levels. Collectively, this rationally designed nano-platform provides a potential therapeutic strategy for cancer metastasis suppression (**Scheme 1**).

Keywords: Golgi apparatus targeting, exocytosis blockade, Monensin, drug reservoir, metastasis suppression



Scheme 1 Schematic illustration of the biomimetic strategy that targeted Golgi apparatus as nanoparticle reservoir for cancer metastasis suppression.

Reference:

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Modulating Autophagy Direction to Enhance Anti-tumor Effect of Endoplasmic Reticulum-targeted Therapy

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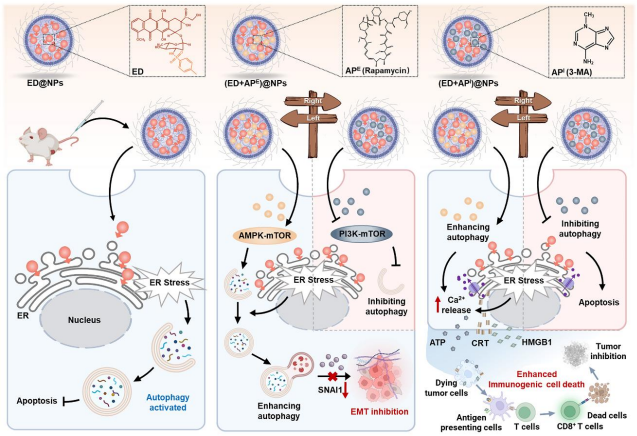
Abstract: Strategies that induce dysfunction in endoplasmic reticulum (ER) hold great promise for anti-cancer therapy. In a previous study, a library of doxorubicin (DOX) derivatives with various targeting subunits were synthesized, redirecting the intracellular fate of DOX from nucleus to ER [1]. This study revealed that ER-targeting efficiency of DOX positively correlated with the capability to induce immunogenic cell death (ICD). However, this strategy remain unsatisfactory due to the compensatory autophagy induction after ER disruption. Moreover, as autophagy could either promote or suppress cell survival, which direction of autophagy better suits ER-targeting therapy remains controversial. Here, we constructed a targeted nano-system that efficiently escorts anti-cancer therapeutics into ER, triggering substantial ER stress and autophagy. Concurrently, we combined autophagy enhancer or inhibitor into the same nanoparticle, and compared their impacts on ER-related activities. In orthotopic breast cancer mouse model, autophagy enhancer increased anti-metastasis effect of ER-targeting therapy and suppressed over 90% of cancer metastasis while autophagy inhibitor had bare effect. Mechanism studies revealed further enhancing autophagy accelerated central protein SNAI1 degradation, suppressing downstream epithelial-mesenchymal transition, while inhibiting autophagy did the opposite. With the same trend, ER-targeting therapy combined with autophagy enhancer provoked stronger immune response and tumor inhibition than autophagy inhibitor. Mechanism studies revealed that the autophagy enhancer elevated Ca^{2+} release from ER and functioned as an cascade amplifier of ER dysfunction, which accelerated Ca^{2+} release, resulted in ICD induction, and eventually triggered immune responses. Together, ER-targeting therapy benefits from autophagy-enhancing strategy more than autophagy-inhibiting strategy for anti-tumor and anti-metastasis treatment (**Scheme 1**).

Keywords: endoplasmic reticulum targeting, autophagy modulation, immunotherapy, drug delivery system, anti-metastasis therapy



Scheme 1 Schematic illustration of the autophagy-modulating drug delivery strategies. ER-targeted ED could induce ER stress, but compensatory autophagy was also activated and decreased its cytotoxicity. ED and autophagy modulators (AP^E or AP^I) were co-loaded into nanoparticles. (ED+AP^E)@NPs accelerated the degradation of central protein SNAI1, leading to the suppression of downstream metastasis-promoting process of EMT. In parallel, (ED+AP^E)@NPs functioned as an amplifier of ER dysfunction → Ca^{2+}release → ICD induction → immune response cascade, provoking stronger immune response. However, (ED+AP^I)@NPs only promoted apoptosis via blocking the PI3K/mTOR pathway.

Reference:

[1] Xiang, Y., Li L*, Huang, Y*, Redirecting Chemotherapeutics to the Endoplasmic Reticulum Increases Tumor Immunogenicity and Potentiates Anti-PD-L1 Therapy. Small, 2022, 18, e2104591.

Gel Loaded with Sildenafil Citrate Solid Lipid Nanoparticles for Skin Wound Healing

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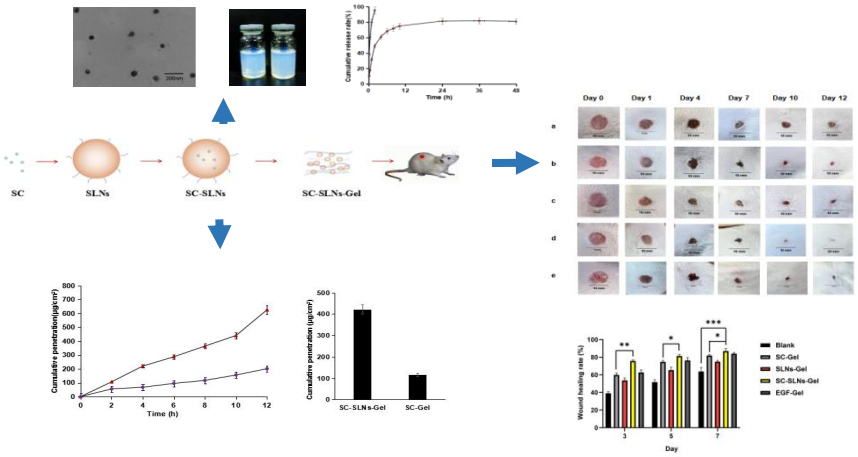
Abstract: It has been reported that sildenafil citrate (SC) can promote skin wound healing. However, the disadvantages of SC such as low stability and poor skin absorption limit its application in wound healing. Solid lipid nanoparticles (SLNs) as nano-carriers have the advantages of increasing drug solubility, reducing irritation, delaying drug release, increasing skin penetration and retention. Sildenafil citrate solid lipid nanoparticles gel (SC-SLNS-Gel) was prepared by mixing SLNs loaded SC into gel for increasing the penetration and absorption of SC and promoting wound healing. The prepared SC-SLNs had moderate particle size, uniform dispersion and sustained-release effect. SC-SLNs-Gel had high drug loading and higher transdermal penetration and skin retention than SC-gel. There was no irritant to normal skin and traumatic skin after transdermal administration of SC-SLNs-Gel. SC-SLNs-Gel can promote skin wound healing significantly compared with SC gel and commercial preparations (EGF-Gel).On the 7th day of treatment, the wound healing rates of blank group, SC-Gel group, SLNs-Gel group, SC-SLNs-Gel group and positive drug group were 63.81%, 81.91%, 74.89%, 86.97% and 83.94%, respectively. The wound healing rate of SC-SLNs-Gel group was significantly higher than that of negative control group (P<0.001) and SC-Gel group (P<0.01). On the 12th day of treatment, the healing status of each group of rats was good. In the same treatment time, SC-SLNs-Gel group rats scab completely shed and hair growth is better. Conclusively, the prepared SC-SLNS-Gel were well designed and may be a promising formulation for transdermal delivery of SC for improving skin wound healing

Keywords: Sildenafil citrate, solid lipid nanoparticles gel, transdermal administration, wound healing

GRAPHICAL ABSTRACT



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pH/Cathepsin B Hierarchical-Responsive Nanocarrier based on proteolytic targeting chimeras (PROTACs) for Cancer Therapy

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Abstract:

Proteolysis targeting chimeras (PROTACs) provide a novel way to degrade specific protein targets for cancer therapy. However, the antitumor efficacy of PROTACs is limited by their insufficient tumor distribution. Undesired distribution of PROTACs at non-target sites leads to uncontrollable protein degradation, limiting their clinical application. We herein report a pH/cathepsin B hierarchical-responsive nanoconjugates (HRNs), sequentially responding to extra- and intracellular stimuli in tumors for programmed delivery of PROTACs. In blood circulation (pH = 7.4), HRNs maintain stable nanostructures (70 nm) facilitating for tumor accumulation through EPR. While tumor extracellular acidity induces a rapid dissociation of HRNs into polymer monomers (< 5 nm), facilitating tumor penetration and cellular internalization. After being trapped into the lysosomes, the polymer monomers are cleaved by cathepsin B to release PROTACs into cytoplasm and degrade specific protein. To investigate anti-tumor efficacy of HRNs, we use cyclin-dependent kinase 4/6 (CDK4/6) which highly expressed in tumors as target-protein. To proof that HRNs could deliver PROTACs to tumor efficiently, we use balb/c mice bearing CT26 as animal models, demonstrating highly accumulation of HRNs in tumor. Specific CDK4/6 degradation efficiently inhibits tumor growth. This study suggests the potential of HRNs for precise protein degradation and provides a potential clinical candidate for cancer PROTAC-therapy.

Keywords: Proteolysis targeting chimeras (PROTACs); pH/Cathepsin B Hierarchical-Responsive Nanocarrier; cyclin-dependent kinase 4/6 (CDK4/6)

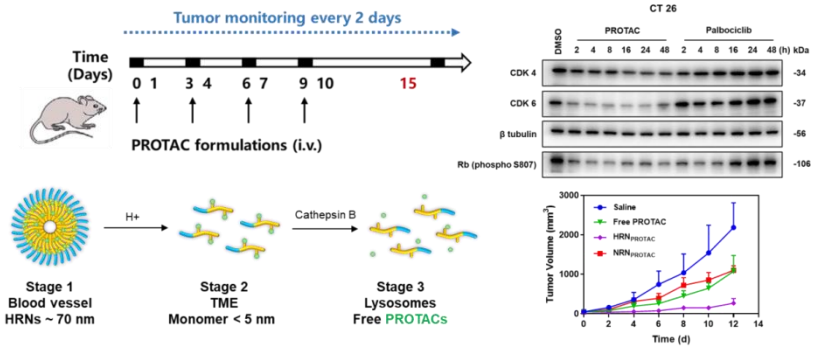

Figure. 1 Schematic illustration of programmed delivery of PROTACs with HRNs (Left); Western blot assay of PROTAC-mediated CDK4/6 degradation and pRb downregulation in CT26 cells after incubation with different times and Anti-tumor efficacy of HRNs in male balb/c mice bearing CT26 (Right).

Reference:

[1] Wang, Y., Zhou, K., Huang, G., Hensley, C., Huang, X., Ma, X., Zhao, T., Sumer, B. D., DeBerardinis, R. J., Gao, J., Nature materials[J], 2014, 13 (2), 204-12

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Dual-line Defensive Non-split HDL Nano System Against Oxidative Stress of Foam Cell and Defunction of HDL

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Abstract: High-density lipoproteins (HDL) possess pivotal antiatherogenic biological properties, including cellular cholesterol efflux, inhibition of atherogenic oxidative low-density lipoprotein (oxLDL) and attenuate inflammation. However, systemic and vascular inflammation may convert HDL to a dysfunctional form that even be pro-inflammatory and pro-oxidant. Herein, a dual-line defensive non-split HDL nano system (T@E-HDLs) with cascading ROS-scavenging function is reported to inhibit the oxidative stress of foam cell and defunction of HDL, in which endogenous nanoparticles from human plasma FIV components were templated as non-split HDL versus exogenous recombinant HDL (rHDL) prepared in vitro. T@E-HDLs are prepared with post-insertion of ebselen (glutathione peroxidase mimic) and TPGS-Tempo (superoxide dismutase mimic) into non-split HDLs, which was proved to be mitochondrial targeted. The surface-modified TPGS-Tempo and phospholipid layer-loaded ebselen of HDL effectively enhanced its resistance against oxidative defunction in the oxidative stressed foam cells derived from macrophages. Specifically, comparing with plain non-split HDLs, T@E-HDLs performed reduced cellular oxidative damage and exerted better HDL functions in oxidative stressed foam cells, including enhanced efficacy for cellular lipid removing, improved inflammation inhibition and reduced lipid deposition and apoptosis. With the antioxidation and consequent anti-defunction effects by cascading enzyme mimics modification, the proposed HDL nano-system provides a promising resolution for the HDL oxidative-defunction dilemma which hindering the application of HDL-targeting therapies in AS.

Keywords: atherosclerosis; non-split HDL; antioxidants; oxidative defunction

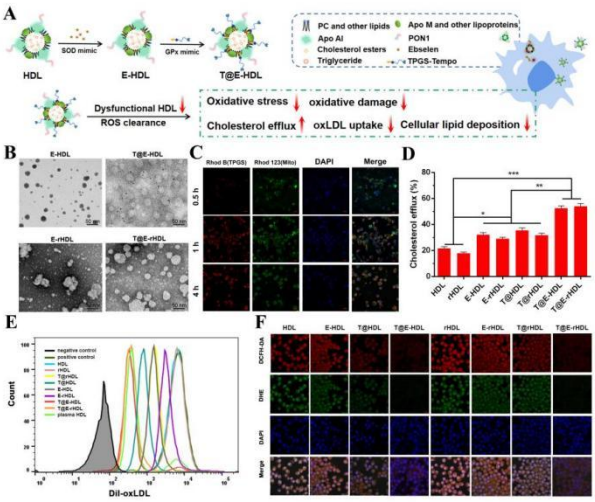

Figure. 1 The T@E-HDL nanosystem mediated antioxidation of foam cell and anti-defunction of HDL.

Reference:

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Intracellular Self-Assembly Driven Nucleus-Targeted Photo-Immune Stimulator with Chromatin Decompaction Function for Robust Innate and Adaptive Antitumor Immunity

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Abstract: Nasopharyngeal carcinoma (NPC) is one of the most common tumors in South China and Southeast Asia. Its development is related to Epstein-Barr virus (EBV) infection. Down-regulation of the latent membrane protein 1 (Lmp1) encoded by EBV can reduce the expression of NF-κB and PI3K, induce cell apoptosis and thus treats EBV-related nasopharyngeal carcinoma. Here, a post cross-linked ROS-responsive poly (β-amino ester) (PBAE) polymeric vector was designed for the delivery of the CRISPR/Cas9 system to cleave Lmp1 oncogene. The diameter of optimized polymer-plasmids polyplex nanoparticles (NPs) were approximately 250nm with good stability. They exhibited efficient cell uptake, high transfection efficiency in EBV-positive C666-1 cells (53.5%), and good gene editing ability against the Mucin2 model gene (*Muc2*) and *Lmp1*, as well as good intracellular ROS levels reducing capability. Besides, the NPs can accumulate in the tumor and significantly inhibit tumor growth in the C666-1 xenograft tumor model via Lmp1 cleavage by CRISPR/Cas9 genome editing technology, indicating the potential in the treatment of EBV-related nasopharyngeal carcinoma.

Keywords: photodynamic immunotherapy; *in situ* self-assembly, chromatin decompaction, nuclear DNA damage

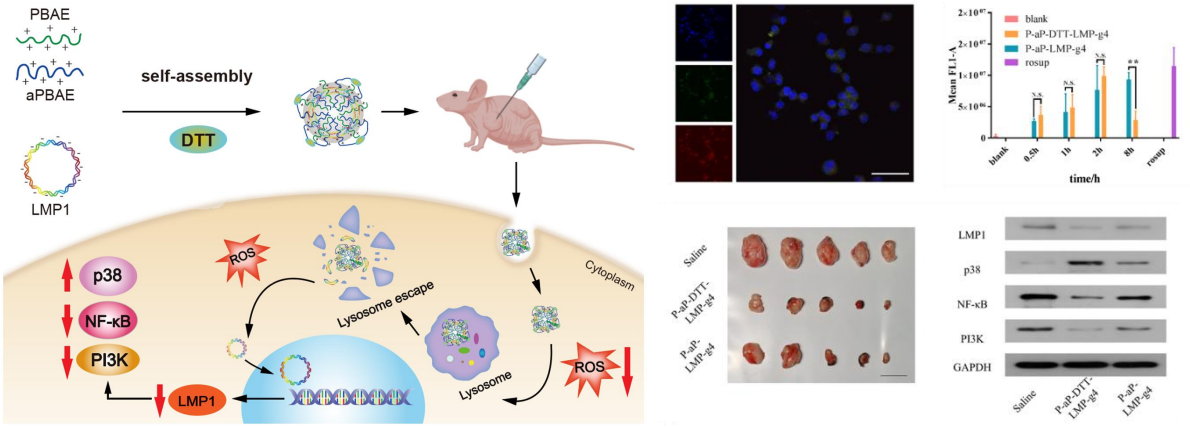

Figure. 1 Schematic illustration of Fabrication of polyplex NPs and mechanism for EBV infection associated NPC treatment. (Left); and cell uptake, intracellular ROS concentration and inhibition of C666-1 xenografts tumor growth in nude mice (Right).

Reference:

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Targeting alveolar macrophages by a phosphatidylserine decorated PLGA nanoparticle loaded with dexamethasone for acute lung inflammation

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Abstract: Acute lung inflammation is a common public health issue with a high morbidity and mortality. The current treatment strategy in clinical is giving glucocorticoids in high dose to suppress the inflammation. However, this strategy might cause serious side effects. Alveolar macrophages that resident in lung alveolus play a crucial role in pathological process of lung inflammation [1]. Targeting delivery of anti-inflammatory drugs to alveolar macrophages is thought to be beneficial for increasing the drug concentration in inflammation site and reducing undesirable side effects. Inspired by the spontaneous phagocyte of macrophages removing apoptotic cells by recognizing the phosphatidylserine “eat me” signal [2], we designed a phosphatidylserine decorated PLGA nanoparticles loaded with dexamethasone (PSNPs) for alveolar macrophages targeting delivery. In this study, the PSNPs were prepared by the anti-solvent precipitation method. The prepared PSNPs had an average size of 189.25 ± 31.40 nm with a spherical morphology. Results demonstrated that phosphatidylserine decorating on nanoparticles could enhance the cellular uptake by macrophages comparing with that of PLGA nanoparticles (NPs). The engulfed PSNPs were mainly transported through lysosomal pathway, and then slowly disintegrated within cells assessing by the Förster resonance energy transfer (FRET) technique. The *in vitro* anti-inflammatory study demonstrated that both NPs and PSNPs could reduce the pro-inflammatory cytokines secretion including TNF-α, IL-6, and IL-1β. The targeting ability of PSNPs was further investigated *in vivo* after pulmonary administration. Results showed that PSNPs had an increased targeting ability to macrophages assessed by fluorescence colocalization of PSNPs with macrophages. In addition, the histopathology of lung tissue confirmed that PSNPs could decrease the infiltration of immune and blood cells and attenuate pathological changes of alveoli for mice suffering from acute lung inflammation. In conclusion, this research indicated that PSNPs might be a promising formulation for lung macrophages targeting delivery, which could increase the drug concentration in inflammation site and improve the therapeutic effect for acute lung inflammation.

Keywords: Phosphatidylserine; Pulmonary delivery; Alveolar macrophages targeting; Acute lung inflammation

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Regulating Photosensitizer Metabolism with DNAzyme-Loading Nanoparticles for Amplified Mitochondria-Targeting Photodynamic Immunotherapy

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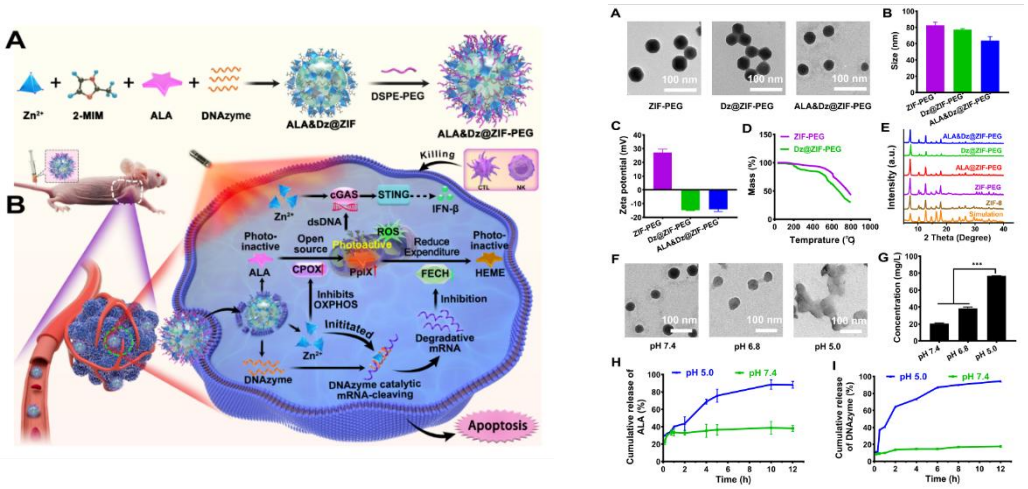
Abstract: Mitochondria-specific photosensitizer accumulation is highly recommended for photodynamic therapy (PDT) and mitochondrial DNA (mtDNA) oxidative damage based innate immunotherapy yet remains challenging. 5-Aminolevulinic acid (ALA, precursor of photosensitizers PpIX) could induce the exclusive biosynthesis of PpIX in mitochondria, nevertheless the efficiency is limited by the intracellular biotransformation of ALA in tumor. Here we report a photosensitizer metabolism regulating strategy with ALA/DNAzyme co-loaded nanoparticles (ALA&Dz@ZIF-PEG) for mitochondria-targeting photodynamic immunotherapy. The Zeolitic Imidazolate Framework (ZIF-8) nanoparticles can be disassembled and produced large amounts of zinc ions (Zn^{2+}) within tumor cells. Notably, the Zn^{2+} could relieve tumor hypoxia for promoting the conversion of ALA to PpIX; and the Zn^{2+} also act as cofactors of rationally designed DNAzyme for silencing excessive ferrochelatase (FECH, catalyzing PpIX into photo-inactive Heme), cooperatively promoting the exclusive accumulation of PpIX in mitochondria via “open source and reduced expenditure” manner. Then the photodynamic effects derived from PpIX lead to the damage and release of mtDNA and subsequent activate the innate immune response. In addition, the released Zn^{2+} further enhance the mtDNA/cGAS-STING pathway mediated innate immunity. The ALA&Dz@ZIF-PEG system induced 3-times of PpIX accumulation more than that of ALA-loaded liposome, achieving significantly enhanced tumor regression in xenograft tumor models.

Keywords: 5-aminolevulinic acid; Photodynamic immunotherapy; Mitochondria-targeting; Photosensitizer metabolism; DNAzyme



Scheme 1. A) Schematic illustration for preparing ALA&Dz@ZIF-PEG nanoparticles, B) Mechanism of promoting mitochondria-targeting photodynamic immunotherapy by ALA&Dz@ZIF-PEG (Left); and characterization of ALA&Dz@ZIF-PEG (Right).

Reference:

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The formulation optimization of lipid nanoparticles for circRNA delivery via microfluidic system through fractional factorial and definitive screening designs

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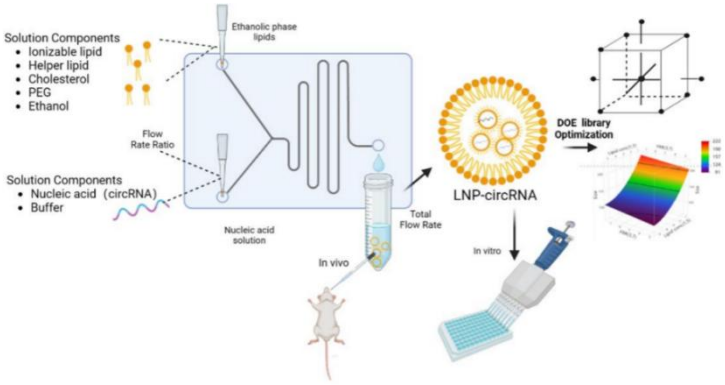
Abstract: circRNA (circular RNA) is a novel type of non-coding RNA, which is distinct with traditional linear RNA, circRNA has a closed loop structure formed by covalent bonds without a 5' -end caps and 3' -end poly (A) tails allows for stable expression and stability against RNA nuclease. It has been demonstrated as the promising vector for the treatment of a variety of diseases. For example, nucleic acids including the circRNA delivery using lipid nanoparticles (LNPs) has been considered a promising strategy in the clinical settings as vaccines or novel therapies for a variety of genetic, infectious diseases or cancers. Despite their great potential, the pharmacokinetics and biological distribution of circRNA loaded by LNPs remain to be studied. Herein, we chose the LNP formulation consisted of amine-containing lipids or lipoid substances, phospholipids, cholesterol, and lipoid modified with polyethylene glycol, whose relative proportions can have a profound effect on the potency of the formulation. In this study, LNP was prepared using a microfluidic system interleaved with herringbone hybrid chip (SHM) by mixing lipids in organic solvents (EtOH) with circRNAs in aqueous phases (weakly acidic buffers) at different controllable parameters, including lipid concentration, flow rate ratio (FRR) between organic and aqueous solutions and total flow rate (TFR). These key determinants are crutial to produce LNPs with high dispersion, reproducibility and heterogeneity and controllable size of, which eventually modulate the biological distribution and specific organ targeting. Therefore, guiding with the design of experiment (DOE) methodologies including definitive screening and fractional factorial designs, lipid concentration, lipid composition and its molar ratio, flow rate ratio (FRR), total flow rate (TFR), different buffers and their pH values were adjusted within a range to obtain optimized conditions. As a result, for example, small LNPs can be formed with > 2 mol% of PEG-lipids, high FRR and TFR and the concentration of PEG-lipids significantly contributed positively to the formation of smaller LNPs. Importantly, under the optimized conditions, the expression of circRNA were demonstrated in vivo and in vitro by cell transfection and in vivo imaging of mice, respectively, which lays important fundamentals for subsequent experiments.

Keywords: microfluidic device; circRNA delivery; DOE Design; LNP; Size control



Reference:

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Lovastatin enhanced the chemo-immunotherapy via synergized stimulation of cGAS STING pathway using a co-loading liposomal delivery system

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Abstract: The cGAS-STING pathway, as an essential immune response pathway, has been demonstrated for a potent target in tumor immunotherapy. However, the low efficiency of conventional STING agonists limits their clinical application. Recent studies have shown that DNA TOPI inhibitor chemodrug SN38 can activate the cGAS-STING pathway and induce an immune response through DNA damage, while traditional statins medication lovastatin was found to inhibit DNA repair, which may in turn upregulate the damaged DNA level. Herein, we have developed a liposomal co-loaded with SN38 and lovastatin (SL@Lip), which can be accumulated and release SN38 and lovastatin in tumor cells, addressing the problems of weak solubility of these two drugs. Importantly, lovastatin can increase DNA damage and enhance the activation of cGAS-STING
pathway coordinating with SN38, and also exhibit the combinational immunotherapy of anti-PD1 antibody by inducing maturation of DC cells and increasing tumor infiltration of CD8+T cells in mouse colorectal cancer model. Overall, this study demonstrates that lovastatin assisted cGAS-STING stimulation via the liposome chemodrug delivery system significantly enhance both chemotherapy and immunotherapy of colorectal cancer, which may provide a clinically translational strategy for antitumor combinational therapy.

Keywords: chemo-immunotherapy, cGAS-STING, DNA damage, SN38, Lovastatin

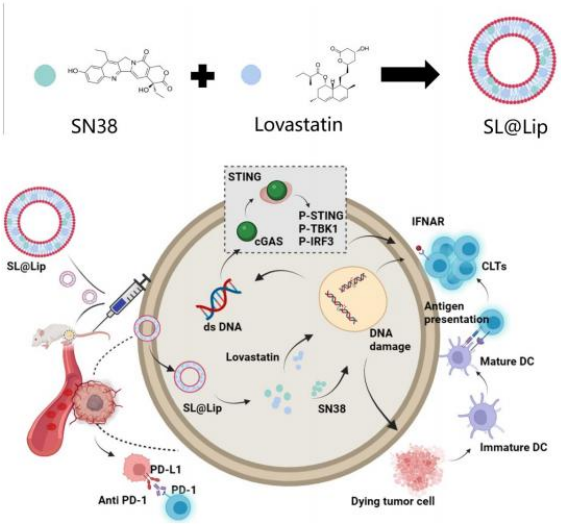

Figure. 1 Schematic illustration of the preparation of SL@Lip and the proposed action of mechanism of SL@Lip enhanced chemo-immunotherapy

Reference:

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Preparation of Angelica sinensis and Sophora flavescens gel and its preliminary study on the treatment of eczema in mice

Rongqia Cui

Abstract: To prepare angelica and sophora flavescens gel and study its effect on eczema in mice. Through orthogonal experimental design, the material liquid ratio, extraction solvent, and extraction frequency were investigated. The content of matrine, oxymatrine, ferulic acid, and dry extract rate were used as evaluation indicators to optimize the extraction process of Angelica sinensis and Sophora flavescens; The central composite design response surface methodology was used to investigate the dosage of carbome-940, glycerol, polyoxyethylene castor oil, and to score the gel to prepare Angelica sinensis and Sophora flavescens gel; DNFB was used to establish mouse eczema model and observe the therapeutic effect of Angelica sinensis and Sophora flavescens gel on mice eczema. The extraction process of Angelica sinensis and Sophora flavescens was as follows: 16 times water, heated and refluxed 3 times, each time for 1 hour; The preparation process of Angelica sinensis and Sophora flavescens gel is: Carbomer 940 1.51%, glycerin 16%, polyoxyethylene castor oil 10%; After being treated with angelica and sophora flavescens gel, the skin inflammation of mice was significantly improved, showing a good therapeutic effect. Angelica sinensis and sophora flavescens gel was successfully prepared, and it was found that it had certain therapeutic effect on eczema in mice.

Keywords: Orthogonal experiment; Star point design; Angelica sinensis and sophora flavescens gel; eczema

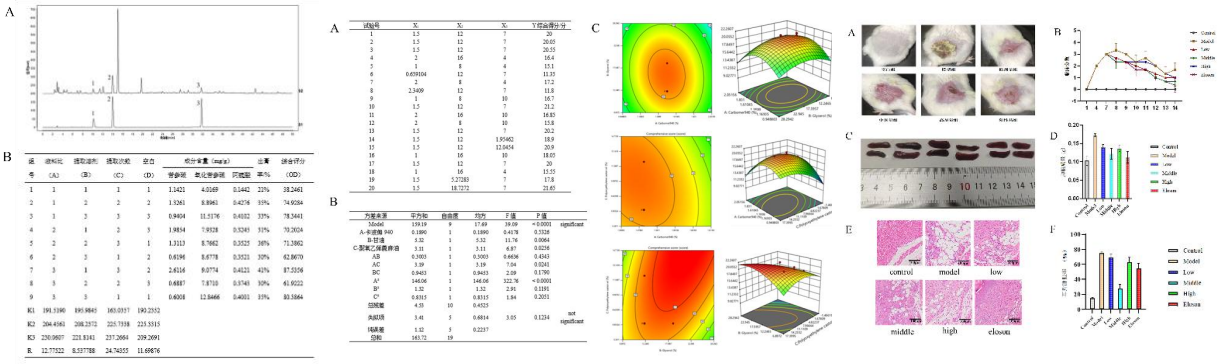

Fig. 1 High performance liquid chromatography of Angelica sinensis and sophora flavescens, orthogonal test design diagram of extraction process (Left) , star point design diagram of Angelica sinensis and sophora flavescens gel (Right).

Fig. 2 Schematic diagram of the therapeutic effect of Angelica sinensis and Sophora flavescens gel on eczema in mice

A Paclitaxel Nanocrystal via π–π Stacking with Enhanced Stability and CD44 Targetability

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Abstract: Efficient Nanocrystals with high drug loading have become a viable strategy for solubilizing drugs with poor aqueous solubility. It remains challenging, however, to synthesize nanocrystals with sufficient stability and targeting potential. Here, we report a novel nanocrystal platform synthesized using paclitaxel (PTX) and Fmoc-8-amino-3,6-dioxaoctanoic acid (Fmoc-AEEA)-conjugated chondroitin sulfate (CS) (CS-Fmoc) via π–π stacking to afford a stable formulation with CD44 targetability (PTX NC@CS-Fmoc). The PTX NC@CS-Fmoc exhibited rod-like shapes with an average hydrodynamic size of 173.6 ± 0.7 nm (PDI = 0.11 ± 0.04) and a drug loading of up to 31.3 ± 0.6%. Next, PTX NC@CS-Fmoc was subjected to lyophilization in the absence of cryoprotectants for long-term storage, and after redispersion, PTX NC@CS-Fmoc displayed an average hydrodynamic size of 205.3 ± 2.9 nm (PDI = 0.15 ± 0.01). In murine Panc02 cells, PTX NC@CS-Fmoc showed higher internalization efficiency than that of PTX nanocrystals without CS modification (PTX NC@F127) ($P < 0.05$) or that of CS-Fmoc micelles ($P < 0.05$). Moreover, PTX NC@CS-Fmoc appeared to accumulate in both lysosomes and Golgi apparatus, while CS-Fmoc micelles accumulated specifically in the Golgi apparatus. In the orthotopic Panc02 tumor-bearing mice model, PTX NC@CS-Fmoc showed higher tumor-specific accumulation than CS-Fmoc micelles, which also demonstrated comparable tumor growth inhibition as to Nab-PTX. Overall, the CS-Fmoc-derived nanocrystals represent a neat and viable formulation strategy for targeted chemotherapy with great potential for translational studies.

Keywords: paclitaxel; nanocrystal; chondroitin sulfate; π–π stacking; pancreatic cancer

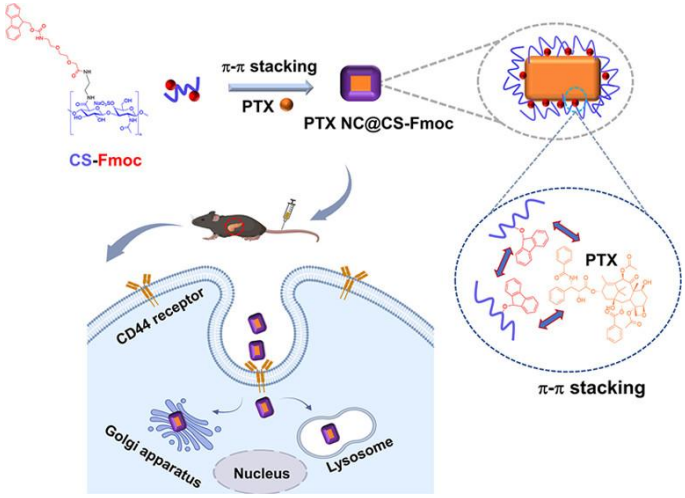

Figure. 1 A schematic diagram of the preparation process of PTX NC@CS-moc and the proposed mechanism.

Cyclosporine A-loaded apoferritin alleviates myocardial ischemia-reperfusion injury by simultaneously blocking ferroptosis and apoptosis of cardiomyocytes

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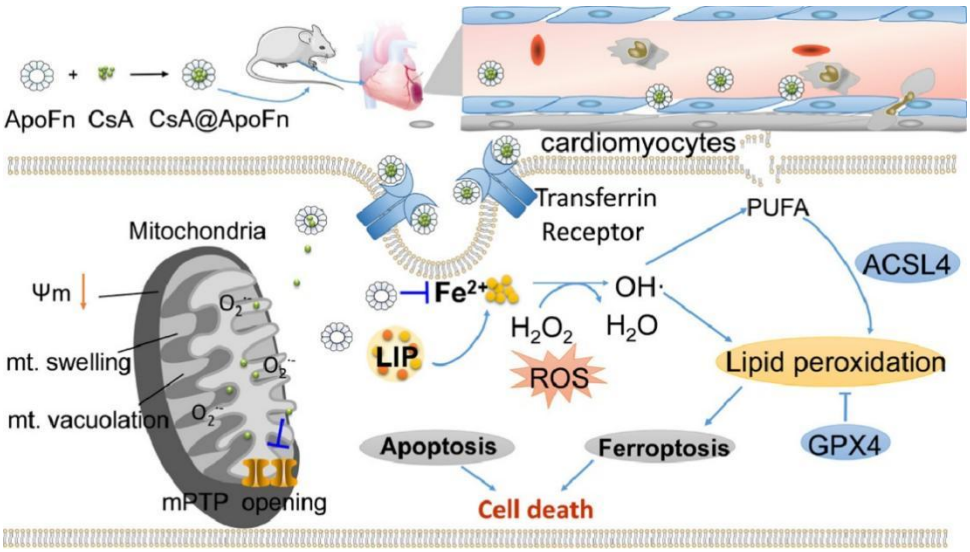
Abstract: Myocardial ischemia-reperfusion injury (MI/RI) seriously restricts the therapeutic effect of reperfusion. It is demonstrated that ferroptosis and apoptosis of cardiomyocytes are widely involved in MI/RI. Therefore, simultaneous inhibition of ferroptosis and apoptosis of cardiomyocytes can be a promising strategy to treat MI/RI. Besides, transferrin receptor 1 (TfR1) is highly expressed in ischemic myocardium, and apoferritin (ApoFn) is a ligand of the transferrin receptor. In this study, CsA@ApoFn was prepared by wrapping cyclosporin A (CsA) with ApoFn and actively accumulated in ischemic cardiomyocytes through TfR1 mediated endoctosis in MI/RI mice. After entering cardiomyocytes, ApoFn in CsA@ApoFn inhibited ferroptosis of ischemic cardiomyocytes by increasing the protein expression of GPX4 and reducing the content of labile iron pool and lipid peroxides. At the same time, CsA in CsA@ApoFn attenuated the apoptosis of ischemic cardiomyocytes through recovering mitochondrial membrane potential and reducing the level of reactive oxygen species, which played a synergistic role with ApoFn in the treatment of MI/RI. In conclusion, CsA@ApoFn restored cardiac function of MI/RI mice by simultaneously blocking ferroptosis and apoptosis of cardiomyocytes. ApoFn itself not only served as a safe carrier to specifically deliver CsA to ischemic cardiomyocytes but also played a therapeutic role on MI/RI. CsA@ApoFn is proved as an effective drug delivery platform for the treatment of MI/RI.



Biomimetic nanoparticle-mediated target delivery of hypoxia-response angiotensin-converting enzyme 2 to pulmonary vascular endothelium reverses hypoxic pulmonary hypertension in rats

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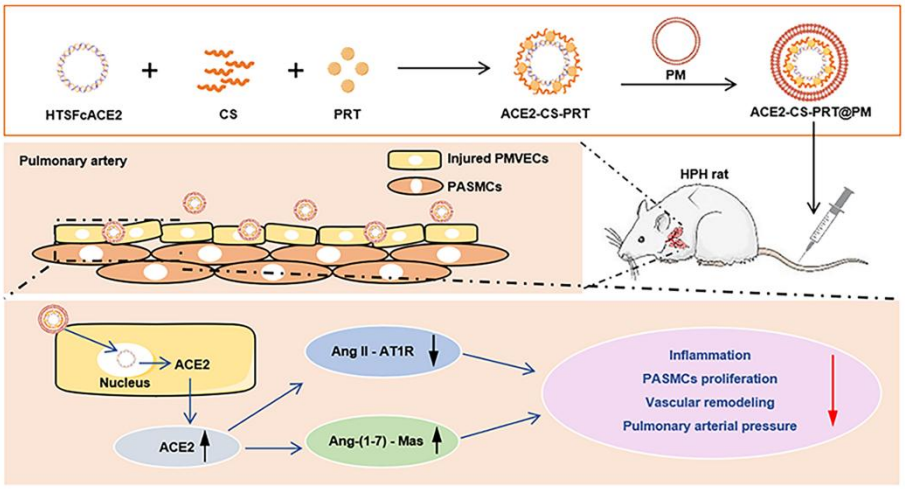
Abstract: Hypoxic pulmonary hypertension (HPH) is characterized by pulmonary vascular sustained constriction and progressive remodeling, which are initiated by hypoxia then plus hypoxia-induced additive factors including pulmonary vascular endothelium injury, intrapulmonary angiotension system imbalance and inflammatory. Now HPH is still an intractable disease lacking of effective treatments. Gene therapy has a massive potential for HPH but is hindered by lacking of efficient target delivery and hypoxia-responsive regulation system for transgene. Herein, we constructed the hypoxia-responsive plasmid of angiotensin-converting enzyme 2 (ACE2) with endothelial specific promoter Tie2 and hypoxia response element, next prepared its biomimetic nanoparticle delivery system, named ACE2-CS-PRT@PM, by encapsulating plasmid of ACE2 with protamine and chondroitin sulfate as core then coating with platelet membrane as shell for targeting to injured pulmonary vascular endothelium. ACE2-CS-PRT@PM had a 194.3 nm diameter with platelet membrane-coating core-shell structure and negative charged surface, and it exhibited the higher delivery efficiency targeting to pulmonary vascular endothelium and hypoxia-responsive overexpression of ACE2 in endothelial cells in hypoxia environment. In vitro, ACE2-CS-PRT@PM significantly inhibited the hypoxia-induced proliferation of pulmonary smooth muscle cells. In vivo, ACE2-CS-PRT@PM potently ameliorated the hemodynamic dysfunction and morphological abnormality and largely reversed HPH via inhibiting the hypoxic proliferation of pulmonary artery smooth muscle cells, reducing pulmonary vascular remodeling, restoring the balance of intrapulmonary angiotension system and improving the inflammatory microenvironment without any detectable toxicity. Therefore, ACE2-CS-PRT@PM is promising for the targeted gene therapy of HPH.



Targeted therapy of glomerulonephritis via salvianolic acid B-loaded biomimetic hybrid nanovesicles driven by homing

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Abstract: Background: Mesangial cell (MC)-mediated immune inflammatory injury is a basic pathological process in glomerulonephritis (GN). However, due to the limited drug accumulation and serious adverse effects, it remains challenging to explore a rational delivery system integrating high efficiency and low toxicity to deliver anti-inflammatory drugs to the glomerular MC region. Results: Salvianolic acid B (SAB)-loaded hybrid membrane biomimetic nanovesicles (SAB@HMVs) were successfully developed by fusing erythrocyte membrane nanovesicles with mesenchymal stem cells biomimetic membrane nanovesicles. SAB@HMVs had a cup-shaped structure, low cytotoxicity, particle size of 143.83 ± 1.33 nm and exhibited a high drug loading capacity (7.02% ± 0.30%) along with a good sustained release function. The *in vitro* anti-inflammatory results revealed that the designed HMVs were effectively taken up by the targeted cells and showed significant anti-inflammatory activity in MCs. Furthermore, *in vivo* pharmacodynamic studies revealed that SAB@HMVs with a targeting ability could deliver SAB to kidney tissue and elicit an effective anti-inflammatory response to improve the pathological changes in the glomerular mesangial region, significantly reducing the levels of cytokines, such as tumor necrosis factor-α and interleukin-1β, alleviating kidney inflammation. Conclusion: We provided a novel strategy to increase nanovesicles accumulation in MCs with the potential to exert anti-inflammatory regulatory effects in GN. Furthermore, this biomimetic hybrid membrane loaded with pure drugs may offer a functional platform to address multiple clinical needs.

Keywords: Mesangial cells, Renal inflammation, Cellular hybrid membrane, Biomimetic drug delivery system, Salvianolic acid B

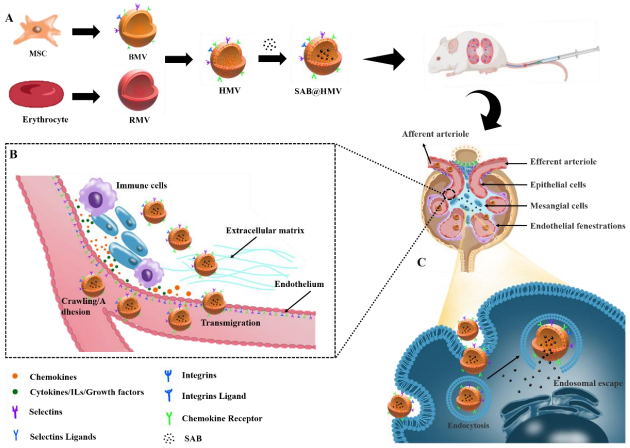

Fig. 1 The hybrid membrane bionic nano-vesicles (HMVs) were composed of MSCs-derived bionic membrane nano-vesicles (BMVs) and erythrocyte membrane nano-vesicles (RMVs). Meanwhile, HMVs-loaded SAB delivery system, termed SAB@HMVs, was constructed by pH-gradient method for the anti-inflammatory targeting therapy of GN. On one hand, SAB@HMVs showed the long circulation effect of erythrocyte membrane; on the other hand, SAB@HMVs inherited the homing property of MSCs, targeting the lesion site to deliver high concentrations of therapeutic SAB.

Preparation of quaternized chitosan magnetic nanoparticles loaded with indocyanine green and their evaluation of characteristics

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Abstract: Objective: To prepare quaternized chitosan magnetic nanoparticles loaded with indocyanine green (ICG@Fe_3O_4@QCS) and to investigate their characteristics. Methods: Through the precipitation method, prepared Fe_3O_4@QCS nanoparticles and evaluated their characteristics through structure, particle size, morphology, and magnetic responsiveness. Through the electrostatic adsorption method prepared, the ICG@Fe_3O_4@QCS nanoparticles and evaluation their characteristics through the particle size, zeta potential, encapsulation rate, drug loading, stability, photothermal conversion efficiency, release, and biosafety of ICG@Fe_3O_4@QCS nanoparticles. The results showed that Fe_3O_4@QCS nanoparticles were successfully prepared in the form of short rods with particle size around (20~30) nm, positively charged, with basic Fe_3O_4 skeleton and particular magnetic responsiveness; ICG@Fe_3O_4@QCS nanoparticles were successfully prepared with particle size around (100~150) nm, positively charged, with encapsulation rate of ≥90% and drug loading capacity of (0.05~2.00)%, slower release compared with ICG solution, all with hemolysis rate less than 2%, heat production under laser irradiation, and NIR imaging function. Conclusion: successfully prepared ICG@Fe_3O_4@QCS nanoparticles by the electrostatic adsorption method, and ICG@Fe_3O_4@QCS nanoparticles are stable, which can improve the bioavailability of ICG.

Keywords: Indocyanine green; Quaternized chitosan; Magnetic nanoparticles; Character evaluation

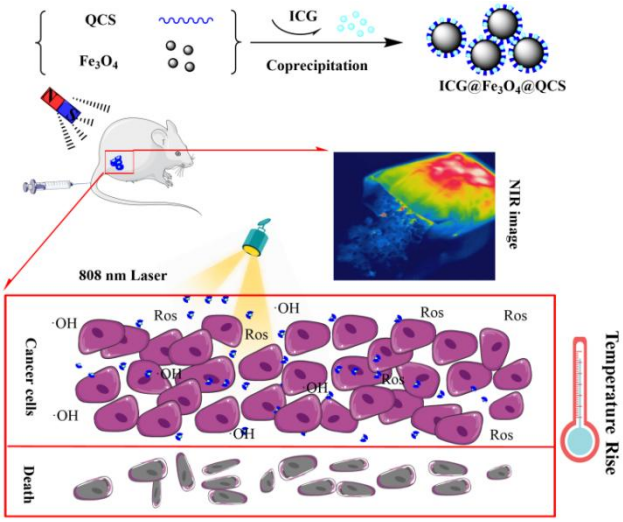

Fig. 1 To improve the bioavailability of ICG, this study proposes to couple ICG with MNPs (ICG@Fe_3O_4@QCS), on the one hand using the inherent properties of nanoparticles to improve the problems of poor stability and fast clearance rate of ICG. On the other hand, MNPs have magnetic targeting, and the coupling of ICG with MNPs can overcome the shortcomings of the non-specific binding of ICG to proteins and the lack of target specificity. MNPs are injected intravenously into the body, the external magnetic field is applied to specific areas, and the laser irradiation produces heat and single-linear state oxygen of ICG to exert phototherapeutic anti-tumor effects while NIR imaging.

Novel lymph node-targeting mRNA vaccines enhance the anti-tumor immunotherapeutic efficacy against the nasopharyngeal carcinoma

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Abstract: The targeting delivery of mRNA vaccines to lymph nodes has great potential to enhance the tumor immunotherapy. In this study, we reported a novel approach to lymph node targeting for mRNA vaccines based on the lipid nanoparticles (LNP) containing a newly-synthesized ionizable lipid (E2-1) (Fig. 1A-1B). E2-1@mRNA obtained by microfluidics showed distinct fingerprint morphology (Fig. 1C), which can selectively express luciferase in the lymph nodes *via* subcutaneous injection (Fig. 1D). The mouse model was firstly constructed by the subcutaneous inoculation of CT26 tumor cells overexpressing the specific antigen of EBV positive nasopharyngeal carcinoma (LMP2). Then the tumor-bearing mice were subcutaneously vaccinated at day 0, 3, 8. The tumor growth was found to be significantly inhibited after treatment by E2-1@LMP2-mRNA (15 μg) compared to control (PBS). In summary, this novel lymph node-targeting mRNA vaccine showed good anti-tumor immunotherapeutic activity, which is worthy of being further investigated as a novel platform of antitumor mRNA vaccines development.

Keywords: mRNA vaccine, lymph node-targeting delivery, tumor immunotherapy.

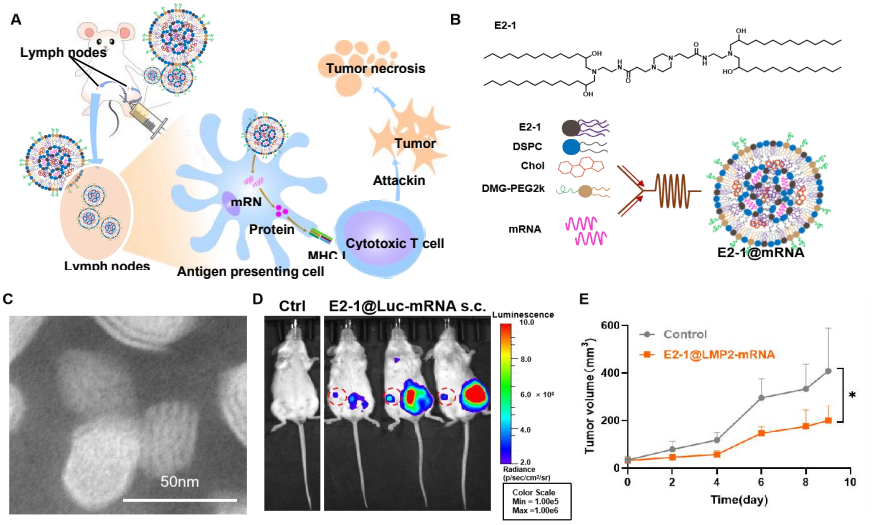

Figure 1. The newly-designed antitumor mRNA vaccine based on ionizable lipid E2-1 effectively inhibited the tumor growth of the model mice bearing CT26 tumor cells overexpressing LMP2. (A) The scheme of the anti-tumor immunotherapeutic effect of E2-1@LMP2-mRNA by targeting delivery to lymph nodes; (B) The self-assembly E2-1@mRNA was prepared by microfluidics, which consisted of E2-1, DSPC, cholesterol (Chol), DMG-PEG2k and mRNA; (C) The morphology of E2-1@mRNA detected by transmission electron microscopy (TEM); (D) The *in vivo* expression of E2-1@mRNA encoding luciferase in mice treated by subcutaneous injection; (E) The tumor growth curves of tumor-bearing mice with the treatment of E2-1@LMP2-mRNA mRNA (15 μg) and control, respectively.

Reference:

[1] Chen K, Fan N, Huang H, Jiang X, Qin S, Xiao W, Zheng Q, Zhang Y, Duan X, Qin Z, Liu Y, Zeng J, Wei Y, Song X. Adv Funct Mater[J]. 2022, 32(39): 2204692.

Glucosyl-modified reduction-responsive dihydroartemisinin nano delivery system targeting intra-erythrocytic Plasmodium and its pharmacodynamics in vivo

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Abstract: Dihydroartemisinin (DHA) has strong therapeutic effects in treating malaria. However, only a small portion of DHA will be able to enter the parasite due to its short half-life. By increasing the expression of the glucose transporter 1 (GLUT1) on the host cell membrane and the hexose transporter (HT) on the parasite membrane, Plasmodium can actively intake large quantities of glucose. In addition, high levels of GSH in the cytoplasm of Plasmodium play a crucial role in protecting the parasite against oxidative damage. In this study, based on the dihydroartemisinin-octadecylamine coupling compound with disulfide bonds as the linking arm, TPGS-GLU (glucose-modified) was added to prepare glucosyl-modified reduction-responsive particles (D@GLU-PMs-SS). Using coumarin 6 (C6) labeled glucose-free modified non-reduction-responsive particles (C6-PMs-CC) as a control, the enrichment of glucose-modified particles in Plasmodium was significantly enhanced after co-incubation with infected erythrocytes in vitro ($P<0.05$). Injecting C6 labeled particles into the infected mice, the C6 content in infected erythrocytes of the C6@GLU-PMs-CC group (glucosyl modified non-reduction-responsive particles) (11.81 ng/ml ± 0.54 ng/ml) was significantly higher than that in the C6-PMs-CC group (9.97 ng/ml ± 0.50 ng/ml) ($P<0.05$). By co-incubating particles and infected erythrocytes in vitro, it turned out that the ROS in infected erythrocytes and the GSH/GSSG ratios in plasmodium of D@GLU-PMs-SS group were 1.27 and 0.49 times respectively of those in the D@GLU-PM-CC control group (glucosyl-modified non-reduction-responsive particles). Compared to DHA-sol, D-PMs-CC (glucose-free modified non-reduction-responsive particles) or D@GLU-PMs-CC, D@GLU-PMs-SS group showed better antimalarial activity and higher safety ($P < 0.05$).

Keywords: malaria; dihydroartemisinin; hexose transporter; reduction triggering drug release

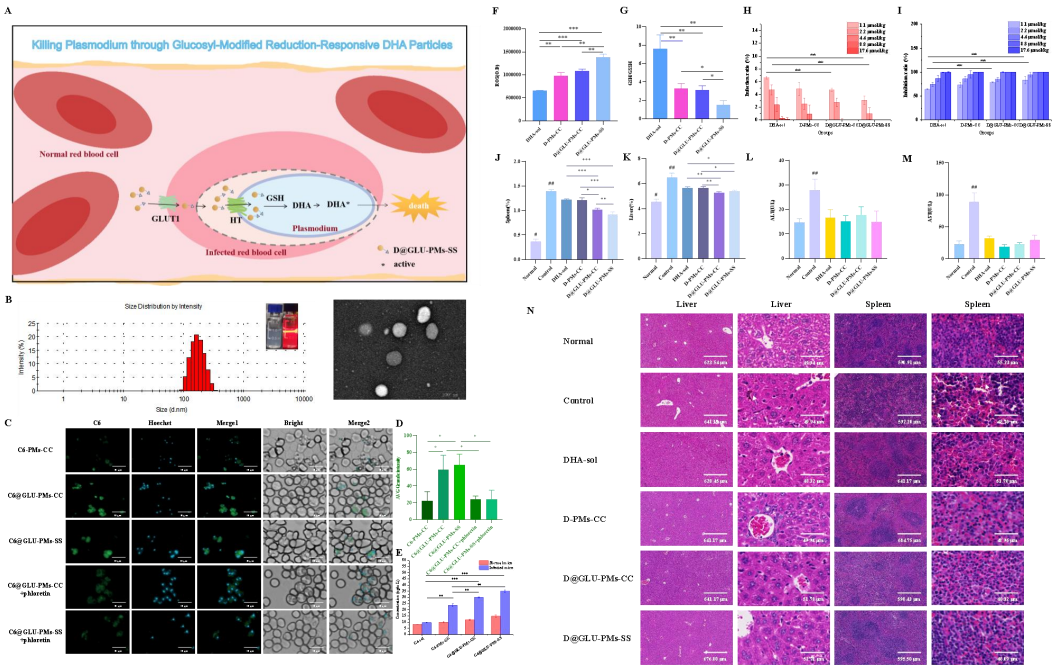

Figure. 1 Schematic illustration of glucosyl-modified reduction-responsive DHA particles for the treatment of malaria (A); particle size distribution, transmission electron microscope and appearance of D@GLU-PMs-SS (B); in vitro targeting (CD), intraerythrocyte targeting (E), ROS in erythrocytes (F), GSH/GSSG ratio in plasmodium (G), infection ratio (H), inhibition ratio (I), organ coefficient (JK), ALT (L), AST (M) and H&E stained images after DHA-sol, D-PMs-CC, D@GLU-PMs-CC and D@GLU-PMs-SS treatment.

A Ovarian Cancer LHRH/Integrin avb3 Receptors Targeting Nanostrategy Enhance in vitro and in vivo Anti-tumor Effect

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Abstract： Ovarian cancer is a kind of malignant tumor that occurs in the female reproductive organs. Due to lack of early diagnostic methods, the probability of death is very high in recent years. LHRH receptors are specially expressed in most ovarian tumors, and the level of integrin avb3 receptors in ovarian tumors is much more than normal tissue cells. Here, we designed LHRH analogues (LHRHa)/RGD co-modified paclitaxel liposomes to increase the targeting to ovarian tumors and to enhance anti-ovarian tumors effect. Result: LHRHa and RGD co-modified paclitaxel (PTX) liposomes (LHRHa RGD-LP-PTX) showed higher cytotoxicity compared with RGD modified PTX liposomes (RGD-LP-C6), LHRHa modified PTX liposomes (LHRHa-LP-C6) and free DTX. LHRHa and RGD co-modified coumarin-6 liposomes (LHRHa-RGD-LP-C6) significantly enhance the cellular uptake compared to RGD modified liposomes and LHRHa modified liposomes, the uptake mechanisms of LHRHa RGD-LP-C6 involved in the way of the actin and clathrin pathways. In addition, RGD and LHRHa reduced the uptake of LHRHa-RGD-LP-C6, which showed that the uptake mechanisms involved integrin αVβ3 receptor and LHRH receptor mediated endocytosis. LHRHa-RGD-LP-C6 displayed better tumor spheroid penetration and tumor spherical inhibition effect than RGD-LP-C6 and LHRHa-LP-C6. LHRHa and RGD co-modified DiR liposomes displayed higher accumulation in tumors than the other groups, the results of in vivo and ex-vivo imaging were consistent. LHRHa and RGD co-modified PTX liposomes showed stronger anti-tumor effect than that of other groups, which might be attributed that LHRHa and RGD co-modified liposomes enhanced cell uptake of ovarian cells through the LHRH receptor and integrin αVβ3 receptor-mediated endocytosis, facilitated intracellular delivery of PTX. Conclusion: LHRHa-RGD-LP-PTX can significantly improve the targeting ability of ovarian cancer and enhance in vitro and in vivo anti- ovarian cancer effect.

Keywords: Modified liposome; LHRHa; RGD; Paclitaxel; ovarian cancer;

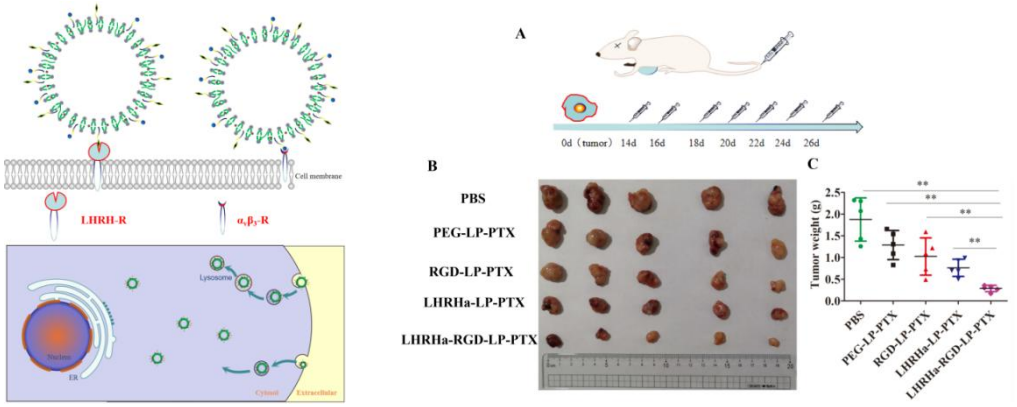

Figure. 1 Schematic representation of LHRHa-RGD-LP entering into tumor cell (Left); Anti-tumor effect of modified PTX liposomes (A) The mode of administration in mice (B). tumors in different groups. (C) tumor weight in different groups (Right).

Reference:

[1] Zou, L.; Liu, X.; Li, J.; Li, W.; Gu, Z. Theranostics[J], 2021, 11 (9), 4171-4186.

Protein/peptide sustained-release system based on injectable pH and reduction sensitive alkylated poly(ortho esters)

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Abstract: Poly(ortho esters) (POEs) are hydrophobic and biodegradable polymers, which possess good injectability and biocompatibility, and are potential platforms for *in situ* delivery of drugs. Herein, alkyl groups and disulfide bond were introduced into the structure of POE to construct pH sensitive and redox sensitive alkylated POEs. In addition, model protein/peptide drugs, such as bovine serum albumin(BSA), lysozyme, bacitracin and cyclosporin, were loaded into the POEs by dispersing the drugs in the oil followed with further mixing with the hydrophobic POEs. In this study, the physical and chemical properties of alkylated POEs, the structural stability of model drugs after preparation, and the release behavior of model drugs were evaluated. Results demonstrated that alkylated POEs have good injectability itself, and possess a unique characteristic of "liquid-solid phase transition" when exposed to water. The prepared injection showed well maintained structure and activity of model drugs after preparation, and a sustained release for 5-7 days. Furthermore, the release rate of model drugs could be flexibly adjusted by variating the composition of alkylated diglycolate building block of alkylated POEs, and were significantly increased in the environment of low pH value and high reduction. Additionally, model drugs with high isoelectric point could significantly promote the degradation of POEs, so as to accelerate the release behavior. In a word, this pH sensitive and reduction sensitive alkylated POEs are an excellent sustained-release carrier for protein/peptide drugs, which have good prospects for the development of *in situ* biomacromolecule drugs deposit.

Keywords: Alkylated POEs; pH sensitivity; Redox sensitivity; Liquid induced phase transition

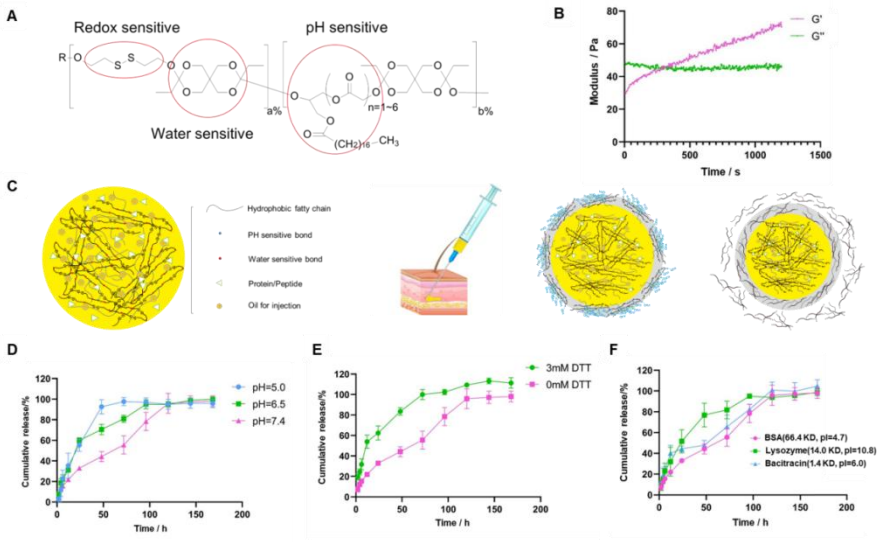

Figure. 1 A) structure of alkylated POE; B) liquid induced phase transition of POEs; C) schematic illustration of sustained-release injection based on alkylated POEs; D) pH sensitive release behavior; E) Redox sensitive release behavior; F) Release behavior of protein/peptide drugs.

Cascade silencing of hif-1α and CD73 with enhancing PDT therapy through a combined fluorinated peptiod complex platform for combined breast cancer therapy

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Abstract: The ubiquitous hypoxic-adenosine aixs in tumor microenvironment is an important factor leading to tumor growth, metastasis and immunosuppression. Reshaping the hypoxic microenvironment and suppressing adenosine concentration is a major challenge to improve immune suppression. In this study, a siRNA+ICG@FLPP with multiple synergistic therapeutic effects was designed to co-deliver siHIF-1α, siCD73 and ICG to alleviate hypoxic-CD73-ADO pathway-mediated tumor suppressive microenvironment. The nanoparticles were prepared by using fluorinated peptoid oligomers as the core carrier and lipid as the shell. Fluorination can achieve efficient gene transfection, and also effectively resist serum complex. The modification of "tumor homing" peptides of CREKA and RGD on DSPE-PEG2000 in lipids improve the tumor targeting. siHIF-1α and siCD73 released in tumor cells jointly act on the hypoxic-CD73-adenosine pathway, synergistically inhibited CD73 expression, and alleviated the tumor immunosuppressive microenvironment. At the same time, fluorinated peptoid oligomers can carry oxygen into the hypoxic environment of the tumor through self-assembly with ICG, thus enhancing the effect of PDT, which alleviates the problem of aggravating hypoxia in the tumor site during traditional PDT treatment. The nanoparticles can achieve effective therapeutic effect in BALB/c 4T1 tumor-bearing mice by i.v. injection. This work provides a new paradigm for the ideal design of combinatorial gene and drug delivery platform based on fluorinated peptoid oligomers-lipid complexes and the synergistic treatment of hypoxia alleviation and CD73 silencing.

Keywords: Fluorinated peptoid; Hypoxia; Combined therapy

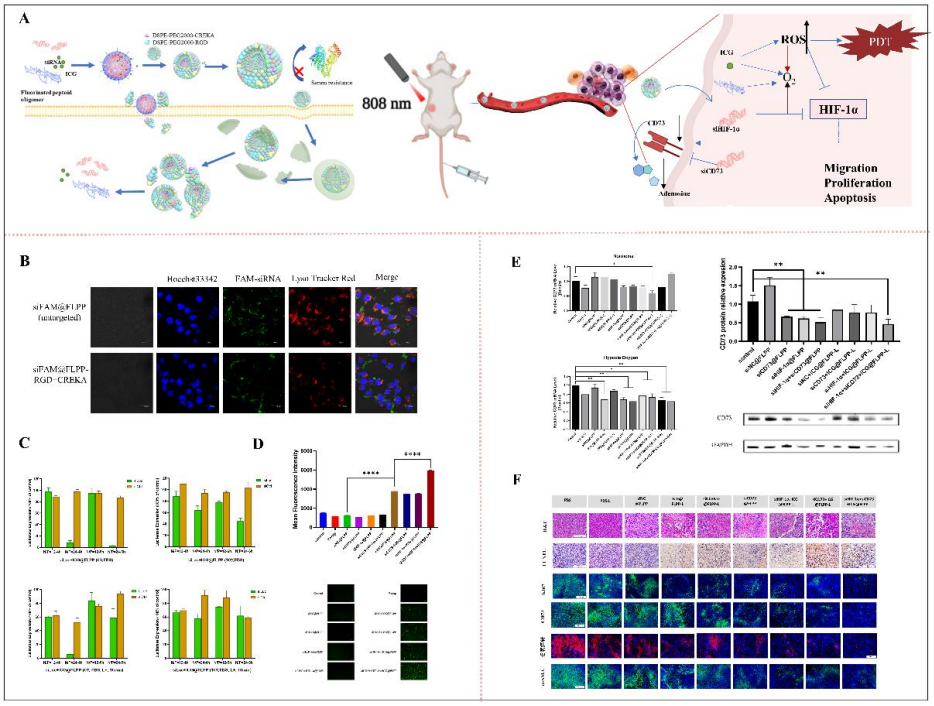

Figure. 1 (A) Schematic illustration of fluorinated peptoid oligomers lipid complexes co-delivery of siRNA and ICG; (B) Endosome-escaping of NPs; (C) In vitro gene transfection in 4T1-luc cells with/without laser irradiation; (D) Detection of reactive oxygen species of 4T1 cells; (E) CD73 inhibition level by q-PCR and WB; (F) Tumor tissue staining.

Optimization and purification of extraction process of terpenoids from Rabdosia rubescens

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Rabdosiae Rubescentis Herba is mainly produced in Henan's specialty medicinal materials. It has the effects of clearing heat and detoxifying, promoting blood circulation and pain, antibacterial and anti -inflammatory. Modern pharmacological research has also proved that it has anti -gastric cancer and anti -esophageal effects. The second -class compound is the main active ingredient of this medicinal material. Therefore, we hope to establish a simple and fast -moving method of the content of the ingredients of the Dongling Caisu, and on this basis, optimize and screen the material extraction process of the valid parts of the Dongling Caisuke, and improve the method of adsorbing resin purification through large holes. The content of the category component provides reference for it to adapt to industrial production.

Keywords: Rabdosia rubescens; process filtering; content measurement

Construction and efficacy study of an oral nano-antimicrobial delivery system based on probiotic spores

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Abstract: Oral antibiotic treatment for colitis induced by *Salmonella typhimurium* (S. Tm) can cause drug resistance, leading to intestinal microbiota imbalance. In this study, an oral microbial inorganic nano antibacterial delivery system based on probiotic spores （BCs@PME-Au) is constructed to treat S. Tm-induced colitis. After oral administration, the system can pass through the gastric acid environment smoothly. Additionally, after BCs@PME-Au reaches the intestine, the PME-AuNPs could fall off with the germination of the spores, which can directly neutralize LPS and then act on TLR 4 / NF-κB pathway to achieve the triple efficacy of antitoxin, antibacterial and anti-inflammatory. BCs could germinate into *Bacillus coagulans* (BC) and colonize competitively with pathogenic bacteria, causing synergistic bactericidal effect. BCs@PME-Au has excellent antibacterial and anti-inflammatory efficacy and provides a new way for the treatment against S. Tm-induced colitis.

Keywords:*Salmonella typhimurium*, oral delivery system, gold nanoparticles, Bacillus coagulans budding, intestinal flora

“Existence is reasonable”: regulation drug release of microspheres based on the nucleophilic attack of PLGA with weakly basic drug

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Abstract: Compared to other material attributes or process parameters, the interaction between poly (lactic-co-glycolic acid) (PLGA) and weakly alkaline drugs has not received much attention in the development of long-acting microspheres. Although the nucleophilic attack phenomenon from weakly alkaline drugs on the chain segments of PLGA was discovered approximately 30 years ago, its effects on microspheres during preparation have not been well investigated to date. We realized this problem again during investigating the different drug loading of naltrexone (NTX) microspheres. The molecular weight (Mw) change of PLGA was observed during the preparation process, and it was found that there was most significantly loss in Mw during the PLGA-NTX solution preparation stage, which stated that the attention should paid to PLGA-NTX solution preparation stage from the microscopic perspective. Therefore, the analysis of PLGA-NTX solution was carried out from three aspects: the organic solvent, the mechanical force used in the dissolution of the organic phase, and the dissolution sequence of the PLGA, NTX and organic solvent. Furthermore, the change in intermolecular force of PLGA, NTX and organic solvent was revealed by molecular dynamics simulation (MDS), and the dissolution sequence of the PLGA, NTX and organic solvent eventually was utilized to achieve demand-oriented drug release. Through the exploration of intermolecular chemistry, the manufacturing process can be adjusted from a micro perspective to obtain a demand-oriented release curve and provide a new research paradigm for the development of small molecule drug loaded PLGA microspheres.

Keywords: microsphere; PLGA; nucleophilic attack; molecular weight; dissolution sequence; demand-oriented drug release.

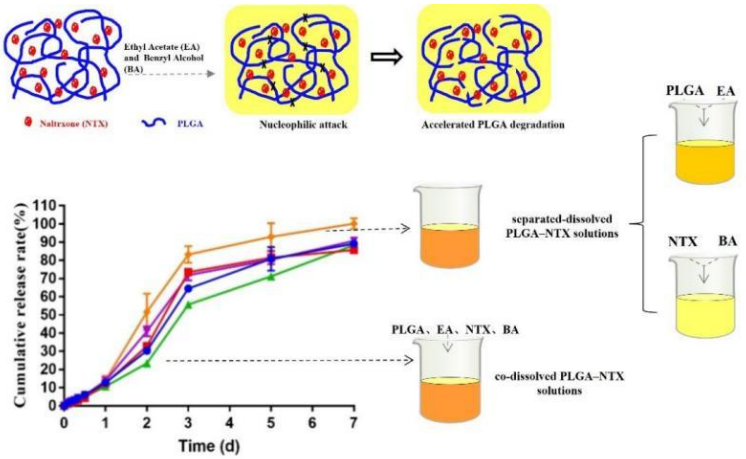

Figure. 1 Illustration of regulation drug release of microspheres based on the molecular interaction between NTX and PLGA. The top line shows the nucleophilic attack of NTX on molecular PLGA and NTX in Ethyl acetate (EA) and benzyl alcohol (BA), which resulted in the degradation of PLGA. The bottom line shows that the molecular interaction between PLGA and NTX was regulated by regulating the process to obtain the demand-oriented drug release.

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Gold Nanorod Drug Delivery System for Prostate Cancer Treatment via Hyperthermia-Chemotherapy

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Abstract: As one of the major diseases recognized worldwide, prostate cancer has become a serious threat to men's health. Traditional chemotherapy and surgical resection have failed to achieve the desired treatment effect.Herein, a combined thermotherapy-chemotherapy approach is reported for the treatment of prostate cancer. Gold nanorods were used as nanomaterials for adjuvant photothermal therapy， HPMA polymer was used as the drug carrier，Doxorubicin as a model drug was attached to HPMA by pH-sensitive hydrazone bonding as a spacer group， to construct a GNRs drug-loaded system modified by HPMA polymer（PDS-pHPMA-DOX@GNRs）. PDS-pHPMA-DOX@GNRs has good photothermal conversion. The results of in vitro release indicated that under the pH 5.0 weak acidic environment, the NIR irradiation would accelerate the fracture of the pH sensitive hydrazone bond and promote the release of small molecular drugs. MTT results indicating that the cytotoxicity of the drug loading system was significantly enhanced after the combined treatment. CLSM results showed that the combined treatment group accelerated the rate of small molecular drugs entering the nucleus. In vivo antitumor activity studies have shown that, Anti-tumor efficiency of the combined treatment group showed significant difference compared with other drug groups (p<0.05). The results of tissue distribution in vivo have showed that that combined therapy could increase the accumulation of drug loading system at tumor site and prolong the retention time at tumor site.

Keywords: Prostate cancer, Gold nanorods, Hyperthermia-chemotherapy combination therapy, HPMA polymer

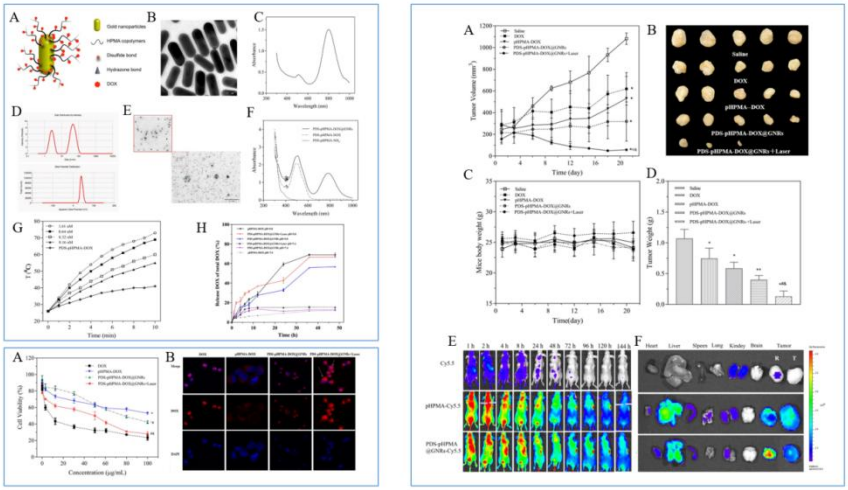

Figure. 1 Synthesis and characterization of PDS-pHPMA-DOX@GNRs (Upper left); In vitro anti-drug resistant tumor activity of PDS-pHPMA-DOX@GNRs(Lower left); In vivo anti-drug resistant tumor activity of PDS-pHPMA-DOX@GNRs (Right).

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Triple crosslinked dynamic responsive hydrogel for accelerating infected wound healing via PI3K/Akt/NF-κB and MAPK signaling pathways

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Abstract: Bacterial infection, excessive oxidative stress, and inflammatory responses can cause chronic nonhealing wounds, which may be a great threat to public health. A multifunctional injectable wound hydrogel have attracted extensive attention, including excellent mechanical properties, remarkable self-healing, remodeling, antibacterial, radical scavenging capabilities. In this study, a pH/ROS dual responsive injectable glycopeptide hydrogel (OHA-PP@CA@ZIF-8) based on oxidized hyaluronic acid (OHA), phenylboronic acid-grafted ε-polylysine (PP) and chlorogenic acid-loaded metal-organic frameworks (CA@ZIF-8) was constructed, which exhibited inherent antibacterial, antioxidant, and angiogenesis-promoting abilities. Due to the dual dynamic-bond cross-linked network based on dynamic Schiff bases and boronic ester bonds, the OHA-PP@CA@ZIF-8 hydrogel has excellent mechanical properties, strong adhesion, good biodegradability, high biocompatibility, stable rheological properties and self-healing ability. Through chelation, ZIF-8 works dually as crosslinker and nano-filler, enhancing the mechanical properties, antibacterial, and antioxidant capacity of OHA-PP@CA@ZIF-8. A series of experiments were carried out with HUVECs cells, including CCK 8, Live/dead cell staining, ROS scavenging, cell scratch experiment, tube formation assay, enzyme-linked immunosorbent assay, immunofluorescent staining and western blot. The OHA-PP@CA@ZIF-8 could be injected directly into the irregular-shaped wounds in a full-thickness skin defect experiment, and the good fitting of the gel to the wound geometries together with the slow and sustainable release of antibacterial CA and Zn^{+}. The OHA-PP@CA@ZIF-8 can significantly accelerate wound healing with more skin appendages appearing by antibacterial, cavenging ROS, and promoting angiogenesis. This study illustrates that the OHA-PP@CA@ZIF-8 hydrogels with an organic inorganic microstructure have great potential in accelerating wound healing.

Keywords: injectable hydrogel, metal-organic frameworks, dual-dynamic-bond, ROS scavenging, wound dressing

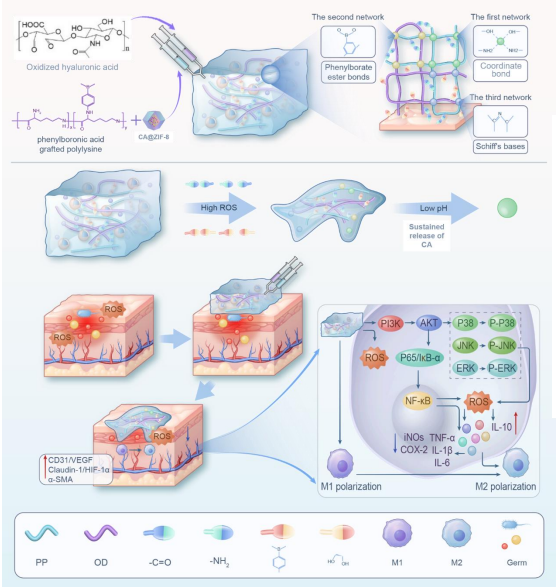

Figure. 1 The tri-crosslinked dynamic response hydrogel with ROS scavenging and pH-regulating ability protects cells from oxidative stress and induces macrophages into M2 polarization to reduce inflammatory cytokines through PI3K/AKT/NF-κB and MAPK pathways, exerting anti-inflammatory effects, reshaping the inflammatory microenvironment, and accelerating S.

Research progress in andrographolide nanoparticles

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Abstract: Andrographolide is a natural diterpenoid product mainly derived from traditional Chinese medicine Andrographis. It can not only inhibit NF- κ B. Signal pathways such as STAT3 reduce the synthesis and release of downstream inflammatory mediators, exhibiting good anti-inflammatory activity, and can act as quorum sensing inhibitors to intervene in the formation of harmful bacterial biofilms.Therefore, andrographolide is also known as a "natural antibiotic". However, due to the poor water solubility and short plasma half-life of andrographolide, its bioavailability is low and its clinical application is limited. Nanodrug delivery systems provide possible solutions to address these issues. Nanocarrier technology can encapsulate andrographolide through microspheres, liposomes, self-emulsification, and other methods, achieving targeted and controlled release of drugs, further improving the bioavailability of drugs. This has a significant reference value for the research and application process of new dosage forms of andrographolide. Although these new drug delivery systems have many advantages, they also have some limitations, such as complex preparation processes, high costs, safety, and stability of effects. This review will delve into the advantages and potential issues of these new drug delivery systems, in order to bring more possibilities for the clinical application of andrographolide.

Keywords: andrographolide, natural antibiotic, nanocarrier technology, targeted therapy, delivery systems .

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Metal-Phenolic Network-Based Self-Assembled Nanoparticles for Synergistic Photothermal/Photodynamic/Chemotherapy

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Abstract: Nanoparticle-based phototherapies, including photothermal therapy (PTT) and photodynamic therapy (PDT). PTT is an attractive method that transfers optical energy to heat energy by photothermal conversion materials, which results in the death of cancer cells. PDT relies on a topical photosensitizer, which can convert tumor tissue oxygen into toxic reactive oxygen species (ROS) with light irradiation. However, the single treatment of PTT or PDT has shown limited therapeutic efficacy in vivo. The combination of PDT and PTT is beneficial for enhanced cancer therapy due to synergistic effects. In addition, PTT and PDT are often combined with chemotherapy to enhance the antitumor effect of monotherapy[1] .

With the aforementioned consideration, we integrated chemotherapy therapy and photo-therapy (PDT and PTT) into one therapeutic strategy by assembling SRF and ICG into nanoparticles by self-assembly. Then complexes containing tannic acid (TA, a natural polyphenol) and Fe^{3+} were used to coat and stabilize the SRF/ICG nanoparticles. In addition, L-Arg is loaded through the electrostatic interaction between TA and L-Arg. Finally, IS@ATF nanoparticles are obtained. The addition of ICG, which endowed the formed IS@ATF NPs with excellent photothermal and photodynamic capability under 808 nm irradiation to perform PTT and PDT. The results of cytotoxicity test in vitro showed that the nanoparticles had synergistic cytotoxicity effects of photothermal/chemotherapy. In addition, the high concentration of TA-Fe membranes has no obvious toxic effect on normal cells and has excellent biological safety. Experimental results of biological distribution in vivo showed that IS@ATF NPs could rapidly accumulate at the tumor site after intravenous injection, and could accumulate at the tumor site 72 h after injection. These results indicate that IS@ATF NPs had excellent biosafety, photothermal and photodynamic properties under 808 nm irradiation, and can effectively reach the tumor site. Therefore, this preparation is expected to better deliver photothermal agent/photosensitizer/drug to the tumor site for synergistic PPT/PDT/chemotherapy of cancer.

Keywords: photothermal therapy; photodynamic therapy, Chemotherapy, Combination therapy

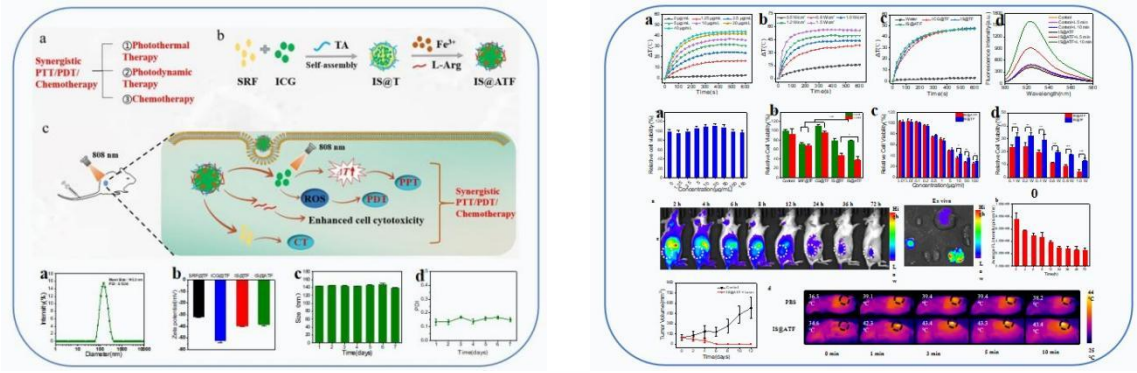

Figure. 1 Diagram of preparation synthesis mechanism and study on photothermal conversion and antitumor effect of nanoparticles in vitro and in vivo.

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Study on anticancer active components and mechanism of pinellia ternata based on network pharmacology

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Abstract: Based on systematic pharmacology, data mining and molecular docking were used to analyze the mechanism of *pinellia* ternata in the treatment of gastric cancer. The chemical components in *pinellia* ternata were obtained by data mining through the Database platform of TCM System Pharmacology (TCMSP) and the chemistry database of Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences. Then the active components were screened by ADME. The target of *pinellia* ternata in the treatment of gastric cancer was predicted by stoichiometric method. The biological functions, diseases and related signaling pathways corresponding to the targets were further analyzed, and the multi-component, multi-target and multi-pathway action mechanism of *pinellia* ternata in the treatment of gastric cancer was further elaborated. A total of 11 effective components were screened out in this study, including 71 targets related to gastric cancer and its complications, and the top 8 related signaling pathways. GO was used to analyze the molecular functions of the top 20 targets with correlation. This study shows that *pinellia* ternata has a variety of effective components, which can regulate the nervous and psychiatric system, cell cycle, cell differentiation and metastasis, enhance anti-inflammatory and immune function, and play a multi-component, multi-target and multi-pathway synergistic anticancer effect in gastric cancer and its related complications, providing a new idea for the follow-up clinical treatment of gastric cancer.

Keywords: Network pharmacology; *Pinellia* ternata; Gastric cancer; Mechanism of action

An oral drug delivery system based on probiotic spore

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Abstract: Ulcerative colitis (UC) is a type of inflammatory disease that is easily transformed into inflammatory colon cancer. At the site of intestinal inflammation, the content of epithelial oxygen increases and the level of reactive oxygen species (ROS) increases. The high level of ROS makes intestinal pathogenic bacteria such as Enterobacteriaceae achieve excessive growth through aerobic respiration, thus destroying the mucosal barrier function and aggravating intestinal inflammation. However, most beneficial intestinal bacteria are obligate anaerobic, which is difficult to survive in the condition of sufficient oxygen and high inflammation. Bacillus licheniformis is a kind of aerobic probiotics. When it enters the intestine, it will consume free oxygen and reproduce in the intestine, which is conducive to the growth of beneficial bacteria that produce short chain fatty acids, so as to regulate the balance of intestinal microbial flora. In this study, baicalin, a natural anti-inflammatory drug, was loaded onto Bacillus licheniformis spores to develop a simple spore - drug delivery system, which has excellent antibacterial and anti-inflammatory effects and provides a new idea for the treatment of colitis by reshading the intestinal microenvironment.

keyword: probiotic spores; oral probiotics; delivery system

Study on bionic nanovaccines based on hybrid membranes to prevent tumor recurrence by enhancing immunogenicity and recruiting dendritic cells

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Abstract: Surgical resection is still the main treatment method for most solid tumors, but postoperative tumor recurrence and metastasis greatly reduce the survival rate of patients, which is the main problem faced in clinical practice. Postoperative recurrence and metastasis are related to the anti-tumor immune status of the body, and tumor vaccine can trigger the systemic immune response and eliminate residual tumor cells, which is a promising therapeutic approach. Some current studies have shown that injected tumor vaccines do not completely inhibit tumor recurrence, which may be related to the weak immunogenicity of tumor antigens, insufficient number of dendritic cells (DC), or immunosuppressive tumor microenvironment and other possible underlying causes.Based on this, we designed a bionic nanovaccine based on antigen and adjuvant delivery of autologous tumor cell membrane (TMS) and Escherichia coli cell membrane (EM). Meanwhile, the hybrid membrane (HM) formed by TMS and EM was wrapped on PLGA nanoparticles loaded with granulocyte macrophage colony-stimulating factor (GM-CSF) to recruit DCs. It is used to deliver antigens and adjuvants to antigen presenting cells. This personalized tumor vaccine is designed to safely enhance the innate immune response, maximize the anti-tumor effect in vivo and in vitro studies, and effectively prevent tumor recurrence, which has potential clinical application value.

Keywords: Nanovaccines; Immunogenicity; Dendritic cells; Tumor recurrence

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Human Serum Albumin Self-Assembly Nanocomposite Potentiates Radiotherapy Efficacy via Boosting Ferroptosis-Induced Tumor Eradication and Anti-tumor Immunity

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Abstract: Although radiotherapy (RT) is a conventional weapon for cancer treatment, its clinical benefit is extensively harnessed by the acquired and intrinsic radioresistance. Ferroptosis has recently been proven to play a crucial role in RT-induced tumor suppression and radioresistance, as well as to bridge RT and immunotherapy. Herein, we synthesized a biocompatible nanocomposite (namely HSA@808-NM2-R837) through the self-Assembly of human serum albumin (HSA), a hypoxic tumor-targeted radiosensitizer (808-NM2) and immunoadjuvant (R837). As results, the nanocomposites (NPs) preferentially accumulate in tumor cells and could serve as a promising contrast agent for tumor near-infrared fluorescence imaging and photoacoustic imaging. Both *in vitro* and *in vivo* results verify that HSA@808-NM2-R837 could effectively sensitize the efficacy of RT. Mechanistically, the combination of HSA@808-NM2-R837 and RT can provoke ferroptosis-mediated tumor cell death via generating excessive reactive oxygen species (ROS) and destroying the GPX4-dependent defense system. Most importantly, the robust anti-tumor immune response was triggered by combination treatment of HSA@808-NM2-R837 and RT. Treatment of liproxstain-1 (a ferroptosis inhibitor) can obviously restrain the maturation of dendritic cells and tumor infiltration of cytotoxic T lymphocytes, indicating that the boosted anti-tumor immunity was partially attributed to ferroptosis-induced pathway. Collectively, our findings provide a promising tumor radiosensitizer and a new avenue for effective radiotherapy through combining ferroptosis and immunotherapy.

Keywords: Radiotherapy; heptamethine; ferroptosis; immunotherapy

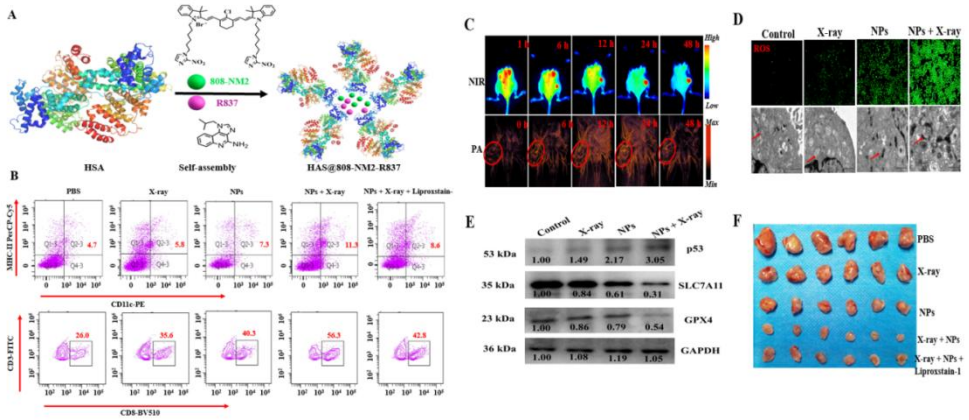

Figure. 1 Schematic illustration of the preparation of HSA@808-NM2-R837 and the anti-tumor immune response (DC maturation and infiltration CD8+ T cells) (Left); and HSA@808-NM2-R837 sensitizes cancer cells to ionizing radiation via ferroptosis-induced cell death (Right).

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PEGylated heptamethine indocyanine dyes for Renal Tumor-Targeted Radiotherapy

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Abstract: Radiotherapy has been clinically proven to be an effective tumor treatment form owing to its high tissue penetration but limited by the anoxic environment of the tumor. The low bioavailability, high toxicity and non-specific targeting of radiosensitizers are the main obstacles to the successful development of radiosensitizers for applications. In our previous work, a series of hydrophobic small-molecule heptamethine indocyanine dyes have been reported for hypoxic tumour-preferential accumulation and radiosensitization, such as 808-NM2. To overcome its hydrophobicity and improve radiotherapy effect, we herein develop its water-soluble derivatives, which are modified with different lengths of polyethylene glycol (PEG) on an unilateral N- alkyl chain of 808-NM2. Such asymmetric PEG modification not only significantly improves its water-solubility, stability and fluorescence emission, but also endows a favorable property of amphipathicity. This property facilitates 808-NM2 available to form small-size nanoparticles via self-assembly in aqueous environment and enhances the tumor targeting accumulation via active/passive dual-modal approaches. Our results demonstrate that PEG2000-808-NM2 exhibits the high fluorescence emission, renal tumor-preferential accumulation and dose-depended radiosensitization by targeting mitochondria. More intriguingly, the PEGylated 808-NM2 also exhibits a remarkable renal clearance, which is attributed to the reduction of aggregates and the formation of well dispersed nanoparticles in physiological conditions. Overall, our findings provide a PEGylated heptamethine indocyanine dye with good water-solubility for renal tumor targeting accumulation, near-infrared fluorescence imaging and radiotherapy, which would also offer a promising platform for imaging-guided precise radiotherapy of other solid tumors.

Keywords: heptamethine; polyethylene glycol; nitroimidazole; tumor targeting; radiosensitization

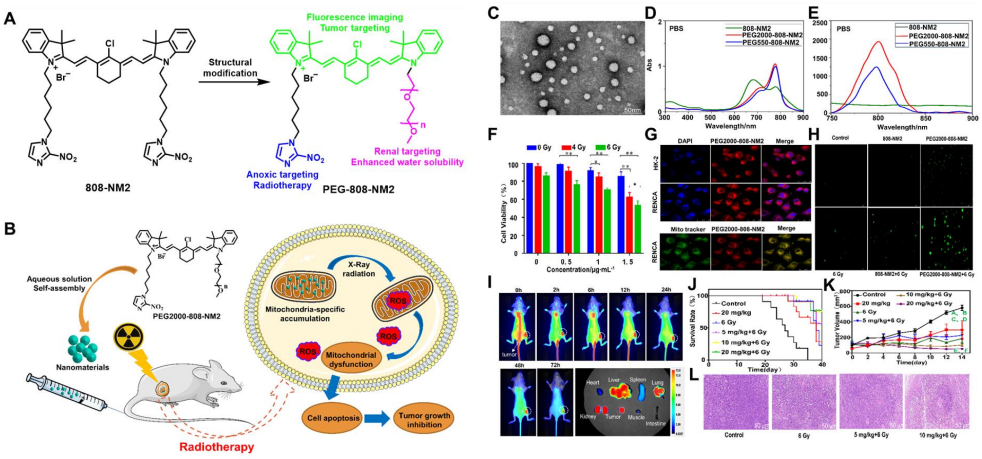

Figure. 1 Schematic illustration of the structural modification from 808-NM2 to PEG-808-NM2 and the proposed mechanism of PEG-808-NM2 mediated radiotherapy (Left). The physical properties of PEG-808-NM2 and its corresponding radiotherapy activity for tumor (Right).

References:

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The NO Donors for Improved Drug Delivery and Enhanced Chemotherapy of Tumor

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Abstract: There are multiple biological barriers in solid tumors. Such as dense extracellular matrix, Interstitial Fluid Pressure, etc. The presence of these biological barriers reduces the osmotic retention effect (EPR effect) of tumor blood vessels. And it makes it difficult for nanodrugs to effectively enrich and penetrate within tumors. Therefore, the tumor treatment effect of nanomedicine is greatly reduced. To this end, we designed to load nitric oxide (NO) donors and cisplatin (CDDP) into poly(L-glutamate)-*g*-methoxypolyethylene glycol polymers to form nanoformulations with the aim of improving drug delivery efficiency and enhancing chemotherapy effects. This nanoformulation is capable of releasing NO in tumor cells. NO and superoxide anions ($O2^{-}$ ˙) react rapidly to form peroxynitrite ($ONOO^{-}$). The resulting $ONOO^{-}$ can significantly enhance vascular permeability and can activate matrix metalloproteinase-mediated extracellular matrix degradation, thereby promoting the penetration and accumulation of nanodrugs in tumors. As this nanodrug is endocytosed by tumor cells, CDDP is further released, inducing apoptosis in tumor cells. This strategy of co-delivery of NO donors and chemotherapy drugs can cross the biological barrier of solid tumors and greatly improve the therapeutic effect of anti-tumor nanodrugs.

Keywords: peroxynitrite; drug delivery; tumor treatment; chemotherapy; vascular permeability

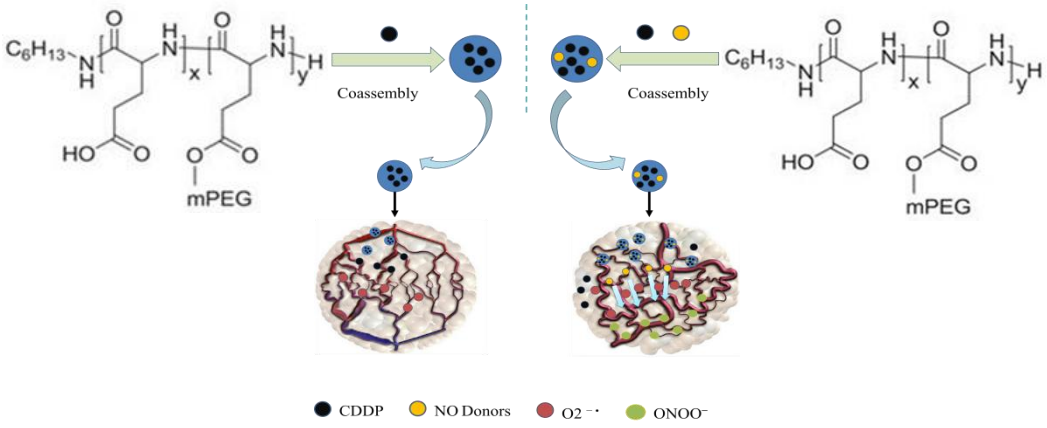

Figure. 1 Nanoformulations enhance vascular permeability.

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Development of separable PEGylated polyglutamic acid-cisplatin nanoformulations

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Abstract: PEGylation has been widely used to extend the circulation time of nanodrugs in the body, thereby increasing the accumulation of drugs in tumors and thus inhibiting tumor growth. However, the therapeutic effect of PEGylated nano formulations would be impaired owing to the poor cellular uptake caused by the spatial rejection of PEG. For this reason, we designed and prepared two poly(L-glutamic acid)-cisplatin nano formulations with separable PEGs, as shown in Figure 1, aiming to enhance the inhibitory effect of the drug on tumor. PEG's removal would be triggered by the specific microenvironment when poly(L-glutamate)-cisplatin nano formulations reach tumor tissues, consequently, nano formulations without PEG can enter tumor cells more quickly and efficiently for intracellular drug delivery. Through this strategy, the nanoparticles can not only obtain a long cycle time in vivo, but also efficiently deliver drugs to target tumor cells, thereby improving the effect of tumor treatment.

Keywords: polyamino acid; polymeric nano preparation; PEGylation

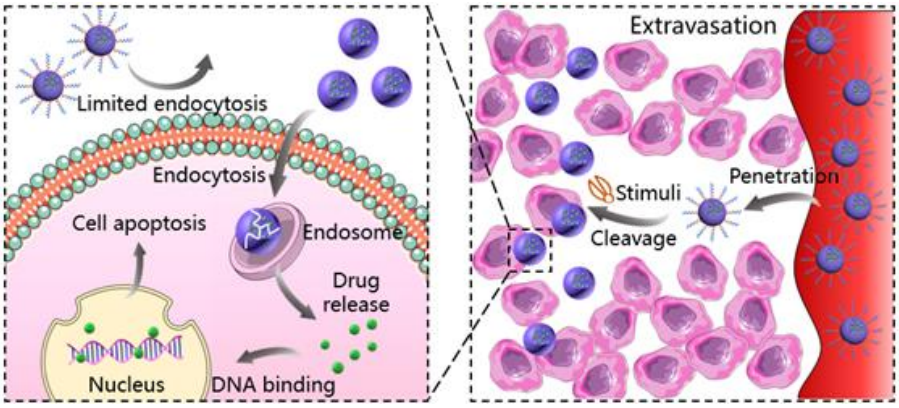

Figure 1. Poly(L-glutamic acid)−cisplatin nanoformulations with detachable PEGylation for prolonged circulation half-life and enhanced cell internalization.

Reference:

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Cocrystal of curcumin and metformin preparation promoted bioavailability and effectiveness on diabetes

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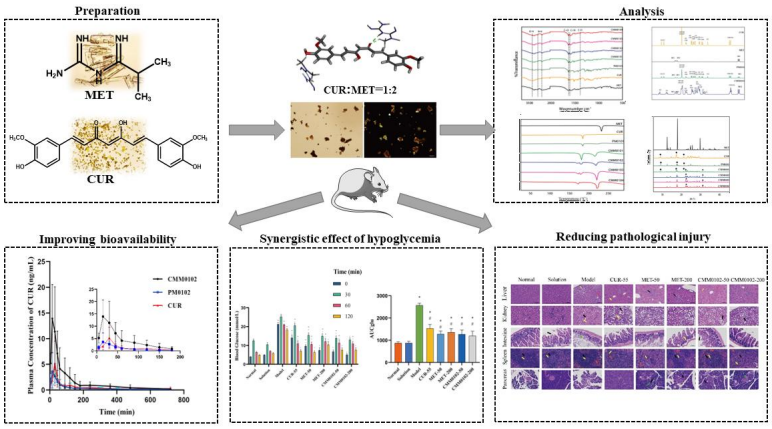
Abstract: Drug-drug cocrystals (DDC) comprise mixture active pharmaceutical ingredients (APIs) with multiple-targeting has been concerned by regulators benefited from promotion of poor water solubility[1] and low bioavailability[2] as well as avoiding pill load triggered adverse. Herein, a novel cocrystal (CMM) was prepared by solvent coprecipitation method with Curcumin (CUR) and Metformin (MET) which were two classic diabetes medicines, aiming to improve the oral bioavailability of CUR and reduce gastrointestinal side effects of high doses of Metformin. The eutectic phases were characterized by differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD), Fourier transform infrared spectroscopy (FTIR) and solid-state nuclear magnetic resonance (13C-MAS-NMR). The pharmacokinetic and pharmacology study was carried out in male SD rats or KM mice. Through DSC, PXRD, NMR, FTIR and other characterization methods, it is proved that the CMM was successfully prepared, and hydrogen bonds were formed between C=O of CUR and C=N of MET. Pharmacokinetic results showed that CMM could effectively increase the plasma absorption of CUR in vivo. Pharmacodynamic evaluation suggested that the 50 and 200 mg/kg cocrystal significantly enhanced hypoglycemic effect in Streptozotocin induced diabetes mice model compared with CUR or MET treatment alone. And glucose or insulin tolerance regulated by CMM possessed the consistent trend. Low doses of CUR or MET isolation is relatively weak on repairing diabetic islet injury, while CMM obviously protected pancreatic islet injury in diabetes possibly through repairing pancreatic islets β cell damage and regulating insulin function. This might be one of important reasons for its stronger hypoglycemic effect. Besides, preparation of cocrystal embodied important research significance and application value because of its definite effectiveness on various diabetic complications including liver, kidney and intestinal injury. In conclusion, CUR-MET cocrystal improved bioavailability with synergistic therapeutic effect on diabetes and complications.

Keywords: Cocrystal; Metformin; Curcumin; Type II diabetes



Graphical Abstract Characterization of CUR-MET cocrystal and its enhancement of CUR bioavailability, improving diabetes treatment.

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Glucose-Sensitive 4-Formylbenzeneboronic Acid-Grafted Chitosan and Phosphoserine Coated Mesoporous Silica Nanoparticles for Oral Delivery of Insulin

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Abstract: Subcutaneous insulin (INS) injection is currently the most extensive treatment method. However, the non-availability of timely adjusting dose according to patient's real-time blood glucose levels (BGLs) as well as the multiple daily injections over a lifetime lead to poor compliance. Herein, 4-formylbenzeneboronic acid-grafted chitosan and phosphoserine coated mesoporous silica nanoparticles (I/MSN/F-C/P) were prepared for the oral glucose-sensitive delivery of insulin. The size of I/MSN/F-C/P was measured to be 338.5 nm. TGA showed the drug loading and coating ratio of 4-formylbenzeneboronic acid-grafted chitosan and phosphoserine (F-C/P) was 35.8% and 10.2%, respectively. INS release profiles of I/MSN/F-C/P in different glucose concentrations showed that only 9.7% INS was released at normoglycemia (1 mg/mL) in 2 h. In contrast, more than 33% INS could be released in 2 h, suggesting I/MSN/F-C/P had glucose-sensitive drug release manner due to the F-C coating. The cellular uptake of I/MSN/F-C/P in mucus producing HT29-MTX-E12 (E12) cells was significantly higher than that of the non-coated MSN (INS/MSN) and non-phosphoserine coated MSN (I/MSN/F-C), indicating that phosphoserine played an important role in penetrating mucus layer. CLSM confirmed that INS was uptaken into cells together with the carrier. The streptozotocin-induced diabetic rat model was used to investigate the hypoglycemic effect. It turned out that I/MSN/F-C/P could remarkedly decrease the BGLs of diabetic rats, while would not decrease the BGLs of normal rats. These results together suggested that I/MSN/F-C/P prepared in this study could effectively orally delivery the loaded insulin, and regulate the drug release according to BGLs.

Keywords: glucose-sensitive; insulin; oral delivery; mesoporous silica nanoparticles; phenylboronic acid

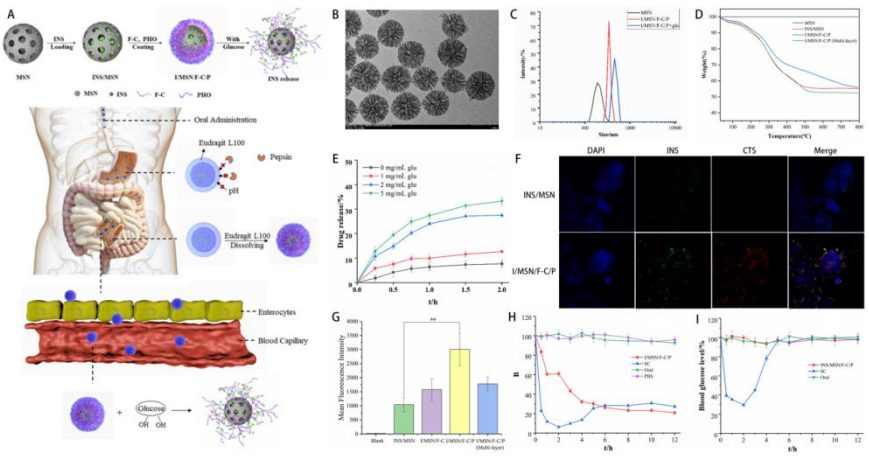

Figure. 1 (A) Schematic illustration of I/MSN/F-C/P. (B) TEM image of MSN. (C) size distributions of I/MSN/F-C/P with or without glucose. (D) TGA for I/MSN/F-C/P. (E) INS released from I/MSN/F-C/P with different glucose concentrations (n=3). (F) CLSM images of E12 cells after incubation with I/MSN/F-C/P. (G) Mean fluorescent intensities of INS/MSN, I/MSN/F-C and I/MSN/F-C/P in E12 cells (n=3). BGLs after oral administration of different insulin formulations to (H) diabetic SD rat and (I) normal SD rat (n = 6).

Allogenic "Zombie Cell" as the Off-the-Shelf Vaccine for Postsurgical Tumor Therapy

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Abstract: Whole-cell cancer vaccines derived from autologous resected tumors provide a full set of tumor-associated antigens, and represent a personalized immunotherapy that overcomes tumor heterogeneity. However, the low immunogenicity of the tumor cell vaccine impedes its application. Previously, we generated a vaccine derived from autologous cancer cells succumbing to oncolysis (ACCO) by a non-viral method that could initiate cell oncolysis and elicit a defined cascade of subcellular events to emit massive “eat me” or “danger” signals [1]. With full set of tumor antigens and self-adjuvanting property, ACCO enabled a long-term and antigen-specific prophylactic effect against autologous tumors [2]. Nevertheless, this strategy cannot treat heterologous tumors. Herein, we develop a stepwise bioorthogonal strategy to deliver an allogenic "zombie cell" as the off-the-shelf vaccine for postsurgical tumor intervention. As a result, heterologous cells that emits adjuvanting signals can be anchored onto the targeted cancer cell surface, which facilitates the phagocytosis of both cell types for subsequent activation of anti-tumor immune response (Fig.1). We denote the strategy as "zombie cell" vaccine (ZCV) because it closely resembles a zombie in the following three aspects: (1) ZCV is essentially walking dead cells undergoing oncolysis; (2) ZCV has the capability to “seize” living tumor cells, and (3) ZCV infects the captured cells with adjuvanting properties.

Keywords: cell vaccine; immunotherapy; oncolysis; bioinspired strategy; postsurgical tumor intervention

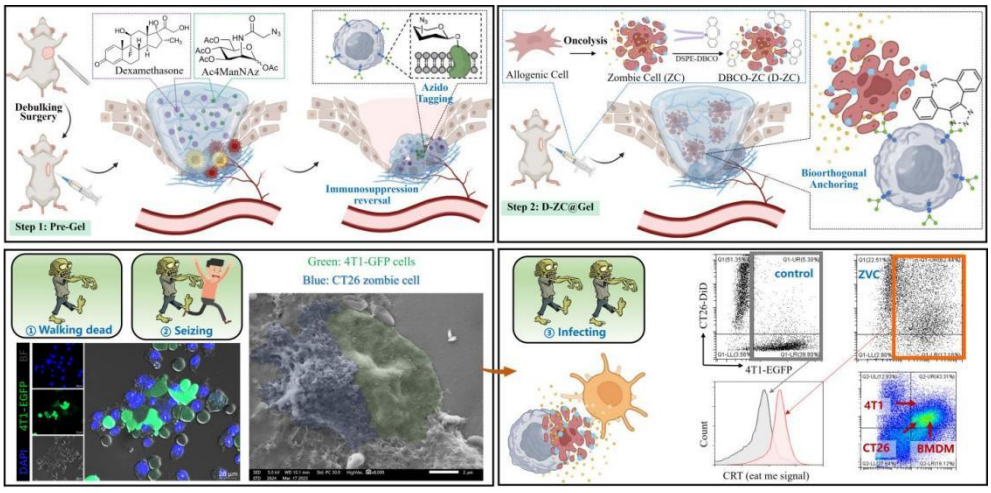

Figure 1. Illustration of a stepwise bioorthogonal strategy to deliver an allogenic "zombie cell" as the off-the-shelf vaccine for postsurgical tumor intervention (up). Corresponding results demonstration the three “zombie” properties: (1) dying, (2) seizing, and (3) infecting.

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Multifunctional Nano-Prodrug Based on TPGS with Integrative Collaborative Therapy and Enhanced Immune Elicitation for Triple Negative Breast Cancer

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Abstract: Triple Negative Breast Cancer (TNBC) is a refractory disease and preferentially leads to metastasis and recurrence. It is hard to be adequately treated by the single agent, due to its malignant cell proliferation, metastasis and low immunogenicity or immunosuppressive microenvironment. It is valuable to use nano-prodrug carriers for multi-drug delivery. Herein, we develop cRGD-modified nanoparticles (cRGD-TDA) of a prodrug of doxorubicin as cytotoxic agent, adjudin as anti-metastasis agent and D-α-tocopherol polyethylene glycol 1000 succinate (TPGS) as reactive oxygen species inducer linked with hydrazone and Schiff base bonds, and then combine it with PD-L1 antagonist to treat 4T1 TNBC. cRGD-TDA NPs present tumor-targeted co-delivery and pH-sensitive co-release of agents. cRGD-TDA NPs combined with PD-L1 antagonist much more significantly inhibit tumor growth and metastasis than single-drug treatment due to their integrative collaborative effect. It is firstly found that TPGS elicits powerful immunogenic cell death (ICD) effect to reverse low immunogenicity and promote maturation of dendritic cells. Meanwhile, PD-L1 antagonist mitigates immunosuppressive environment and has a synergistic effect with cRGD-TDA NPs. The study provides a new strategy to treat refractory cancer integratively and collaboratively.

Keywords: prodrug, D-a-tocopheryl polyethylene glycol succinate, immunogenic cell death, multi-drug treatment; chemoimmunotherapy

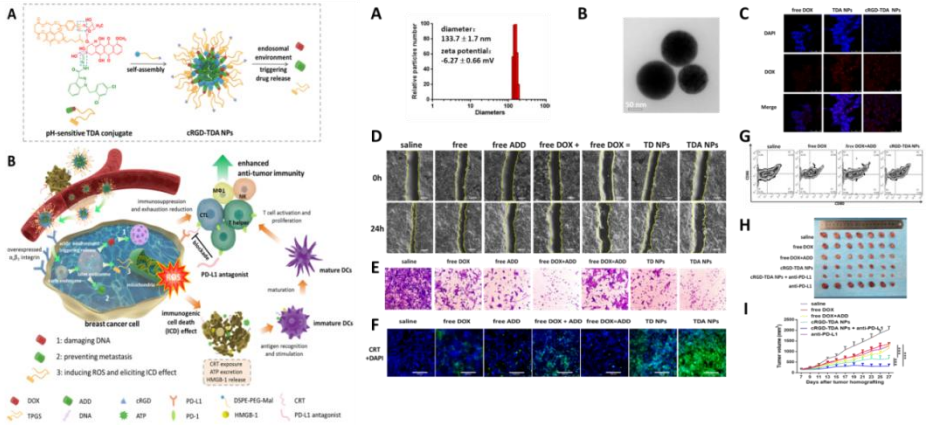

Figure 1 Schematic illustration of construction and mechanisms of cRGD-TDA NPs (Left); and characterization, uptake, immunostimulation, anti-metastasis and anti-tumor efficacy of cRGD-TDA NPs (Right).

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Single-atom nanozyme with diatomic active sites as a potent ROS scavenger for rheumatoid arthritis therapy*

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Abstract: Excess ROS are mainly produced by macrophages in the synovial membrane in rheumatoid arthritis (RA) patients' lesions, and the high levels of ROS promote macrophages polarization into proinflammatory M1 phenotype, increase the secretion of proinflammatory cytokines, create a hypoxic microenvironment, and aggravate osteoarticular erosion and cartilage damage. Therefore, simultaneous regulation of inflammation levels and alleviation of hypoxia may be an effective strategy for RA treatment. We herein designed a potent antioxidant nanozyme with single atom Cu and single atom Se as dual active centers on a nitrogen-doped carbon support (CuSe/CN), modified dextran sulfate (DS) by electrostatic adsorption to efficiently target the proinflammatory M1macrophages and scavenge extra ROS in the inflamed joints. Preliminary observation of the structural properties by TEM and XRD showed that Cu and Se are homogenously and atomically distributed throughout the support, no obvious nanoparticles or clusters are observed. And the content of Cu and Se is as high as ~0.99 wt% and ~4.84 wt%, respectively. Further characterization by XPS spectrum of the Cu 2p analysis, it can be seen that the Cu mainly exists in the form of positive monovalent and divalent. The Se 3d XPS spectrum of CuSe/CN shows a peak at 58.4 eV, which can be assigned to C-Se-C units. Furthermore, investigation demonstrated that single-atom nanozyme with diatomic active sites maximizes exposure of the catalytic active site, resulting in superior enzyme-mimicking activity in scavenging excess ROS. The SOD-like activity enabled CuSe/CN to scavenge 80% of $O_2^{\cdot-}$. Meanwhile, the resulting byproduct H_2O_2 was rapidly degraded to O_2 which was attributed to the catalase- and GPx-like activities of CuSe/CN. Moreover, CuSe/CN eliminated ~90% of ·OH promptly. The developed CuSe/CN not only eliminate the extra ROS but also produce abundant O_2, which would facilitate the recovery of synovial microenvironment, highlighting the potential application in the reprograming the synovial microenvironment for efficient RA therapy.

Keywords: antioxidant, single-atom nanozyme, ROS, rheumatoid arthritis

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Progress in the oral delivery system of probiotics

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Abstract: Probiotics promote the absorption of nutrients and maintain intestinal health by regulating the mucosal and systemic immune function or by regulating the balance of the intestinal flora in the host mucosa. In recent years, more and more research has been focused on probiotics. Oral administration of probiotics is widely considered to be beneficial for intestinal and systemic health. However, the acidic environment in the stomach, the presence of various digestive enzymes and bile salts in the intestinal tract seriously threaten the viability and function of probiotics, leading to poor intestinal delivery. How to protect the successful transport of probiotics through the stomach remains a challenge. At present, many studies have successfully constructed probiotic delivery systems to achieve the successful introduction of a large number of highly active probiotics into the gut. Therefore, this review summarizes the current drug delivery systems used for oral delivery of probiotics, while also analyzing the advantages and disadvantages of various drug delivery systems.

Keywords: probiotics; oral probiotics; delivery system

Magnetic Driven Biological Hybrid Free Radical Generator for Antitumor Therapy

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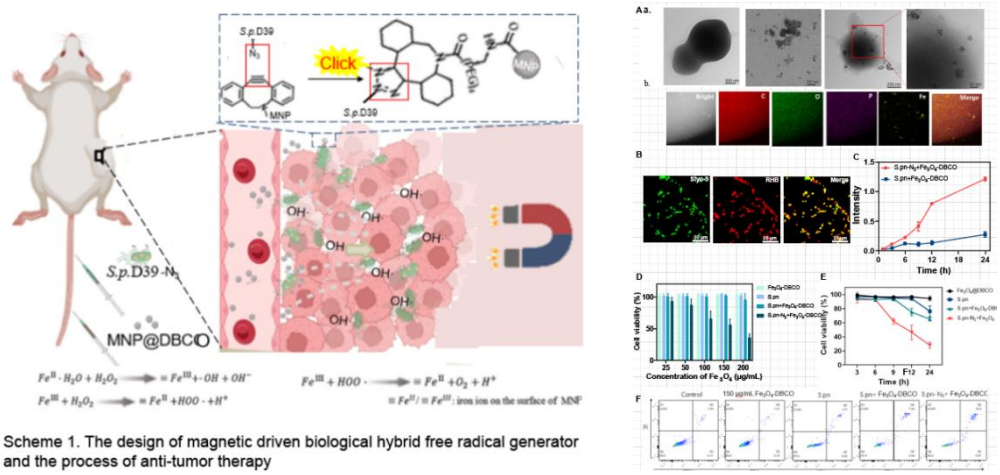
Abstract: Free radical therapy has become a key strategy in cancer treatment. Among them, compared with other free radical therapies, chemo-kinetic therapy has the advantages of no penetration limitation and wider application range. Enough H_2O_2 content is highly recommended to enhance the free radical therapy by providing more raw materials for free radical production yet remains challenging. Despite the high expression of H_2O_2 in tumor tissues, it is far from the amount required to achieve the desired free radical treatment efficiency. Existing strategies are mainly to directly deliver exogenous H_2O_2 or enzymes to catalyze the production of H_2O_2 in tumor sites to increase the concentration of H_2O_2. However, existing strategies are difficult to provide a large amount of H_2O_2 continuously and the drug is easy to leak, causing damage to normal tissues. Due to the short half-life of free radicals, the limited diffusion distance and the non-specific distribution of exogenous drugs, free radicals only have a good killing effect on neighboring cells. Due to the narrow range of action of free radicals, extracellular vesicles or in situ release of small size photosensitizers are mainly used to make free radicals uniformly distributed. However, due to insufficient light penetration, it is difficult to achieve the ideal therapeutic effect. Therefore, how to simultaneously solve the endogenous H_2O_2 deficiency from the root and expand the range of free radical action is the key to improve the efficiency of free radical treatment. Herein, inspired by the spontaneous and continuous production of H_2O_2 by *S. pneumoniae*, we designed a magnetically driven biofusion free radical generator. The azido-modified *S.P.* D39 preanaerobically targeted self-propulsion to the tumor site for early residence. Bioorthogonal with alkynyl modified Fe_3O_4 magnetic nanoparticles to form a magnetically driven biofusion free radical generator in situ. Under the action of external magnetic field, bio-fusion microrobots move uniformly in the tumor matrix, continuously produce ·OH, enhance the uniform distribution of ·OH, expand the range of free radicals, and greatly improve the treatment efficiency of free radicals.
Keywords: free radical therapy; continuous supply of ·OH, biological hybrid robots, magnetic targeting



Scheme 1. The design of magnetic driven biological hybrid free radical generator and the process of anti-tumor therapy

Figure. 1 Schematic illustration of the design of biological hybrid free radical generator (Left); and synthesis and characterization of functional biofusion systems (Right).

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Supramolecular pharmaceutical excipients and pulmonary drug deliveries

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Abstract: Metal-organic framework (MOF) is a new type of pharmaceutical supramolecular carrier, while the MOF formed with cyclodextrin (CD) as the organic linker and potassium ion as the inorganic metal center, namely, CD-MOF shows the characteristics of highly regular morphology and high porosity of special interest to be used as the DPI inhalation carrier. After loading Budesonide (BUD), Paeonol (PAE) and Tetrahydropalmatine (THP) with CD-MOF, the particle size, release behaviors and stability of the active pharmaceutical ingredients could be improved *in vitro*. Besides, the bioavailability can be enhanced through lung delivery *in vivo* and pulmonary inflammation could be significantly reduced in the meantime. After CD-MOF encapsulation, Glycyrrhetinic Acid (GA) exhibited obvious sustained-release characteristics both *in vitro* and *in vivo*, which can be used to treat idiopathic pulmonary fibrosis (IPF) after pulmonary inhalation. In addition, glycoside scutellarin enhanced CD-MOF anchoring for laryngeal targeted delivery when co-loaded with Dexamethasone. The water-insoluble CL-MOF particles of cross-linked CD-MOF not only can preserve the characteristics of MOF, but also slow down the release of the drug molecules from the particulate systems. The fluorescence micro-optical sectioning tomography (fMOST) system was applied to visualize the three-dimensional spatial distribution of inhaled particles cross the whole lung *in situ* for the first time using CL-MOF, revealing the particle distributions and achieving a breakthrough in the methodology of studying the distribution of inhaled particles in the whole lungs. Furthermore, RCLD, another nano-particle system of cross-linked CD-MOF can highly target lung tumors under the mechanisms of pH-responsive aggregation/dissociation, supramolecular recognition and cell recognition, thus inhibiting lung metastasis of melanoma remarkably with good biosafety. In conclusion, a series of pharmaceutical supramolecular carriers synthesized based on CD-MOF have important and smart application prospects in pulmonary drug deliveries.

Keyword: Metal-organic framework; Pulmonary drug delivery; Cyclodextrin; Supramolecular carriers.

Functional lipid excipients – lipopeptides

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Abstract: Functional lipid excipients, the cornerstone of novel lipid-based delivery systems[1], play a key role in achieving efficient and safe delivery of bioactive molecules. In recent years, we have focused on building lipid materials and developing multifunctional lipid-based biomolecule delivery systems. To improve the lack of functional properties of conventional phospholipids, we synthesized modified phospholipids with composite functions such as pH-responsiveness in disease microenvironment and mitochondrial targeting[2], followed by the construction of multifunctional biomolecule delivery systems based on those lipids through the “multi-component synergistic self-assembly” strategy. Besides, based on the structural and functional characteristics of peptide dendrimers and their derivatives, we combined the phospholipids with low-generation peptide dendrimers to create the dendritic lipopeptides and construct a series of biomimetic lipid-based delivery systems for tumor and oxidative stress-induced disease treatment[3,4]. In summary, functional lipid excipients endow lipid-based drug delivery systems with new functions and advantages and improve the treatment efficacy of diverse diseases.

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Study on injectable HA-SF biphasic co-crosslinked hydrogel for facial soft tissue filling

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Abstract: With the rapid development of the national economy and the rise of the appearance level economy and Internet celebrity economy in recent years, the penetration rate of medical beauty has increased greatly, and the medical beauty market has developed rapidly with broad market prospects. Skin and soft tissue injection filling is one of the leading technologies of light medical beauty and has the most development potential. It mainly improves the aging and depression of the middle face by injecting natural or synthetic biological materials into the dermis or subcutaneous layer. Polymer hydrogels based on hyaluronic acid (HA) are widely used in skin beauty and facial adjustment. HA hydrogel has the advantages of natural effect, reversibility, metabolism, and wide clinical use, but its half-life in vivo is short, and its adhesion to a variety of cells in vivo is insufficient. SF is a kind of structural protein extracted from natural silk. It is composed of 18 amino acids. It has good biocompatibility and excellent mechanical properties and has a strong adhesion ability to various cells. These advantages of SF complement the limitations of HA. Therefore, the combination of SF and HA to prepare dual-phase co-crosslinked hydrogel for facial soft tissue filling can not only reflect the advantages of the traditional HA hydrogel itself but also have many advantages such as high mechanical properties, good adhesion, excellent moisturizing performance, promoting cell adhesion and skin type Ⅲ collagen regeneration. The prepared dual-phase co-crosslinked hydrogel can achieve a filling effect with long maintenance time, high biological activity, and improved skin condition.

Keywords: Hydrogel; Hyaluronic acid; Cosmetic medicine.

药物制剂的体内外相关性探究:缓释制剂及中成药之尝试

香港中文大学 左中

摘要：In-vitro in-vivo correlation （IVIVC）是利用药物制剂体外溶出反映药物体内吸收乃至药效发挥的前提条件。其关键步骤是建立一个有预测作用的精确的数学模型来描述制剂体外溶出和体内药动学参数之间的关系。近年来，IVIVC 广泛应用在药物制剂开发、评价的过程中，并被药物监管部门普遍接受。这种 IVIVC 建立方法在药物的溶出和吸收过程较简单时（如 BCS I 类药物）可以获得较好的预测效果。若由于吸收或溶出过程存在复杂机制(比如 BCS III 类药物或中药多组分药物的溶出、吸收过程存在相互作用时)，导致药物的溶出和体内吸收之间不是简单的线性关系，这时建模的结果很容易受建模方法的影响。这种二步的 IVIVC 方法会将实验误差在多步数据分析过程中被放大，从而导致无法最终建立 IVIVC。在中药制剂中超过 30%的有效成分为 BCS III 类成分，使得中药制剂的 IVIVC 建立更具有挑战性。针对传统 IVIVC 建立方法的不足，我们团队建立了一种基于卷积的一步 IVIVC 方法。该方法通过非线性混合效应建模工具包（NONMEM）实现了体外溶出曲线与体内药动学曲线的直接关联，不仅灵活、快速，还可以根据药物体内吸收与体外溶出时间不同的特性，灵活的选择各种经验的相关方程进行测试，加快了建模的过程，十分适用于存在复杂溶出和吸收机制的 BCS III/IV 类药物。同时，我们以这种新的 IVIVC 建模技术应用于中药多组分溶出的体内外相关性评价。我们以银杏叶片为例，第一次尝试了建立中成药制剂中多成分的 IVIVC。

克服双重屏障的口服超分子聚合物递送系统：非侵入式脑靶向潜能的探究

叶田田 沈阳药科大学

摘要：口服纳米载体在粘膜覆盖上皮中的渗透行为受到很大影响，因此设计一种能够持续克服黏液和细胞屏障的口服递送系统，仍然是一个挑战。本研究构建了一系列亲疏水性质可变的“壳-核结构”超分子聚合物，并发现其具有优异的黏液穿越能力和上皮吸收能力。在黏液蛋白的范德华力驱动下，亲水纳米衣与脂质核心逐步分离，暴露脂质核心，从而实现有效的上皮摄取，克服口服黏液层-上皮层双重屏障。同时，通过索马鲁肽的包载，探索了这种超分子聚合物通过口服途径，实现非侵入式脑靶向递送的潜力。

Hemoglobin-Crowned Nanomedicnes for Tumor Associated Macrophage-Targeted Cancer Treatment

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Abstract: Tumor-associated macrophages (TAMs) are a promising therapeutic target for cancers, but achieving multitarget therapy of TAMs is still challenging. Here, we develop a protein-crowned micelle system for targeted and synergistic TAM reprogramming to enhance cancer treatment. The doxorubicinloaded micelles with a hemoglobin crown (Hb-DOXM) can bind with endogenous plasma haptoglobin to realize specific M2-type TAM targeting. Under the tumor hypoxic and acidic environments, Hb-DOXM can responsively release O2 and DOX to reduce the recruitment of TAMs by hypoxia remission and release DOX to kill M2-type TAMs and cancer cells. To reprogram TAMs adequately, the TAM-modulating drug celecoxib is further encapsulated (HbDOXM@Cel) to repolarize M2-type TAMs. The targeted and synergistic TAM reprogramming by Hb-DOXM@Cel can remodel the tumor microenvironment (TME) to an immunostimulatory microenvironment and augment the antitumor effect of cytotoxic T lymphocyte, thus strongly enhancing the DOX-based chemotherapy. The protein-crowned micelle strategy presents a targeted and synergistic TAM therapy tool for enhanced cancer treatment.

Keywords: photodynamic immunotherapy; *in situ* self-assembly, chromatin decompaction, nuclear DNA damage

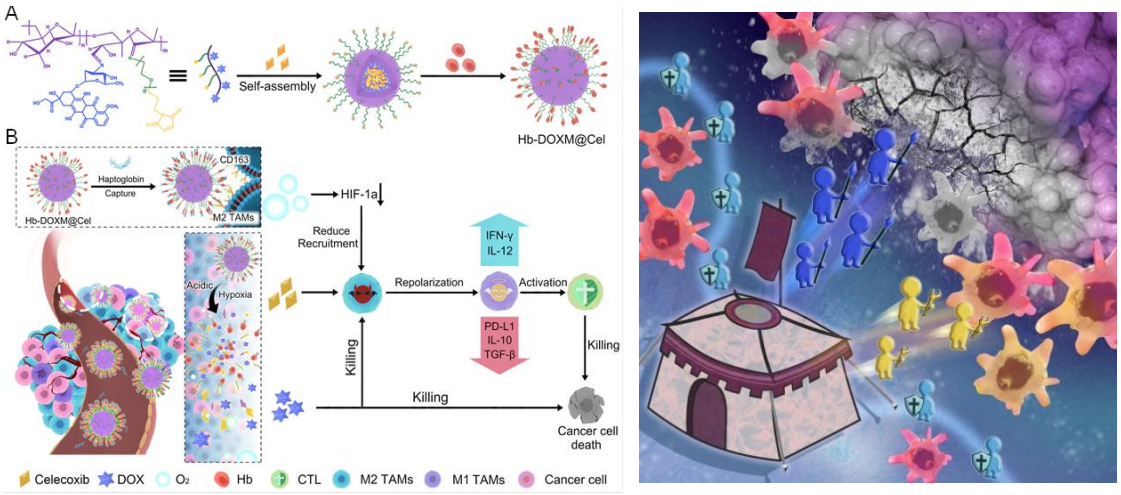

Figure. 1 Schematic Illustration of Hemoglobin-Crowned Micelles for Targeted and Synergistic TAM Reprogramming to Enhance Cancer Treatment.

Reference:

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Preparation of a Sunitinib Loaded Microemulsion for Ocular Delivery and Evaluation for the Treatment of Corneal Neovascularization *in Vitro* and *in Vivo*

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Abstract: Corneal neovascularization (CNV) is a pathological condition that could disrupt corneal transparency thus harm to visional acuity. However, there is no potent drug to treat CNV. Sunitinib (STB), a small molecule multiple receptor tyrosine kinase inhibitor, was shown to have effect on CNV. This study aimed to develop an STB microemulsion (STB-ME) eye drop to inhibit CNV by topical application. The STB-ME was successfully prepared by the phase inversion emulsification method, and the physicochemical properties of STB-MEs were investigated. Short-term storage stability, the human corneal epithelial cells cytotoxicity, drug release, ocular irritation, ocular pharmacokinetics and the inhibiting effect on CNV were evaluated *in vitro* and *in vivo*. The optimal formulation of STB-ME is composed of oleic acid, CRH 40, Transcutol P, water and sodium hyaluronate (SH). It is a uniform spherical particle with a mean droplet size of 18.74 ± 0.09 nm and a polydispersity index of 0.196 ± 0.004. In the *in vitro* drug release results, STB-ME showed sustained release and was more suitable for Korsmeyer-Peppas fitting (R^2 = 0.9960). The results of the ocular pharmacokinetics in rabbits showed that the formulation containing SH increased the bioavailability in the cornea (2.47-fold) and conjunctiva (2.14-fold). STB-ME following topical administration more effectively suppressed the alkali burn-induced CNV in mice than saline, and the high dose (0.1%) STB-ME had the similar efficacy with dexamethasone (0.025%). Moreover, that vascular endothelial growth factor (VEGF-A) and platelet-derived growth factor-BB (PDGF-BB) in the cornea were significantly decreased on days 3 and 7 in STB-ME groups compared with the saline group, and the inhibitory effect of 0.1% STB-ME had no significantly difference compared with the dexamethasone group. This study provides a promising formulation of STB-ME for the inhibition of CNV by topical administration, which has the excellent characteristics of effective, sustained release and high ocular bioavailability.

Keywords: sunitinib, microemulsion, ocular delivery, corneal neovascularization, ocular pharmacokinetics

Self-Assembly of Peptide Lipid-Based Nanoparticles for Gene Delivery

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Abstract: Combination of photothermal therapy (PTT) and gene therapy (GT) shows great potential to achieve synergistic antitumor activity. However, the lack of controlled release of genes from carriers remains a severe hindrance. Herein, peptide lipid (PL) and sucrose laurate (SL) were used to coat single-walled carbon nanotubes (SCNTs) and multi-walled carbon nanotubes (MCNTs) to form bifunctional delivery systems (denoted SCNT-PS and MCNT-PS, respectively) with excellent temperature-sensitivity and photothermal performance. CNT/siRNA suppressed tumor growth by silencing survivin expression while exhibiting photothermal effects under near-infrared (NIR) light. SCNT-PS/siRNA showed very high anti-tumor activity, resulting in the complete inhibition of some tumors after 21 days of treatment. It was highly efficient for systemic delivery to tumor sites and to facilitate siRNA release owing to the phase transition of the temperature-sensitive lipids, due to PL and SL coating. Furthermore, neither SCNT-PS nor MCNT-PS nanoparticles had any discernible cytotoxic effect at concentrations as high as 60 μg/mL or toxicity to mice. Thus, SCNT-PS/siRNA is a promising anti-tumor nanocarrier for combined PTT and GT.

Keywords: temperature-sensitive lipids, carbon nanotubes, photothermal therapy, gene therapy, synergistic therapies

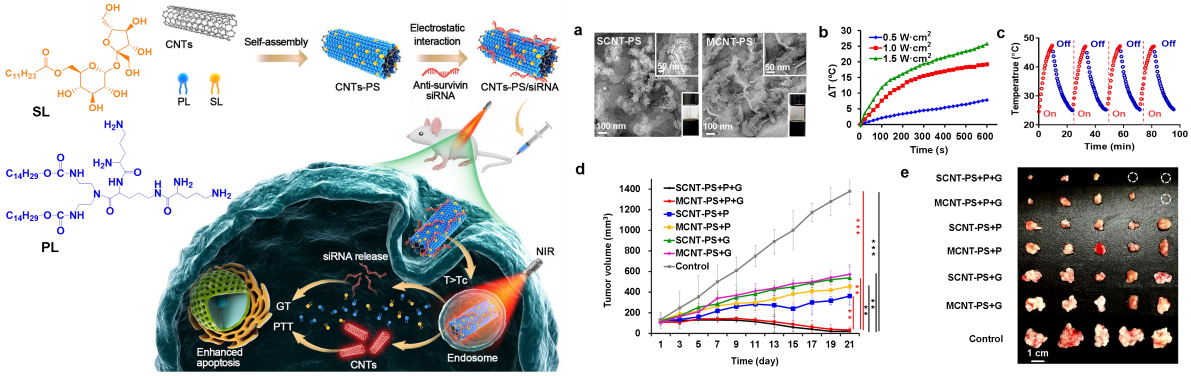

Figure 1. Schematic diagram of the temperature-sensitive CNT-PS/siRNA nanoparticle for synergistic PTT and GT for cancer cells (Left); Characterization of CNT-PS and *In vivo* antitumor study (Right).

Reference:

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明胶蛋白：平台型药物载体材料用于肿瘤治疗

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摘要：

明胶蛋白（Gelatin）是胶原的水解产物，是一种无脂肪的高蛋白，在食品、化妆品及医药等领域应用广泛。实体肿瘤微环境中高表达的基质金属蛋白酶2/9可水解胶原及明胶蛋白，促进肿瘤侵袭、转移。近年来，我们通过明胶蛋白改性，成功构建明胶蛋白-阿霉素前药及“AND”逻辑门控递送系统，可有效降低化疗药物对正常组织的毒副作用，实现肿瘤治疗药物的“减毒增效”。并探究将明胶蛋白作为一种平台型构筑单元，与其它功能性生物医药材料（如聚多巴胺、磁性蒙脱石、碳酸钙及免疫节点抑制剂）组装成为局部植入剂，在肿瘤术中窗口期局部缓释给药，可实现肿瘤局部治疗、全身治疗及长期治疗的效果。

关键词：明胶蛋白；药物递送；水凝胶；肿瘤免疫治疗

Self-Assembling Paclitaxel-Mediated Stimulation of Tumor-Associated Macrophages for Postoperative Treatment of Glioblastoma

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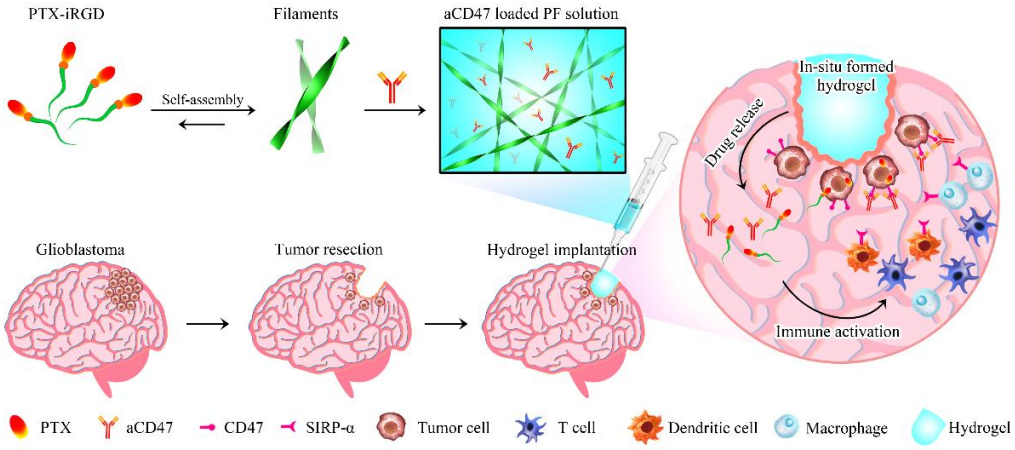
Abstract: The unique cancer-associated immunosuppression in brain, combined with a paucity of infiltrating T cells, contributes to the low response rate and poor treatment outcomes of T-cell-based immunotherapy for patients diagnosed with glioblastoma multiforme (GBM). Here, we report on a self-assembling paclitaxel (PTX) filament (PF) hydrogel that stimulates macrophage-mediated immune response for local treatment of recurrent glioblastoma. Our results suggest that aqueous PF solutions containing aCD47 can be directly deposited into the tumor resection cavity, enabling seamless hydrogel filling of the cavity and long-term release of both therapeutics. The PTX filaments elicit an immune-stimulating tumor microenvironment and thus sensitizes tumor to the aCD47-mediated blockade of the anti-phagocytic “don’t eat me” signal, which subsequently promotes tumor cell phagocytosis by macrophages and also triggers an antitumor T cell response. As adjuvant therapy after surgery, this aCD47/PF supramolecular hydrogel effectively suppresses primary brain tumor recurrence and prolongs overall survivals with minimal off-target side effects.

Keywords: cancer immunotherapy, local delivery, self-assembling, hydrogel, anti-CD47



Construction of polydopamine-based modular back-to-back Janus nanomaterials and evaluation of their performances in anti-tumor applications

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Abstract: The modular self-assembling Janus nanoparticles that can carry different therapeutic molecules have received widespread attention due to their advantages such as diversity, controllability, and selectivity. This paper consists of the design, precise synthesis, and biomedical applications of Janus nanoparticles, with the goal to develop a novel modular Janus nanoparticle synthesis method and to clarify the formation mechanism of nanomaterials. Depending on individual needs, the desired modules with specific composition and function are selected and assembled via condensation reaction to prepare the back-to-back “A”/polydopamine-polydopamine/“B” (“A”/PDA-PDA/“B”, where A and B represent inorganic materials) Janus nanoparticles. For these unique nanoparticles, dual drugs with different hydrophilic-hydrophobic properties can be loaded into different modules (independent regions) of the same nanocarrier system, and the release of each drug does not affect the other, achieving the inhibition of malignant tumor growth and metastasis. The combination of multi-modal imaging and therapies, as well as biosafety of Janus theranostic agent will be systematically investigated at the cellular and animal levels. This synthetic approach provides a novel strategy for assembling modular back-to-back PDA Janus nanoparticles with unique morphologies and structures, thereby promoting the research progress of multifunctional Janus nanoparticles in cancer diagnosis and treatments.

Key Words: polydopamine; back-to-back Janus; hydrophilic-hydrophobic drug carrier; modular construction; liver cancer

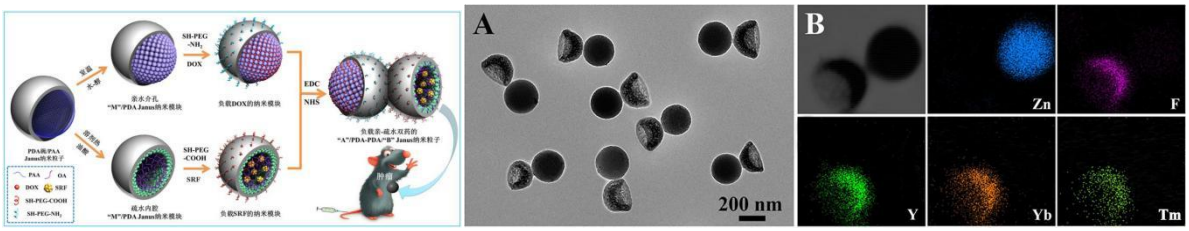

Figure. 1 Schematic diagram for the fabrication of multifunctional back-to-back Janus nanoparticles as pH and NIR dual-stimuli responsive hydrophobic and hydrophilic drug vehicles for multi-modal imaging-guided chemo-photothermal synergistic cancer therapy(Left); and TEM image (Right).

Reference:

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Construction of chemotactic system of polymer nanomotors and their application in the treatment of brain diseases

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Abstract: More than 50% of deaths can be attributed to chronic inflammatory diseases, so it is important to construct a drug delivery system based on the effective interaction of highly expressed substances specific to the inflammatory microenvironment with the artificial chemotaxis system. Therefore, a chemotactic system based on polymer nanomotors is proposed for precise targeting of inflammatory diseases, in which high levels of reactive oxygen species (ROS) and induced nitric oxide synthase (iNOS) at inflammatory sites are used as chemical attractants. It reacts with the active components in the polymer nanomotors to produce nitric oxide (NO), thus inducing the chemotactic system to actively search for the inflammatory site and achieve effective targeting [1-5]. This chemotactic system based drug delivery strategy is expected to improve drug utilization and may be applicable to a variety of inflammatory diseases. Subsequently, this chemotactic system was applied to the immunotherapy of glioblastoma and the treatment of Parkinson's disease [6-8].

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[8] Mimi Wan#; Qi Wang#; Xiaoyun Li; Bo Xu; Dan Fang; Ting Li; Yueqi Yu; Leyi Fang; Yue Wang; Meng Wang; Fenghe Wang; Chun Mao*; Jian Shen*; Jia Wei*; Angew. Chem. Int. Ed., 2020, 59: 14458

Dendritic Polylysine with Paclitaxel and Triptolide Codelivery for Enhanced Cancer Ferroptosis Through the Accumulation of ROS

Yuanyuan Wen [a], Mengnan Ni [b], Hui Jiang [b], Haisi Wu [b], Qinqi Yu [c], Jinyu Li [c], Xiaolin Li [c], Jifu Wei [a*], Wei Wu [d*], Huae Xu [a, b*]

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Abstract: Recently, paclitaxel (PTX) was reported to increase intracellular lipid reactive oxygen species (ROS) levels triggering cancer cell ferroptosis. Based on this, some efforts had been made to improve the treatment of PTX for non-small cell lung cancer (NSCLC). Our previous studies demonstrated that Triptolide (TPL) could improve the antitumor effect of PTX. Nevertheless, the poor solubility and side effects often limit the application of chemotherapy drugs. In this paper, we constructed a novel nano-drug delivery systems (NDDSs) chemosynthesis by PEGylated generation 3 (G3) dendritic polylysine co-loaded with PTX and TPL (PTX-TPL-PEG-PLL, PTPP), which was endowed with the ability of tumor targeting and favourable solubility. In addition, we demonstrated that TPL could induce ROS by regulating NF- κ B signaling pathway, so that enhanced the ferroptosis-induced effect of PTX, which illustrated the possible mechanisms underlying the synergistic effect of PTX and TPL for the first time. In general, PTPP may be a potential system for NSCLC treatment.

Keywords: dendritic polylysine, drug delivery, oncotherapy, NF-κB signaling pathway, ferroptosis

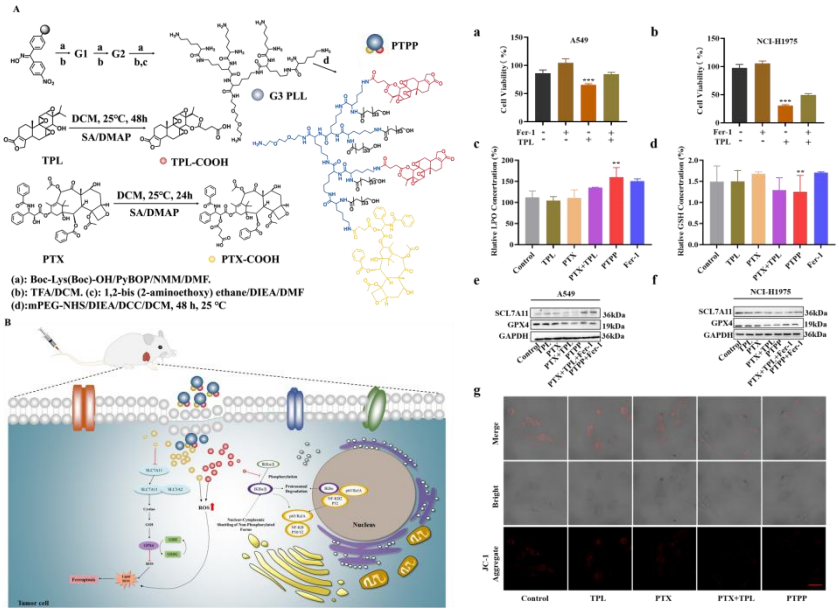

Figure. 1 Scheme of the PTPP system (Left) and the mechanism of ferroptosis-induced effect of PTPP (Right).

Reference:

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Hypoxia-responsive nanocarriers for cancer diagnosis and precision therapy

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Abstract: Hypoxia is associating with tumor development and progression, as well as highly related to therapeutic resistance. Therefore, there is clinical demanding of diagnosis hypoxia in tumors, predicting its responses to therapies, as well as overcome its influence to therapies, such as chemotherapy, radiotherapy and immunotherapy. Recently, we employ MR contrast amplification (MR-CA) nanoprobes for quantitative hypoxia imaging to achieve precise early detection of pancreatic tumor, and effective prediction of therapeutic responses, as well as the normalization of the hypoxic TME to promote therapeutic efficacy. Besides, we created novel tumor-targeted polymeric micelles sensing hypoxia in tumor microenvironment to activate strong cytotoxicity and immunogenic responses for effectively eradicating hypoxic and advanced breast tumors (*e.g.*, metastasis). In all, the hypoxia-sensitive nanocarriers demonstrated high performance for tumor diagnosis and therapy.

Keywords: Hypoxia, stimuli-responsive, nanocarriers, diagnosis, therapy, tumor

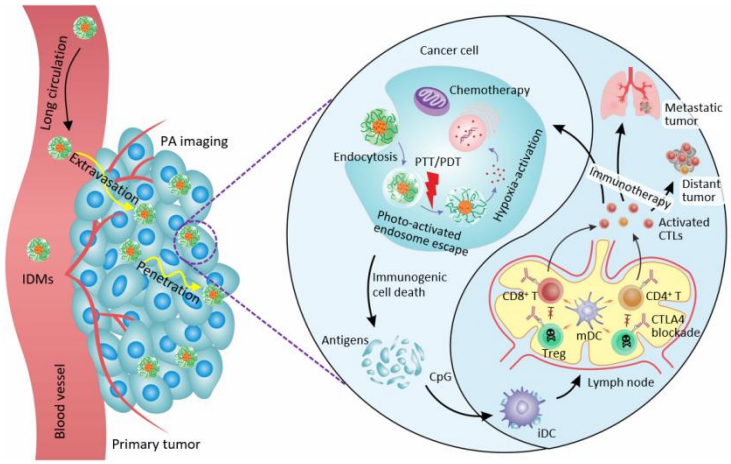

Figure 1. The development of hypoxia-responsive nanocarriers for cancer theranostics.

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Biological chemotaxis-guided self-thermophoretic nanoplatform augment colorectal cancer therapy through autonomous mucus penetration

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Abstract: Oral drug delivery systems have great potential to treat colorectal cancer (CRC). However, the drug delivery efficiency is restricted by limited CRC related intestine positioning and dense mucus barrier. Herein, we present a biological chemotaxis-guided self-thermophoretic nanoplatform (BCTN) facilitates precise intestinal positioning and autonomous mucus penetration. The nanoplatform introduces asymmetric platinum sprayed mesoporous silica to achieve autonomous movement in intestinal mucus. Furthermore, inspired by the intense interaction between pathogenic microbes and CRC, the nanoplatform is camouflaged by *Staphylococcus aureus* membrane (SAM) to precisely anchor in CRC related intestine. Owing to 4.3-fold higher biological chemotactic anchoring of CRC related intestine and 14.6-fold higher autonomous mucus penetration performance, the nanoplatform vastly improves the oral bioavailability of cisplatin, leading to a tumor inhibition rate of 99.1% on orthotopic CRC-bearing mice. Taken together, the exquisitely designed nanoplatform to overcome multiple physiological barriers provides a new horizon for the development of oral drug delivery systems.

Keywords: oral drug delivery system; colorectal cancer, nanomotors, intestinal mucus, bacterial biomimetic.

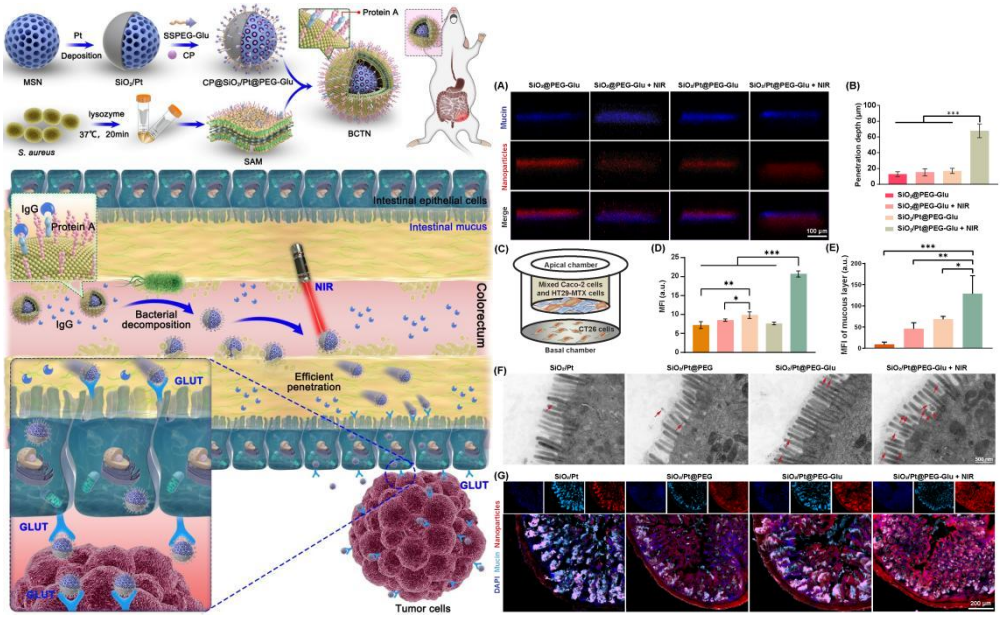

Figure. 1 A schematic of the synthetic procedure for biological chemotaxis-guided self-thermophoretic nanoplatform augment CRC therapy (Left); and self-thermophoresis driven autonomous mucus penetration (Right).

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Mucus Penetrating and Cell-Binding Polyzwitterionic Micelles as Potent Oral Nanomedicine for Cancer Drug Delivery

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Abstract: Orally administrable anticancer nanomedicines are highly desirable due to their easy and repeatable administration, but are not yet feasible because the current nanomedicine cannot simultaneously overcome the strong mucus and villi barriers and thus have very low bioavailability (BA). Herein, this work presents the first polymeric micelle capable of fast mucus permeation and villi absorption and delivering paclitaxel (PTX) efficiently to tumors with therapeutic efficacy even better than intravenously administered polyethylene glycol based counterpart or free PTX. Poly[2-(*N*-oxide-*N*,*N*-diethylamino)ethyl methacrylate] (OPDEA), a water-soluble polyzwitterion, is highly nonfouling to proteins and other biomacromolecules such as mucin but can weakly bind to phospholipids. Therefore, the micelle of its block copolymer with poly(ε-caprolactone) (OPDEA-PCL) can efficiently permeate through the viscous mucus and bind to villi, which triggers transcytosis-mediated transepithelial transport into blood circulation for tumor accumulation. The orally administered micelles deliver PTX to tumors, efficiently inhibiting the growth of HepG2 and patient-derived hepatocellular carcinoma xenografts and triple-negative breast tumors. These results demonstrate that OPDEA-based micelles may serve as an efficient oral nanomedicine for delivering other small molecules or even large molecules.

Keywords: oral nanomedicine; polyzwitterionic micelle; mucus penetrating; transcytosis; cancer drug delivery

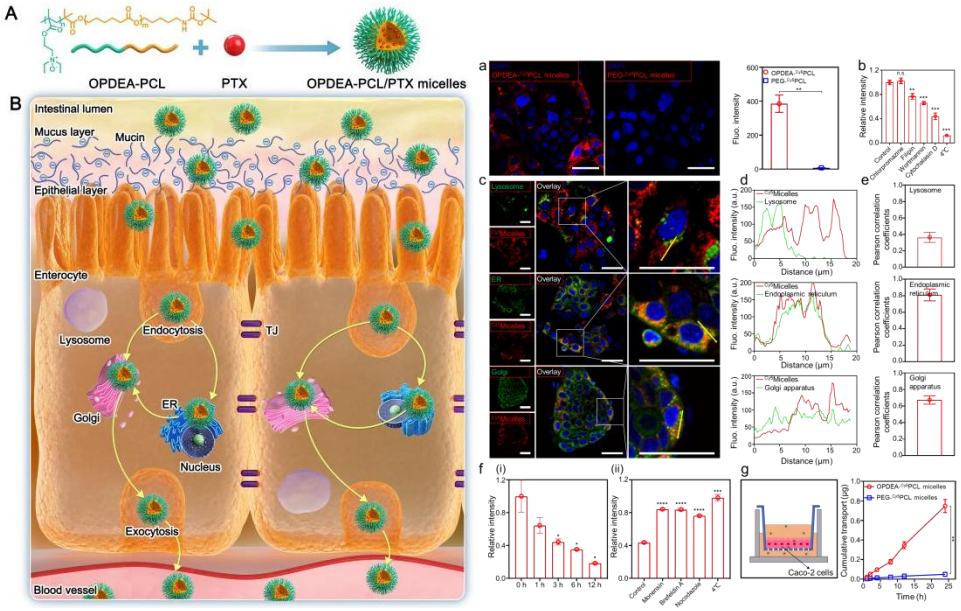

Figure. 1 Schematic illustration of intestinal mucus penetration and transepithelial transport of OPDEA-PCL micelles (Left); and Caco-2 cell intracellular trafficking and in vitro transcellular transport of OPDEA-^{Cy5}PCL micelles (Right).

Reference:

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Growth and agglomeration mechanisms of spherical crystals and granulation strategies

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Abstract: Spherical crystallization technology is able to complete granulation in the crystallization unit, with high product performance, low energy consumption and short production cycles, realizing high-end products and green processes. The research on spherical crystallization has common problems of unclear mechanism, blind trials and errors in preparation process, and uncontrollable shape and size of spherical crystals. In response to this problem, a spherical crystal growth model is proposed by simulating the structure and behavior of molecular clusters using molecular dynamics; a crystal agglomeration model is proposed by analyzing the structure and behavior of clusters using online/offline monitoring of process; and the quantitative relationship between key parameters of spherical crystal formation and the spherical crystal morphology is established based on the spherical crystal growth and agglomeration model. A variety of common strategies are developed for the efficient preparation of spherical crystals: the spherical growth strategy accurately produces spherical crystals with radial branching structure, which is widely applicable to organic molecular crystals in pharmaceutical, food and military industries; the spherical agglomeration strategy designs a two-step bridging mechanism and proposes key indicators such as wetting energy and adhesion energy to enable spherical crystals with high throughput screening of ternary solvent systems, which is particularly suitable for needle-like crystals in pharmaceuticals. The agglomerated abrasion strategy enables the formation of spherical crystals in a single solvent (water) system and within the conventional crystallization supersaturation range, which is suitable for inorganic salt crystals in the food, daily chemical and fertilizer fields; the oiling-out crystallization strategy produces multi-component functional spherical crystals by a one-pot method with uniform and adjustable spherical components, which is suitable for drug combination and functional food development. Based on the above strategies, the green and efficient crystallization and granulation of high-end functional spherical crystals of multiple materials has been achieved.

Keywords: Spherical crystallization; Granulation; Spherulitic growth; Agglomeration; Particle design

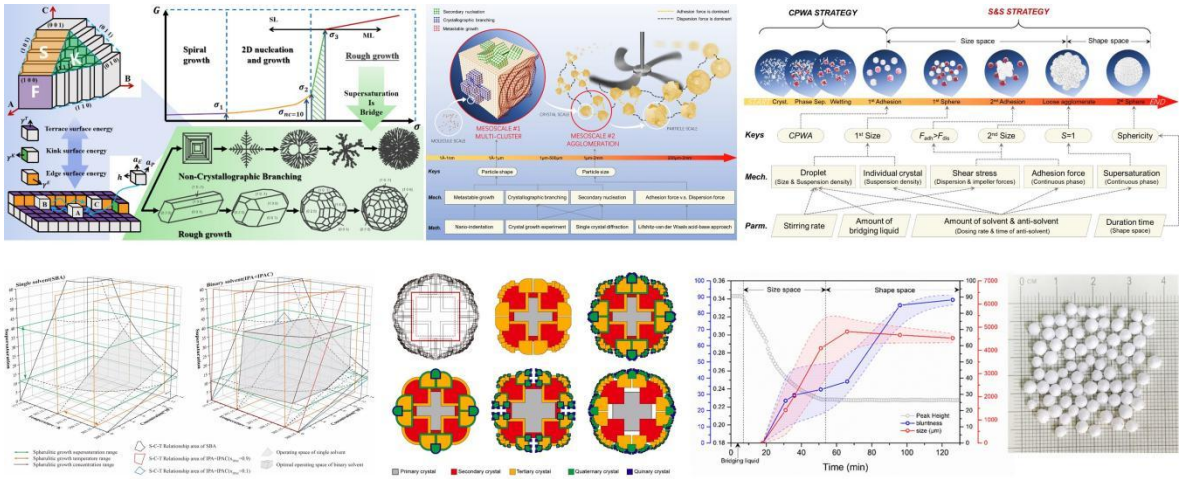

Figure. 1 Schematic representation of the preparation strategy (top) and formation mechanism (bottom) of spherical crystals.

Reference:

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Apatinib and Gamabufotalin Co-loaded Lipid/Prussian Blue Nanoparticles for Synergistic Therapy to Gastric Cancer with Metastasis

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Abstract:

Introduction: Due to the non-targeted release and low solubility of anti-gastric cancer agent, Apatinib (Apa), a first-line drug with long-term usage in a high dosage can induce multi-drug resistance and cause serious side effects, as well. In order to avoid those drawbacks of Apa, Gamabufotalin (CS-6) and drug delivery system were selected for combinational therapy to gastric cancer by reducing the dose of Apa, while maintaining the therapeutic effect and improving bioavailability. **Objectives:** This study aimed to develop an effective nanocarrier for synergistic Apa/CS-6 delivery in gastric cancer. **Methods:** Apa and CS-6 were co-loaded by Lipid/Prussian blue, which were prepared by hydrothermal synthesis method and thin-film hydration method. The biocompatibility and biosafety evaluation of HA-Apa-Lip@CPB-CS-6 NPs were evaluated by hemolysis assay, H&E staining and blood test. The targeting effect of nanoparticles was examined by an *in vivo* imaging system in BGC-823 xenograft models. To evaluate the antitumor activity and mechanism of HA-Apa-Lip@CPB-CS-6 NPs, MTT, transwell assay, cell cycle analysis, western blotting analysis, immunofluorescence and immunohistochemistry tests were performed in BGC-823 cells *in vitro* and *in vivo*. **Results:** *In vitro* assays indicted synergistic effect of Apa/CS-6 and the inhibitory effect of HA-Apa-Lip@CPB-CS-6 NPs on the BGC-823 cell proliferation and invasion/metastasis via downregulation of VEGF and MMP-9. *In vivo* assays, HA-Apa-Lip@CPB-CS-6 NPs showed strongest anti-tumor and anti-metastasis ability in BGC-823 cells-bearing nude mice due to the excellent penetration performance and outstanding synergy effects. Besides, HA-Apa-Lip@CPB-CS-6 NPs demonstrated favorable biosafety. **Conclusion:** We developed an effective strategy for synthesizing HA-Apa-Lip@CPB-CS-6 NPs, which displayed highly efficient accumulation in tumor sites, controllable drug release, and low side effect of the chemotherapy, providing an alternative for malignant gastric cancer therapy.

Keywords: Apatinib; Gamabufotalin; Co-delivery; Gastric cancer

Association of the effect of immunosuppressive therapy and the diversity of gut microbiota after hematopoietic stem cell transplantation

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Abstract: The mechanism of gastrointestinal tract adverse reactions in hematopoietic cell transplantation remains unclear. We evaluated the effects of immunosuppressive therapy on the structure, composition and biodiversity of intestinal microflora after hematopoietic stem cell transplantation (HSCT) and explored the mechanism of action of intestinal microflora from the perspective of drug concentration. Immunosuppressive therapy protects the gut microbiota after transplantation by reversing the dysbiosis at phylum, genus and species levels. Among them, the types of intestinal flora showed differences between the high and low concentration groups. The abundance of bacteria, micrococcus, peptostreptococcus and sphingolipid bacteria in feces early after transplantation was related to the concentration requirement of immunosuppressive agents in hematopoietic stem cell transplantation recipients.

Keywords: hematopoietic stem cell transplantation; intestinal flora; immunosuppressive drug

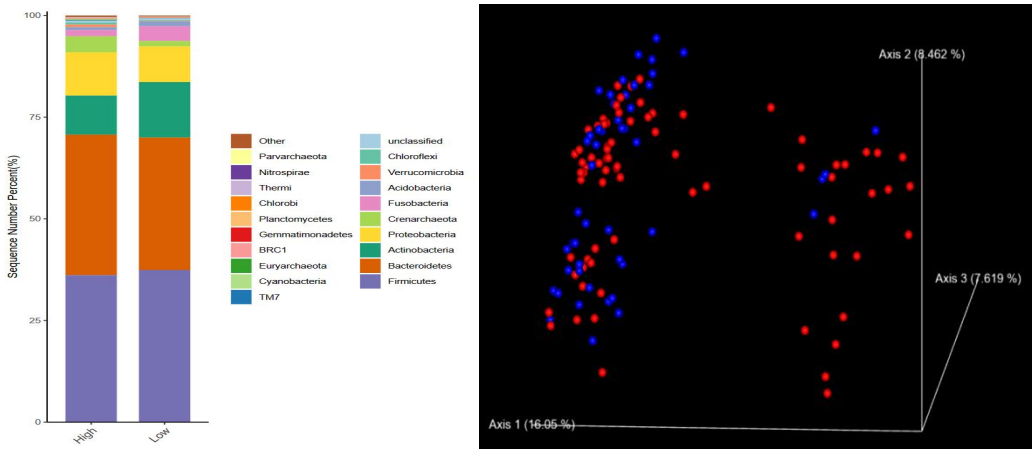

Figure. 1 (A) The abundance of the top 20 dominant flora in the high and low concentration groups. (B) 3D map of PCoA based on Unweighted Unifrac.

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Functional Au nanoparticles for drug delivery and Long-Term CT Imaging Tracking of MSCs in Pulmonary Fibrosis Treatment

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Abstract: Idiopathic pulmonary fibrosis (IPF) is a common chronic progressive interstitial lung disease with a high fatality rate. Mesenchymal stem cells (MSCs) therapy has been proven to be a potentially effective approach for IPF treatment. However, this strategy is currently limited by the poor survival and insufficient comprehending of the in vivo condition of the transplanted MSCs in IPF remedy. After transplantation, the mitochondrial membrane of MSCs is destroyed in the reactive oxygen species (ROS) environment of fibrotic lung, resulting in the leakage of membrane interstitial proteins (cytochrome C) into cytoplasm, which bind to apoptotic protease activator factor-1 and then trigger the formation of apoptotic complexes. This process further activates the downstream apoptosis executive protein Caspase 3, ultimately leading to apoptosis, which is known as the internal mechanism of apoptosis. In addition to the internal mechanism of apoptosis triggered by ROS, the tumor necrosis factor receptor on the cell surface, in combination with the corresponding ligand, stimulates the death receptor to form a death-inducing signaling complex, activates the apoptosis executive protein Caspase 3, and induces the occurrence of the external pathway of apoptosis. Moreover, the lack of suitable tracking tool for transplanted stem cells makes it hard to detect the distribution, migration, and survival of stem cells in vivo, limiting medical evaluation and timely intervention. To address these issues, herein, a novel multifunctional nanocarrier (AuPPT) is fabricated for survival increasing and real-time tracking of MSCs in MSC-based IPF therapy. First, AuNPs surface is functionalized with cationic polymer PEI for the loading of negatively charged retinoic acid (RA) and miRNA drugs. In order to reduce the cytotoxicity caused by PEI, the surface of AuNPs is further modified with PEG, followed by the modification of trans-activator of transcription (TAT) to increase the intracellular nucleic acid delivery efficiency. The drug-loaded AuPPT was co-incubated with the MSCs and then transplanted into the lungs of IPF mice. In the presence of RA, AuPPT down-regulated the ROS level in the lesion site. Meanwhile, the effective delivery of miRNA largely reduced the expression of intracellular Caspase 3, thus decreasing the apoptosis of transplanted MSCs, as a consequence, improving the effect of MSC therapy on IPF. Moreover, after cellular uptake of AuPPT, the labeled MSCs could be detected by CT technology, achieving continuous monitoring of the distribution and migration of MSCs. Overall, this work reports AuPPT that combine the drug delivery and imaging tracking of MSCs, which may provide a strategy for the stem cell-based treatment of IPF.

Keywords: idiopathic pulmonary fibrosis; mesenchymal stem cells; Au/mesoporous silica core/shell type Janus nanoparticles; reactive oxygen species; CT imaging

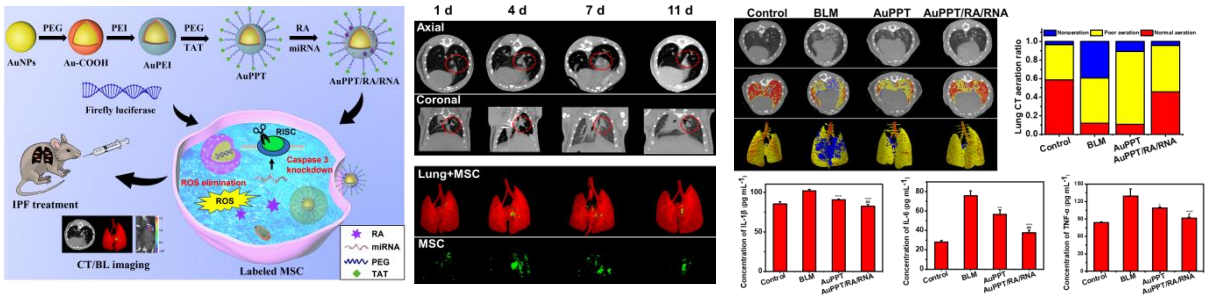

Figure. 1 Schematic diagram of the preparation of multifunctional AuPPT and CT imaging tracking of the transplanted MSCs combined with drug delivery for the improved therapy of BLM-caused IPF mouse.

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Occam’s Razor-inspired Nb2C delivery platform potentiates breast cancer therapy and inhibits lung metastasis

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Abstract: Breast cancer exhibits a high rate of lung metastasis and is one of the leading causes of cancer-related mortality in women. Hence, it is critical to develop innovative therapeutic strategies to combat breast cancer and lung metastasis. The physical and optical properties of niobium carbide (Nb_2C) nanosheets endow them with excellent photothermal conversion properties and the capacity for drug delivery, making them ideal for photothermal therapy (PTT) in breast cancer and its lung metastasis. To explore a new synergistic strategy for subcutaneous tumor ablation and lung metastasis inhibition in breast cancer, an Occam’s Razor-inspired nanocomposite (Nb_2C-BBR) was fabricated based on functionalized Nb2C nanosheets and berberine (BBR), a natural inhibitor that regulates metastasis-related proteins in the tumor microenvironment. The Nb_2C nanosheets were ultrathin (thickness of ~ 124 nm), could be endocytosed into subcellular organelles, showed desirable photothermalconversion efficiency (38 % and 59 % at 808 nm and 1064 nm, respectively), and achieved multi-modal imaging in the near-infrared (NIR-II) biowindow. With a size of 130.4 nm, the Nb_2C-BBR nanocomposites exhibited favorable biocompatibility and reduced the dose of Nb_2C nanosheets required under NIR-II irradiation while maintaining photothermal performance and anticancer efficacy. Combined chemotherapy and PTT with the Nb_2C-BBR nanocomposites not only eradicated cancer cells notably but also significantly suppressed cell proliferation by activating the mitochondrial apoptotic pathway. By regulating the expression of proteins associated with the epithelial-mesenchymal transition and extracellular matrix both in vitro and in vivo, Nb_2C-BBR nanocomposites significantly inhibited the migration and invasion of breast cancer cells following NIR-II irradiation. The functionalized nanoplatform for synergistic therapy efficiently destroyed cancer cells, inhibited metastasis, and induced only minor local tissue damage, demonstrating its potential as a treatment approach for metastatic
tumors.

Keywords: Breast cancer, lung metastasis, niobium carbide, NIR-II biowindow, synergistic therapy, epithelial-mesenchymal transition

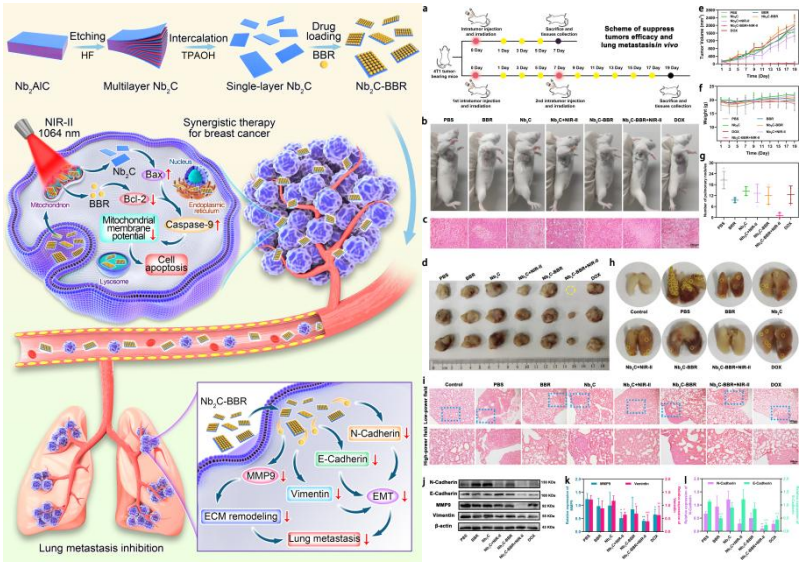

Figure. 1 Schematic diagram showing the Occam’s Razor-inspired Nb_2C delivery platform for synergistic therapy against breast cancer and lung metastasis (Left); and anti-tumor and anti-metastasis effects of Nb_2C-BBR nanocomposites under NIR-II laser irradiation (Right).

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Chemical messenger-based nanomodulators for cancer immunotherapy

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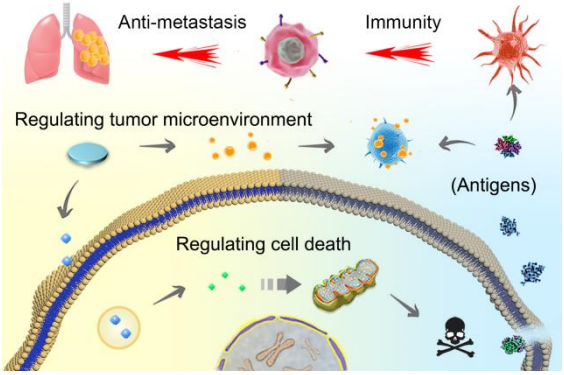
Abstract: The critical challenge for tumor therapy is metastasis and recurrence. Developing immunomodulatory drugs to build systematic antitumor immunity is highly sought for tumor treatment.[1] Chemical messengers have been one of the hot research topics in biomedicine and biochemistry due to their versatile of regulatory activity on multiple biological processes.[2] However, under tumor specific microenvironment, a majority of chemical messengers usually present limited activity in regulating immune responses. In our recent work, reprogramming tumor microenvironment has been demonstrated an efficient strategy to amplify the outcomes of therapeutic agents. Thus, we assume that the antitumor immunity with chemical messengers would be achieved *via* reprogramming tumor microenvironment. In this work, we propose nanomodulators based on chemical messengers, and explore its potential in regulating antitumor immunity. Upon exposure to tumor acidic microenvironment, the nanomodulators reshaped the tumor immunosuppresive microenvironment. With metal ions as the chemical messengers, the nanomodulators retard cellular metabolism of tumor cells, thereby releasing tumor-associated antigens *via* tumor immunogenic death. Meanwhile, the nanomodulators reversed tumor immunosuppressive microenvironment, allowing the intratumoral infiltration of immune cells to fabricate systemic immunity against tumor metastasis and relapse. All these features make chemical messenger-based nanomodulators possess obvious advantages over traditional immunotherapeutic agents. These findings raise the prospects of chemical messengers for tumor vaccination, which provides new opportunities for tumor treatment.

Key words: chemical messenger; cancer; immunotherapy; nanomodulator



Scheme 1. Chemical messenger-based nanomodulators for cancer immunotherapy

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Tumor Microenvironment-mediated Nanoplatform for Cancer Theranostics

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Abstract: Cancer therapy has become a worldwide problem and hot topic, and every year lots of people will suffer from various kinds of cancer. With the development of nanotechnology and novel functional nanomaterials, some new type of cancer therapy methods has been developed successfully, such as phototherapy, sonodynamic therapy. Tumor microenvironment (TME), which consists tumor cells, many other types of cells, cytokines, small molecules, and abnormal blood vessels, is considered a complex internal environment for the occurrence and development of tumors. In recent years, great progress has been made to regulate these various micro-environmental hallmarks such as hypoxia, acidic pH, high H_2O_2, and GSH levels, vascular malformations and so on. Utilizing the unique physical and chemical properties, various kinds of inorganic nanomaterials have been used for cancer therapy [1-6]. Herein, I will briefly introduce functional transition metal complex nanomaterials (for example, transition-metal dichalcogenides, transition metal carbides, transition metal oxides, and metal coordination nanocomplex) for cancer imaging and therapy. Then, I will talk about some methods to tune the TME and enhance cancer therapy. Last, I will give some information about the clearance behavior of inorganic biomaterials for cancer theranostics. Therefore, our work highlights the promise of functional inorganic nanomaterials for biomedical applications.

Keywords: Biomaterials, transition metal complex nanomaterials, tumor microenvironment, cancer therapy, toxicity

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Atomic-Level Modulation of Functional Metal Nanomaterials for Tumor-Specific Therapy

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Abstract: Functional metal nanomaterials featuring unique physical/chemical properties have been widely used as effective anticancer agents and/or drug delivery vehicles to treat cancer. However, how to accurately control the biological performances of metal nanomaterials in complex environments in vivo, that is, exerting anti-tumor activity exclusively in tumor tissues while keeping biocompatible in normal tissues, is a major challenge to the implementation of precision oncology. By fine-tuning the interaction between the metal center and the surrounding atomic configuration, the catalytic properties of metal nanomaterials could be tailored. In recent years, we mainly focus on atomic-level modulation of metal nanomaterials to confer them with structure-dictated catalytic capacities and stimulus-responsive performances for tumor-specific therapy. We hope it would pave the way for the fabrication of intelligent nanomaterials through correlation of therapeutic behaviors with the chemical structures to combat serious or life-threatening diseases.

Keywords: Functional metal nanomaterials; atomic-level modulation; stimulus-responsiveness; tumor-specific therapy; biocompatibility

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Surface biomimetic modification improves the therapeutic function of drug carrier in vivo

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Abstract: Drug delivery is a key link in the process of new drug research and development. The interactions between drug delivery systems (DDS) and biomolecules, cells and tissues are closely related to their fate in vivo and in vitro. How to accurately regulate the biological behavior of DDS is crucial to improve the therapeutic effect of drugs. The DDS can be modified by using the components of living organisms. We found that biomimetic modifications on the surface of drug delivery vectors, including cell membrane coating, yeast microcapsule and functional protein modification, can regulate the interaction between the vectors and cells, improve the distribution of the vectors in vivo tissues and organs, and improve the targeting of focal sites. In addition, extracellular vesicles (EVs) play an important role in the transmission of biological information and material between cells. We found that extracellular vesicles can mediate the delivery of drug carriers among cells. Along with the transmission of biological information, EVs can simultaneously promote the transfer of drugs between cells, realize the penetration of drugs into the deep part of tumors, and exert excellent anti-tumor effects.

Keywords: surface modification; biomimetic modifications, extracellular vesicles, drug delivery

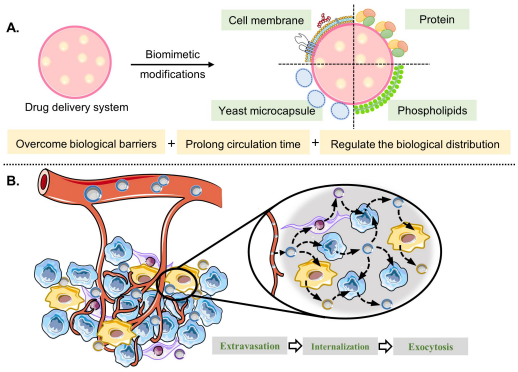

Figure. 1 (A)Schematic illustration of the effects of surface biomimetic modification to improves the therapeutic function of drug carrier; (B) Schematic illustration of intercellular and intracellular transportation of nanoparticles via EVs.

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Spatiotemporal management of functional alveolar bone regeneration by nano-bone powder delivering abaloparatide and calcium

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Abstract: Post-extraction alveolar bone atrophy greatly hampers the later orthodontic tooth movement (OTM) or implant placement. In this work, we have synthesized a bioactive “nano-bone powder” that served as bone filler with sequential delivery of abaloparatide (ABL) and calcium ion (Ca^{2+}), namely ABL@nanoflower. The nanoflower has presented desirable porous hierarchical structure, high drug encapsulation efficacy (92.4%) and good cell biocompatibility. ABL is coated within the porous surface of nanoflower, and released in the first stage to promote bone remodelling, then Ca^{2+} is sustainedly released later to further enhance mineralization. In vitro, recruitment and proliferation of bone marrow mesenchymal stem cells (BMSCs) have been improved by ABL, and sequential delivery of Ca^{2+} synergistically has promoted the osteoblastic differentiation of BMSCs. In vivo, micro-CT and histology analysis has revealed that ABL@nanoflower restored morphologically and functionally active alveolar bone without affecting OTM. In conclusion, the ABL@nanoflower as bone filler with sequential delivery of ABL and Ca^{2+} demonstrates favourable bone regeneration effects, which may have great clinical application potential.

Keywords: nanoflower, tooth extraction, orthodontic tooth movement, abaloparatide, alveolar bone regeneration

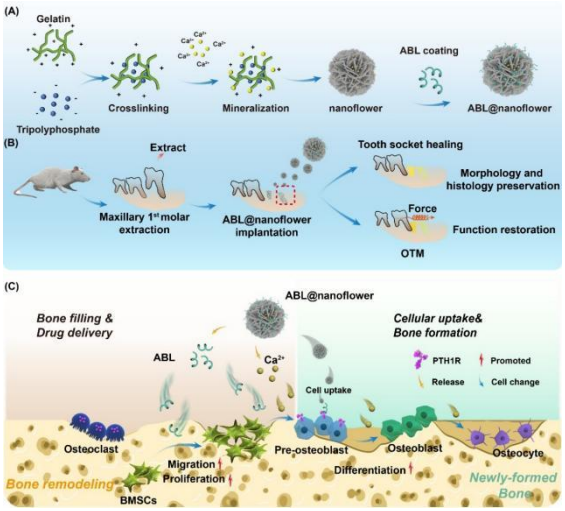

Figure. 1 Illustration of ABL@nanoflowers applied for tooth extraction site preservation and followed alveolar maintenance during orthodontic tooth movement.

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Engineering extracellular vesicles for nucleic acid delivery

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Abstract: Immunotherapy has revolutionized the treatment of tumor malignancies. However, single cancer immunotherapy frequently leads to treatment failure due to adaptive immune resistance. Herein, a synergistic cancer immunotherapy modality was established by synergizing P21-activated kinases 4 (PAK4) silencing with immunogenic phototherapy in engineered extracellular vesicles. PAK4 is known as a driver for the proliferation and progression of tumors. More recently, it is identified as a tumor-cell-intrinsic “guard” associated with immune exclusion. Therefore, PAK4 silencing can not only directly inhibit the survival of cancer, but also is able to boost intratumoral immune infiltration. To trigger potent antitumor immunity, siRNA against PAK4 (siPAK4) was complexed with the Ce6-conjugated, thioketal-linked polyethyleneimine (TPC) to obtain the photoactivatable nanocomplex (TPCS). Subsequently, TPCS was encapsulated by M1 macrophage-derived extracellular vesicles (EVs) to generate the engineered EVs (TPCS@EV). The results confirmed that TPCS@EV induced potent PAK4 silencing and robust immunogenic phototherapy, thus contributing to effective immune activation and intratumoral immune infiltration for enhanced antitumor effects. Moreover, the antitumor synergism of the combined treatment was quantitatively demonstrated by using the Compusyn approach. Together, this study presents a synergistically potentiated cancer immunotherapy modality of engineered EVs, which is promising for boosting antitumor efficacy.

Keywords: engineered extracellular vesicles; cancer immunotherapy; nucleic acid delivery

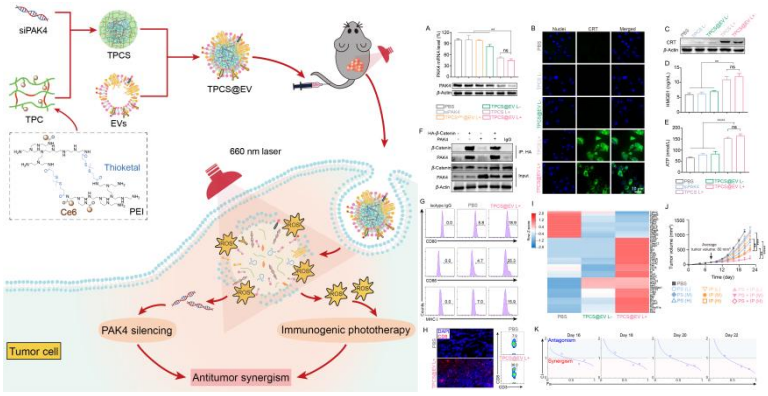

Figure. 1 Schematic illustration of the engineered extracellular vesicles to synergize PAK4 silencing and immunogenic phototherapy, which simultaneously boosts immune activation and intratumoral immune infiltration to synergistically enhance the antitumor effect.

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Rational design of heptamethine cyanines to promote the photostability for high performance antitumor phototherapy

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Abstract: Heptamethine cyanines have been discovered for anticancer phototherapy with advantages of deep tissue penetration by near-infrared light and tumor-targeted capability. However, they would be easily decomposed under laser irradiation. Common attempts to protect cyanine away from the light-driving reaction are performed on the meso site of the cyanine. Herein, for more flexible design, we modify the cyanine at two sites of meso position and indole ring, and study the influence of steric shielding, electronic deactivation and solubility on the phototherapy outcome. Based on a mitochondria-targeted cyanine of Cy7-TPP, we conjugated dodecyl side chain with the indole ring (Cy7-TPP-C_{12}) for steric protection strategy. For electronic deactivation strategy, we connect tetraphenylethylene (TPE) at the meso site of the two dyes above and obtain Cy7T-TPP and Cy7T-TPP-C_{12}. Among the four molecules, Cy7-TPP is less stable than other dyes. Cy7T-TPP and Cy7T-TPP-C_{12} showed higher photothermal response and improved photostability. The two molecules displayed OATP transporters-mediated cell uptake, however, they behaved differently in vivo. Cy7T-TPP showed preferential tumor accumulation and retention, while Cy7T-TPP-C_{12} was prone to accumulate in liver, which indicated that tumor targeting ability of cyanines requires balance between hydrophilicity and lipophilicity. Ultimately, Cy7T-TPP was optimized and intravenously injected to tumor-bearing mice, which showed long-term tumor retain for strengthened phototherapy, even on large tumors. In a word, this work explored design feasibility on two sites of cyanine to facilely optimize steric hindrance, electron deactivation and solubility for improving cyanine performance, and consequently we obtained Cy7T-TPP as promising candidate for anticancer phototherapy.

Keywords: phototherapy; cyanines; molecular design; photostability

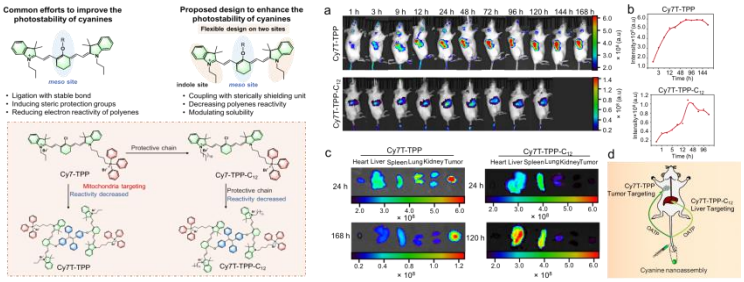

Figure. 1 Structural design of heptamethine cyanines for high performance anticancer phototherapy. A triphenylphosphine (TPP)-modified heptamethine cyanine, Cy7-TPP as the model cyanine in this work. (Left); and *in vivo* imaging of Cy7T-TPP and Cy7T-TPP-C_{12} in 4T1 breast tumor-bearing BALB/c mice. (Right).

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Study on biological/mechanical dual-immune checkpoint nano-blocker for melanoma immunotherapy

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Abstract: Melanoma is a serious threat to human health, immune checkpoint blockade (ICB) restores the ability of cytotoxic T lymphocytes (CTLs) to kill tumors by biologically blocking the receptor-ligand signaling pathway, and has been shown good therapeutic efficacy in melanoma treatment. However, clinical data show that only about 20% of patients are responsive to ICB therapy, so increasing patient response rates is the key to ICB therapy.It has been found that in addition to biological blockade, tumor cells can mechanically block T cell-mediated killing. after sensing the mechanical properties of target cell cortical structures, T cells exert forces at immune synapses, which in turn cause target cells to undergo lysis. However, cancer cells, especially melanoma cells, evade T cell-mediated cytotoxicity by enriching the cholesterol content of the plasma membrane to soften the cortical structures. Therefore, biological blockade of tumor cell immune checkpoints along with resistance to mechanical immune escape would be more beneficial for tumor immunotherapy. Based on this, a biological/mechanical dual immune checkpoint nanoblocker CaNP@T@Pra was designed to restore and improve the killing ability of T cells against tumor cells by biologically and mechanically blocking tumor immune checkpoints. It effectively solved the problem of low efficiency of killing cancer cells due to the weakened T cell function in melanoma immunotherapy, and provided a new strategy for melanoma immunotherapy.

Key words: Cancer Immunotherapy; Immune checkpoint blockers; Pravastatin sodium; Biomechanical pathways; Targeted

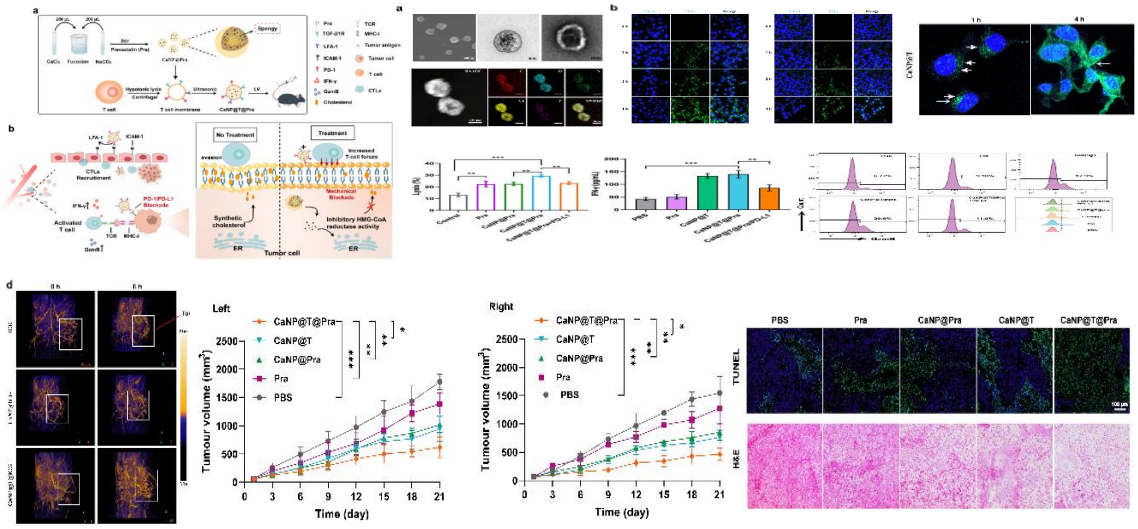

Figure. 1 Preparation process and in vivo mechanism diagram of biological/mechanical nano immune checkpoint double blocker ;and CaNP@T@Pra- mediated co-activation of innate and adaptive immunity.

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Engineered bacterial outer membrane vesicles encapsulating oncolytic adenoviruses enhance the efficacy of cancer virotherapy by augmenting tumor cell autophagy

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Abstract: Oncolytic adenovirus (Ad) infection promotes intracellular autophagy in tumors. This could kill cancer cells and contribute to Ads-mediated anticancer immunity. However, the low intratumoral content of intravenous-delivered Ads is far from to activate tumor over-autophagy. Herein, we report bacterial outer membrane vesicles (OMVs)-encapsulating Ads as microbial nanocomposites that are biomineral engineered for autophagy-cascade-augmented immunotherapy. Biomineral shells cover the surface antigens of OMVs to circumvent the clearance during in vivo circulation and enhance intratumoral enrichment. After entering tumor cells, there is excessive H_2O_2 accumulation through the catalytic effect of overexpressed pyranose oxidase (P_2O) from microbial nanocomposite. It increases oxidative stress levels and triggered tumor autophagy. The autophagy-induced autophagosomes further promote Ads replication in Ads-infected tumor cells, leading to Ads-overactivated autophagy. Moreover, OMVs are powerful immunostimulants for remolding the immunosuppressive tumor microenvironment, facilitating autophagic antitumor immune response. Therefore, the present autophagy-cascade-boosted immunotherapeutic method can expand OVs-based immunotherapy.

Keywords: oncolytic adenoviruses, autophagy, intravenous injection, microbial nanocomposite, autophagy-cascade-augmented immunotherapy

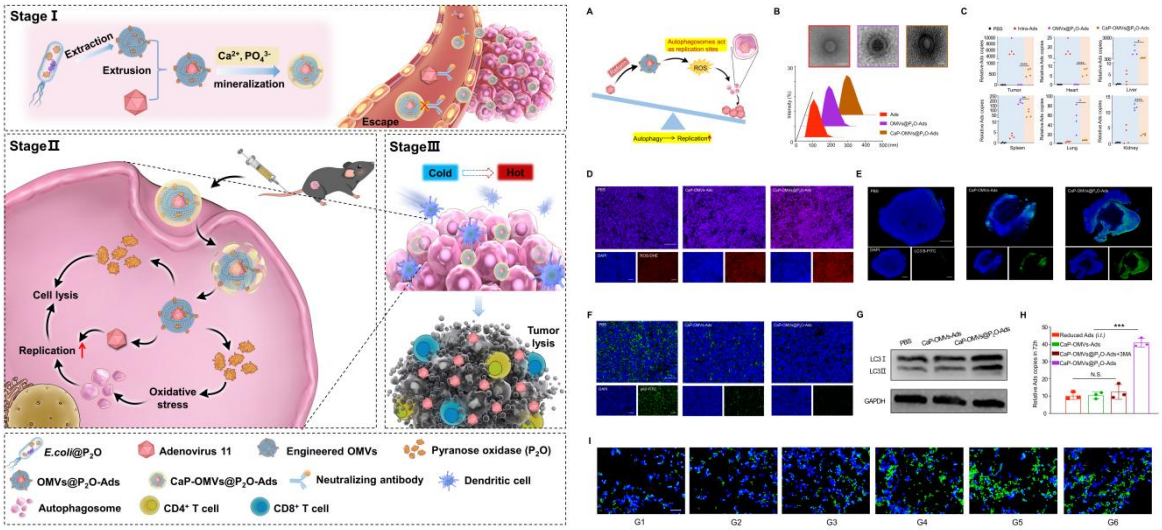

Figure. 1 Schematic diagram. The biomineralized microbial nanocomposite engineered from OVs for autophagy-cascade-augmented immunotherapy. (Left); and the biomineralized microbial nanocomposite increase the replication of Ads and enhance the response of antitumor immunity (Right).

Intratumoral pharmacokinetics: microenvironment-driven drug delivery systems

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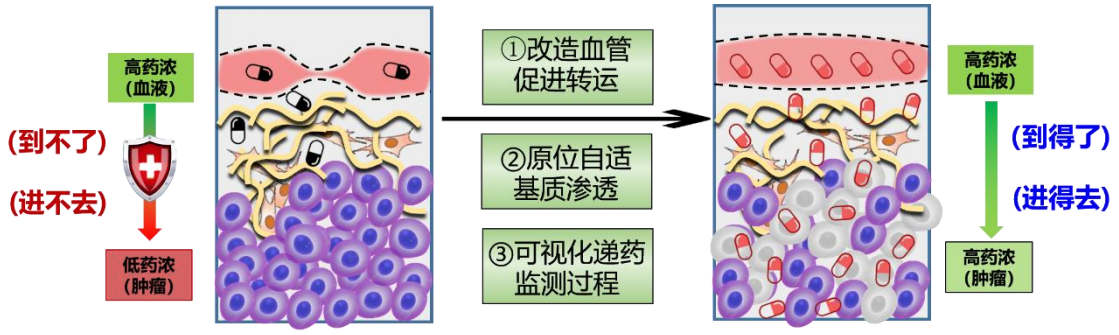
Abstract: Intratumoral step is the most crucial procedure in determining the efficacy. However, the current classic principle, such as enhanced penetration and retention (EPR) effect, mostly concentrated the prior-tumoral behavior. The post-tumoral procedures are still greatly short of systematic research. The bottlenecks restricting the drug penetrating and pharmaceutical optimization mainly include intratumoral transporting barrier from vessels, intratumoral permeating barrier from stroma, and the accurate evaluating technique for monitoring the barrier crossing. Aiming at the above three key scientific questions, we developed: actively remodeling the new vessels to improve the transporting, in-situ self-adapting to cross the stroma, visible drug delivery strategies, in order to realize the barrier crossing and deep penetrating, uncover the general rules among the neovascularization regulation, cascade adaption to matrix and the drug transporting efficacy. Theoretical reliance in realizing the rational intratumoral drug distribution have been provided. Based on the former research, we are also trying to develop drug delivery systems that can actively modulate the microenvironment. During the procedures of intratumoral responsiveness and drug-release, the active dialogue will be initiated for microenvironment remodeling, and the barrier effect will be reduced in a spatiotemporal way with an improved penetration. A multi-target, multi-level and multi-dimension therapeutic effect will be achieved, while the basic theory for penetrating drug delivery will be enriched.

Key words: drug delivery system; tumor barrier; enhanced permeability and retention effect; tumor angiogenesis; visible drug delivery



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Microneedle arrays for intradermal delivery of biologics: cases of nucleic acid vaccine and peptide drug

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Abstract: The epidermis of the skin contains abundant professional antigen-presenting cells and efficient draining lymphatic and capillary vessels underlying the epidermis, all of which can enhance the delivery of vaccines and drugs. Microneedle (MN) patches have been developed for transdermal and intradermal delivery of a variety of bio-macromolecules, but the clinical translation is limited by the limited antigen presentation for nucleic acid vaccines and low delivery dose for drug delivery [1].

In the first case, we report an ultra-low-cost microneedle electrode array for DNA vaccination. The low cost and small size are achieved by combining a piezoelectric pulser that emits microsecond, bipolar, oscillatory electric pulses and a MN array that targets delivery of high electric field to the skin’s epidermis. The microneedle electrode facilitated antigen presentation and induced strong antibody responses in mice which enabled at least 10-fold dose sparing compared to conventional intramuscular or intradermal injection of the DNA vaccine.

In the second case, we developed a dissolving liraglutide pure drug MN patch for the treatment of diabetes. This pure drug MN patch could load up to 2 mg of drug in a patch size of 1 cm^2, which was 10 to 100-fold of conventional MN patches of the same size. The pure drug MN had sufficient mechanical strength to penetrate the stratum corneum and epidermis and showed a delivery efficiency of up to 85% with dosing viability of less than 8%. The pure drug MN patch could deliver at least 1.0 mg liraglutide into porcine skin ex vivo, which is in the range of liraglutide dose in human clinical use. Pure drug MN achieved a bioavailability of 60.5% and 46.3% relative to subcutaneous (S.C.) injection in rats and minipigs, respectively, but showed a similar pattern of hypoglycemic effect as S.C. injection in diabetic rats. The pure drug MN was well tolerated, and no skin irritation except erythema within 4 hours was observed when administered once daily for 7 days at the same site. To the best of our knowledge, this is the first study for delivering peptide drug using pure drug MN patch and achieved pharmacokinetics suitable for clinical translation.

Keywords: Microneedles, piezoelectric pulser, nucleic acid vaccine, liraglutide, dissolving pure drug microneedle patch

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Study on the taste masking mechanism of novel polymer materials at the molecular level for multiple bitter components of traditional Chinese medicine

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Background: Taste masking of traditional Chinese medicines (TCMs) containing multicomponent bitter substances remains an important challenge. **Methods:** Berberine (BER) and phillyrin (PHI) were selected as model drugs. The bitter drugs were taste-masked using chitosan (CS). The taste masking mechanisms between CS and bitter model drugs was elucidated using multiple characterization techniques, including differential scanning calorimetry (DSC), X-ray diffraction (XRD), and Fourier transform infrared (FTIR) analyses, combined with molecular simulation software such as Materials Studio and Discovery Studio. The taste-masking effect was evaluated by both electronic tongue and gustatory sensation test. Also, the characteristics of *in vitro* release and *in vivo* pharmacokinetics were investigated. **Result:** Physicochemical characterization showed that the taste-masking compounds formed by CS with BER (BER/CS) and PHI (PHI/CS) were irregular in appearance (Figure 2). The drug binding efficiencies of BER/CS and PHI/CS were 50.15 ± 2.63% and 67.10 ± 2.52%, respectively. The results of DSC, XRD, and FTIR analyses and molecular simulation further indicated CS mainly masks the bitter taste by affecting the binding site of the bitter drugs and bitter receptors in the oral cavity through formation of hydrogen bonds between the hydroxyl or amine groups of CS and the nucleophilic groups of BER and PHI (Figure 1-5). The taste masking evaluation results by both electronic tongue and gustatory sensation test confirmed the excellent taste masking effects on alkaloids, flavonoid glycosides or the mixture of the two kinds bitter components (Figure 6 a-c). The *in vitro* release and *in vivo* pharmacokinetic results (Figure 6 d-e) suggested that the taste-masked compounds evaluated in this study could achieve rapid drug release in the gastric acid environment and did not influence the *in vivo* pharmacokinetics of the drug. **Conclusion:** The investigated technique may have potential for taste-masking of traditional Chinese medicinal compounds containing multi-bitter components.

Keywords: berberine, phillyrin, taste-masking, chitosan, hydrogen bond, molecular simulation

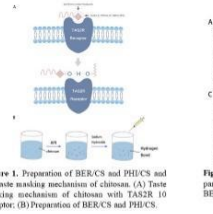

Figure 1. Preparation of BER/CS and PHI/CS and the taste masking mechanism of chitosan. (A) Taste masking mechanism of chitosan with TAS2R 10 receptor; (B) Preparation of BER/CS and PHI/CS.

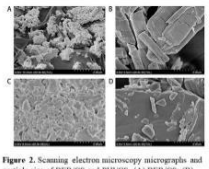

Figure 2. Scanning electron microscopy micrographs and particle size of BER/CS and PHI/CS. (A) BER/CS; (B) BER (C) PHI/CS (D) PHI

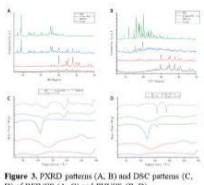

Figure 3. PXRD patterns (A, B) and DSC patterns (C, D) of BER/CS (A, C) and PHI/CS (B, D).

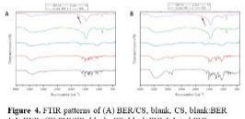

Figure 4. FTIR patterns of (A) BER/CS, blank, CS, blank:BER 1:1, BER; (B) PHI/CS, blank, CS, blank:PHI 1:1 and PHI.

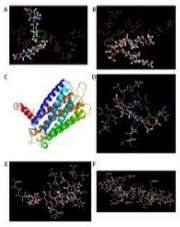

Figure 5. Materials Studio patterns with chitosan of (A) BER; (B) PHI; (C) The predicted model of TAS2R10; Discovery Studio patterns with TAS2R of (D) BER; (E) PHI; (F) CS.

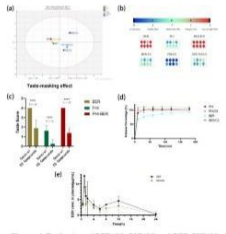

Figure 6. Evaluation of BER/CS, PHI/CS and BER-PHI/CS. (A) Electronic tongue test of BER, PHI, BER-PHI, BER/CS, PHI/CS, and BER-PHI/CS; (B)-(C) Volunteer sensory test of BER, PHI, BER-PHI, and CS compounds (BER/CS, PHI/CS, and BER-PHI/CS); (D) Dissolution profiles of BER, BER/CS, PHI and PHI/CS; (E) BER and BER/CS blood concentration–time curve.

Fabrication of multi-functional hydrogels and study of their application in biomedical field

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Abstract： Hydrogels have gained increasing attention in the biomedical fields owing to their unique three-dimensional network structure. In our team, a series of hydrogels with different mechanical strengths have been developed, including nanogels, injectable physical/chemical hydrogels, and ultra-stretchable hydrogels. Also, their applications in vivo animal models were evaluated. The results showed that the prepared hydrogel has multiple functions including, effectively preventing postoperative tissue adhesion; significantly preventing the recurrence and lung metastasis; improving the CNV in eye treatment and significantly improving fibrosis in the lungs. To expand the application field, a stretchable hydrogel with excellent frost resistance and conductivity was developed. the hydrogel adhesion hydrogel has a good gastrointestinal repair effect function under wet conditions. In summary, a series of hydrogels were developed and investigated in detail by our team, which showed that hydrogel is an ideal material for solving practical clinical problems in the field of biomedicine.

Keywords： hydrogel; biomaterials; biomedical; injectable; stretchable

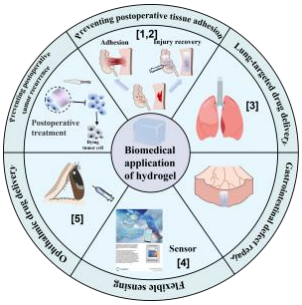

Figure. 1 Schematic illustrating the applications of hydrogel in preventing postoperative tissue adhesion[1, 2], lung protection[3], gastrointestinal defect repairment, flexible sensing[4], eye treatment[5], and preventing tumor recurrence post-operation.

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Engineered tumor cell-derived microparticles for enhanced anti-tumor efficacy

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Abstract: Tumor cell-derived microparticles (MPs) can function as anticancer drug delivery carriers. However, short blood circulation time, large size-induced insufficient tumor accumulation and penetration into tumor parenchyma as well as limited cellular internalization by tumor cells and cancer stem cells (CSCs), and difficult intracellular drug release restrict the anticancer activity of tumor cell-derived MP-based drug delivery systems. Here, hydrophobicity-adaptive polymers based on poly(*N*-isopropylacrilamide) are anchored to tumor cell-derived MPs for enhanced delivery of anticancer drug doxorubicin (DOX). The polymers are hydrophilic in blood to prolong the circulation time of DOX-loaded MPs (DOX@MPs), while rapidly switch to hydrophobic at the tumor acidic microenvironment. The hydrophobicity of polymers drives the fission of tumor cell-derived MPs to form small vesicles, facilitating tumor accumulation, deep tumor penetration and efficient internalization of DOX@MPs into tumor cells and CSCs. Subsequently, the hydrophobicity of polymers in acidic lysosomes further promotes DOX release to nuclei for strong cytotoxicity against tumor cells and CSCs. Our work provides a facile and simple strategy for improved anticancer drug delivery of tumor cell-derived MPs.

Keywords: Tumor cell-derived microparticles; cancer stem cells; hydrophobicity-adaptive; Tumor deep penetration

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Engineered NanoAlum for efficient cancer metalloimmunotherapy

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Abstract: Magnesium aluminum layered double hdyroxides (LDH) is a two-dimensional material composed of divalent magnesium ion/trivalent aluminum ion hydroxide layers, and anions/water located between the layers.[1] As an antigastric drug (Talcid, Bayer), LDH has been widely used clinically. Recently, our group found that LDH can also be obtained by hydrothermal treatment of commercial aluminum adjuvant (Imject Alum, Thermofisher). As a new type of nano-aluminum adjuvant (NanoAlum), LDH can effectively help antigens induce strong cytotoxic T lymphocyte (CTL) response.[2] Meanwhile, optimization of the physicochemical properties of LDH enables it to efficiently deliver antigens to lymphoid organs, thereby rapidly inducing strong and durable anti-tumor immune response against advanced solid tumors.[3-5] Furthermore, the intrinsic antacid properties of LDH and its variability in metal ions enable it to directly remodel the suppressive tumor immune microenvironment (TIME). Our recent research found that peritumoral injection of LDH can neutralize the acidic TIME while supplementing Mg^{2+}, which greatly promotes the recruitment and activation of peripheral CTLs into the tumor to inhibit the growth of solid tumors.[6] Upon LDH is taken up by tumor cells, it can neutralize intracellular acidic lysosomes to block the tumor autophagy pathway, thereby inducing tumor apoptosis.[7] Interestingly, partial replacement of Mg^{2+} in LDH by nutritional metal ions (M) such as Zn^{2+} results in nutritional NanoAlum (NanoMAlum) Zn-LDH, which can not only activate anti-tumor immune cells in TIME, but also induce tumor immunogenic death by activating the tumor cGas-STING signaling pathway and down-regulating the expression of tumor immune checkpoints.[8] These results show that the acid-resistant LDH NanoAlum obtained from the clinical aluminum adjuvant owns the most simple components but highly integrated functions. It is expected to significantly enhance tumor immunotherapy by efficiently delivering antigens to lymphoid organs and systematically remodeling the immunosuppressive TIME.

Keywords: NanoAlum; vaccine delivery; tumor microenvironment; metalloimmunotherapy

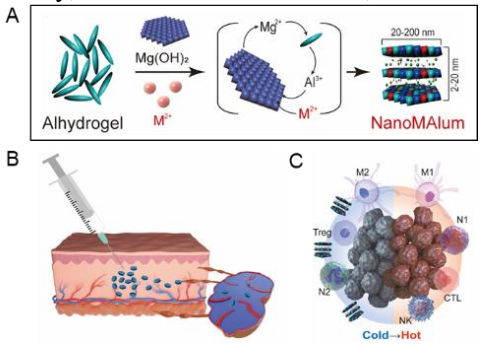

Figure. Synthesis and application of NanoMAlum in cancer immunotherapy.

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Adhesive membrane protein-mediated countermeasure therapy

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Abstract: Cells employ diverse adhesive membrane proteins to sense the tissue surface to accurately decide on where to land. During this process, the surface expression of adhesive proteins is dynamically manipulated to counter the complex *in vivo* environment. Using cell membrane coating technology, the adhesive proteins are concomitantly transplanted to the drug carrier's biointerface. The adhesive protein-decorated drug carrier mimics the adhesive behavior of the mother cells, and therefore can achieve targeted drug delivery. Good examples of its biomedical applications include: 1) Use diverse, low avidity bacterial outer membrane protein-decorated drug carriers to achieve specific targeting to gastric epithelial cells, blocking 85% of bacteria adherence without using antibiotics. 2) transplant neutrophil's diverse, high avidity adhesive proteins onto drug carriers, leading to the firm attachment to the inflamed endothelium and cartilage. The carrier itself can broadly neutralize pro-inflammatory cytokines and thus blocks joint damage in rheumatoid arthritis. 3) using negatively charged red blood cell membrane to formulate a crosslinked colloidal gel that fully retains the nanoparticles at the site of injection for 3 days. The retention allows the gel to locally neutralize a large amount of bacterial pore-forming toxins which minimizes the lesion size caused by bacterial skin infection.

Keywords: Cell membrane coating; adhesive membrane protein; drug delivery; biomaterials; countermeasure therapeutics.

Net-neutral Nanoparticles-Extruded Microcapsules for Oral Delivery of Insulin

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Abstract: Oral delivery of insulin could widely improve the quality of life of diabetic patients but still requires further exploration. Commonly utilized oral delivery vehicles hardly penetrate the intestinal mucus barrier, thus greatly hurdling their therapeutic efficacy. State-of-the-art technology shows that coating particles with neutral surface charge could reduce adsorption of mucins and improved the transport of particles within mucus. However, the synthesis of net-neutral particles (NNs) usually need complex purification and processing procedure. Herein the NNs were conveniently constructed by simply adjusting the ratio of positive (chitosan) and negative (γ-glutamic acid) materials. To further achieve the optimal bioavailability of NNs, NNs formed materials were package in to wild chrysanthemum pollens (WCPs), obtaining pH-triggered nanoparticles-extruding microcapsules (PNMs@insulin). At the small intestine pH value (~6.0), the amino groups of CS deprotonate gradually and trigger the swelling, followed by the rapid extrusion of NNs through nano-orifices on the pollens' surface. After oral administration of the microcapsules, plasma insulin levels were enhanced significantly with a high oral bioavailability of >40%, leading to a remarkable and longer-sustained blood glucose-reducing effect. Moreover, we discovered that the empty pollen shells could act as a potential saccharide-adsorbing agent, which helps to manage sugar intake. This oral strategy of insulin will provide a vast potential for daily and facile diabetes treatment.

Key words: insulin, net-neutral nanoparticles, saccharide-absorbing

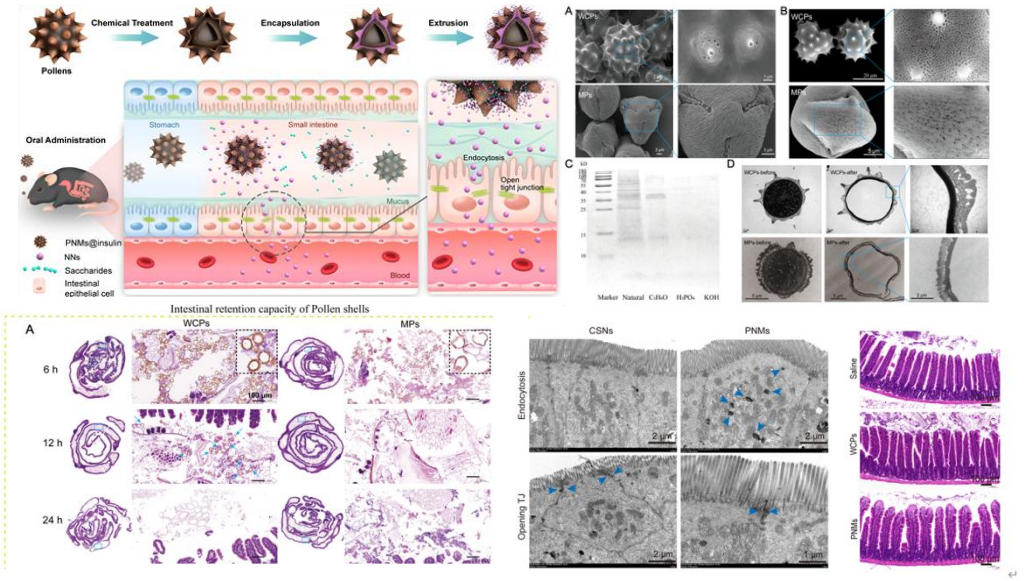

Figure. 1 Schematic illustration of pH-triggered NNs-extruding microcapsules (PNMs) for oral insulin delivery; and Representative TEM image of epithelial tissues after oral administration.

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Engineered macrophages as near-infrared light activated drug vectors for chemo-photodynamic therapy of primary and bone metastatic breast cancer

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Abstract: Patients with primary and bone metastatic breast cancer have significantly reduced survival and life quality. Due to the poor drug delivery efficiency of anti-metastasis therapy and the limited response rate of immunotherapy for breast cancer, effective treatment remains a formidable challenge. In this work, engineered macrophages (Oxa(IV)@ZnPc@M) carrying nanomedicine containing oxaliplatin prodrug and photosensitizer are designed as nearinfrared (NIR) light-activated drug vectors, aiming to achieve enhanced chemo/photo/ immunotherapy of primary and bone metastatic tumors. Oxa(IV)@ZnPc@M exhibits an antitumor M1 phenotype polarization and can efficiently home to primary and bone metastatic tumors. Additionally, therapeutics inside Oxa(IV)@ZnPc@M undergo NIR triggered release, which can kill primary tumors via combined chemo-photodynamic therapy and induce immunogenic cell death simultaneously. Oxa(IV)@ZnPc@M combined with anti-PD-L1 can eliminate primary and bone metastatic tumors, activate tumor-specific antitumor immune response, and improve overall survival with limited systemic toxicity. Therefore, this all-inone macrophage provides a treatment platform for effective therapy of primary and bone metastatic tumors.

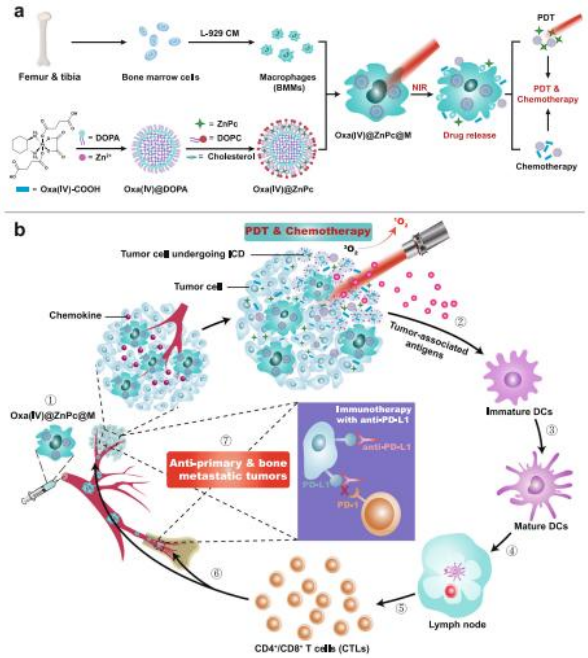

Fig. 1 The preparation and mechanism of the artificially engineered macrophages.

The Application and Mechanism of Cellular Communication in Engineering Cell-Based Drug Delivery Systems

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Abstract: Cell-based biomimetic delivery systems inherited specific protein, lipid and RNA contents from donner cells, have the natural properties of high biocompatibility. Based on its complex structural components, cell-based biomimetic delivery systems which can exchange information with the surrounding environment, deliver drug at a different manner. However, the detailed cellular mechanisms underlying cell-based drug delivery have not been explicitly reported. Understanding the drug release mechanism is of great significance to improve the therapeutic efficiency of biomimetic drug delivery systems and develop more intelligent drug carriers. In this paper, six engineering cell-based drug delivery systems are designed from three perspectives of tunneling nanotubes, gap junctions, and extracellular vesicles are investigated.

Tunneling nanotube-dependent transport. (1) Lipopolysaccharide-anchored macrophages hijack tumor microtube networks for selective drug transport. (2) Mesenchymal stem cells transfer mitochondria via tunneling nanotubes to reprogram macrophage metabolism.

Gap junction-dependent transport. (1) Mesenchymal stem cells revitalize endothelial cells through gap junction-medicated mitochondrial replacement. (2) “Cytokine-microfactories” recruit DCs and deliver tumor antigens via gap junctions for immunotherapy.

Extracellular vesicle-dependent transport. (1) Proinflammatory macrophage-derived microvesicles promote drug delivery via SNARE-mediated membrane fusion. (2) Mesenchymal stem cells-derived microvesicles delivery eNOS agonists to enhance endogenous nitric oxide generation

Keywords: Biomimetic drug delivery systems, Tunneling nanotubes, Gap junctions, Extracellular vesicles, Macrophages, Mesenchymal stem cells

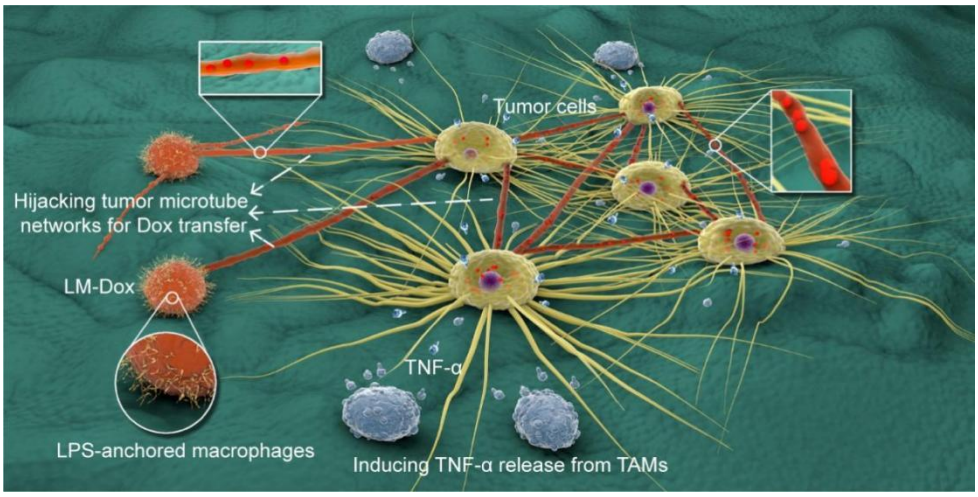

Figure. 1 The mechanism for lipopolysaccharide-anchored macrophage-mediated antitumor ability: transport of Dox between tunneling nanotube-connected cells

D-lactate modulates M2 tumor-associated macrophages and remodels immunosuppressive tumor microenvironment for hepatocellular carcinoma

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Abstract: Current immunotherapy has limited efficacy in hepatocellular carcinoma (HCC) due to the immunosuppressive tumor microenvironment (TME). Increasing evidence confirms the role of M2 tumor-associated macrophages (TAMs) as a key regulator of immunosuppressive TME for contributing tumor progression. The polarization of TAMs from M2 to M1 demonstrates great potential for remodeling the immunosuppressive TME. D-lactate (DL) is a gut microbiome metabolite, and acts as an endogenous immunomodulatory agent that enhances Kupffer cells for clearance of pathogens. In this study, the potential of DL for transformation of M2 TAMs to M1 was confirmed for the first time, and the mechanisms underlying such polarization were mainly due to the inhibition of phosphatidylinositol-3-kinase (PI3K)/protein kinase B (Akt) pathway and the activation of nuclear factor kappa B (NF-κB) pathway. To deliver DL to M2 TAMs in HCC, a poly(lactic-co-glycolic acid) (PLGA) nanoparticle (NP) was used to load DL, and the DL-loaded NP was modified with HCC membrane and M2 macrophage-binding peptide (M2pep), forming a targeted biomimetic nanoformulation (DL@NP-M-M2pep). DL@NP-M-M2pep could accumulate in the tumor *via* HCC membrane-associated homing function and deliver DL to M2 TAMs *via* M2pep-mediated targeting capacity, which transformed M2 TAMs to M1 and remodeled the immunosuppressive TME. The combination of anti-CD47 antibody (CD47 is an anti-phagocytic molecule) with DL@NP-M-M2pep achieved long-term animal survival. These findings reveal a potential TAM-modulatory function of DL and provide a combinatorial strategy for HCC immunotherapy.

Keywords: gut microbiome metabolite; macrophage repolarization; nanoparticle; drug delivery; combination therapy

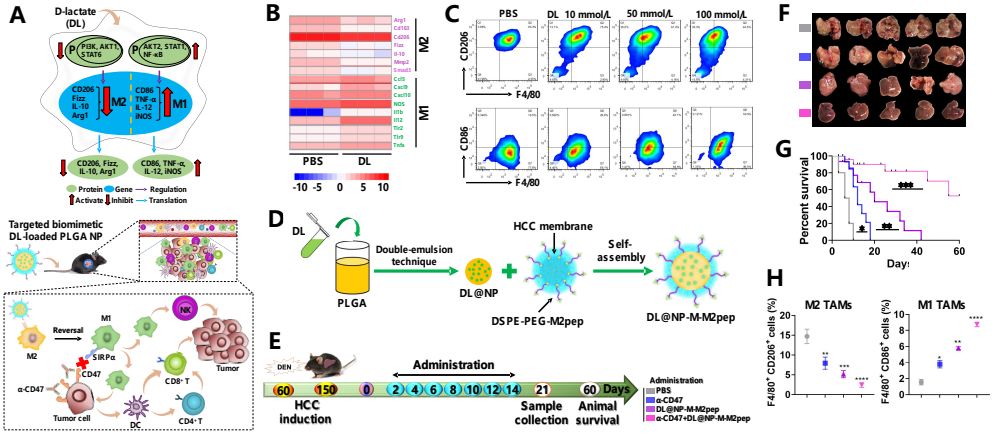

Figure. 1 DL@NP-M-M2pep polarizes TAM from M2 to M1 for HCC immunotherapy. (A) The proposed mechanism of TAM modulation achieved by DL@NP-M-M2pep. (B and C) The efficacy of DL on macrophage transformation. (D) The preparation of DL@NP-M-M2pep. (E to H) The anti-HCC efficacy based on M2-to-M1 modulation achieved by DL@NP-M-M2pep.

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NIR-II Photo-Amplified Sonodynamic Therapy Using Sodium Molybdenum Bronze Nanoplatform Against Subcutaneous *Staphylococcus Aureus* Infection

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Abstract: Ultrasound (US)-mediated sonodynamic therapy (SDT) has the advantages of non-invasiveness and deep tissue penetration. Nanosystems are prominently used in sonosensitization; however, most nano-sonosensitizers have a low reactive oxygen species (ROS) yield, thus restraining the application of SDT. We developed sodium molybdenum bronze nanoparticles (SMB NPs) with rich oxygen vacancies and expanded interlayer gaps of molybdenum trioxide nanobelts. Owing to the increased oxygen vacancy density and wide interlayer gap-induced narrower band gap of SMB NPs, the electrons (e-) and holes (h+) generated by US are separated more rapidly, and oxygen vacancies prevent electrons-holes recombination under US irradiation. SMB NPs exhibit a second near-infrared (NIR-II) photothermal effect to promote the generation of ROS by the sonosensitizer. The SMB NPs system was successfully realized to eliminate *Staphylococcus aureus* (*S. aureus*) and dissipate biofilm. Therefore, multimodal therapy using SMB NPs serves as an effective and promising regimen for deep-seated bacterial infections. The newly developed Mo-based sonosensitizer is presented for the first time to demonstrate excellent antimicrobial activity through hyperthermia-promoting SDT therapeutics. This work proposes a novel strategy in the field of NIR-II photo-amplified SDT with Mo-based materials for bacterial eradication and other important biomedical applications.
Keywords: sodium molybdenum bronze, oxygen vacancy, sonodynamic, photothermal, anti-infection

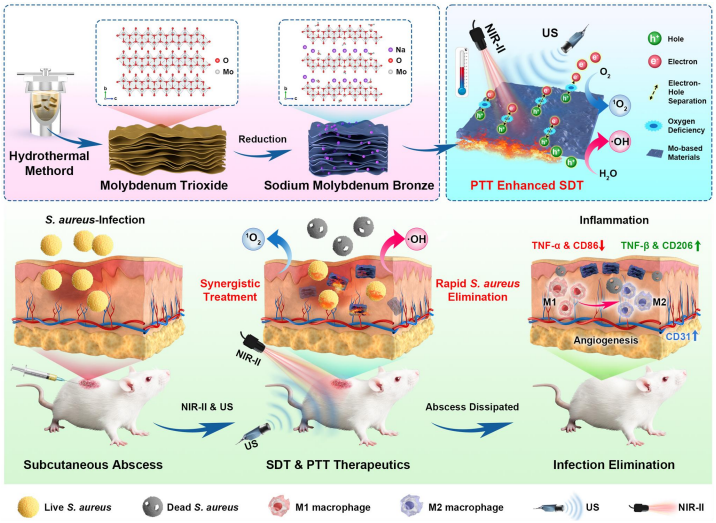

Figure. 1 Schematic illustration of the main synthesis procedure of oxygen vacancy and wide interlayer gap sodium molybdenum bronze nanoplatform, and NIR-II-mediated ROS generation for enhancing the SDT efficacy against subcutaneous *S. aureus* infection.

Reference:

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[2] **X. J. He**, J. T. Hou, X. S. Sun, P. Jangili, J. An, Y. N. Qian, J. S. Kim, J. L. Shen*, Advanced Functional Materials[J], 2022, 2203964.

Multi-drug Loaded Yolk-Shell Liposome for Synergistically Enhanced Tumor Chemo-immunotherapy

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Abstract: Tumor immunotherapy (e.g., immune checkpoint blockade (ICB)) is an innovative strategy that can specifically activate the body's immune system to achieve a highly effective antitumor effect. However, only a small portion of patients have a significant response rate to PD-L1-based ICB, which is due to that antibodies and small molecule inhibitors hardly struggle to penetrate inside tumors influenced by the dense tumor microenvironment. Herein, in order to overcome multiple tumor barriers and achieve multi-loading of drugs with different properties and targets, we designed a charge reversal yolk-shell liposome co-loaded with doxorubicin (DOX) and the bromodomain and extra-terminal domain (BET) inhibitor (JQ1) to enhance tumor chemotherapy by blocking the PD-L1 pathway from the transcriptional level and reducing immune resistance. The developed yolk-shell liposomes successfully encapsulated JQ1 into PLGA yolk by physical loading and greatly improved the encapsulation rate and drug loading of JQ1, and then PLGA yolk and DOX were co-loaded into the lumon of the liposomes. The release of JQ1 was less under physiological conditions (pH 7.4) and more in acid microenvironment. After yolk-shell liposome accumulated in the tumor through the enhanced permeability and retention (EPR) effect, a rapid reversal for zeta potentials responding to the acidic tumor microenvironment was utilized to enhance cellular internalization. After taken up by tumor cells, charge reversal yolk-shell liposome could induce immunogenic cell death (ICD), potent cytotoxicity and intrinsic cell apoptosis. In addition, DOX-induced ICD could initiate damage-associated molecular patterns (DMAPs) and promote tumor cytotoxic T lymphocytes (CTLs) infiltration into tumors. Combined JQ1 blockade of the PD-L1 pathway further enhanced the antitumor immune response by alleviating the immunosuppressive tumor microenvironment. We believe that this charge-reversing yolk-shell liposome is expected to achieve enhancement of hydrophobic drug loading and stability and efficient chemo-immunotherapy by inducing ICD and reversing PD-L1-mediated immunosuppressive pathways.

Keywords: yolk-shell liposome, immune checkpoint blockade, immunogenic cell death, PD-L1, chemo-immunotherapy

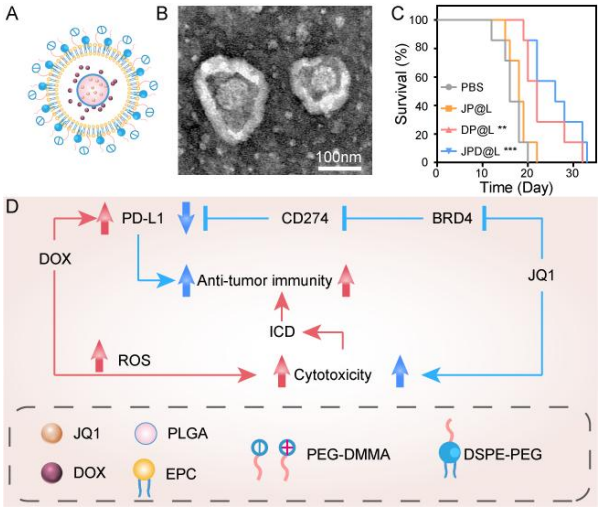

Figure 1. (A) Structure of yolk-shell liposome. (B) The TEM images of JPD@L. Scale bar: 100 nm. (C) The survival curves of mice bearing B16-F10 tumor after intravenous injection of different formulations. ** $P<$ 0.01, *** $P<$ 0.005, compared with other groups. (D) Schematic illustration of charge reversal yolk-shell liposome co-loaded with DOX and JQ1 for enhancing chemo-immunotherapy through blockade PD-L1 pathway.

Active modulation of cellular and humoral immunity through a multistage targeted antiviral nanovaccine

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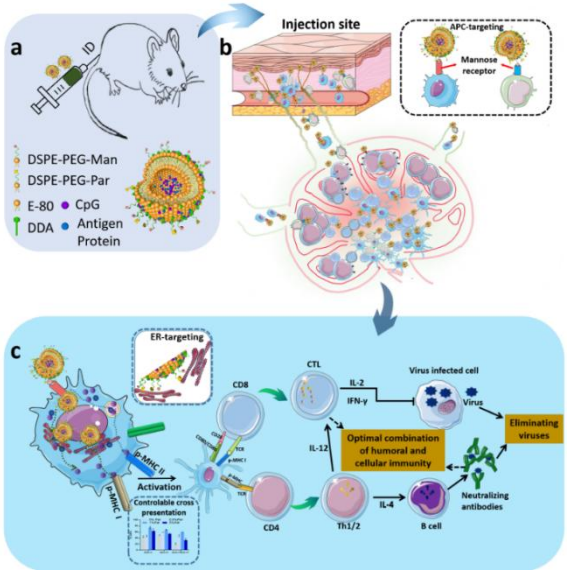
Abstract: Viruses such as COVID-19 are highly infectious, pathogenic, and lethal, posing a serious global health risk. Despite the tremendous development of antiviral vaccines, most current research focuses mainly on investigating the mechanism of action and effect of antiviral humoral immunity, with preliminary investigation and mobilization of cellular immunity, which has greatly limited the antiviral effect of vaccines. A multistage targeted antiviral nanovaccine that can actively regulate cellular and humoral immunity was prepared in this study, which could be a new direction for the design and optimization of more efficient forms of delivery of antiviral vaccines. BriflieA liposome (LIPO) vaccine to deliver the SARS-CoV-2 spike RBD protein (S) for possible prevention of COVID-19 has been constructed. CpG DNA, a Toll-like receptor 9 (TLR9) agonist, is an adjuvant to assist the rational distribution of humoral and cellular immunity. After endowing the LIPO with lymph nodes (LNs) targeting and precisely orientating it to DC's endoplasmic reticulum (ER), the vaccine can actively modulate the presentation pathway of exogenous antigen and alter the priming of CD8+ and CD4+ T cells. With highly efficient lymphatic transport and precise ER-targeting, the LIPO vaccine has mediated potent both humoral and cellular immune responses in vivo. Furthermore, it has been proven that the LIPO vaccines could elicit protective immune responses by establishing strong, long-lived germinal center reactions. This project provides a reference for designing and optimizing antiviral vaccines with high efficiency and outstanding safety. It is highly accessible and can be used to design vaccines for other viruses.

Keywords: Virus, subunit vaccine, humoral and cellular immunity, cross-presentation, ER targeting



Scheme : Construction of the LIPO vaccine and its immune response mechanism in vivo. (a) Preparation and administration of S+CpG@PM-LIPO; (b) Schematic diagram of S+CpG@PM-LIPO internally transport to LNs; (c) Specific antigen release of S+CpG@PM-LIPO on ER of DCs mediating precise cross-presentation for optimal combination of humoral and cellular immunity.

GSH Depletion-Induced Activation of Dimersomes for Potentiating the Ferroptosis and Immunotherapy of “Cold” Tumor

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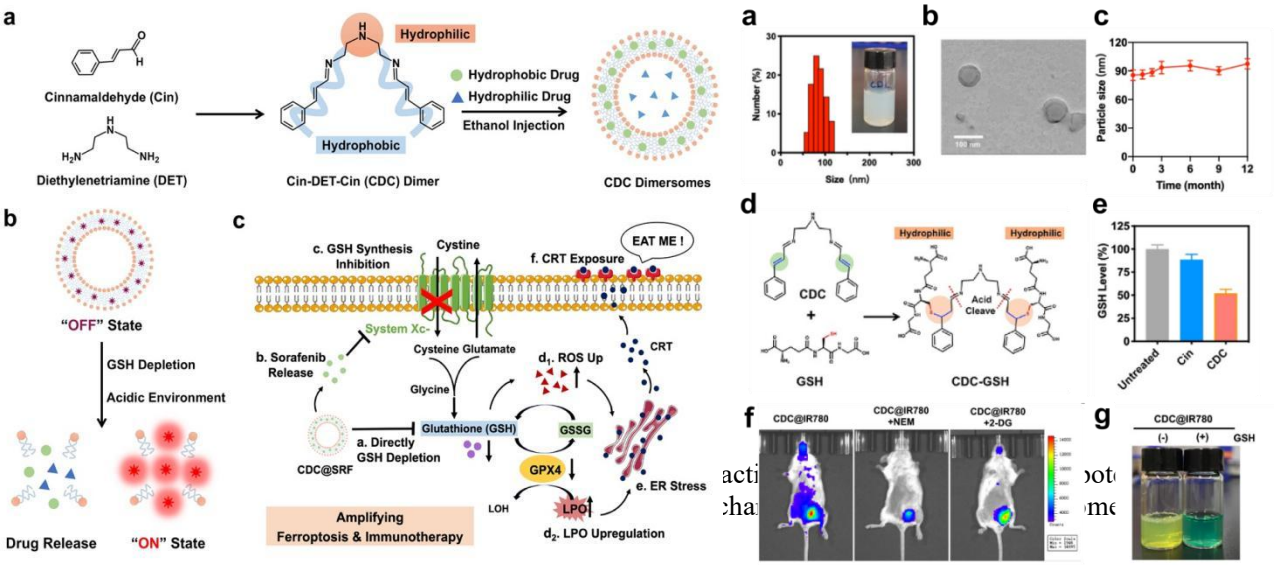
Abstract: The abundant glutathione (GSH) in “cold” tumors weakens the ferroptosis therapy and the immune response. Herein, inspired by lipids, we fabricated cinnamaldehyde dimers (CDC) into lipid-like materials to form dimersomes capable of depleting GSH and delivering therapeutics to potentiate the ferroptosis and immunotherapy of breast cancer. The dimersomes exhibited superior storage stability for over one year. After reaching the tumor, they quickly underwent breakage in the cytosol owing to the conjugation of hydrophilic GSH on CDC by Michael addition, which not only triggered the drug release and fluorescence switch “ON”, but also led to the depletion of intracellular GSH. Specifically, it significantly enhanced the ferroptosis after combination with sorafenib (SRF) and elicited a robust immune response in vivo by promoting the maturation of dendritic cells and the priming of $CD8^+$ T cells. As a result, the CDC@SRF dimersomes cured breast cancer in all the mice after four doses of administration.

Keywords: vesicles; drug delivery; GSH depletion; ferroptosis; cancer immunotherapy



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Dual isolated single-atom nanozymes efficiently regulate the ocular surface microenvironment and inhibiting inflammation in dry eye disease

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Abstract: Dry eye disease (DED) is a common chronic ocular surface disease driven by impaired eye lubrication and inflammation. DED can cause severe itching, dryness and visual impairment, impaired vision and reduced quality of life, affecting up to 5-50% of the population. The current treatment is mainly palliative care, relying heavily on lubricating eye drops and anti-inflammatory drugs, which may need to be used for long periods of time. The main pathological features of DED are loss of tear film homeostasis, tear hyperosmosis and ocular surface inflammation, which can further induce reactive oxygen species (ROS) production in ocular surface tissues, resulting in redox imbalance of ocular tissues. ROS can activate the NLRP3 inflammasome and produce a cascade reaction to promote the secretion of IL-1 β , resulting in ocular surface inflammation and forming a " inflammatory vicious cycle " in DED. In this study, we prepared FeMn dual isolated single-atom nanozymes (FeMn-DAzymes) in which Fe and Mn atoms were monodispersed on the surface of N-doped carbon materials with pointed dodecahedron structure. Through the synergistic effect between bimetallic Fe and Mn, FeMn-DAzymes can efficiently remove excessive ROS in the ocular surface microenvironment (OSME) with high oxidative stress, effectively regulate the OSME, reduce ROS level, and further block the oxidative damage. *In vitro* experiments, FeMn-DAzymes effectively reduced the ROS level of human corneal epithelial cells (HCEC) under hypertonic stimulation. NLRP3 inflammatory body activation is blocked and IL-1 β inflammatory factor is activated to protect HCEC from oxidative stress damage, and the "inflammatory vicious cycle" is cut off from the root to achieve the effect of DED treatment. *In vivo* experiments observed that FeMn-DAzymes effectively repaired corneal defects. FeMn-DAzymes provide a new strategy and method for the treatment of DED.

Keywords: Dual isolated single-atom nanozymes, dry eye disease, reactive oxygen species, NLRP3.

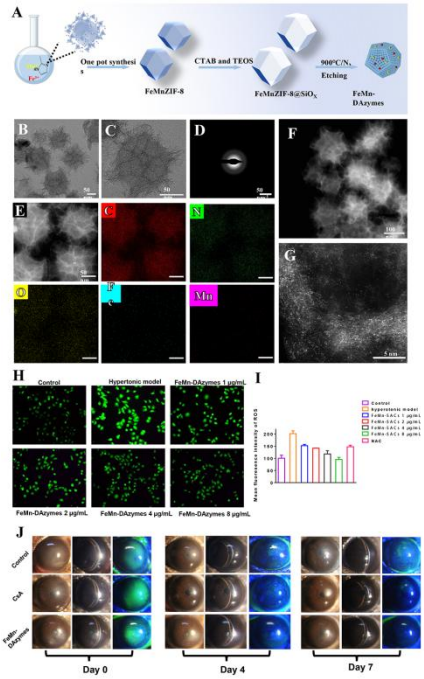

Figure 1. (A) Schematic illustration of the synthetic procedure of FeMn-DAzymes; (B-G) Characterization of FeMn-DAzymes; (H,I) The effect of scavenging ROS *in vitro.* (J) Effect of FeMn-DAzymes for DED *in vivo.*

Reference:

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Numerical investigation on the realistic pulmonary drug delivery process in the pediatric intersubject realistic upper airway models

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Abstract: Credible regional deposition is crucial to develop an *in vitro-in vivo* correlation (IVIVC) for orally inhaled drugs yet research on the child remains limited. Computational fluid dynamics coupled with discrete phase model was established and validated based on the idealized MT model to provide credible methodology for the study. Four realistic mouth-throat (MT) models as well as the geometry of the DPI Breezhaler® was reconstructed based on CT data. MT deposition fraction in all models increased with the increasing flow rate (30, 60, 90L/min) and particle size (1-30um), indicating that the inertial impact plays a dominant role in the MT region. The complex geometry of the realistic MT led to an asymmetric flow field and more voices in the oral cavity region than that in the idealized model, resulting in a different particle spatial distribution and higher MT deposition fraction. The trend of relative position parameter between the inhaler and MT (i.e the vertical distance L_m from the mouthpiece of the inhaler to the tongue surface) is opposite to the MT deposition fraction. The smaller L_m is, the deeper the mouthpiece in the oral cavity, the higher the collision and deposition of particles on the tongue surface. Underestimated MMAD obtained by NGI led to higher lung deposition fraction compared with the fine particle fraction (FPF) and experimental results, especially at low flow rate. Input parameter should be calibrated to get better prediction results because MMAD can’t stand for the true particle properties. It is expected that the results may be useful to industry during product development for the child, and it enhanced the understanding of the relationship between the reginal deposition and *in vivo* data prior to clinical trials.

Keywords: orally inhaled drugs; dry powder inhalers; the upper airway of children; Computational Fluid Dynamics (CFD) models, particle deposition mechanism;

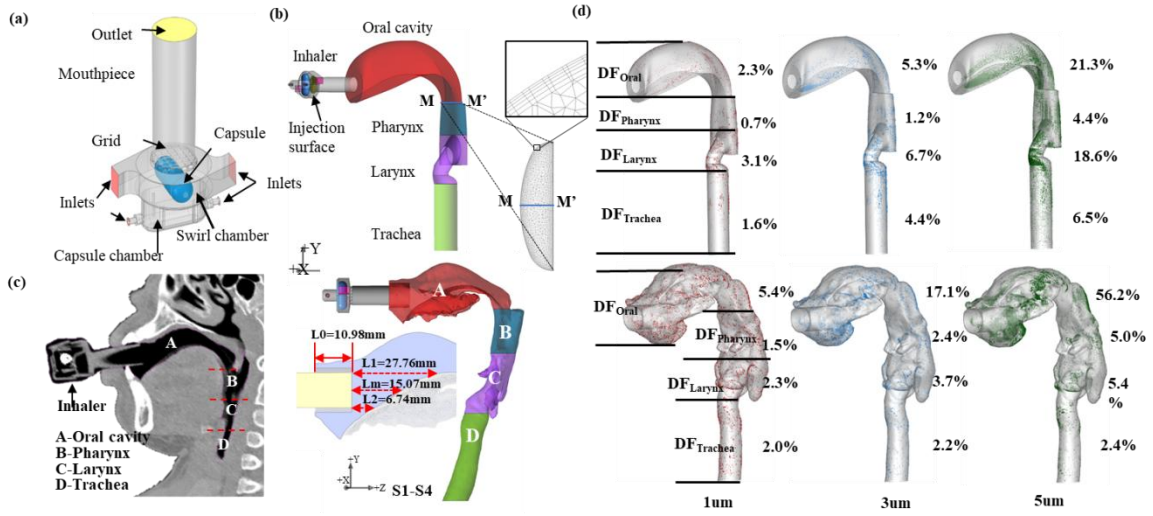

Figure 1. Geometric schematics of the models and regional deposition results :(a) Geometry of Breezhaler®; (b) Idealized airway model; (c) Realistic airway models; (d) Reginal deposition distribution between idealized and realistic airway model at 60L/min;

Intrinsically bioactive and biomimetic nanoparticle-derived therapies alleviate asthma by regulating multiple pathological cells

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Abstract: Asthma is a serious global public health concern. Airway neutrophilic inflammation is closely related to severe asthma, for which effective and safe therapies remain to be developed. Here we report nanotherapies capable of simultaneously regulating multiple target cells relevant to the pathogenesis of neutrophilic asthma. A nanotherapy LaCD NP based on a cyclic oligosaccharide-derived bioactive material was engineered. LaCD NP effectively accumulated in the injured lungs of asthmatic mice and mainly distributed in neutrophils, macrophages, and airway epithelial cells after intravenous or inhalation delivery, thereby ameliorating asthmatic symptoms and attenuating pulmonary neutrophilic inflammation as well as reducing airway hyperresponsiveness, remodeling, and mucus production. Surface engineering via neutrophil cell membrane further enhanced targeting and therapeutic effects of LaCD NP. Mechanistically, LaCD NP can inhibit the recruitment and activation of neutrophils, especially reducing the neutrophil extracellular traps formation and NLRP3 inflammasome activation in neutrophils. Also, LaCD NP can suppress macrophage-mediated pro-inflammatory responses and prevent airway epithelial cell death and smooth muscle cell proliferation, by mitigating neutrophilic inflammation and its direct effects on relevant cells. Importantly, LaCD NP showed good safety performance. Consequently, LaCD-derived multi-bioactive nanotherapies are promising for effective treatment of neutrophilic asthma and other neutrophil-associated diseases.

Keywords: neutrophilic asthma, nanotherapy, neutrophil extracellular traps, inflammasome, precision therapy

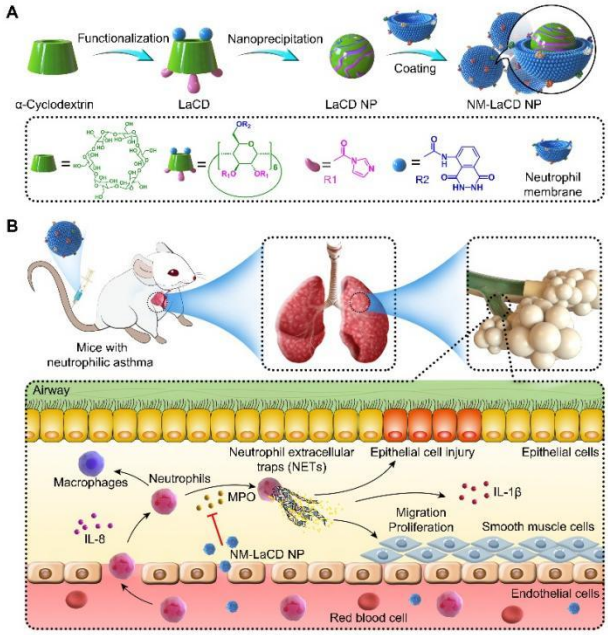

Figure 1. Schematic illustration of engineering of multifunctional bioactive nanoparticles derived from a luminol-conjugated α-cyclodextrin (LaCD) material. (A) Chemical structure of LaCD as well as engineering of LaCD nanoparticles (LaCD NP) and neutrophil membrane-coated LaCD NP (NM-LaCD NP). (B) A sketch showing accumulation of NM-LaCD NP in the injured lungs and targeted treatment of neutrophilic asthma by regulating multiple pathologically relevant cells.

Polydopamine-coated mesoporous silica nanoparticles co-loaded with Ziyuglycoside I and Oseltamivir for synergistic treatment of viral pneumonia

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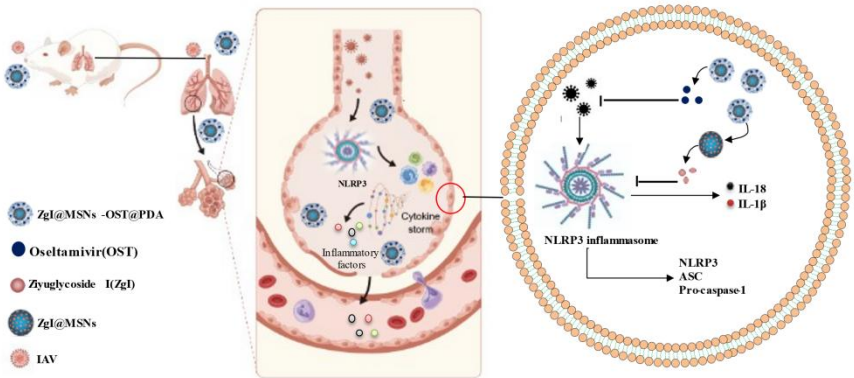
Abstract: Viral pneumonia (VP) is a serious health risk to humans, but there is still a lack of specific treatment for VP. The spread of the virus in the body induces an excessive inflammatory response that can easily cause chronic or even irreversible damage to the lungs. Hence, treatment of VP requires rapid clearance of the virus and sustained control of inflammation. In this paper, an innovative mesoporous silica medication delivery system co-loaded with ziyuglycoside I and oseltamivirv(OST) in a fast and slow monomeric form (ZgI@MSNs-OST@PDA) was prepared for targeted treatment of VP. The prepared ZgI@MSNs-OST@PDA nanoparticles have an homogeneous and membrane-encapsulated spherical structure with an average particle size of about 760 nm. The *in vitro* release and *in vivo* pharmacokinetic studies demonstrated that ZgI@MSNs-OST@PDA achieved immediate release of OST and sustained release of ZgI, and it was readily taken up by cells. *In vitro* anti-H1N1 virus experiments showed that nanoparticles rapidly killed the virus in host cells, while the anti-inflammatory effect was indeed sustained and long-lasting, and it provided excellent protection to host cells. *In vivo* antiviral pneumonia experiments likewise confirmed the rapid clearance of influenza viruses from mice lungs and the effective control of over-activated immune responses of ZgI@MSNs-OST@PDA nanoparticles. Through mechanism study we found that the treatment of viral pneumonia with nanoparticles was associated with inhibition of the NLRP3inflammasome pathway. In conclusion, the constructed nanoparticles were able to achieve synergistic therapeutic effects of ZgI and OST on VP, i.e. rapid killing of influenza viruses by OST and effective control of virus-induced hyperinflammatory response by ZgI.

Keywords: Viral pneumonia; ZiyuglycosideI; Oseltamivirv; Nanoparticles; Synergistic treatment



LLOMe promote therapeutic effect of nanovaccine for cervical cancer

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Abstract: HPV vaccine is a promising option for treatment of advanced cervical cancer, and how to enhance the vaccine therapeutic effect remains the main challenge. In this current study, we co-loaded peptide HPV16E7$_{44\text{-}62}$ and a dipeptide LLOMe as the adjuvant by constructing a novel liposome nanovaccine termed as E7/L@V. E7/L@V effectively induced the maturation of bone marrow-derived dendritic cell *in vitro*. LLOMe in nanovaccine promoted the lysosomal escape of antigen peptide, and enhanced the antigen-presentation efficacy. In the subcutaneous xenograft model of cervical cancer, E7/L@V effectively initiated specific immune responses against cervical cancer, therefore inhibiting the growth of cervical cancer. This study demonstrated that LLOMe could enhance the anti-cervical cancer of nanovaccine, which provides new potent strategy for the treatment of advance cervical cancer.

Keywords: cervical cancer; nanovaccine; LLOMe; antigen presentation

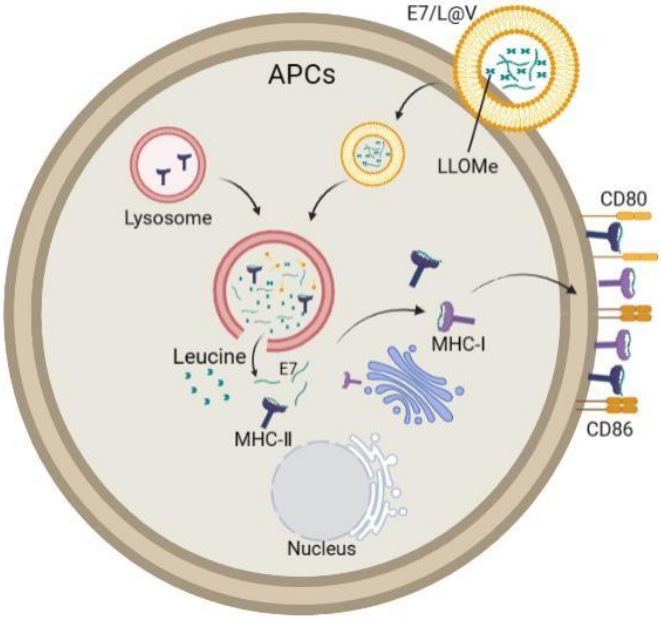

Figure. 1 Schematic illustration of LLOMe promotes nanovaccine inducing the maturation of antigen-presenting cells.

An in vitro release strategy of polyester microspheres simulating physiological environment to achieve "real" IVIVC

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Abstract: The reported *in vivo-in vitro* correlation (IVIVC) could not predict the impact of organism-microsphere interactions on drug release reliably, as the *in vitro* release method only provided an environment for drug dissolution but ignored the contribution regarding *in vivo* factors. Here, we attempted to replicate the underlying physicochemical processes of microspheres *in vivo*, and established a bio-relevant *in vitro* release method to attain real IVIVC. For naltrexone microspheres, the osmolarity exhibited a decisive role in regulating the release kinetics. In terms of drug release behavior, the release rate constant in the first stage (r=-0.9981), the release rate constant in the second stage (r=0.9626), and the release delay period (r=0.9965) were all linearly correlated with the osmolarity. As well for polymer degradation (r=0.9999). Thus, it could be inferred that the formation of drug mass transfer channels in an osmolarity-dependent manner drove the drug release kinetics mainly rather than the degradation process of polymer. Further, the release trend of microspheres under the 10% fetal bovine serum (FBS) method showed a similarity factor of 64 to the *in vivo* cumulative release profile, and the morphological change and degradation mechanism were also consistent. For thiophenorphine microspheres, the release method containing FBS accurately described the high burst release and honeycomb-like microstructure *in vivo*. However, unlike the simulation mechanism of naltrexone, the extremely high plasma protein binding (95%) of thiophenorphine dominated the regulation of drug release kinetics. Collectively, we took a new multi-route *in vivo* simulation strategy to address the dilemma of unrelated *in vivo* and *in vitro*. The simulation of physiological environment affecting drug release *in vivo* and the regulation of key factor affecting drug mass transfer allowed the replication and prediction of the microspheres evolution pattern *in vivo*.

Keywords: microsphere; PLGA; IVIVC; release kinetics; osmolarity

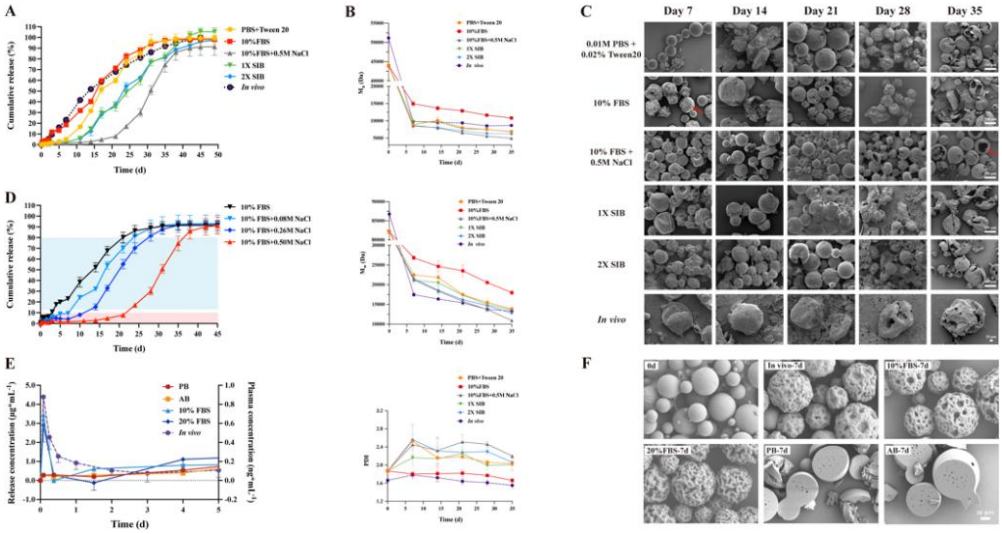

Figure. Characterizations of microspheres in different release methods and *in vivo*. (A) Release behaviors of naltrexone microspheres; (B) M_n, M_w and PD of naltrexone microspheres; (C) Morphology of naltrexone microspheres; (D) Release behaviors of naltrexone microspheres in different osmolarity methods; (E) Thiophenorphine concentration; (F) Morphology of thiophenorphine microspheres at day 0 and day 7.

Self-assembly of TPGS Polymeric Micelles as Maduramicin Carriers has Enhanced Anticancer and Anti-metastatic Capabilities for Canine Breast Cancer Therapy

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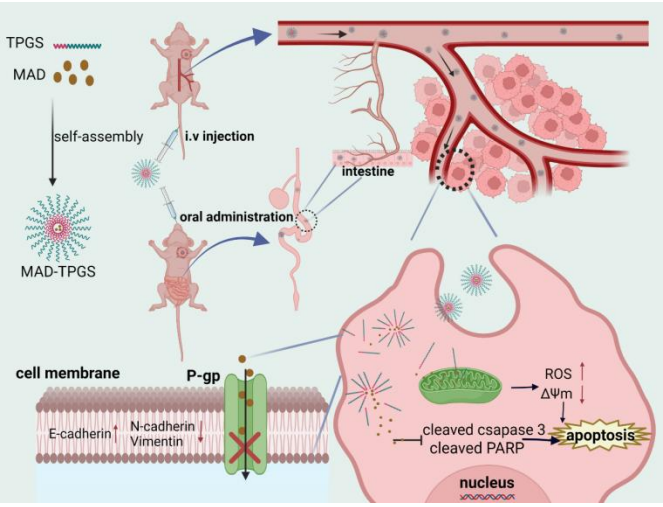
Abstract: Canine mammary tumors (CMT) can severely compromise the quality of life of the affected dogs due to local recurrence, distant metastases and finally death. Maduramicin has received recent attention for its ability to anti-metastasis of breast cancer. However, its poor aqueous solubility and toxicity to normal tissue limit its clinical application. Therefore, in order to enhance the anticancer and anti-metastasis effect of MAD, MAD loaded TPGS polymeric micelle (MAD-TPGS) were prepared by a thin-film hydration technique. The optimized MAD-TPGS exhibited excellent size distribution, stability and improved water solubility. MAD was almost entirely encapsulated in TPGS polymer micelles as characterized by Fourier transform infrared spectroscopy and X-ray diffraction spectroscopy. Cellular uptake assays showed that TPGS polymer micelles could enhance drug internalization. Moreover, TPGS synergistically improved the cytotoxicity of MAD by targeting mitochondrial organelles, improving reactive oxygen species level and reducing the mitochondrial transmembrane potential. More importantly, MAD-TPGS significantly impeded the metastasis of tumor cells. In vivo results further confirmed that MAD-TPGS exhibited a much higher antitumor efficacy than free MAD and had excellent biocompatibility. Interestingly, MAD-TPGS possessed better ability in CMT suppression via tail vein injection than oral administration, indicating that MAD-TPGS was more suitable for intravenous administration. Taken together, MAD-TPGS could be applied as a potential anti-metastasis cancer agent for CMT by tail vein injection.

Keywords: Maduramicin; Canine mammary tumors; Polymer micelle; Anti-metastasis



Scheme 1 Schematic illustration for the self-assembly process of MAD-TPGS and their treatment against metastatic of canine breast cancers.

Investigation on Surface Properties of Uniform Lactose Microsphere for Carrier-based Pulmonary Drug Delivery via Inverse Gas Chromatography

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Abstract: Dry powder inhaler (DPI) has increasingly attracted increasing attention in the field of pulmonary drug delivery. Carrier-based DPI (cbDPI), i.e. blended fine micronized active pharmaceutical ingredient with carrier materials is the main type of commercial product. Lactose monohydrate microparticle is the solely approved carrier, whose size, morphology and surface properties play a crucial role in the drug delivery efficiency of cbDPI[1]. Herein, uniform lactose microsphere (LM) with tailorable surface properties were fabricated by a self-designed micro-fluidic jet spray dryer combined with mixed-solvent post-treatment process. Then fine micronized tiotropium bromide as the model drug were blended with a series of LM samples. The LM surface properties, including surface energy, surface roughness, acid base properties and surface energetic heterogeneity were systematically explored using inverse gas chromatography and correlated with in vitro aerosol performance of mixed dry powder evaluated by next generation impactor. This study provides new insight in developing cbDPI products.

Keywords: pulmonary drug delivery, micro-fluidic jet spray drying, surface properties, in vitro aerosol performance, inverse gas chromatography.

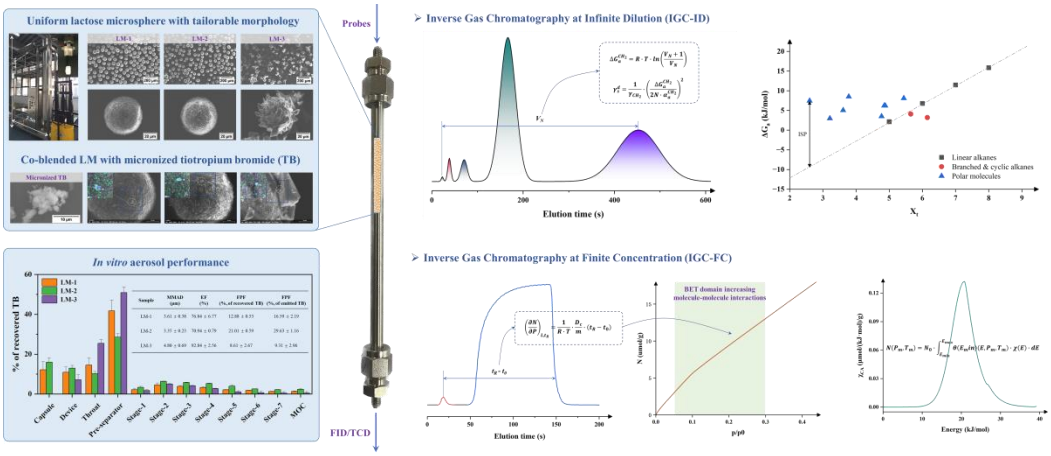

Figure. 1 Schematic graph of IGC for evaluating surface properties of lactose microsphere.

Reference:

[1] S. Mangal, H. Park, R. Nour, et al., Correlations between surface composition and aerosolization of jet-milled dry powder inhaler formulations with pharmaceutical lubricants, Int. J. Pharm., 2019, 568: 118504.

Spray freeze dried niclosamide nanocrystals embedded dry powder for high dose pulmonary delivery

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Abstract: Based on the drug repositioning strategy, niclosamide (NCL) has shown potential applications for treating COVID-19[1]. However, the development of new formulations for effective NCL delivery is still challenging. Herein, NCL-embedded dry powder for inhalation (NeDPI) was fabricated by a novel spray freeze drying technology. The addition of Tween-80 together with DSPC showed the synergistic effects on improving both the dispersibility of primary NCL nanocrystals suspended in the feed liquid and the spherical structure integrity of the spray freeze dried (SFD) microparticle. The SFD microparticle size, morphology, crystal properties, flowability and aerosol performance were systematically investigated by regulating the feed liquid composition and freezing temperature. The addition of leucine as the aerosol enhancer promoted the microparticle sphericity with greatly improved flowability. The optimal sample (SF-80D-N20L2D2T1) showed the highest FPF of ~ 47.83%, equivalently over 3.8 mg NCL that could reach the deep lung when inhaling 10 mg dry powders.

Keywords: NCL-embedded dry powder for inhalation (NeDPI), spray freeze drying, fine particle fraction, particle formation mechanism, structure-performance relationship

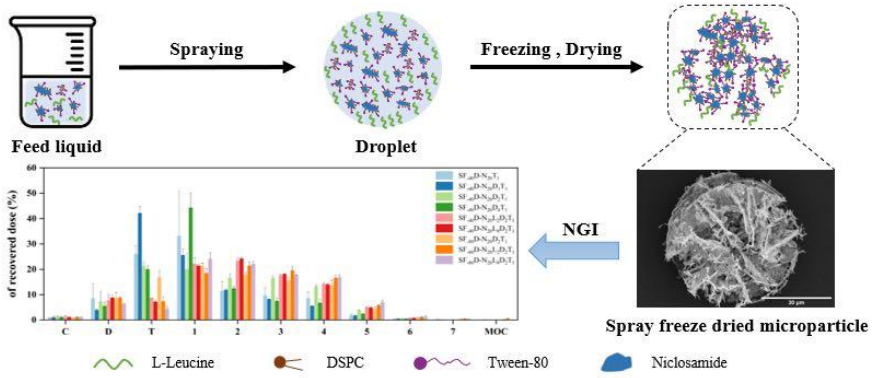

Figure. 1 Schematic graph of microparticle formation mechanism and in vitro aerosol performance of NeDPI.

Reference:

[1] L. Braga, H. Ali, I. Secco, E. Chiavacci, et. al., Drugs that inhibit TMEM16 proteins block SARS-CoV-2 spike-induced syncytia, Nature, 2021: 88–93.

Insoluble salt of memantine with unique fluorescence phenomenon

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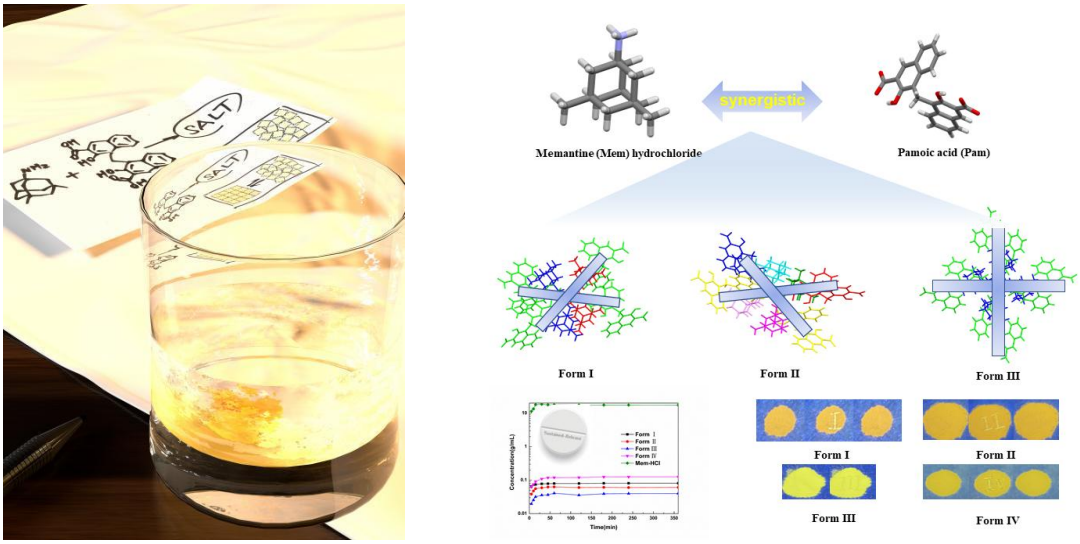
Abstract: Alzheimer's disease is a chronic disease, and long-term treatment of chronic diseases has always been a concern. Memantine (Mem) is approved by the US Food and Drug Administration drug for the treatment of moderate to severe Alzheimer's disease. In this study, reactions of Memantine (Mem) with Pamoic acid (Pam) to form insoluble salts (Mem-Pam). Four polymorphic forms (Form I, II, III, IV) of Mem-Pam were successfully obtained through polymorphic screening, and systematically characterized by X-ray powder diffraction (PXRD), thermal analysis (TGA and DSC), single-crystal X-ray diffraction (SXRD), and Solid-State Fluorescence. Compared with the hydrochloride form, the dissolution and release rate of these four forms is lower. The presence of pamoic acid reduces the rate of release of memantine and makes it possible to achieve a sustained release of the drug. Interestingly, because of the presence of memantine, each polymorphic solid crystal of Mem-Pam has unique fluorescence emission. Therefore, memantine and pamoic acid have a synergistic effect in fluorescence performance and maybe can expect to real-time monitoring in continuous and controlled release drug delivery systems. In addition, the polymorphic solid crystals also exhibit reversible mechanochromic luminescence under the fumigation of acetonitrile vapor, which has a guiding role in the fluorescent design and synthesis of Pam substances and is expected to be used for information security, visual inspection of organic substances, etc.

Keywords: Memantine, Pamoic acid, Insoluble Salts, Polymorphism, Physicochemical Property



(a) (b)

Figure. 1 (a): Concept diagram, (b): Molecular structure diagram of memantine and pamoic acid (top), the Crystal Structure of Multicomponent Salts (middle), and dissolution and Optical Properties of Multicomponent Salts (bottom).

Development of a green and efficient drug spherical agglomeration technology for the production of high quality tablet products

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Abstract: Among various drug products, oral tablets are the most preferred product forms dominating the market because of their high patient compliance and wide acceptance. However, most of drug crystal products prepared by simple crystallization methods are needle-like and thin flake crystal habits, which are defective in terms of powder and mechanical properties, seriously affecting formulation efficiency and tablet quality. Spherical crystals are special crystalline products which offer advantages over normal crystals in terms of microscopic properties and efficiency of downstream product handling. In pharmaceutical industry, spherical crystals present high flowability and compressibility achieving direct tableting. At present, two main technologies for preparing spherical crystals of drugs have been developed: traditional granulation technology and ternary solvent spherical agglomeration technology. Nevertheless, the two technologies possess their own insuperable limitations in the application of complex equipment and biohazardous solvents, respectively. In order to overcome the shortcomings of traditional technologies, we developed an oiling-out spherical agglomeration technology that simply relies on heating and quenching operations in water. Spherical crystals of 14 drugs have been successfully prepared with good powder properties, high yield and adjustable particle size distribution. More importantly, in the case of celecoxib, the oiling-out spherical agglomeration technology achieved zero organic solvent addition (the amount of organic solvent required per unit of product is reduced by 63.8 g/g) and a 52.9% reduction in operating temperature compared to the traditional ternary solvent spherical agglomeration and melt granulation technologies, which is expected to result in a 41.2% reduction in energy consumption per ton of product. Meanwhile, the technology enables the assembly of drugs with synergistic effects into spherical co-agglomerates, resulting in drug combination. In addition, no punch sticking or capping occurs during tableting for the drug spherical product with excellent tableting performance, which is expected to meet the requirements of the direct tableting.

Keywords: Crystallization; Spherical agglomeration; Drug combination; Tableting performance; Direct tableting

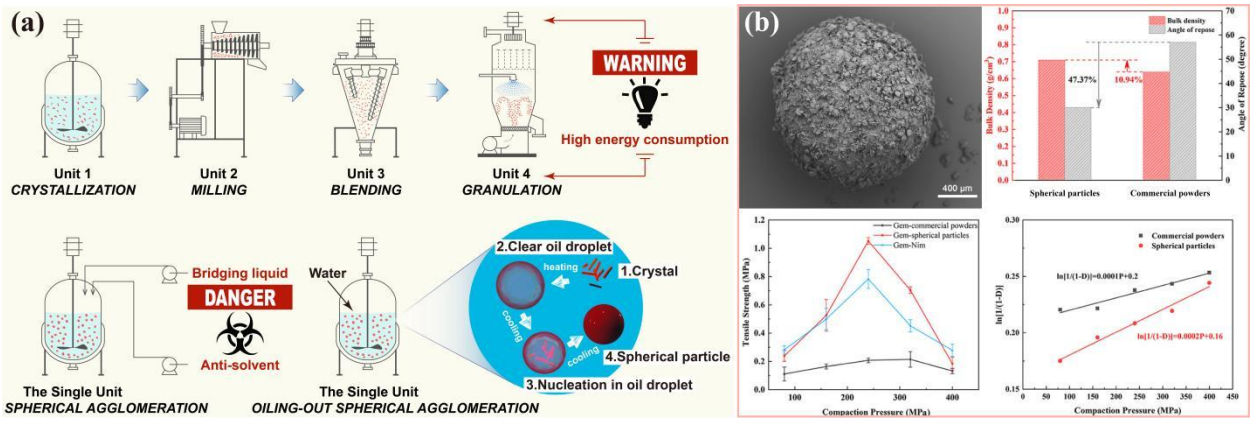

Figure. 1 (a) Schematic diagram of the advantages of the oiling-out spherical agglomeration technology developed in this work compared to conventional technologies. (b) Characterization results of drug spherical crystals in terms of external morphology, powder properties and tableting performance.

Reference:

[1] Guo, S., Yu, C., Feng, S., Wei, J., Tong, L., Li, K., Gao, Y., Zhao, P., Li, T., Chen, M., Gong, J., International Journal of Pharmaceutics[J], 2022, 626(15), 122180.

A Multicomponent Crystal Strategy to Improve Dissolution Rate and Tabletability Property of the Antiepileptic Drug Gabapentin Tablets

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Abstract: Pharmaceutical materials are regarded as a crucial part in contemporary medication manufacturing, processing, and formulation. Intermolecular interactions can be purposely modified to produce new solid forms with improved functional properties using the present understanding of the interaction topology in solid states. Drugs come in a variety of dosage forms, such as granules, capsules, tablets, and so on. Tablets continue to be the preponderant dosage form because of their physical and chemical stability, high manufacturing efficiency, and low manufacturing cost. Gabapentin (GBP), an analogue of the neurotransmitter gamma-aminobutyric acid, is used to treat partial seizures. Cocrystals are homogeneous crystalline solids containing pharmaceutically acceptable cocrystal coformers and an active pharmaceutical ingredient (API), according to the definition given by the pharmaceutical industry. The pharmaceutically acceptable *p*-aminobenzoic acid (PABA) was selected to form a 1:1 cocrystal with GBP, resulting in a cocrystal tablet that can successfully slow down the dissolution rate of the original drug and reduce the intrinsic dissolution rate. Therefore, GBP-PABA was thought to have enormous promise for the development of sustained-release formulations. Meanwhile, GBP exhibits poor compaction behavior, which increases the possibility of capping or laminating during compression. The incorporation of water molecules into multicomponent crystals gives them different molecular conformations as well as multiple packing arrangements. Then, all powder samples were subjected CTC (compressibility, tabletability, compactibility) profiling in order to identify the behavior of bulk powder deformation. According to analysis of crystal structure, GBP·H_2O displays comparable improved compaction properties owing to the slip planes which enable us to explore how regulating molecular packing at the molecular level can improve the tableting performance. As a result, the association between the crystal topology structure, mechanical properties, and its tabletability properties established in this work is an indispensable step toward the ultimate goal of precise performance design of tablet products.

Keywords: Gabapentin; Crystallization; Multicomponent crystals; Intrinsic dissolution rate; Tabletability

Reference:

[1] Li, M., Sun, J., Kuang, W., Zhou, L., Han, D., Gong, J., Crystal Growth & Design [J], 2022, 22(8), 5027-5035

Toxic protein capture-driven microglial regulation using carrier-free DNA/RNA nanocomplexes for intracerebral haemorrhage therapy

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Abstract: Disability or death due to intracerebral haemorrhage (ICH) is attributed to blood lysis, haemoglobin (Hb) liberation, and consequently activated microglia-mediated neuroinflammation. However, despite decades of effort, effective therapies for the clinical treatment of ICH are still lacking 1. Herein, we present carrier-free nanocomplexes (named h-DRNS) composed of Hb aptamers and microRNA-124 via simple self-assembly for efficient ICH therapy. The h-DRNS selectively targeted ICH lesions and efficiently captured toxic Hb, preventing Hb-mediated nerve cell damage. Moreover, the surface Hb crown formed by the specific capture drove the h-DRNS to actively target the microglia via strong affinity between Hb and scavenger receptors expressed on the surface of the microglia, realizing precise microRNA-124 delivery and efficient phenotype regulation of inflammatory microglia. After treatment with the h-DRNS, the haematoma size was reduced by 21.98-fold, and neurological inflammation was substantially mitigated with significant functional recovery in Hb-induced and collagenase-induced ICH mouse models. Collectively, the h-DRNS showed a promising improvement in the clinical outcomes of ICH and may serve as a precise gene-delivery platform for treatment of various brain diseases.

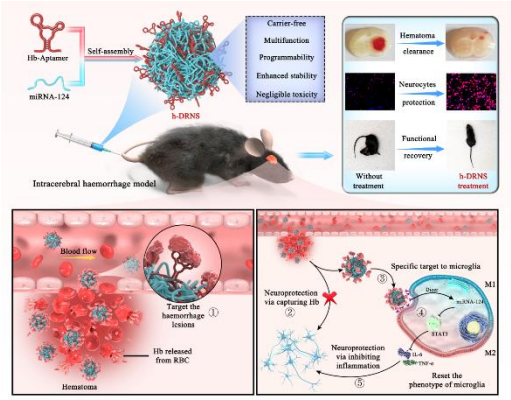

Figure 1. Schematic of the carrier-free DNA/RNA nanocomplexes (h-DRNS) for efficient ICH therapy.

Keywords ： Nucleic acid nanocomplexes delivery; Haemoglobin capture; Microglia-targeted; Neuroprotection; Intracerebral haemorrhage therapy

References:

[1] Xue, M. & Yong, V. W. Neuroinflammation in intracerebral haemorrhage: immunotherapies with potential for translation. The Lancet Neurology 19, 1023-1032, doi:10.1016/s1474-4422(20)30364-1 (2020).

Reversing Fibrotic Immune Exclusion of Solid Tumor by Multivalent CXCR4 Antagonistic Nano-Permeator for Chemoimmunotherapy

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Abstract: Fibrosis is one of the key factors that lead to the immune exclusion of solid tumors. Although degradation of fiber is a promising strategy, its application was still bottlenecked by the side effects of causing metastasis, resulting in the failure of immunotherapy. Here, we developed an antimetastatic polymer (HPA) for the delivery of chemo-drug and antifibrotic siPAI-1 to form the nano-permeator. Nano-permeator shrank after protonation and deeply penetrated into the tumor core to down-regulate the expression of PAI-1 for antifibrosis, and further promoted the sustained infiltration and activation of T cells for killing tumor cells. Moreover, metastasis after fiber elimination was prevented by multivalent CXCR4 antagonistic HPA to reduce the attraction of CXCL12 secreted by distant organs. The administration of stroma-alleviated immunotherapy increased the infiltration of CD8+ T cells to 52.5% in tumor tissues, inhibiting nearly 90% metastasis by HPA in distant organs. The nano-permeator reveals the mechanism and correlation between antifibrosis and antimetastasis, and was believed to be the optimizing immunotherapy for solid fibrotic tumors.

Keywords: Immune exclusion, Fibrosis, Deep penetration, CXCR4/CXCL12, Metastasis

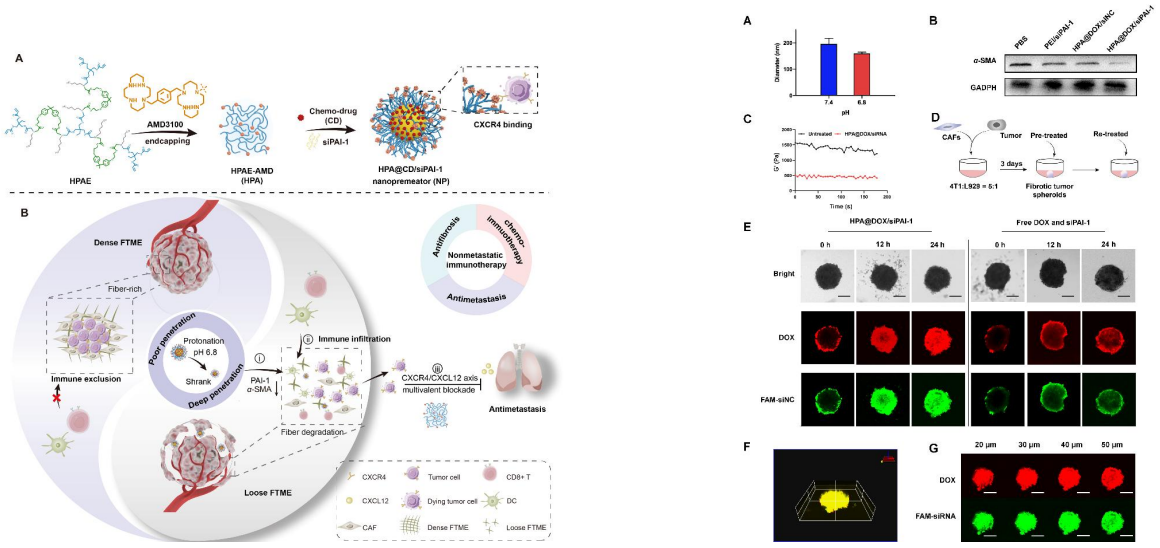

Figure. 1 Schematic illustration of the working mechanism of nano-permeator HPA@DOX/siPAI-1 by antifibrosis for enhancing immunotherapy (Left); and antifibrotic HPA@DOX/siPAI-1-mediated deep penetration of adaptive immunity (Right).

Reference:

[1] Sun X, Wu B, Chiang H, Deng H, Zhang X, Xiong W, et al., Nature[J] 2021, 599, 673-678.

Bioinspired Nanosystems Delivered by Transdermal Delivery System to Boost Antitumor Immunotherapy

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Abstract: Tumor metastasis and recurrence remain the leading cause of treatment failure and tumor-related death. Herein, we report a novel strategy by fabricating a photo-immune nanoparticle decorated with immune cell membrane (BD@LM NPs) for the treatment of primary tumor and prevention of tumor recurrence and metastasis after surgical resection. By integrating photosensitizer and chemotherapeutic drug into the biomimetic nanovectors, a combinational antitumor effect is obtained due to the synergy of chemotherapy and phototherapy. By further loading the bioinspired BD@LM NPs into a microneedle patch, an enhanced antitumor performance can be produced due to the direct destruction of skin barrier, which accelerates the delivery of BD@LM NPs into solid tumor tissue locally. Moreover, a powerful antitumor immunity is generated due to the initiation of immunologic cell death (ICD) cascade, which boosts the infiltration of cytotoxic T lymphocytes and decreases the amounts of immunosuppressive cells. Overall, the prepared nanoparticle-loaded microneedle patch (BD@LM MN) exhibits strong tumoricidal effect, which not only inhibits the tumor growth of primary tumor, but also protects the body from tumor recurrence and metastasis post-surgery by using two different superficial tumor models.

Keywords: photo-immunotherapy; microneedle; bioinspired drug delivery system

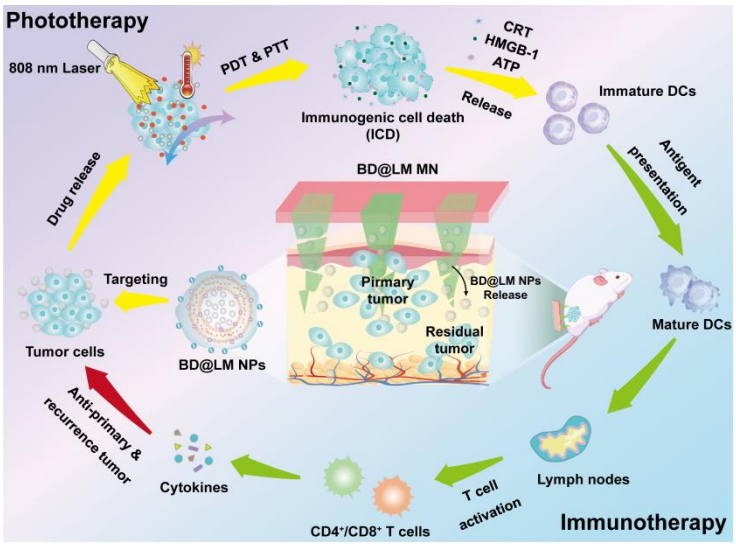

Figure. 1 Schematic illustrates the mechanism of BD@LM MN on promoting immunologic cell death for cancer phototherapy and immunotherapy.

Reference:

[1] Xu, J., Lv, J., Zhuang, Q., Yang, Z., Cao, Z., Xu, L., Pei, P., Wang, C., Wu, H., Dong, Z., Chao, Y., Wang, C., Yang, K., Peng, R., Cheng, Y., & Liu, Z., Nature nanotechnology[J], 2020, 15(12), 1043–1052.

Pathogenesis-Guided Engineering of Multi-Bioactive Hydrogel Co-delivering Inflammation-Resolving Nanotherapy and Pro-Osteogenic Protein for Bone Regeneration

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Abstract: There are still great challenges in promoting bone defect repair via regeneration strategies. In view of delayed bone healing due to local inflammation, herein we propose pathogenesis-guided engineering of multi-bioactive hydrogel therapy for bone regeneration, by simultaneously improving the osteoimmune environment and enhancing osteogenic differentiation of stem cells. After discovering the pivotal role of persistent inflammation and bone loss in the pathogenesis of periodontitis by transcriptomics, a multi-bioactive nanotherapy based on self-assembled nanomicelles (PP5 NMs) is first developed. PP5 NMs effectively rescue osteogenesis of human periodontal ligament cells under pathological conditions and promote bone formation in rats with mandibular or cranial bone defects. By integrating PP5 NMs, a pro-osteogenic protein rhBMP9, and a hydrogel-forming temperature-responsive material, a multifunctional hydrogel therapy is further engineered, which can regulate the pro-inflammatory/oxidative microenvironment and accelerate bone regeneration. The obtained multi-bioactive hydrogel capable of co-delivering and sustainedly releasing PP5 NMs and rhBMP9 displays excellent bone regeneration capability, by synergistic effects of inflammation-resolving and pro-osteogenic differentiation of stem cells. Mechanistically, this hydrogel therapy improves the osteoimmune environment by attenuating pathogenesis and enhancing stem cell differentiation via the TLR4/NF-κB/HO-1 axis and activating the Smad1/5/8 protein complex. Our hydrogel is promising for treating different inflammatory bone diseases.

Keywords: bone defect, osteoimmune environment, inflammation, osteogenesis, nanotherapy, hydrogel

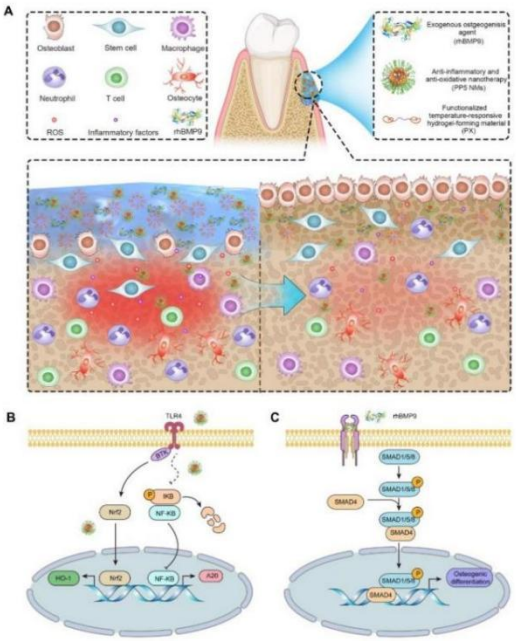

Figure 1. Schematic illustration of engineering multi-bioactive thermosensitive hydrogel for bone regeneration. (A) A sketch showing the formulation of multiple active hydrogel for promoting bone formation at a mandibular defect by inhibiting inflammatory response and enhancing osteogenic differentiation of stem cells. The multi-bioactive hydrogel was formulating by rationally integrating inflammation-resolving nanomicelles (PP5 NMs) and rhBMP9 into a temperature-responsive hydrogel derived from PX that can be delivered via local injection. While the bioactive nanomicelles can normalizing the pro-inflammatory microenvironment by eliminating excessive ROS and simultaneously generating an anti-inflammatory active pharmaceutical ingredient, rhBMP9 may recruit stem cells in situ and promote their differentiation into osteoblasts, thus enhancing bone formation. (B-C) Diagrams illustrate signaling pathways dominating anti-oxidative and anti-inflammatory effects of PP5 NMs as well as pro-osteogenic activity of rhBMP9 in hPDLCs.

Neutrophil-Mediated Delivery of Chemotherapy Drug Enhances Pancreatic Cancer Response to Irreversible Electroporation

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Abstract: Pancreatic cancer is an abysmal malignancy with a fibrotic stroma that restricts an efficient delivery of therapeutic agents. Irreversible electroporation (IRE) is a novel ablative technique that kills cancer cells by releasing high-intensity electric pulses to irreparably damage cell membrane. It also induces a strong anti-tumor immunity and shows efficacy along with immunotherapies [1]. However, tumor relapse is still common after IRE treatment. IRE induces a massive infiltration of neutrophils into pancreatic tumor. Therefore, we hypothesized that neutrophil mediated delivery of chemotherapy drugs would lower to the risk of tumor relapse after IRE. Doxorubicin (DOX) was first encapsulated into bovine serum albumin (BSA) nanoparticles, and loaded into murine neutrophils to give the resultant formulation (NP@NEs). Drug release was achieved by incubation with IRE-treated tumor lysate, during which the carrier neutrophils was activated to undergo apoptosis and eventually structural disintegration. NP@NEs exhibited a prolonged retention in circulation. Its accumulation in IRE-treated Panc02 murine pancreatic tumors was 2.6 times that in the untreated tumors. Within the IRE-treated tumors, the DOX-BSA NPs were diffusively scattered surrounding the neutrophils, suggesting a timely release of the NP payloads. In subcutaneous models established using Panc02 or $Kras^{G12D/+}$;$Trp53^{R172H/+}$;Pdx-1-Cre (KPC) murine pancreatic cancer cells, the combination of IRE and NP@NEs suppressed tumor growth more effectively that either monotreatment without excessive toxicity reactions. Immunohistochemical staining (IHC) revealed that the IRE + NP@NEs combination significantly reduced the frequency of $Ki67^{+}$ proliferating cells, and increased the frequency of $TUNEL^{+}$ apoptotic cells. Our data demonstrated that neutrophil-mediated delivery of DOX-BSA nanoparticles was an effective approach to the improvement of IRE efficacy against pancreatic cancer.

Keywords: Irreversible electroporation; neutrophils; Doxorubicin, pancreatic cancer

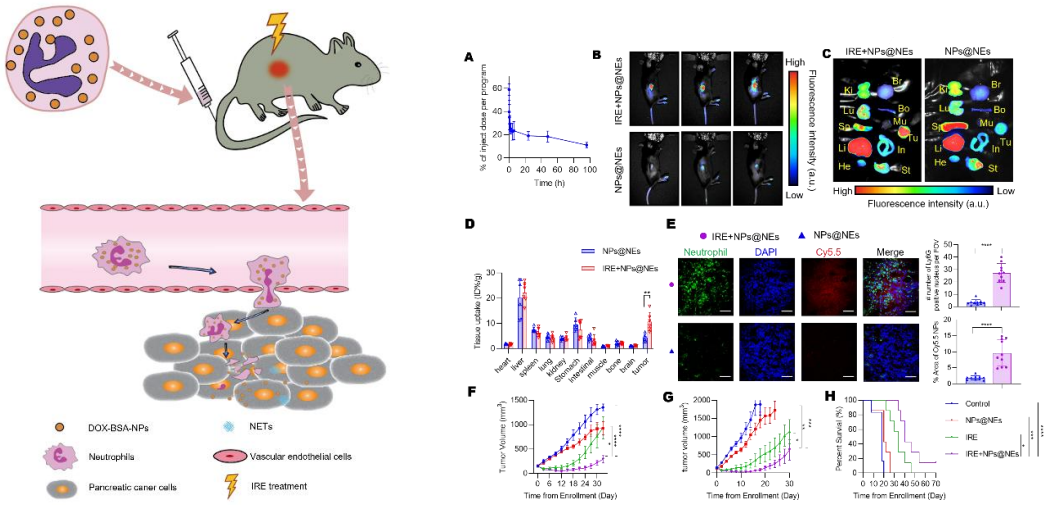

Figure. 1. (Left) Schematic illustration of the NPs@NEs delivery system. (Right) Pharmacokinetics (A), biodistribution (B-E) and antitumor efficacy of NPs@NEs (F-H).

Reference: [1] **Zhao, J.**†; Wen, X. F.†; Tian, L.; Li, T.; Xu, C.; Wen, X. X.; Melancon, M. P., Gupta, S.; Shen, B.; Peng, W.; Li, C*. Irreversible electroporation reverses resistance to immune checkpoint blockade in pancreatic cancer. Nature Communications 2019, 10:899

Hypoxia-Responsive Host-Guest Pharmaceutical Excipients

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Abstract: Excipients used in medicines are crucial components that can impact the quality, safety, and effectiveness of drugs. One important trend in the development of pharmaceutical excipients is their ability to act as carriers for targeted and controlled drug release. Supramolecular hosts including cyclodextrins, calixarenes and cucurbiturils have emerged as promising excipient candidates. They have some advantages such as easy preparation, precise molecular structure and weight, and excellent chemical stability. The host-guest loading process is mild, simple, and repeatable. The host-guest formulations offer several benefits, including the quantitative loading of drug, high percentage of encapsulation, and reproducibility because of the exact cavity-loading pattern and quantifiable host-guest binding constant. Due to the dynamic and reversible nature of supramolecular interactions, host-guest formulations also possess modular characteristics, which are well-suited for personalized medicine. These lead to predictable therapeutic indices and excellent application prospects in both scientific research and industry.

As part of our ongoing research, which explores biomedical application by taking advantages of the molecular recognition of calixarene macrocycles, we have developed a hypoxia-responsive excipient based on azocalixarenes. These azocalixarenes possess a deepened cavity, resulting in high binding affinities and high encapsulation efficiencies towards therapeutic agents. Azocalixarenes can significantly increase the solubility of drugs at an equivalent level, with a high degree of solubility enhancement and a long stability period. The azo group can be specifically reduced under hypoxic microenvironments, a common feature of many diseases, which confers the excipient with hypoxia-triggered release due to the remarkable decrease in binding affinities following reduction. The fast release kinetics further facilitates the efficient accumulation of drugs at the lesion site. Furthermore, azocalixarenes offer a broad molecular modification space, allowing for the enhancement of targeting, biocompatibility, and adaptability to different diseases.

Keywords: Pharmaceutical Excipients; Hypoxia-responsive; Supramolecular chemistry; Host-guest; Azocalixarene

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One-pot green fabrication of multifunctional chlorella-peg-gelatin hydrogels with anti-dreezing, infection-preventive, and immunomodulatory properties for diabetic wound healing

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Abstract: Wound dressings need to inhibit the accumulation of reactive oxygen species, inflammation and bacterial infection in the hyperglycemic microenvironment of wounds, which leads to a complicated and expensive preparation process that does not cater to the problems of commercial production. Therefore, a multifunctional wound dressing that can solve these problems is required to facilitate diabetic wound healing. In this study, a one-pot hydrogen bonding-guided self-assembly method was performed to prepare injectable hydrogels (CPGel hydrogels) with infection prevention, immunomodulation and extreme low temperature tolerance by compounding PBS-Chlorella extract and PEG-Chlorella extract with gelatin. The PEG introduced to hydrogels enables the application range of -100 °C and, furthermore, both injectability and robust mechanical properties. Chlorella provided hydrogels with efficient anti-infective, reactive oxygen species scavenging, and immunomodulatory effects, thereby protecting cells from oxidative damage and suppressing inflammation by inducing M1-to-M2 macrophage polarization. In addition, the synergistic effect of the two contributes to the excellent antimicrobial and high-quality healing properties of CPGel for wound healing (massive collagen I deposition and skin appendage regeneration). This indicates that the CPGel hydrogel has the potential to be a bioactive dressing for diabetic wounds while being produced on a large industrial scale.
Keywords: Chlorella; anti-freezing; immunomodulation; anti-infection; diabetic wound healing

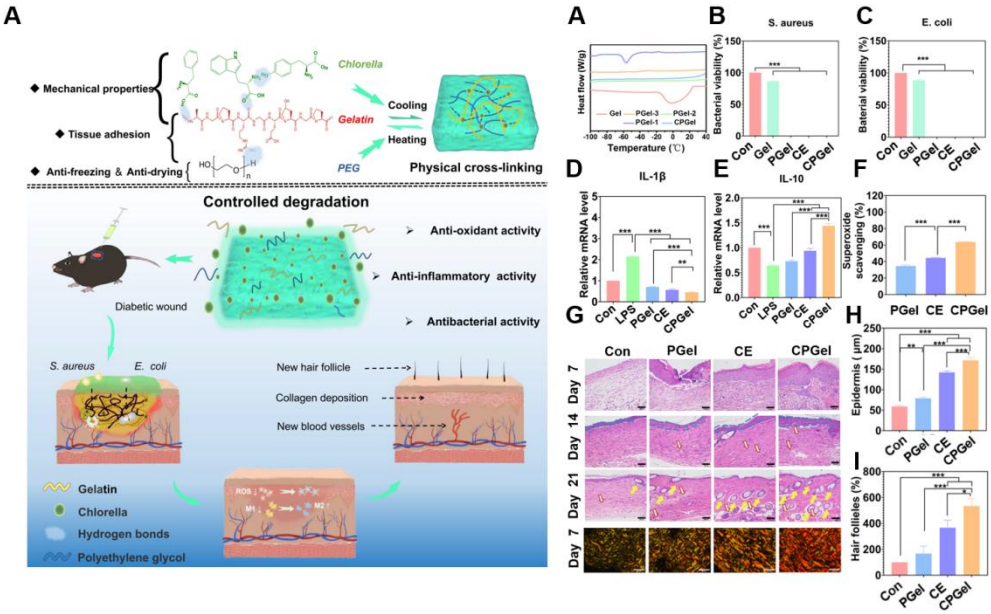

Figure. 1 Molecular design of the CPGel hydrogels and schematic representations of their multifunctional treatment of diabetic wound healing (left) and CPGel hydrogel for infection prevention, immunomodulation and extreme low temperature tolerance (right).

Precise engineering of disulfide bond-bridged prodrug nanoassemblies to balance antitumor efficacy and safety

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Abstract: Prodrug-based nanoassemblies, which combine the merits of prodrug technology and nanocarriers, are regarded as promising platforms for cancer treatment. Notably, the chemical structure of prodrugs is closely associated with antitumor efficacy and safety, and the intrinsic relationships among them need further exploration. Herein, paclitaxel was conjugated with 2-octyldodecan-1-ol through different positions of disulfide bond to construct the prodrug nanoassemblies. Interestingly, the minor differences in chemical structure not only dominated the assembly performance and drug release of nanoassemblies, but also significantly impacted the pharmacokinetics, antitumor efficacy, and safety. It was worth noting that prodrug nanoassemblies with one carbon atom between disulfide bond and ester bond had faster drug release and better antitumor effect, while prodrug nanoassemblies with three carbon atoms between disulfide bond and ester bond possessed moderate antitumor effect and better safety. Our findings illustrated the structure-function relationships of self-assembled prodrugs and provided a promising paradigm for the precise engineering of advanced prodrug nanoplatforms.
Keywords: disulfide bond; prodrug-based nanoassemblies; efficacy; safety; antitumor therapy

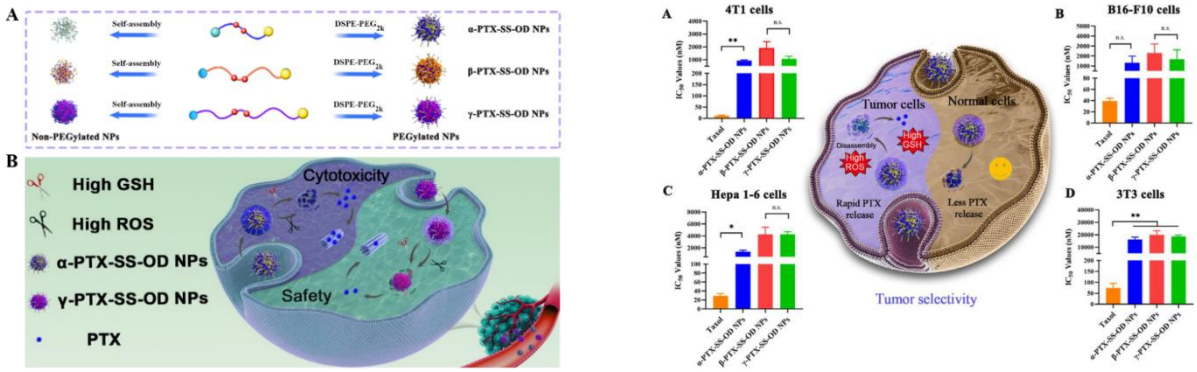

Figure. 1 Schematic illustration. Precise engineering of disulfide bond bridged prodrug nanoassemblies to balance antitumor efficacy and safety (Left); and cytotoxicity of prodrug nanoassemblies (Right).

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P7C3 Ameliorates Bone Loss by Inhibiting Osteoclast Differentiation and Promoting Osteogenesis

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Abstract: Bone homeostasis, the equilibrium between bone resorption and formation, is essential for maintaining healthy bone tissue in adult humans. Disruptions of this process can lead to pathological conditions such as osteoporosis. Dual-targeted agents, capable of inhibiting excessive bone resorption and stimulating bone formation, are being explored as a promising strategy for developing new treatments to address osteoporosis. In this study, we investigated the effects of P7C3 on bone remodeling and its potential therapeutic role in osteoporosis treatment in mice. Specifically, P7C3 can remarkably suppress receptor activator of nuclear factor-kB (NF-kB) ligand (RANKL)-induced osteoclast differentiation in bone marrow macrophages via the Akt-NF-κB-NFATc1 signaling pathway. Additionally, RNAseq analysis revealed that P7C3 promoted osteoblast differentiation and function through the Wnt/β-catenin signaling pathway, thereby enhancing bone formation. Furthermore, micro-CT analysis and histological examination of bone tissues from P7C3-treated mice showed attenuation of both Ti-induced bone erosion and OVX-induced bone loss. These findings suggest that P7C3 may have a novel function in bone remodeling and may be a promising therapeutic agent for the treatment of osteoporosis.

Keywords: P7C3, osteoporosis, osteoclast differentiation, osteoblast differentiation

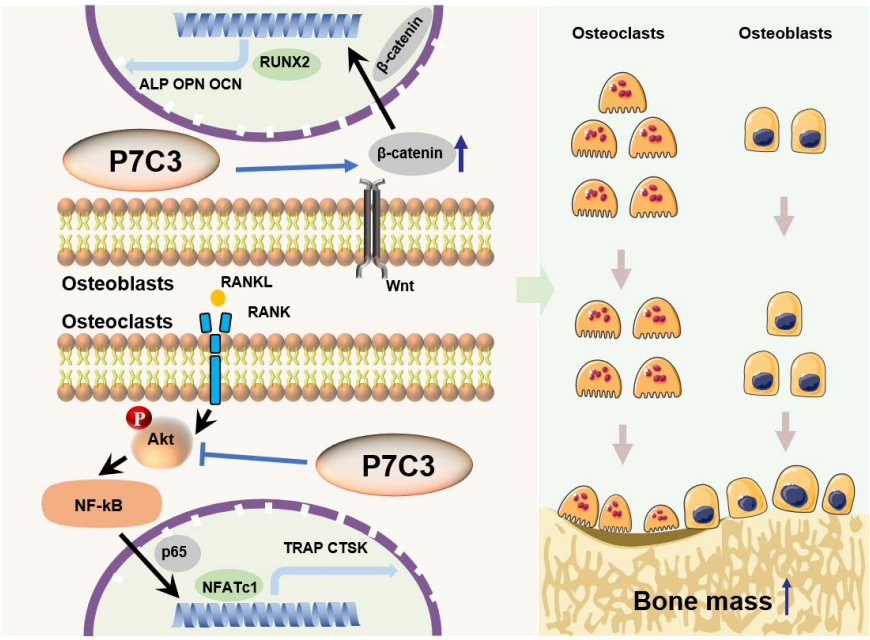

Figure. 1 Schematic model outlining the actions of P7C3 on bone. The molecular mechanism of P7C3 in inhibiting osteoclast differentiation and promoting osteoblast differentiation (left) and regulating bone remodeling by suppressing bone resorption and promoting bone formation to increase bone mass (right) have been demonstrated.

Microbe-assisted materials for the treatment of major diseases

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Abstract: The symbiotic microbial communities within the human body are highly prevalent in various regions, including the intestines, oral cavity, and skin. Once the symbiotic microbial community is imbalanced, it can affect various physiological functions in the human body, such as energy absorption, endotoxin production, short-chain fatty acid production, and can lead to diseases such as malignant tumors and metabolic disorders[1] Currently, one of the most promising methods for regulating these microbial communities is through active microbial therapy. However, these therapies are hindered by issues related to the poor functionality and safety of the active microorganisms, thus necessitating further improvements. From a chemical perspective, microbes are complex macromolecular systems composed of nucleic acids, proteins, and polysaccharides. By utilizing mild polymer modification methods, it is possible to construct multifunctional and highly safe microbe-assisted materials for the treatment of major diseases. Based on this design concept, we have conducted a series of systematic studies focused on the construction methods and application areas of active microbial materials. To merge the advantages of polymer materials and microorganisms, we have developed a range of methods for preparing microbe-assisted materials using biorthogonal chemistry, Schiff base chemistry, physical forces such as hydrophobic interactions and host-guest interactions. For this reason, we introduced the advanced functions of microbes to construct a series of microbe-assisted materials known as microbe-assisted materials for disease treatment: 1) developed construction methods for microbe-assisted materials by integrating the advantages of polymeric materials and microbes; 2) proposed a new treatment strategy based on microbe-assisted materials, "treating bacteria with bacteria," to regulate the tumor microbiota for improved efficacy; 3) introduced a new concept of treatment based on "bacteria replacement therapy" to orally degrade toxins in kidney failure.

Keywords: Life-unit involved polymer; Microbe-assisted materials; Polymer/microbes hybrid materials; Symbiotic microbiota; Cancer treatment

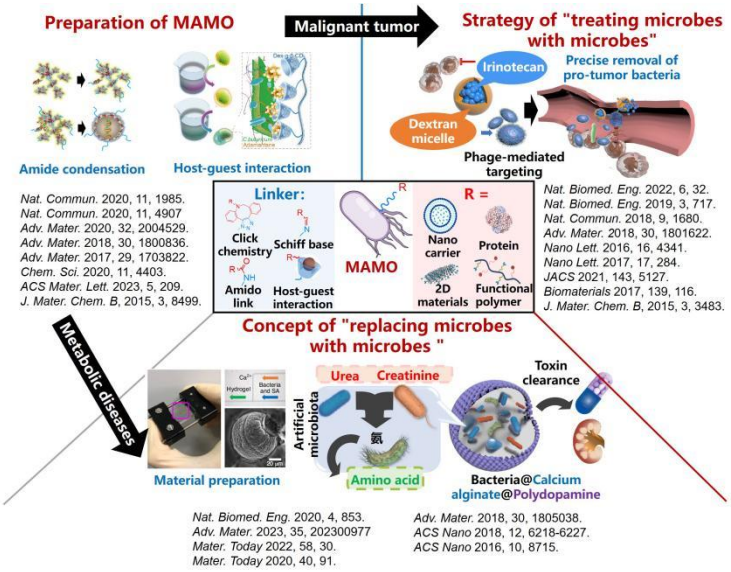

Figure. 1 Research directions for microbe-assisted materials.

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Novel targeted resveratrol nanocrystal liposomes for anti-hepatic fibrosis

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Abstract: Nanocrystals (NCs) enable the delivery of poorly water-soluble drugs with improved dissolution and bioavailability. In this study, a drug delivery system composed of nanocrystal and liposome is presented, which merges the advantages of drug nanocrystals (high drug loading) and liposomes (easy surface functionalization and high stability) for targeted delivery of hydrophobic drugs to liver fibrosis site. Resveratrol (3,5,4′-trihydroxy-trans-stilbene) is a polyphenolic compound that has been shown to exert various pharmacological actions, such as inhibiting collagen deposition, improving liver function, and alleviating hepatic injury. However, resveratrol has limited its application in the medical field due to its poor water solubility and low bioavailability. In the present work, resveratrol nanocrystals were prepared by micro-media milling method, which improved the dissolution rate and bioavailability of resveratrol. The resveratrol nanocrystals were loaded into vitamin A-modified liposomes, which further improved the stability of the nanocrystals and endowed the nanocrystals with the ability to target hepatic stellate cells. VA-Lipo@Res-NC combines many advantages of nanoparticles and liposomes, and has its own unique advantages, such as the advantages of high drug loading efficiency, good stability, facile modification of lipid layers and excellent biocompatibility, which improved the bioavailability and significantly enhance the anti-hepatic fibrosis effect of Res.

Keywords: Resveratrol, Nanocrystals, liposomes, mini-media milling technique, anti-hepatic fibrosis

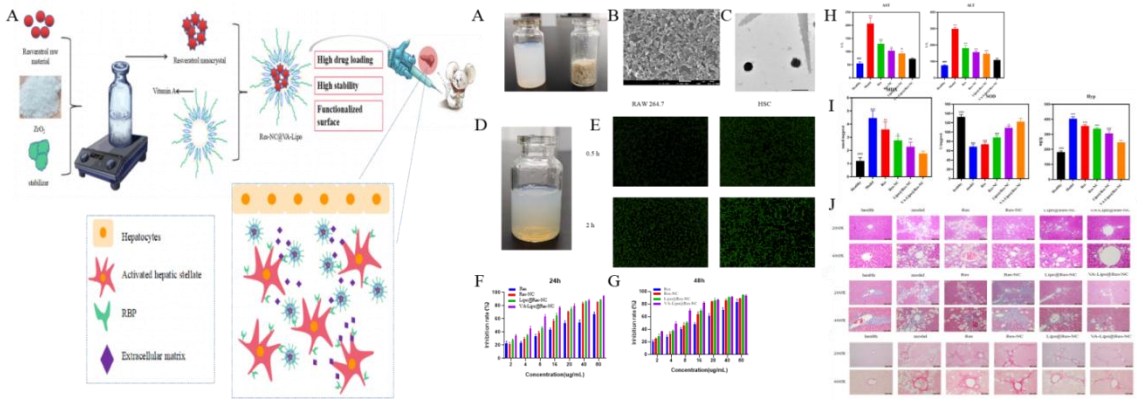

Figure. 1 The construction of resveratrol nanocrystalline liposome targeted drug delivery system (VA-Lipo@Res-NC)with its drug release mechanism (Left); and The characterize of drug delivery system and the results of drug delivery system at animal and cellular levels (Right).

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Localized imaging of PD-L1 on individual tumor-derived exosomes for prediction of immunotherapy response

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Abstract: Tumor-derived exosomal PD-L1 is a promising biomarker for prediction of immunotherapy response. However, conventional bulk measurement can hardly analyze the expression of PD-L1 on individual tumor-derived exosomes. Herein, a method for localized imaging of tumor-derived individual exosomal PD-L1 (LITIE) is developed. In this assay, exosomes in plasma were directly captured by a biochip. Then a liposome-mediated membrane fusion strategy was used to image miR-21 in exosomes to discriminate tumor-derived exosomes from the whole exosome populations. Subsequently, primer exchange reaction (PER) is applied to generate localized and amplified fluorescent signals for imaging PD-L1 on identified tumor-derived exosomes. When applied in clinical sample test, LITIE assay could effectively distinguish breast cancer patients from healthy donors or patients with benign tumors. Interestingly, in a mice melanoma model, LITIE showed ability to predict immunotherapy response even before drug treatment. Thus, we think the strategy of measuring individual tumor-derived exosomal PD-L1 could serve as a promising way for screening of clinical responders suitable for immunotherapy.

Keywords: exosomal PD-L1, predictive biomarker, liquid biopsy, dual-target recognition, signal amplification

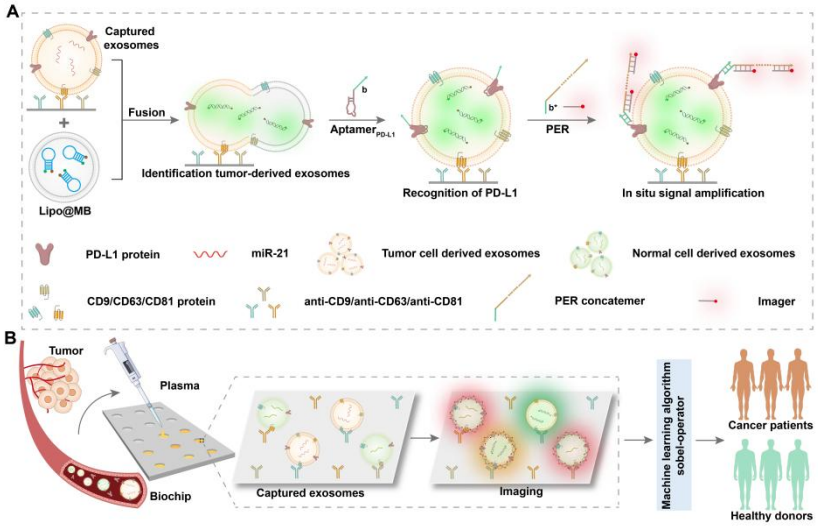

Figure. 1 Concept and design of LITIE assay. (A) The workflow illustration of LITIE assay for simultaneous detection of PD-L1 protein and miR-21 in individual exosomes. (B) Schematic procedure of LITIE assay.

Reference:

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Mitochondrial targeted prodrug nanoparticles for chemo-photodynamic combinational tumor therapy

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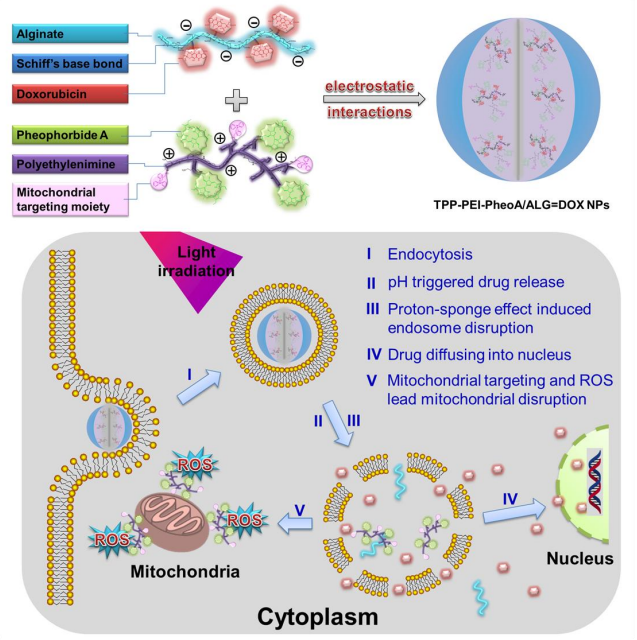
Abstract: Nanoparticles have been explored recently as an efficient means of delivering chemotherapeutic drugs and photosensitizers for cancer chemotherapy and photodynamic therapy. Herein, pH and light dual responsive mitochondrial targeted prodrug nanoparticles were designed to delivery both chemotherapeutic drugs and photosensitizers for enhanced antitumor efficacy. The prodrug nanoparticles (TPP-PEI-PheoA/ALG=DOX NPs, TPPAD NPs) are composed of a light responsive mitochondrial targeted prodrug (triphenylphosphonium and pheophorbide A modified polyethyleneimine, TPP-PEI-PheoA) and a pH-responsive prodrug (doxorubicin conjugated alginate with Schiff's base bond, ALG=DOX). TPPAD NPs were prepared through electrostatic interaction. This prodrug nanoparticles platform owns the following key characteristics: (1) TPPAD NPs could simultaneous delivery DOX and PheoA to the tumor site by passive targeting effect, (2) TPPAD NPs could release drugs in a designed mode and delivery drugs to the target organelles, (3) TPPAD NPs based PDT could induce immunogenic cell death of the tumor cells, thus activating the immune system, (4) TPPAD NPs greatly enhanced antitumor efficacy by combinational therapy. Taken together, this prodrug nanoparticle platform has appeared to be a simple and smart nanomedicine for targeted tumor combinational treatment.

Keywords: pH responsive; light responsive; prodrug nanoparticles; mitochondria-targeting; combined therapy



Alkyl chain length-regulated *in situ* intelligent nano-assemblies with AIE-active photosensitizers for photodynamic cancer therapy

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[1] L. Shen and Q.-L. Zhang contributed equally to this work.

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Abstract: Photodynamic therapy (PDT) bring new hope for the treatment of breast cancer due to few side effects and and highly effective cell killing, but the poor biocompatibility, low tissue penetration, low tumor specific targeting, and their dependence on oxygen severely limits of traditional photosensitizers (PSs) with, leading to their limited application in vivo. In this study, a series of Aggregation-induced emission (AIE) photosensitizers based on pyridinium-substituted triphenylamine salts (abbreviated to TTPA **1-6**) with different alkyl chain lengths are synthesized. Results reveal that TTPA **1-6** promote type I and type II reactive oxygen species (ROS) generation, including ·OH and $^1O_2$, implying their potential for photodynamic therapy under both aerobic and anaerobic conditions. Moreover, TTPA **4-6** with longer alkyl chains can assemble with albumin thereby forming nanoparticles (TTPA **4-6** NPs) in situ in blood, which significantly facilitates mitochondrial-targeting and strong ROS generation ability. In addition, the TTPA **4-6** NPs are pH responsive allowing for increased accumulation or endocytosis of the tumor, enhancing the imaging or therapeutic effect. Therefore, the in vivo distributions of TTPA **4-6** nanoparticles are visually enriched in tumor sites and exhibited excellent photodynamic cancer therapy efficacy. This work demonstrates a novel strategy for AIE photodynamic therapy, and has the potential to play an essential role in clinical applications using nano-delivery systems.

Keywords: Aggregation-induced emission; Photosensitizers; Photodynamic therapy; ROS generation; Self-assembled nanoparticles

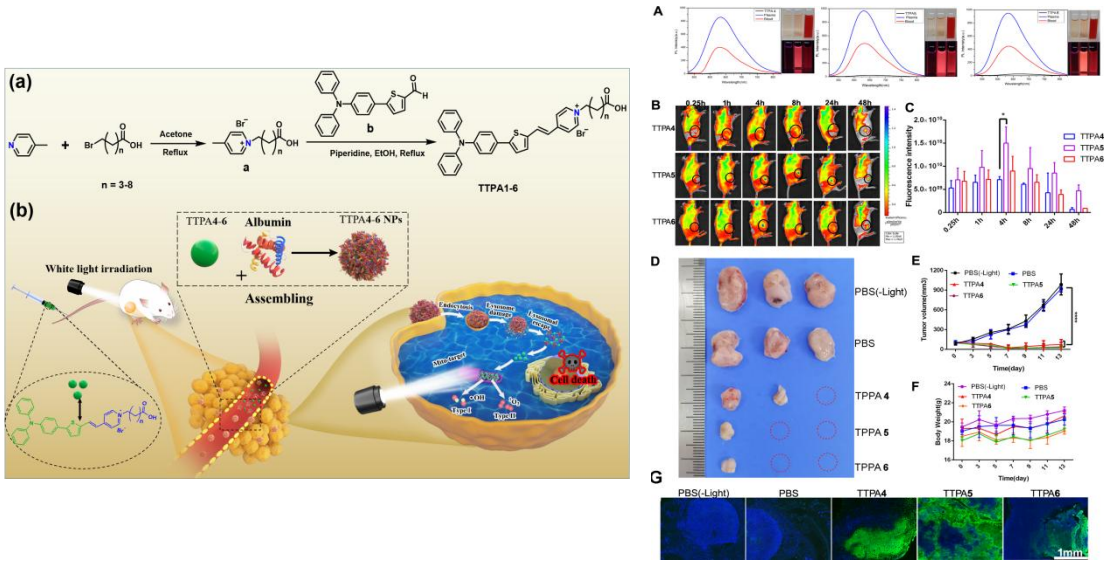

Figure. 1 Schematic diagram of the synthesis of TTPA **1-6** (left); and AIE-active photosensitizers mediated photodynamic cancer therapy (right).

PLGA particle-based drug or vaccine delivery system: our efforts on the basic and applied research

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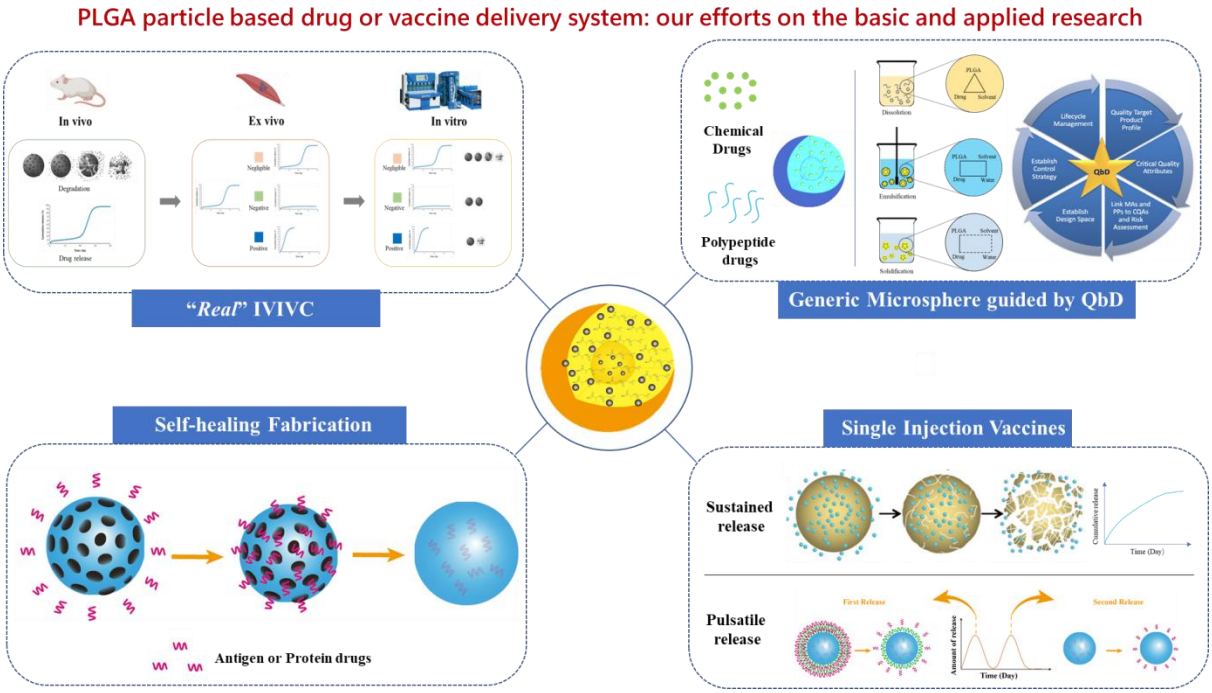
Abstract: PLGA, as a famous biodegradable and biocompatible pharmaceutical excipient, has been widely used in various delivery carriers. PLGA microspheres can sustainedly release active pharmaceutical ingredient, making them a dosage form with significant clinical advantages and a hot topic in the modified new drugs research area. However, PLGA microspheres are also a formulation difficult to develop. The *in vivo* release complexity greatly limited PLGA microsphere development. Not only is there a lack of innovative microspheres, generic microspheres have not yet been listed on the marketed.

Changes in polymer and drug properties and process parameters may change the *in vivo* performance, while the current *in vitro* release methods can hardly respond to the *in vivo* changes of microspheres in material attributes or process parameters. We established an *in vitro* release method that revealed not only the drug cumulative release but also the morphology change of PLGA microspheres, in order to achieve high-throughput PLGA microsphere screening that closely correlates with the *in vivo* performance.

Based on the understanding of the forming and release mechanism, we further extended our research work on PLGA particles from loading chemical drug to the peptide drug and to the construction of novel pulsatile release vaccine. A drug delivery technology platform based on PLGA particle formulations took an initial shape though our work in past 5 years.

Keywords: PLGA; microparticle; innovative vaccine; modified new drugs; generic drugs; release kinetics



Self-Assembly of a Linear-Dendritic Polymer Containing Cisplatin and Norcantharidin into Raspberry-Like Multi-Micelle Clusters for the Efficient Chemotherapy of Liver Cancer

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Abstract: Combination chemotherapy has been proved to be an effective strategy in the clinic, and nanoformulations have drawn much attention in the field of drug delivery. However, conventional nanocarriers suffer from shortcomings such as inefficient co-loading and undesired molar ratio of the combined drugs, pre-leakage of cargoes during systemic circulation, and lack of cancer-selective drug release. To achieve tumor-specific codelivery of cisplatin (CDDP) and norcantharidin (NCTD) for synergistic treatment of liver cancer, a novel linear-dendritic polymer, termed as G1(PPDC)x, was designed and synthesized, where a prodrug consisting of CDDP and NCTD was conjugated to PEG2000 via ester bond to fabricate linear polymer-drug conjugates, and the conjugates were subsequently grafted to the terminal hydroxyls of a dendritic polycarbonate core. Benefiting from the hydrogen bond interactions, G1(PPDC)x could spontaneously self-assemble into a unique type of raspberry-like multi-micelle clusters in solution (G1(PPDC)x-PMs). G1(PPDC)x-PMs possessed an optimal synergistic ratio of CDDP and NCTD, and without obvious premature release or disassembly in biological environments. Intriguingly, upon extravasation into the interstitial tumor tissues, G1(PPDC)x-PMs (132 nm in diameter) could disassemble and reassemble into smaller micelles (40 nm in diameter) in response to the mildly acidic tumor microenvironment, which would enhance the deep tumor penetration and cellular accumulation of drugs. In vivo delivery of G1(PPDC)x-PMs leaded to significantly prolonged blood circulation half-life, which is beneficial to achieve sufficient tumor accumulation through the enhanced permeability and retention (EPR) effect. G1(PPDC)x-PMs displayed the best antitumor activity in H22 tumor-bearing mice with a tumor inhibition rate of 78.87%. Meanwhile, G1(PPDC)x-PMs alleviated both myelosuppression toxicities of CDDP and vascular irritation of NCTD. Our results demonstrated that G1(PPDC)x-PMs could serve as an effective drug delivery system for co-delivery of CDDP and NCTD to treat liver cancer efficiently.

Keywords: cisplatin, norcantharidin, raspberry-like multi-micelle clusters, penetration, myelosuppression

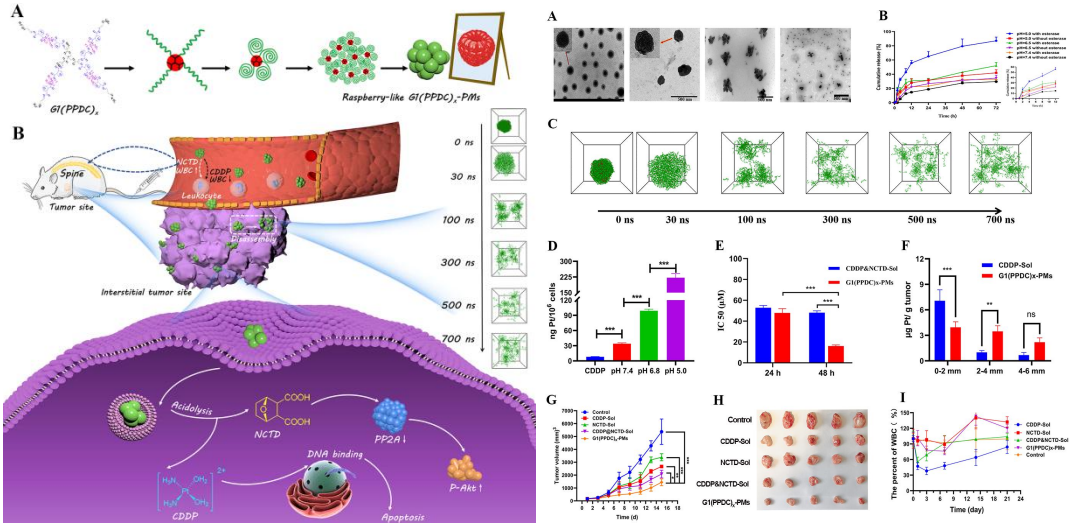

Figure. 1 Schematic illustration of raspberry-like G1(PPDC)x-PMs formation from G1(PPDC)x and its *in vivo* synergetic treatment of liver cancer (left); and the enhancement of intracellular uptake and penetration into deep tumor sites by the pH and esterase-triggered size reduction of G1(PPDC)x-PMs, and the superior antitumor effect as well as the alleviative myelosuppressive toxicity of G1(PPDC)x-PMs (right).

基于喷雾干燥技术制备 Q1/Q2 型长效控释 PLGA 微球：粒子形成、长效释放与体内外突释效应

时念秋

摘要：长效释放（LAR）制剂是控制生物大分子（如多肽蛋白类）释放的重要策略。LAR 制剂已经有多款产品成功上市，如 Lupron Depot®（LD）等。喷雾干燥技术属于可控的连续制备技术，具有复杂的时空动力学和热质转换特征，呈现独特的粒子设计及形成特性。根据美国 FDA 新药注册要求，基于 PLGA 研发的微球制剂必须定性地（Q1）和定量地（Q2）与参考药物相同。深入理解喷雾干燥过程参数对微粒工程化特性及释药行为等性质影响至关重要。本研究利用 ProCepT 4M8-TriX 型双流喷头/共流式雾化气流模式的喷雾干燥仪进行基于 Q1/Q2 理念的长效微球研发，考察喷雾干燥过程参数的影响，并探讨其粒子形成特征、长效释放及体内外突释效应机制。前期通过“反向工程”识别市售 LD（7.5mg，1 个月缓释）的关键成分。本课题利用喷雾干燥设备综合考虑喷头动力学、雾化动力学与送料动力学等方面制备众多符合 Q1/Q2 标准的 PLGA 亮丙瑞林微球。综合分析了雾化室温度（T_{inlet}）、送料浓度（C_{feed}）、喷头气流（AF_{nozzle}）、气液流速比（$Ratio_{A/L}$）、喷头尺寸（S_{nozzle}）及送料温度（T_{feed}）等过程参数对于工程化微粒性质、药物长效释放动力学及体内外突释效应的影响。本研究阐明了喷雾干燥过程参数对微球理化性质及释药行为的综合影响，有助于理解利用喷雾干燥进行微粒设计的工程化特征、时空动力学及药物释放行为，并为应用喷雾干燥技术进行符合 Q1/Q2 理念的长效微球研发提供了重要理论参考。

基于细菌的抗肿瘤递药系统

金义光

目前活菌制剂主要是调节肠道微生态平衡的益生菌制剂和免疫接种用活菌疫苗。本文研究了基于活菌和菌影的抗肿瘤递药系统及其在肺癌治疗中的应用。

细菌具有抗肿瘤作用，但抗肿瘤效果有限，普通给药方式易被免疫系统清除。本文用电致孔法将紫杉醇脂质体载入大肠杆菌和干酪乳杆菌，包封率高，细菌活性好。两种载药细菌制剂具有促进 A549 细胞凋亡效果，表明细菌作载体增强了紫杉醇脂质体进入细胞。将细菌、紫杉醇脂质体、细菌和紫杉醇脂质体混合物以及载紫杉醇脂质体细菌制剂对原发性肺癌大鼠进行肺部给药，各组制剂均促进肿瘤细胞凋亡，减少 VEGF 表达，促进 TNF-α、IL-4、IFN-γ等因子产生，其中载紫杉醇脂质体细菌制剂效果最强。因此肺吸入载药细菌制剂可通过化疗和免疫增强作用发挥抗肺癌作用。

针对细菌制剂可能存在的安全性问题，本文进一步制备了以大肠杆菌菌影作为药物载体的递药系统。通过电致孔法将紫杉醇脂质体载入菌影，进一步包裹了 4T1 乳腺癌细胞膜，得到 LP@BG@CCM，体外表现出高效进入 4T1 细胞能力和显著抗 4T1 细胞效果。在 4T1 转移性肺癌小鼠模型上，静脉注射的 LP@BG@CCM 可靶向分布于肺，对转移性肺癌有强的抑制作用，有效激活脾脏中 $CD4^+$ T 细胞和 $CD8a^+$ T 细胞。LP@BG@CCM 通过靶向、免疫刺激和高效抗发挥抗肿瘤作用，为抗肿瘤治疗提供了新策略。

冻溶结晶法制备超细晶体吸入剂研究

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报告简介：

药物的吸收除了受其自身性质影响外，在很大程度上还取决于药物颗粒尺寸、形貌、分散性以及表面状态等。固体药物经过超细化加工后，与常规药物相比较，具有提高口服制剂的溶出速率、增强药物的靶向性和定位能力、实现药物的控释、增加吸入药物的肺部沉积量等优点。本研究报告了使用冻溶结晶法制备粒度可调的吸入型超细晶体。研究了目标药物结晶溶液的初始浓度、冻溶体积、搅拌、添加剂对制备超细晶体的关键影响参数。结果表明，冻溶法可以所得超细晶体产品为粒度均一，圆度值在 0.6~1.0 之间， CV 值在 20%~30%，平均粒径范围可调控在 1~10μm，晶型唯一，适合将其开发为吸入给药剂型，尤其适合开发为干粉吸入剂，工艺稳健，无须气流粉碎等后造粒过程，节能环保，可实现规模化制备生产。

Mesenchymal Stem Cells as Targeting Drug Delivery System for Pulmonary Disease Treatment

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Abstract: Pulmonary disease, such as lung metastasis, pulmonary fibrosis, and acute respiratory distress syndrome, is one of the most common diseases in clinic, facing challenges of high lethality rate and limited therapeutic options. Mesenchymal stem cells (MSCs) have elicited considerable attentions for the treatment of lung disease, showing advantages of inherent lung accumulation through systemic administration and inflammatory cells-selected homing, as well as a relative long-term adhesion in diseased lungs. We previously demonstrated that MSCs can be a potent gene delivery carrier to treat lung metastasis, showing the ability of not only targeting to the metastatic sites but also penetrating into the inside of metastatic nodules. We further developed the iron oxide nanoparticles (IONPs) modified MSCs for a highly efficient and targeted mitochondrial delivery to injured alveolar epithelial cells, providing a novel strategy to mitigate the pulmonary fibrosis. The engineering using IONPs was observed to augment both the homing and intercellular drug delivery capability of MSCs, which was mainly due to the overexpression of both C-X-C chemokine receptor type 4 and connexin 43 by engineered MSCs. In addition, we recently developed a biomimetic nanovehicle hybridizing the cell membrane of MSC with liposome. This hybrid nanovehicle shows advantages of both highly efficient inflammation targeting and good drug loading capacity, achieving a specifically targeted delivery of methylprednisolone to inflammatory damaged lung cells and resulting in a prominent suppression of lung inflammation. To conclude, MSCs as well as their biomimetic nanovehicles can be a novel cellular vehicle for the targeting therapy of pulmonary disease.

Keywords: Mesenchymal stem cell; Targeting; Drug delivery; Vehicle; Pulmonary disease;

基于仿生策略的纳米递送系统

魏华

报告摘要：

基于“原料仿生”、“拓扑结构仿生”和“功能仿生”三位一体的新型药物递送策略，发展了一系列兼具胞外血液循环稳定性和胞内可高效释放治疗试剂的智能仿生载体，在体内外实现了针对肝癌等重大疾病的高效治疗。通过“原料仿生”策略，发展了一系列基于环糊精的超分子纳米递送系统，实现了高效的化疗和联合治疗[1-3]。通过“拓扑结构仿生”策略，发展了一系列具有增强胶体稳定性的环状拓扑结构纳米载体，实现了优于传统线形拓扑结构纳米载体的治疗效果[4-6]。通过“功能仿生”策略，发展了具有线粒体靶向功能的自递送系统，高效逆转肿瘤耐药[7]。

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Proton-Catalyzed Self-Assembly of Peptides for Combating Drug Resistance of Cancer

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Abstract: Formed by noncovalent interactions and not defined at the genetic level, the self-assembly of small molecules is emerging as a novel biological entity. However, spatiotemporal control of the formation of intracellular assemblies of small molecules in living cells remains challenging due to the heterogenous, crowded, dynamic cellular microenvironment. To address this long-standing challenge, we developed proton-catalyzed self-assembly to control intracellular assemblies formation in living cells. Taking advantage of the acid-catalyzed hydrolysis of phosphodiamidate derivatives and the acidic environment of the lysosome, the designed precursors resist the hydrolysis by extracellular and cytoplasmic enzymes. In the acidic environment of living cells, the hydrolysis of the P-N bond of precursors releases the native substrate of the enzyme, thus enabling the enzyme to induce the nanofiber formation inside the living cell where the enzyme exists. Furthermore, introducing a pH-sensitive host-guest complex in our system could control the assemblies formation kinetically in cancer cells selectively and escape from lysosomes to self-assemble on mitochondria, which generates cytotoxic nanostructures on the mitochondria of cancer cells and induce cancer cell death mainly through ferroptosis. The established design strategy promises a fundamentally new approach to designing functional assemblies in biological systems with high spatiotemporal specificity.

Keywords: self-assembly; peptide; proton-catalyzed; cancer therapy

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Construction of BCS Classification System for Natural Products Based on Prediction and Verification of Physical and Chemical Properties and Exploration Drug-like Properties

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Abstract: Natural products are treasures of ethnic medicine, in which a huge number of new structural entities have been discovered. In further drug efficacy screening, high biological activity is often pursued excessively, while absorption, distribution, metabolism, excretion, and toxicity (ADMET) are neglected. ADMET can be predicted using compound structure based software with good accuracy. However, the above calculation models are based on a large number of drug molecules obtained through chemical synthesis methods and validated through ADMET experiments. To address the issue of uncertainty in the accuracy of natural product prediction models, we conducted a correlation verification project between the predicted and measured results of 2432 active natural products from 49 plant species and 9 major structural types. On this basis, a BCS classification database for natural products was constructed, which can provide reference for further evaluation of drug-like properties. The above achievements provide support for ensuring the accuracy of the predicted physical and chemical properties of natural products.

Orally administrable H2S-scavenging metal-organic framework prepared by co-flow microfluidics for comprehensive restoration of intestinal milieu

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Abstract: Intestinal milieu disorders are strongly related to the occurrence of inflammatory bowel diseases (IBDs), which results from mucosa destruction, epithelium disruption and tight junction (TJ) proteins loss[1]. Excess of H_2S in the intestinal milieu produced by sulfate-reducing bacteria metabolism contributes to IBDs development *via* epithelial barrier breakdown. Conventional interventions, such as surgery and anti-inflammatory medications, are considered not completely effective because of frequent recurrence and other complications[2]. Herein, a novel oral delivery system, a hydroxypropyl methylcellulose acetate succinate (HPMCAS)-based polymer-coated Zr-based metal-organic framework (UiO-66) with a Cu_x-rhodamine B (CR) probe (hereinafter referred to as HUR), was produced *via* co-flow microfluidic assistance with ability to reduce H_2S levels, thus restoring the intestinal lumen milieu. HPMCAS serves as an enteric coating that exposes UiO-66@CR at the pH of the intestine but not the acidic pH of the stomach. The synthesized HUR exhibits notable therapeutic efficacy, including mucosa recovery, epithelium integrity restoration and TJ proteins up-regulation *via* H_2S scavenging to protect against intestinal barrier damage and microbiome dysbiosis. Thus, HUR has been verified to be a promising theranostic platform able to decrease the H_2S content for intestinal milieu disorder treatment. The presented study therefore opens the door for further exploitation for IBDs therapy.

Keywords: intestinal milieu restoration, hydrogen sulfide scavenging, Zr-MOF, microfluidic technology, inflammatory bowel disease

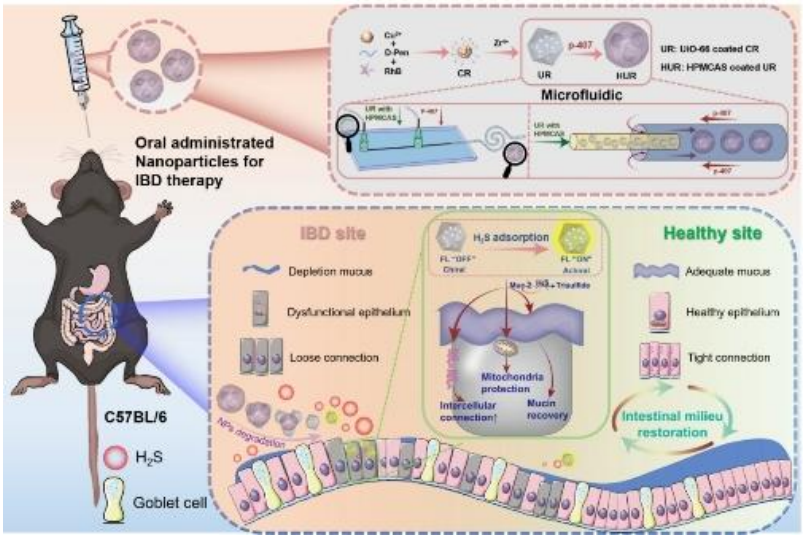

Figure. 1 Schematic illustration of the preparation of HUR and mechanisms of its activity in the treatment of IBDs.

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Construction of HPMC-modified supramolecular assembly for oral administration and evaluation of brain targeting ability

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Abstract: This study utilized HPMC and soybean phospholipids to self-assemble into a HPMC-modified supramolecular assembly(HPMC/SAS) with a shell-core structure by van der Waals force. The self-assembly technology was achieved through the "emulsification dispersion-solvent evaporation" method. The conformation, energy, and steady state of HPMC/SAS were first predicted using molecular dynamics simulations. The structure of the supramolecular assembly was then confirmed by TEM and DSC. Finally, indocyanine green (ICG) was used as a fluorescent probe to evaluate the potential of HPMC/SAS as a novel brain targeted drug delivery system through oral delivery. The results showed that the self-assembled structures of HPMC and phospholipid were mainly maintained by van der Waals interaction (vdW), and the electrostatic interaction was relatively weak.The hydrophilic heads of the phospholipid molecules were exposed to the solvent environment, and the hydrophobic tails were wrapped by HPMC molecules, forming a tight complex system which showed a spherical shell-core structure by TEM observation. After oral administration of ICG loaded HPMC/SAS, the distribution of fluorescence in the whole brain and brain sub-regions were evaluated at 15min and 45min, and the brain targeting potential of oral HPMC/SAS was investigated compared with conventional oral liquid preparations such as ICG solution, liposome suspension and emulsion. At 15min and 45min, HPMC/SAS group had the most fluorescence distribution in the whole brain compared with solution group, liposome suspension group and emulsion group. By semi-quantitative analysis, the fluorescence intensity of the HPMC/SAS group was 2 times at 15min and 1.17 times at 45min than that of the liposome group. After oral administration of ICG-loaded HPMC/SAS, the fluorescence signals were mainly distributed in the medulla oblongata, cerebral cortex and striatum. This specific distribution of brain sub-regions showed that the fluorescence signal increased with time, and some fluorescence distribution was also observed in the hippocampus, midbrain and thalamus, which confirmed that oral HPMC/SAS had a tendency to distribute along the brainstem region to the parietal cortex. The results of this study indicated that HPMC/SAS, as a supramolecular polymer, has specific brain accessibility after oral administration, and is expected to become a new oral brain targeted drug delivery system.

Keywords: self-assembly, oral administration, HPMC, supramolecular polymer, brain targeting

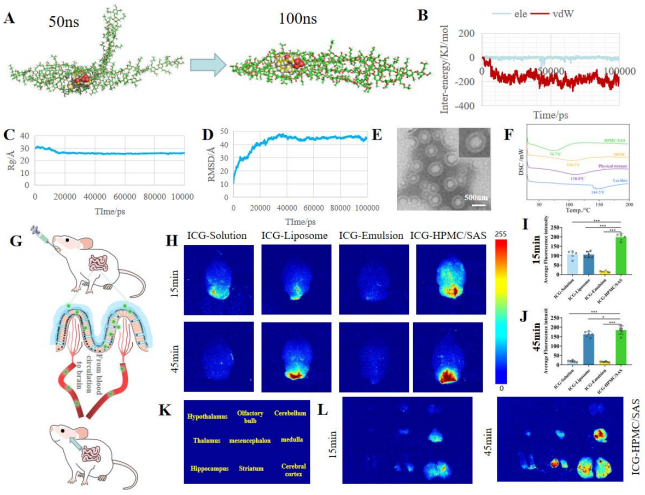

Figure 1.Construction, characterization analysis and brain targeting ability of HPMC-modified supramolecular assembly for oral administration

Functionalized SWCNTs as targeted co-delivery carriers to enhance the anti-ancer efficacy by mediating chemotherapy in coordination with photothermal therapy

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Abstract: Nowadays, more and more nanomaterials are widely used in antitumor research and application field. Among these, single-walled nanotubes (SWCNTs) can be utilized for targeted drug delivery as the potent vehicles. In addition, SWCNTs have an excellent light absorption characteristic in the near infrared area (NIR, 700-1400 nm), which can increase the temperature in medium environment to reach or exceed the thermal ablation temperature of tumor cells to realize the hyperthermia. In this study, pristine SWCNTs were acidized by nitric acid and the shortened products (CNTs) were modified with NH_2-PEG_{2000}-NH_2 and folic acid (FA), to improve their biocompatibility and targeting effect. The resulting SWCNTs-PEG-FA were further coated by phase-change material (PCM)-1-Tetradecanol (TD) to adsorb photosensitizer indocyanine green (ICG) on the surface of nanotubes. The final SWCNTs-PEG-FA-ICG/TD (CNTs-PFI/T) and other functionalized carriers were characterized and assessed in term of various properties. The results showed that compared with the pristine ones, all the modified SWCNTs had better monodispersity, stability and biocompatibility. Especially, CNTs-PFI/T exhibited the more excellent physical and chemical properties, as well as prominent photothermal conversion performance under NIR laser irradiation (808 nm). *In vitro* experiment results demonstrated that CNTs-PFI/T@DOX could induce the apoptosis of MCF-7 cells and affect the cycle distribution more efficiently than free DOX or other SWCNTs nano-formulations, by mediating the coordination of chemotherapy and hyperthermia. In tumor-bearing model animals, CNTs-PFI/T@DOX similarly exhibited the highest antitumor activities among all the treatment groups. Thus, the functionalized CNTs-PFI/T designed in this study could be the promising delivery systems to realize cooperative chemotherapy and photothermal therapy (PTT).

Keywords: Single-walled nanotubes; Photothermal therapy; Indocyanine green; nano delivery carriers; Synergetic effect

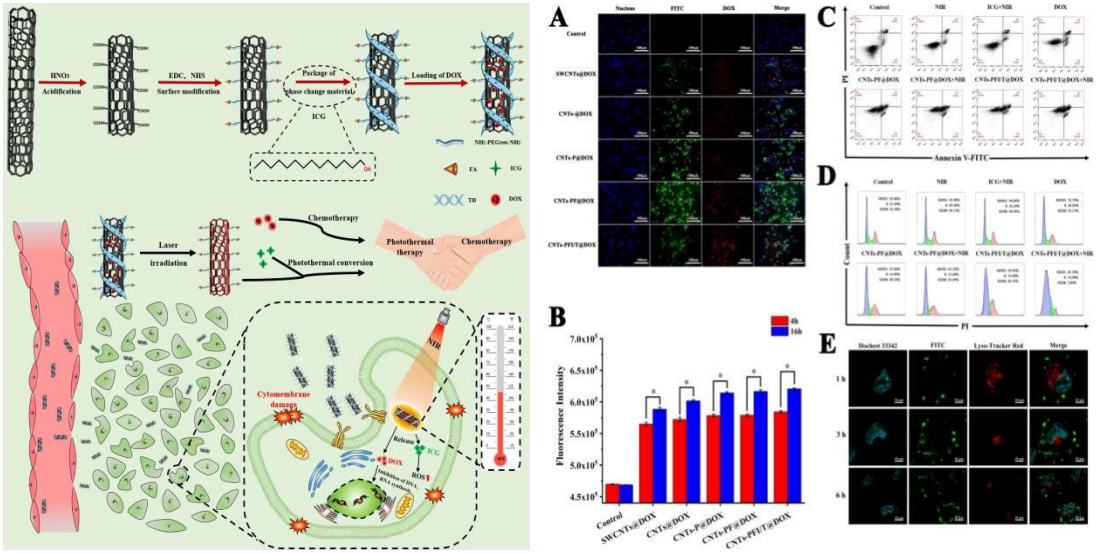

Figure.1 Schematic illustration of the development procedure of CNTs-PFI/T@DOX and the proposed antitumor mechanism by mediating the coordination of chemotherapy and PTT (Left); and the cellular uptake of various CNTs delivery systems and their effect on cell apoptosis and cycle distribution (Right).

Anti-GPC3 Antibody and Cell-penetrating Peptide CPP44 Dual-functional Liposomes Mediate Targeted Delivery of Arsenic Trioxide Against Liver Cancer

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Abstract: Arsenic trioxide (ATO), the active ingredient in Chinese arsenic, can effectively inhibit the growth of hepatocellular carcinoma (HCC) cells, but the biggest bottleneck in application is the lack of a tumor-targeted delivery system. Phosphatidylinositol proteoglycan 3 (GPC3) is a protein specifically expressed in HCC, and CPP44 is a tumor lineage-homing cell-penetrating peptide that specifically penetrates HCC cells. In this study, we developed a liposome with ATO as a model drug and dual surface modification by anti-GPC3 antibody and CPP44 penetrating peptide. The system was firstly enriched and localized at the liver tumor site after entering the body through passive targeting by EPR and active targeting by specific binding of anti-GPC3 antibody to GPC3 protein, and then the specific penetration of CPP44 into HCC cells ensures the delivery of ATO to the interior of HCC cells. *In vitro*, Dl-ATO-Lp exhibited higher cell uptake rate and stronger tumor cell killing effect. In a mouse model of HCC, Dl-ATO-Lp showed good *in vivo* targeting and anti-tumor effects, and the tumor inhibition rate of Dl-ATO-Lp was up to 63.43%. The proposed strategy and the constructed liposome drug delivery system realized the spatial targeting delivery of ATO and improved the therapeutic effect of ATO on HCC, which indicated a new development direction and provided a practical basis for promoting the application of ATO in solid tumor therapy.

Keywords: arsenic trioxide; phosphatidylinositol proteoglycan 3 (GPC3); CPP44; liver cancer

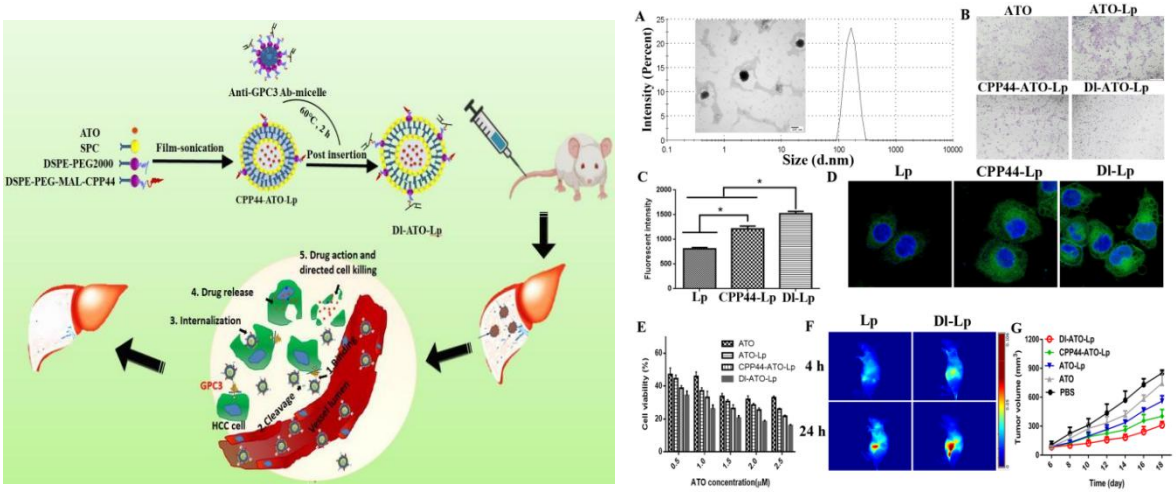

Figure. 1 Schematic illustration of the synthetic procedure of Dl-ATO-Lp and the proposed mechanism of dual-functional liposomes mediate targeted delivery of ATO against liver cancer (Left); and Dl-ATO-Lp anti-cancer effects *in vitro* and *in vivo* (Right).

Smart Liposomal Nanocarrier Enhanced the Treatment of Ischemic Stroke Through Neutrophil Extracellular Traps and cGAS-STING Inhibition of Ischemic Penumbra

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Abstract: Brain inflammation is regarded as one of the leading causes that aggravate secondary brain injury and hinder the prognosis of ischemic stroke. After ischemic stroke, high quantities of peripheral neutrophils are recruited to brain lesions and release neutrophil extracellular traps (NETs) leading to the aggravation of blood–brain barrier (BBB) damage, activation of microglia and ultimate neuronal death. Herein, a smart multifunctional delivery system has been developed to regulate immune disorders in ischemic brain. Briefly, Cl-amidine, an inhibitor of peptidylarginine deiminase 4 (PAD4), is encapsulated into self-assembled liposomal nanocarriers (C-Lipo/CA) that are modified by reactive oxygen species (ROS)-responsive polymers and fibrin-binding peptide to achieve targeting ischemic lesions and stimuli-responsive release of drug. In the mouse model of cerebral artery occlusion/reperfusion (MCAO), C-Lipo/CA can suppress NETs release process (NETosis) and further inhibit cGAS-STING pathway in ischemic brain. In addition, MCAO mice treated with C-Lipo/CA significantly mitigated ischemic and reperfusion injury, with reducing the area of cerebral infarction to 12.1%, compared with the saline group of about 46.7%. These results demonstrated that C-Lipo/CA, which integrated microglia regulation, BBB protection and neuron survival, exerts potential therapy strategy to maximize ameliorating the mortality of ischemic stroke.

Keywords: Brain targeted drug delivery system; Nanomedicine; NETs; cGAS-STING; ROS-responsive; liposome

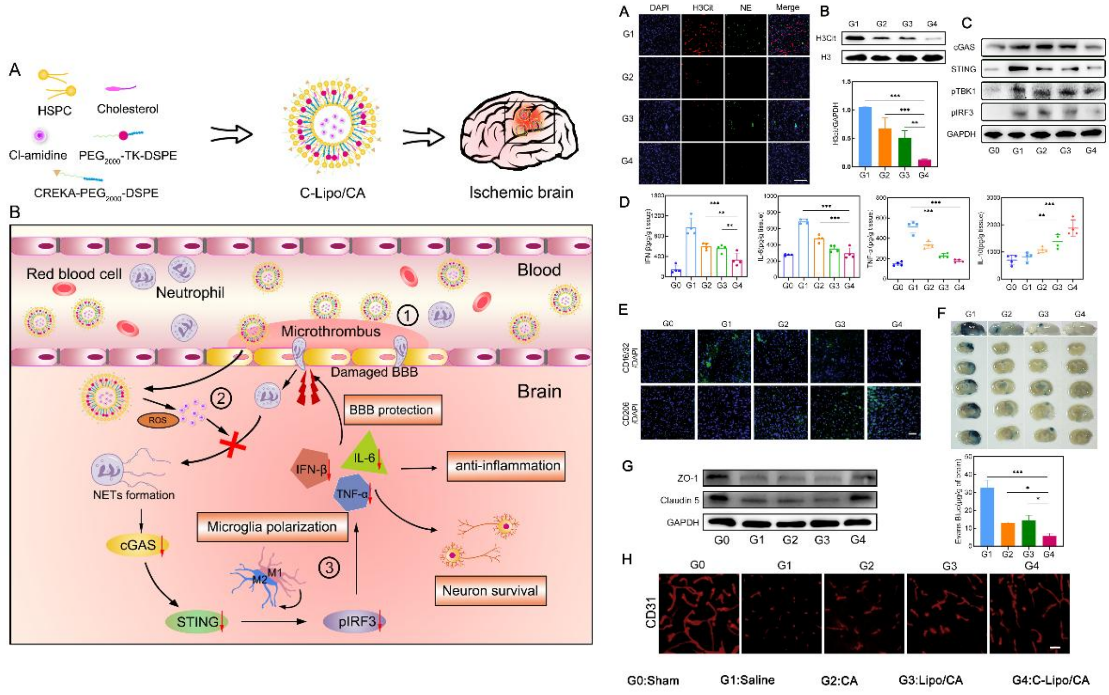

Figure. 1 Illustration of C-Lipo/CA liposomes construction and the proposed mechanism of C-Lipo/CA-mediated immunotherapy (Left); and C-Lipo/CA-mediated immune microenvironment modulation in ischemic brain (Right).

A Sodium Alginate-Based Multifunctional Nanoplatform for Synergistic Chemo-Immunotherapy of Hepatocellular Carcinoma

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Abstract: Efficient hepatocellular carcinoma (HCC) treatment remains a significant challenge due to the inherent limitations of traditional strategies. The exploration of polysaccharides' natural immunity for immunotherapy of HCC has been rarely explored. For this purpose, we reported in this study facile construction of a multifunctional nanoplatform, biotinylated aldehyde alginate-doxorubicin nano micelle (BEA-C=N-DOX-M) for synergistic chemo-immunotherapy by the use of constant β-D-mannuronic acid (M) units and modulated α-L-guluronic acid (G) units in the alginate (ALG) structure. The constant M units show natural immunity and specific binding ability with mannose receptor (MR) via strong receptor-ligand interactions, and the modulated G units serve as highly reactive conjugation sites for biotin (Bio) and DOX. This formulation not only integrates natural immunity of ALG and ICD triggering function of DOX, but also shows dual targeting properties to HCC cells via MR and Bio receptor (BR)-mediated endocytosis pathways. Notably, BEA-C=N-DOX-M at an equivalent dose of 3 mg/kg of DOX mediated tumor inhibitory efficiency 12.10% and 4.70% higher than free DOX and aldehyde alginate-doxorubicin nano micelle (ASA-C=N-DOX-M), respectively, in Hepa1-6 tumor-bearing mice. This study reported the first example of integrating natural immunity of ALG and ICD effect of anticancer drugs for enhanced chemo-immunotherapy of HCC.

Keywords: hepatocellular carcinoma, alginate, M unit, G unit, natural immunity, ICD, chemo-immunotherapy

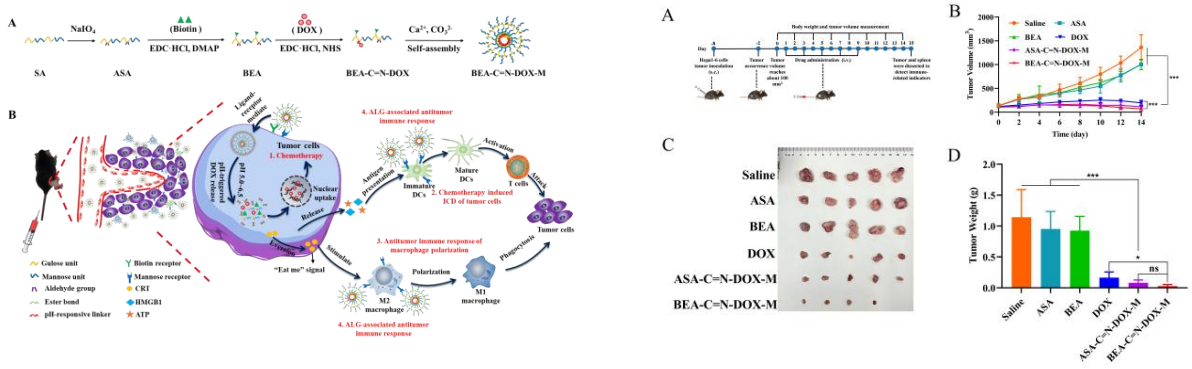

Figure. 1 Schematic illustration of the preparation of BEA-C=N-DOX-M for synergistic chemo-immunotherapy of hepatocellular carcinoma. (Left); and In vivo evaluation of the antitumor efficiency (Right).

Sequential Delivery of Nanomedicines to Macrophages by Controlling Phagocytosis Rates

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Abstract: Macrophages comprise an important target for treating metabolic diseases including hepatic steatosis. However, efficient drug delivery to macrophages is limited by a high metabolic rate. Nevertheless, phagocytosis can be inhibited by the interaction between CD47 and signal regulatory protein α, namely the “don't-eat-me” signal. Thus we propose a sequential drug delivery system realizing delicate control of phagocytosis rates by the organization of the conventional liposomes (Lip) and those modified by CD47-derived self-peptide (SLip) with optimized ratios. The liposome surfaces were covered with collagenase 1 (C1) and loaded with silibinin (C1-MLip/silibinin) to alleviate the pathological state of hepatic fibrosis. Fluorescence imaging and phagocytosis index revealed that the mixed liposome (MLip) significantly regulated the phagocytosis rates and relevant internalization mechanisms. An optimal inhibition of inflammatory macrophage polarization was achieved at a Lip/SLip ratio of 1:1, along with a significant attenuation of early liver fibrosis verified in vivo. In summary, we developed an effective sequential drug delivery system to macrophages by combining slow and fast phagocytosis rates through controlling the “don't-eat-me” signal, and its conciseness and robust therapeutic effect suggest promising potential in the clinical treatment of hepatic steatosis.

Keywords: Macrophage, phagocytosis, liposome, SIRPα, self-peptide

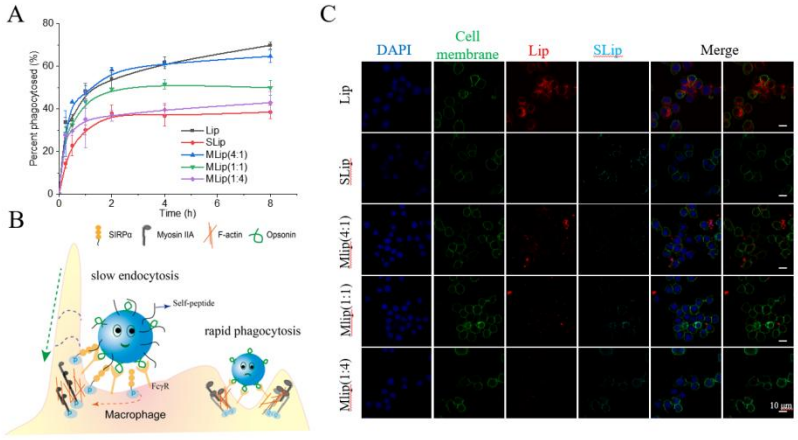

Figure. 1 A novel sequential nanomedicine delivery system to macrophages is developed by controlling the phagocytosis rate. CD47-derived self-peptide modified liposomes (SLip) and conventional liposomes (Lip) were mixed and incubated with macrophages. Then, Lip will quickly be phagocytosed while phagocytosis of SLip is inhibited by the interaction of self-peptide to SIRPα, achieving a sustained delivery efficacy.

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Biomimetic Strategies for Intravenous Delivery of Oncolytic Virus

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Abstract: Intravenous delivery of oncolytic virus (OVs) is promising in cancer treatment. Unfortunately, fast clearance of OVs and the severe cytokine release syndrome impedes its wide application. It has been shown that nanoparticles coated with cell membranes display less toxicity and slower clearance. However, different from conventional nanoparticles, the characteristic spike-like structure and abundant antigens on the surface make it difficult for intravenous-delivered OVs to take advantage of cell membrane coating to shield its surface antigens. To overcome this challenge, we developed three biomimetic strategies for its intravenous delivery. It was found the erythroliposome coating strategy, artificial virus-protein corona strategy, and the erythrocyte-leveraged strategy could significantly prolong the circulation of OVs in the blood and tumor accumulation of OVs, resulting in enhanced oncolytic efficacy to metastatic and refractory tumors. These studies provide new perspectives to empower OVs to combat deep tumors or metastases.

Keywords: Intravenous delivery; Oncolytic virus; erythroliposome; erythrocyte; artificial virus-protein corona; tumor therapy

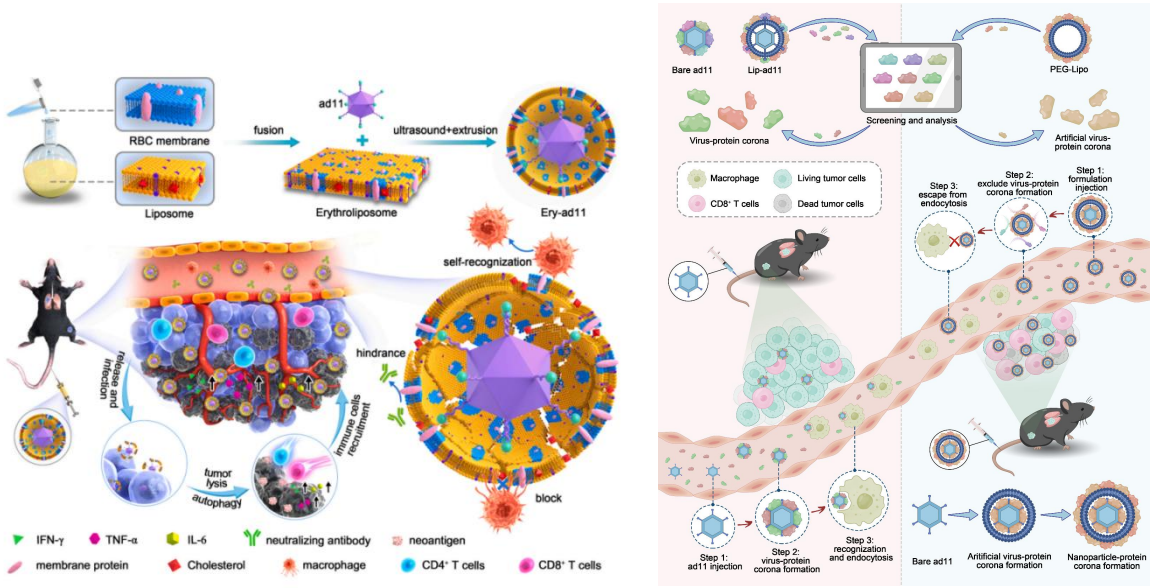

Figure. 1 Schematic illustration of the erythrosome coating strategy (Left) and the artificial virus-protein corona strategy (Right) for intravenous delivery of OVs to combat deep tumors or metastases.

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The effect of charges on the corneal penetration of solid lipid nanoparticles loaded econazole after topical administration in rabbits

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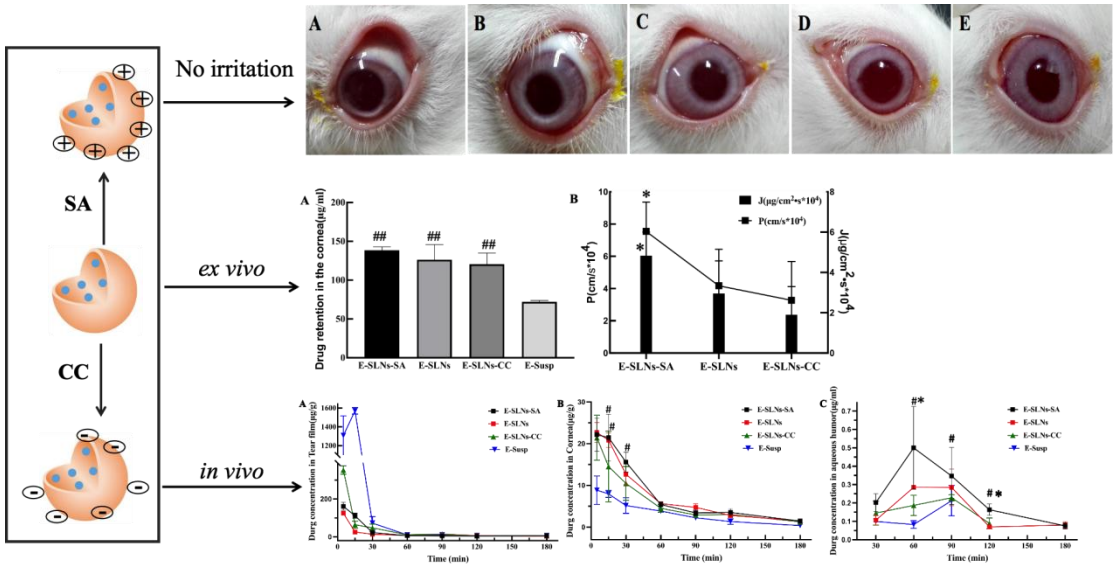
Abstract: Fungal keratitis is an infectious disease caused by pathogenic fungi with a high blindness rate. Econazole (ECZ) is an imidazole antifungal drug with insoluble ability. Econazole-loaded solid lipid nanoparticles (E-SLNs) were prepared by microemulsion method, then modified with positive and negative charge. The mean diameter of cationic E-SLNs, nearly neutral E-SLNs and anionic E-SLNs were 18.73±0.14, 19.05±0.28, 18.54±0.10 nm respectively. The Zeta potential of these different charged SLNs formulations were 19.13±0.89, -2.20±0.10, -27.40±0.67 mV respectively. The Polydispersity Index (PDI) of these three kinds of nanoparticles were about 0.2. The Transmission Electron Microscopy (TEM) and Differential Scanning Calorimetry (DSC) analysis showed that the nanoparticles were a homogeneous system. Compared with Econazole suspension (E-Susp), SLNs exhibited sustained release capability, stronger corneal penetration and enhanced inhibition of pathogenic fungi without irritation. The antifungal ability was further improved after cationic charge modification compared with E-SLNs. Studies on pharmacokinetics showed that the order of the AUC and $t_{1/2}$ of different preparations was cationic E-SLNs > nearly neutral E-SLNs > anionic E-SLNs > E-Susp in cornea and aqueous humor. It was shown that SLNs could increase corneal penetrability and ocular bioavailability while these capabilities were further enhanced with positive charge modification compared with negative charge ones.

Keywords: solid-lipid nanoparticles; topical administration; modified by different charge, corneal penetration; ocular bioavailability.



Self-Propelled Janus Nanomotors for Neurological Diseases

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Abstract: With the discovery of Janus materials, individuals were found that Janus materials has shown great potential in the treatment of neurological diseases. Janus materials was used to design novel particle emulsifiers, heterogeneous catalysts, self-driving nanomotors. It can also be used as a new dosage form, which works by being assembled as a superstructure. We designed asymmetric coated nanoenzymes by spraying ultra-thin metal layers (including platinum (Pt), palladium (Pd) and molybdenum (Mo)) on carbon nanospheres. They can effectively catalyze endogenous hydrogen peroxide, which induces movement as fuels to promote them to deep brain lesions for further nanocatalyst-mediated cascade-blocking therapy. The results demonstrate that the JCNs successfully block the inflammatory cascades, reversed multiple behavioral deficits, and significantly reduced mortality in sTBI mice. This work offers a revolutionary strategy for sensing brain damage.
Keywords: Janus nanomotor, catalytic therapy; nanozymes; oxidative stress; brain injury

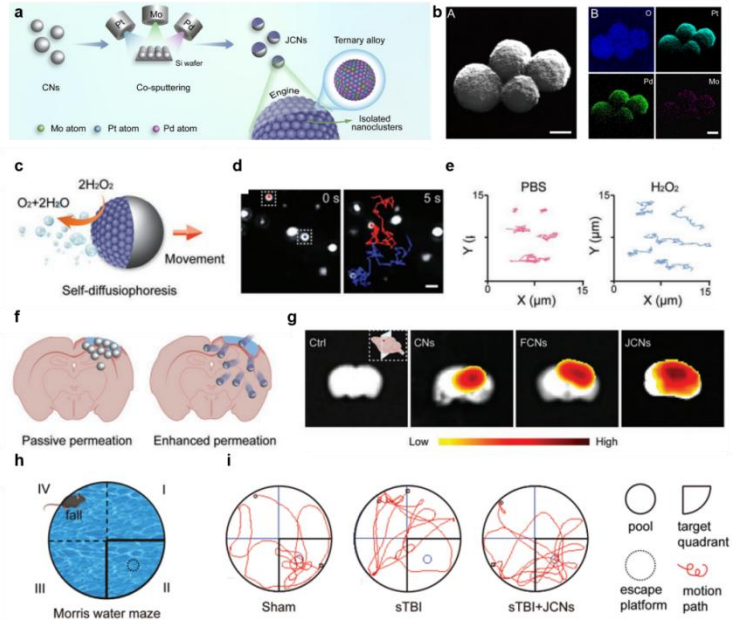

Figure. 1 Janus nanomotor is self-driven into the brain. a. Schematic diagram of nanomotor preparation; b. TEM diagram and EDS mapping of nanomotor; c. Schematic diagram of nanomotor catalytic decomposition of hydrogen peroxide to produce oxygen to achieve self-drive; d. Self-propelled process of catalytic decomposition of hydrogen peroxide by nanomotor; e. Tracking trajectory of hydrogen peroxide catalyzed by nanomotors; f. Schematic diagram of self-driving nanomotor with passive nanoparticle penetration in brain tissue; h. Schematic diagram of the water maze experiment; i. Schematic illustration of the synthetic procedure of SMTA and the proposed mechanism of SMTA-mediated photodynamic immunotherapy (Left); and SMTA-mediated co-activation of innate and adaptive immunity (Right).

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Orally Administrated Pharmaceutical Cocrystal of Gefitinib Improved Its Physicochemical and Therapeutic effect against Lung Cancer by increased level of DNA damage

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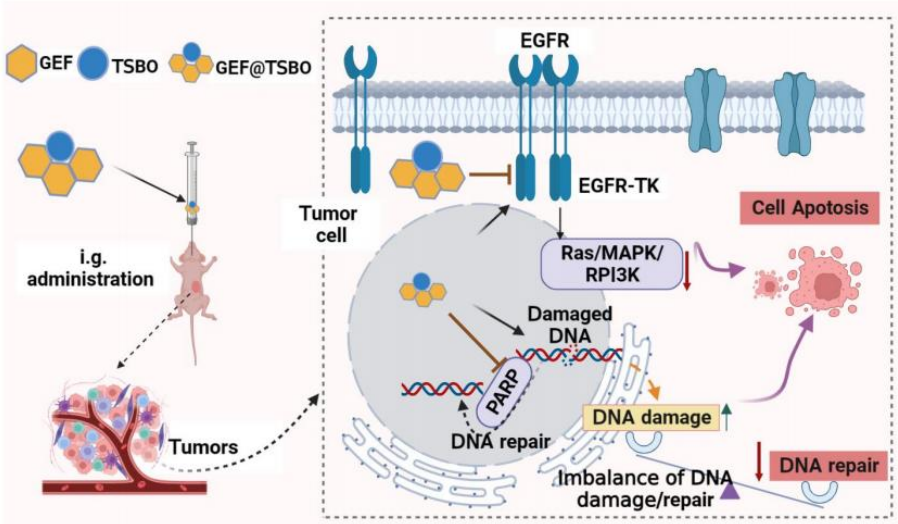
Abstract: Gefitinib (GEF) is a clinically used medication that inhibits the epidermal growth factor receptor (EGFR) for the lung cancer treatment. However, its effectiveness is limited due to low solubility and dissolution rates. Herein, we have successfully synthesized two cocrystals of GEF with 3-thiosemicarbano-butan-2-one-oxime (TSBO) and Nicotinamide (NCA) using recrystallization method. Powder X-ray diffraction, Fourier transform infrared spectroscopy (FT-IR), 2D NOESY and scanning electron microscopes (SEM) were utilized to characterize the cocrystals. The solubility and dissolution rates of the cocrystals in deionized water with a pH of 7.0 were found to be 2 to 2.5 times higher compared to free GEF. The in vitro cytotoxic effect revealed that cocrystal enhanced the inhibition of cell proliferation and apoptosis of A549 and H1299 cells compared to free GEF. In mouse models, GEF@TSBO is proven targeted, safe and effective antitumor medication that suppressed tumor growth. Mechanically, the newly synthesized GEF cocrystals showed to increase the cellular level of damaged DNA, meanwhile, the potentially downregulated PARP further impaired the DNA repair machinery, therefore casing imbalance of DNA damage and restoration. These findings suggested that cocrstalization of GEF with TSBO and biocompatible NCA could be a capable adjuvant to remarkably improve the physicochemical and biopharmaceutical performance in the lung cancer treatments.

Keywords: Crystal Engineering; Cocrystal; DAN damage and repair; Docking; Anticancer



Graphical Abstract : The EGFR inhibitor Gefitinib cocrystals has been prepared for improve its biophysical properties and stability and bioavailability, which can be orally administrated and exhibit stronger antitumor effect towards lung cancer by inducing the DNA damage and suppress the DNA repair in the meantime, compared to the Gefitinib API itself.

Pharmaceutical technology for patient centric drug therapy and better human life

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One of the important key words in pharmaceutical studies for drug therapy is patient centric therapy. To meet this purpose in pharmaceutical engineering researchers, following their important research subjects are listed up; 1) Patient friendly dosage form design 2) Use of suitable drug administration routes in designing dosage forms 3) Development of novel drug delivery methods including nano-drug carrier system.

There are several types of patient friendly dosage forms such as orally disintegrating tablets (ODTs) or films (ODFs), and jelly, which are convenient for patients to be administered. These dosage forms are specified in Japanese pharmacopeia 18th revised version, suggesting that the recent tendency in developing dosage forms is well reflected in the regulatory side.

While the special preparation methods such as a wet mass molding method or so called WOWTAB method have been developed to prepare commercial products, usual tableting methods are now popular to prepare commercial products of ODTs based on the fundamental studies on compaction and the formulation study. Development of fillers for direct tableting has also contributed to this type of ODT preparation.

Pharmaceutical technology is able to applied to preparation of supplement products. One of the key technologies is for improving dissolution properties of components of natural products. Some trials are introduced in the presentation. Pharmaceutical technology can also contribute for better life by applying to dosage form design of supplements as well as drugs.

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Ion-responsive Nano-probes

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Abstract：Ions play important roles in physiological and pathological processes in vivo. The occurrence and development of most diseases are accompanied by changes in ion levels, forming a microenvironment with ion differences [1]. We innovatively developed methods of ion-responsive ligand-mediated nano-assembly and constructed a series of high-performance ion-responsive nanomaterials that realized the response of biological functions to ionic microenvironment differences for sensitive and specific imaging and efficient and safe treatment of diseases [2,3]. For the acidic tumor microenvironment, a series of H^+-responsive antitumor nanodrugs were designed [4,5]. For example, a H^+-responsive platinum nanodrug targeting tumor nucleus and blocking DNA repair pathway was prepared that could expose surface nuclear targeting groups under acidic microenvironment and enter the nucleus to induce DNA platinization. Meanwhile, the nuclease-mimetic platinum nanodrug inhibited the inherent nucleotide excising repair pathway, realizing the reversal of platinum-based drug resistance [4]. Based on the high level of K^+ in tumor microenvironment, a K^+-responsive fluorescence/magnetic resonance dual-mode probe was constructed that could distinguish the pathological states of tumors by specifically identifying the fluorescence signal of high potassium concentration. Combining the tumor location and structure information obtained by magnetic resonance imaging, non-invasive bimodal imaging and malignancy differentiation of tumors was realized [6]. In addition, a highly sensitive and specific K^+-responsive nano-probe was developed for real-time brain imaging to realize dynamic monitoring of neural activity and early warning and classification of epilepsy in freely moving mice [7]. Based on the high level of free radicals in tissue injury microenvironment, a free radical ion responsive theranostic probe is constructed that achieved excellent efficacy in liver injury and hair regeneration [8-10]. The above strategies of regulating nano-biological functions based on specific ions in disease microenvironment provide new ideas for breaking the bottleneck of theranostics of major diseases.

Key Words: nano-probe；disease microenvironment；in vivo imaging；theranostics；nano-biological effects

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Determination of the Mechanical Properties of Polymeric Microneedles by Micromanipulation

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Abstract: Precise characterization of the mechanical properties of polymeric microneedles is crucial for their successful penetration into skin and delivery of the loaded active ingredients. However, most available strategies for this purpose are based on compression of the whole patch, which only provide the average rupture force of the needles and can not give information on the variations across individual microneedles in the patch. In this study, we determined the mechanical strength of individual microneedles of two types of hyaluronic acid microneedles with or without loaded model drugs using a micromanipulation technique. The applied force as a function of displacement of the microneedles was recorded, which was used to determine the rupture displacement, rupture force, and then to derive and calculate normal stress-deformation curve, rupture stress and Young's modulus of individual microneedles. The obtained data suggest that the molecular weight of the polymer and the loading of drug into the microneedles can significantly affect the rupture behavior and mechanical properties of the microneedles, which provides a foundation for preparing sufficiently strong microneedles for controlled drug delivery.

Keywords: mechanical properties; polymeric microneedles; micromanipulation; rupture force; normal stress

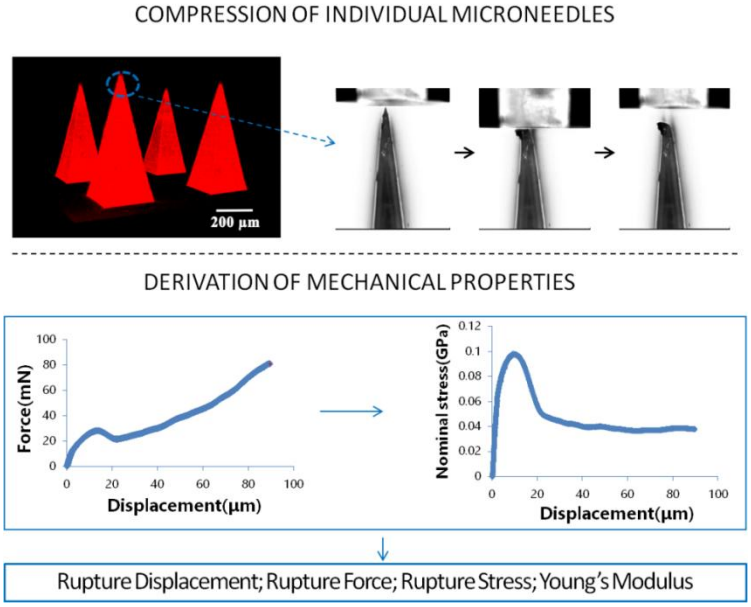

Figure. 1 Schematic illustration of using micromanipulation for characterizing rupture behavior and mechanical strength of individual microneedles, including rupture displacement, rupture force, rupture stress and Young's modulus.

Reference:

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Metal-based Nanomedicine in the Specific Therapy for Breast Cancer

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Abstract: Breast cancer is a malignant tumor occurring in the mammary epithelium of the breast and how to treat breast cancer specifically remains a huge challenge. According to the biological characteristics, we developed a series metal-based nanomedicine for the specific therapy and reversal of chemoresistance of breast cancer. It is reported that the reduced ferroportin-induced abnormal iron metabolism provides an opportunity for combating triple negative breast cancer (TNBC) via iron-dependent production of reactive oxygen species (ROS) by Fenton reaction. Nevertheless, the efficiency of current Fenton reagents is largely restricted by the lack of specificity and low intracellular H_2O_2 level of cancer cells. Herein, core-shell-satellite nanomaces (Au@MSN@IONP) are fabricated [1], as near-infrared (NIR) light-triggered self-fueling Fenton reagents for the amplified Fenton reaction inside TNBC cells, demonstrating the proof-of-concept of NIR-light-triggered self-fueling Fenton reagents against TNBC with low ferroportin levels. In addition, ferroptosis has recently become an attractive strategy to combat the chemoresistance of cancer cells, but the clinic samples analysis revealed the enhanced intracellular ferroptosis defense system of chemoresistant breast cancer, which greatly challenges the efficient ferroptosis induction Herein, we report a ferrous metal-organic framework-based nanoagent that inhibits the intracellular upstream glutathione synthesis and induces self-amplified ferroptosis of cancer cells [2], for reversing chemoresistance and boosting chemotherapy, providing a self-amplified ferroptosis strategy via inhibiting intracellular upstream glutathione synthesis, which is effective to reverse cancer chemoresistance. Finally, we designed and synthesized a virus-spike tumor-activatable pyroptotic agent for the treatment of breast cancer [3]. The spiky structure of VTPA facilitated the tumor intracellular lysosomal rupture and subsequently exploited the tumor overexpressed GSH for the degradation to release Mn ions and IONPs, leading to the synergistic activation of pyroptotic tumor cell death, providing a new paradigm for the future development of cancer-specific pyroptotic nanomedicine [4].

Keywords: breast cancer; specific therapy; metal-based nanomedicine; ferroptosis; pyroptosis

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Hybrid Chalcogen Bond as the “Double-Control Switch” of Homodimeric Prodrug Nanoassemblies to Address Tumor Redox-Heterogeneity

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Abstract: Sulfur bonds, especially trisulfide bond, have been found to ameliorate the self-assembly stability of homodimeric prodrug nanoassemblies and could trigger the sensitive reduction-responsive release of active drugs. However, the anti-tumour efficacy of homodimeric prodrug nanoassemblies with single reduction-responsivity may be restricted due to the heterogeneous tumour redox microenvironment. Herein, we replace the middle sulfur atom of trisulfide bond with an oxidizing tellurium atom or selenium atom to construct redox dual-responsive sulfur-tellurium-sulfur and sulfur-selenium-sulfur hybrid chalcogen bonds. The hybrid chalcogen bonds, especially the sulfur-tellurium-sulfur bond, exhibit ultrahigh dual-responsivity to both oxidation and reduction conditions, which could effectively address the heterogeneous tumour microenvironment. Moreover, the hybrid sulfur-tellurium-sulfur bond promotes the self-assembly of homodimeric prodrugs by providing strong intermolecular forces and sufficient steric hindrance. The above advantages of sulfur-tellurium-sulfur bridged homodimeric prodrug nanoassemblies result in the improved antitumor efficacy of docetaxel with satisfactory safety. The exploration of hybrid chalcogen bonds in drug delivery will deepen insight into the development of prodrug-based chemotherapy to address tumour redox heterogeneity, thus enriching the design theory of prodrug-based nanomedicines.

Keywords: Homodimeric prodrug; Chalcogen; Hybrid bond; Redox-responsive; Tumour heterogeneity

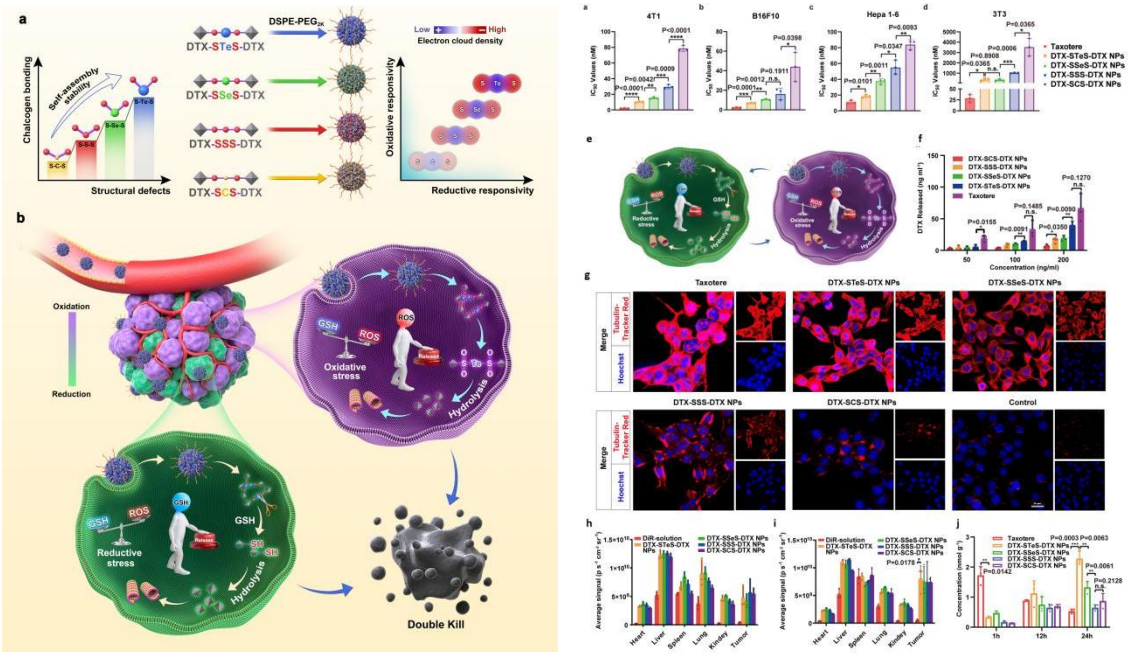

Figure. 1 Schematic illustration. a The self-assembly stability and redox-responsivity of STeS, SSeS, SSS, and SCS bonds. b Hybrid chalcogen bond bridged HPNAs with ultrahigh redox dual-responsivity to address tumor heterogeneity (Left); and cytotoxicity and intracellular bioactivation and biodistribution of HPNAs (Right).

Reshape the tumor microenvironment for increasing the distribution of glucose oxidase in tumor and inhibiting metastasis

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Abstract: The poor penetration of solid tumors hinders the development of hunger therapy represented by glucose oxidase (GOx). To address this limitation, we have constructed a GOx/Dex@ZIF-TA nanosystem consisting of tannic acid (TA), carrier ZIF-8, encapsulated GOx and dexamethasone (Dex). In this nanosystem, the loaded Dex can not only expand the pores of the nucleus to promote GOx to enter the nucleus, filling the shortcomings of short life of reactive oxygen species, but also inhibit the production of collagen to reshape the tumor microenvironment and inhibit lung metastasis. In vivo experiments proved that Dex could inhibit the production of collagen, which increased the accumulation and penetration of the tumor tissues and inhibited lung metastasis. In addition, cell experiments showed that Dex could also enlarge the nuclear pores of the nucleus and promote the entry of drugs into the nucleus. More importantly, Dex as a broad anti-inflammatory drug, the results here should be easily transformed to obtain clinical benefits. Together, this work provided a way to address the limitations of hunger distribution in tumor tissues.

Keywords: Dexamethasone, Metastasis, Starvation therapy

ROS responsive stepwise targeted drug release platform for inhibiting oxidative stress levels and inflammation in ischemic stroke and improving neurological function

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Abstract: Ischemic stroke is a common cerebral disease in which neurons are damaged due to reduced or interrupted blood supply to the brain and there are no sufficient treatments and drugs currently. Here, we report a step-targeting ROS responsive nanoplatform consisting of recombinant angiotensin II (ANG)-targeting the blood-brain barrier and stroke homing peptide (SHp) targeting targeted brain injury regions to load Danshensu with ROS response for anchoring vascular injury sites and ischemic neurons. The resulting nanoparticles first cross the BBB to the damaged area under the action of two peptides, after which the nanoparticles respond to release and remove excess ROS, thereby reducing the oxidative stress environment. Danshensu was released and act on microglia and damaged nerve cells, promoting the transformation of anti-inflammatory phenotype M2 of microglia and reverse the inflammatory environment, saving damaged nerve cells. The self-assembled brain targeting system of prodrugs and peptide chains with cross-linking properties exhibits good cellular uptake and free radical scavenging abilities at the cellular level, effectively reducing cellular oxidative damage and clearing intracellular ROS. It can improve the inflammatory environment in the brain injury area, reduce cerebral infarction, restore brain nerve function in animal level, and provide a simple strategy for the treatment of ischemic stroke.

Keywords: Danshensu; ROS response; stepwise targeted; neurological function

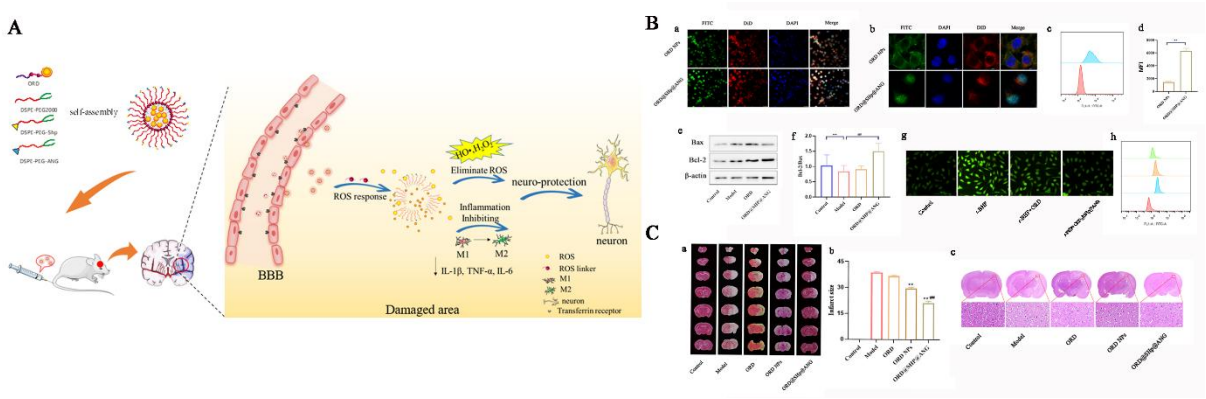

Fig.1 (A)The release mechanism of nanoparticles; (B) Effects of nanoparticle on ROS clearance and apoptosis at cell level. (C) Improvement of cerebral infarction at the animal level.

Small changes in the length of diselenide bond-containing linkages exert great influences on the antitumor activity of docetaxel homodimeric prodrug nanoassemblies

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Abstract: Homodimeric prodrug-based self-assembled nanoparticles, with carrier-free structure and ultrahigh drug loading, is drawing more and more attentions. Homodimeric prodrugs are composed of two drug molecules and a pivotal linkage. The influence of the linkages on the self-assembly, in vivo fate and antitumor activity of homodimeric prodrugs is the focus of research. Herein, three docetaxel (DTX) homodimeric prodrugs are developed using different lengths of diselenide bond-containing linkages. Interestingly, compared with the other two linkages, the longest diselenide bond-containing linkage could facilitate the self-delivery of DTX prodrugs, thus improving the stability, circulation time and tumor targeting of prodrug nanoassemblies. Besides, the extension of linkages reduces the redox-triggered drug release and cytotoxicity of prodrug nanoassemblies in tumor cells. Although the longest diselenide bond-containing prodrug nanoassemblies possessed the lowest cytotoxicity to 4T1 cells, their stable nanostructure maintained intact during circulation and achieve the maximum accumulation of DTX in tumor cells, which finally “turned the table”. Our study illustrates the crucial role of linkages in homodimeric prodrugs, and gives valuable proposal for the development of advanced nano-DDS for cancer treatment.

Keywords: diselenide bond; homodimeric prodrug; docetaxel; self-assembly; redox responsive

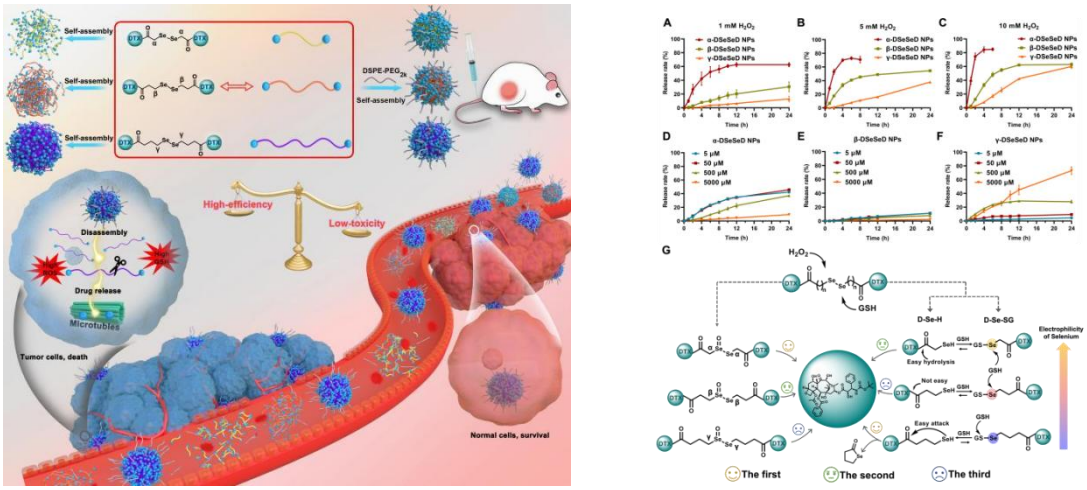

Figure. 1 Schematic illustration of α-/β-/γ-diselenide bonds-bridged DTX homodimeric prodrug nanoassemblies for efficient chemotherapy (Left); and redox-responsive mechanism of α-diselenide bond, β-diselenide bond and γ-diselenide bond bridged prodrugs (Right).

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Study on the substance basis of Artemisia argyi essential oil against A549 cells based on the spectrum-effect relationship

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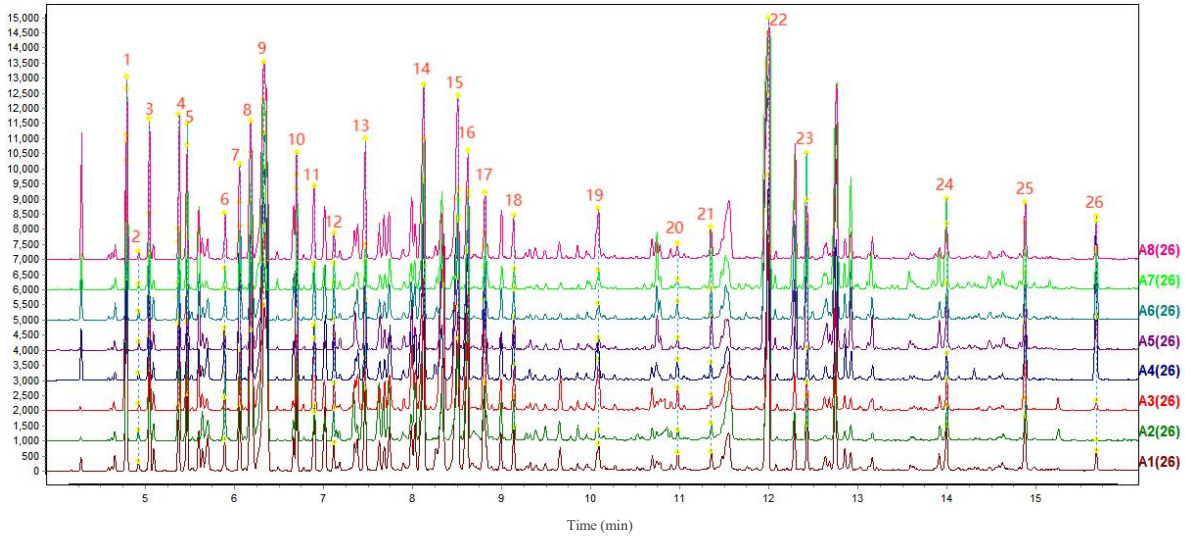
Objective: To establish a mathematical model of the spectro-effect relationship between the peaks of the *Artemisia argyi* essential oil (AAEO) extracted at different harvesting times and the inhibition of proliferation viability of A549 cells, and to reveal the substance basis of the inhibition of proliferation viability of A549 cells of AAEO.
Methods: The volatile oils from eight batches (S1-S8) of *Artemisia argyi* extracted at different harvesting times were detected by GC-MS, and the fingerprints of the volatile oils from the eight batches of *Artemisia argyi* were established. The inhibition rate of AAEO against A549 cells was used as the parent sequence, and the normalized peak areas of the shared characteristic peaks were imported into the online SPSSPRO website for grey correlation analysis（GRA）. The tumour inhibition rate represented by the IC50 value of A549 cells was used as Y and the peak area of the shared characteristic peak of each batch of AAEO was used as X. Partial least squares regression (PLSR) analysis was performed using SIMCA 14.0 software. The statistical analysis methods of visual comparison, GRA and PLSR were used to correlate the "spectrum" and "potency" information, and finally to identify the important active ingredients of AAEO in inhibiting A549. **Results:** A total of 26 common peaks were obtained in the GC fingerprint, and GRA showed that 10 peaks had association values greater than 0.8. PLSR used a regression coefficient greater than 0 and a VIP value greater than 1 as screening conditions to obtain three peaks, P1, P7 and P25. Combining the three analytical methods, peaks 1 and 25 were obtained, which may be important effective substances for AAEO to inhibit A549. **Conclusion:** The established spectral-effect relationship model provides the basis for studying the pharmacological effects of AAEO on A549 cells.
Keywords: *Artemisia argyi* essential oil, Anti-tumour, Fingerprinting, Spectroscopic-effect relationship



Co-injection of PEGylated rapamycin nanoparticles for mitigating anti-drug antibody production for augmenting anticancer efficacy of protein toxin

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Abstract: The induction of anti-drug antibody (ADA) is a formidable challenge for protein-based therapy. Trichosanthin (TCS) as a class of ribosome-inactivating proteins (RIPs) has been widely studied in tumor treatment. However, the immunogenicity can induce the formation of ADA, which can cause hypersensitivity reactions and neutralize the efficacy of TCS, thus limiting its clinical application in cancer therapy. Here we present a promising solution to this issue by co-administration of the rapamycin nanoparticles and TCS. PEGylated rapamycin amphiphilic molecule was designed and synthesized as a prodrug and a delivery carrier, which can self-assemble into a nanoparticle system with encapsulation of free rapamycin, a hydrophobic drug. It was found that co-injection of the PEGylated rapamycin nanoparticles and TCS could mitigate the formation of anti-TCS antibody via inducing durable immunological tolerance. Importantly, the combination of TCS and the rapamycin nanoparticles had a synergistic effect to inhibit the growth of breast cancer. Our work provides a promising approach for protein toxin-based anticancer therapy and for promoting the clinical translation.

Keywords: Trichosanthin, rapamycin nanoparticles, anti-drug antibody, immunological tolerance, synergistic effect

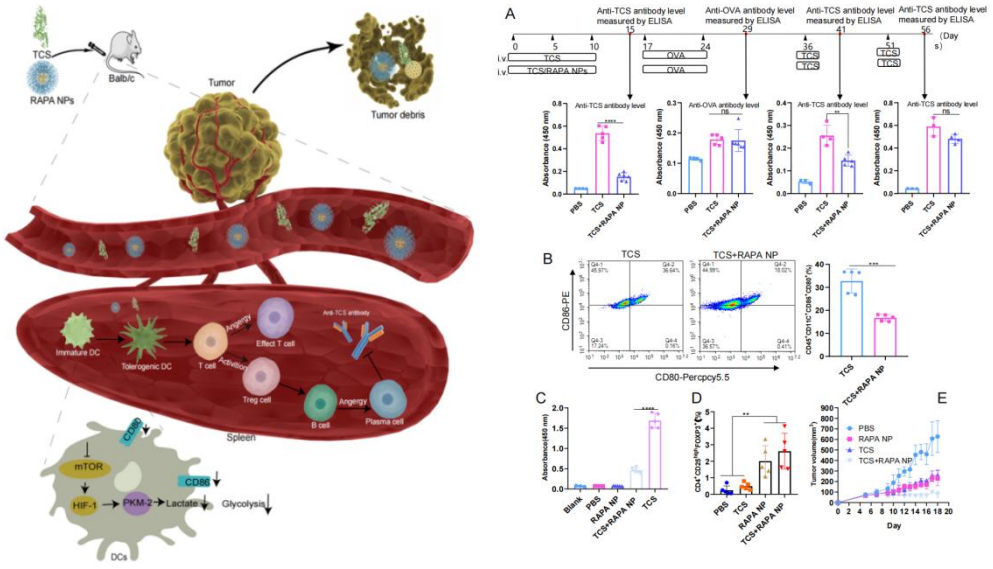

Figure. 1 Schematic illustration of the combination strategy based on RAPA NPs and TCS for enhanced tumor treatment (Left); and PEGylated rapamycin nanoparticles induced an antigen-specific immunological tolerance and augmented anticancer efficacy of TCS (Right).

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Self-assembled nanoparticles with bilirubin/morin accelerate chronic diabetic wound healing by promoting local anti-inflammatory and antioxidant responses

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Abstract: Chronic diabetic wounds pose a serious threat to human health and safety due to their refractory nature and high recurrence rate. The formation of refractory wounds is associated with wound microenvironmental factors such as increased expression of proinflammatory factors and oxidative stress. Bilirubin is a potent endogenous antioxidant, and morin is a natural active substance which possesses anti-inflammatory and antioxidant effects. Both of them hold potential for diabetic wound treatment through intervening the pathological process. In this study, we developed a bilirubin/morin based carrier free nanoparticle (BMNPs) for chronic diabetic wound treatment. In vitro study showed that BMNPs could effectively scavenge overproduced ROS and suppress the elevated inflammation, exerting protective effect. BMNPs was then loaded into Collagen/PVAgel in in vivo study for maintaining a moisture environment for skin and convenient biomedical application. In type I diabetic mice, BMNPs-loaded hydrogel restored skin function and promoted wound healing through epithelial regeneration, collagen deposition, and blood supply restoration. This study provides a promising therapeutic alternative for diabetic wound healing.
Keywords: bilirubin; morin; chronic wound; anti-inflammatory; antioxidant

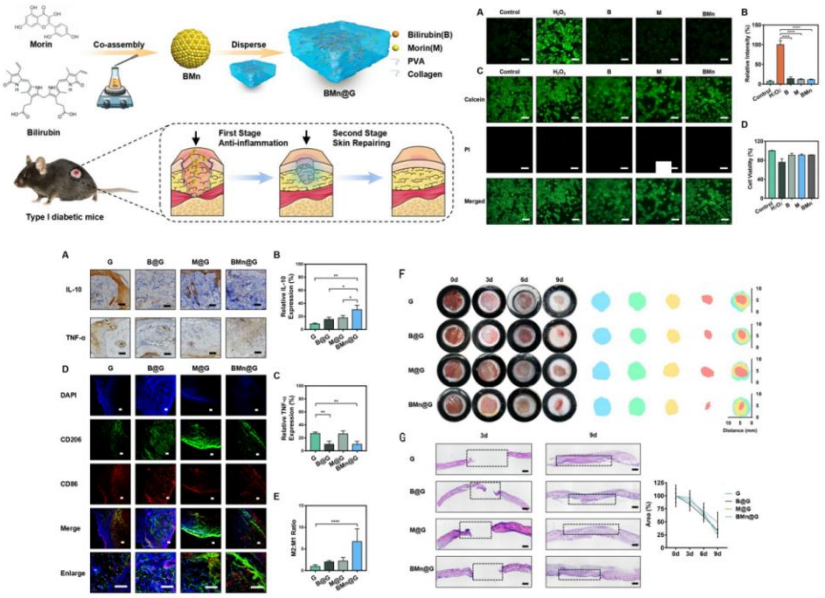

Figure. 1 Schematic illustrations for the preparation and the application of BMn@G for chronic diabetic wounds therapy and study on antioxidant properties of nanoparticles in vitro（Up）; and Anti-inflammatory effect of the preparation and its effect on wound repair（Down）.

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Liver Carboxylesterase-triggered Cationic Triadic Copolymer Deliver Cas9-mRNA/sgPCSK9 for Ameliorating Hyperlipidemia

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Abstract: Proprotein convertase subtilisin/kexin type 9 (PCSK9) is an important regulator that controls plasma cholesterol levels via impacting low-density lipoprotein receptor (LDL-R) metabolism both within and outside of the hepatocytes. Inhibition of PCSK9 expression to ameliorate hyperlipidemia by mRNA delivery and gene therapy is a favorable strategy. However, due to the lack of a safe and site-oriented release RNA delivery system, how to effectively and permanently down-regulated PCSK9 remains a challenge. Herein, we designed and synthesized a novel biguanide nano micelle, term as mPEG-b-P(Met/n-PMA), for delivery of mRNA. Multiple interactions between mPEG-b-P(Met/n-PMA) and nucleic acid serve to stable mRNA with a potent ability to deliver in vivo. The developed mPEG-b-P(Met/n-PMA) also demonstrates super intelligent mRNA liver selective release resulting from carboxylesterase 1 (CES1) active destabilized strategy. After loaded with Cas9-mRNA/sgPCSK9, mPEG-b-P(Met/n-PMA)/Cas9-mRNA/sgPCSK9 led to inhibition of PCSK9 in vitro by ~60%. Furthermore, this modality successfully targeted the liver where PCSK9 is highly expressed and led to effective inhibition of PCSK9 and ~20% of plasma LDL-C decrease in mice. Besides the lipid-lowering treatment, mPEG-b-P(Met/n-PMA) even owns multi-effects in controlling mouse blood glucose and weight. This work established a novel pattern to realize mRNA stable loading, delivery safely and intellectual liver fixed-point release, which may expand the application of the smart mRNA delivery system in the utility of metabolic diseases that occur in the liver.

Keywords: PCSK9, mRNA delivery, CES1 active destabilized strategy, CRISPR/Cas9, liver fixed-point release

Supramolecular Cell-Hitchhiking Nanomedicines for Targeted Delivery

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Abstract: It has been a fantasy that nanomedicine may significantly improve the delivery efficiency of medicine into the targets. The reality is harsh, as numerous clinical data have suggested that only modest improvement was observed. Scientists are searching for better ways of delivering medicine in a more precise manner. Cells are a basic unit of living organisms and using them as drug carriers has unique advantages. For instance, it can significantly improve the targeting efficiency due to the homing effects of selected cells or improve the systemic circulation. There are currently two strategies to construct cell-hitchhiking delivery systems. One is to directly phagocytose drugs (including nano-drugs) via endocytosis, and the other is to use covalent bonds or biological ligand-receptor interactions to conjugate nanomedicine to the surface of live cells. However, the cells that phagocytize medicines may degrade the drug before reaching the target. Covalent binding involves a complex synthetic process on the cell surface, which may impair the physiological function of the carrier cells. The ligand-receptor interaction is often limited to specific cells, and competitive ligand displacement occurs in vivo as well. During the past a couple of years, we have developed several supramolecular approaches to tackle these above-mentioned issues and to enable targeted delivery of various nanomedicines to inflammatory tissues (including solid tumors), driven by the inflammatory tropism of immune cells. We show that these unique systems may significantly improve the delivery efficiency of medicine into the targeted tissues and effectively treat several inflammatory diseases including acute pneumonia and atherosclerosis, and solid tumors such as melanoma.

Keywords: cell-hitchhiking, self-assembly, host-guest interactions, inflammation, targeted therapy

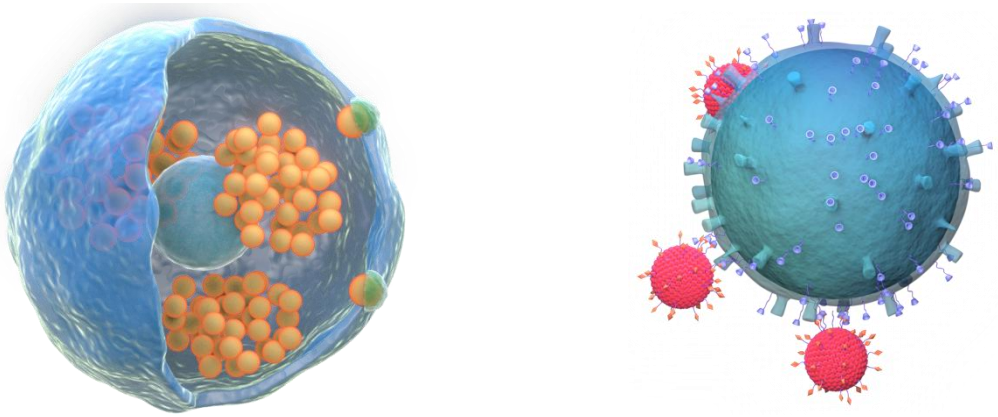

Figure. 1 Schematic illustration of cell-hitchhiking nanomedicine’ intracellular self-assembly (Left); and cell-hitchhiking via extracellular “hand-holding” (Right).

Engineered Cryo-shocked Cells as Drug Delivery Vehicles

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Abstract: The cryo-shocked cells that were obtained by rapid immersion of live cells in liquid nitrogen have been developed as a novel kind of biomedical materials for the treatment of various diseases. After quick-shocking, the cryo-shocked cells lost proliferation capability while preserving transiently the integrity of cellular structure, enabling the possibility of drug loading and cargo release. Moreover, the cryo-shocked cells retained similar protein expressions as live cells, thus preserving protein-derived biofunctions to some extent. Our previous work has proved the efficacy of cryo-shocked tumor cell as the bone marrow targeting vehicle and tumor vaccine to mediate chemoimmunotherapy in treatment of acute myeloid leukemia, as well as cryo-shocked mononuclear macrophages as lung targeting vehicle and mixed antibodies of cytokines for attenuation of cytokine storm in pneumonia. The proposed liquid nitrogen-shocking strategy is simple and possible for large scale production and standardization, thus is promising in clinical use.

Keywords: cryo-shocking, dead cell, targeting delivery, cancer treatment, immunoactivation, immunosuppression

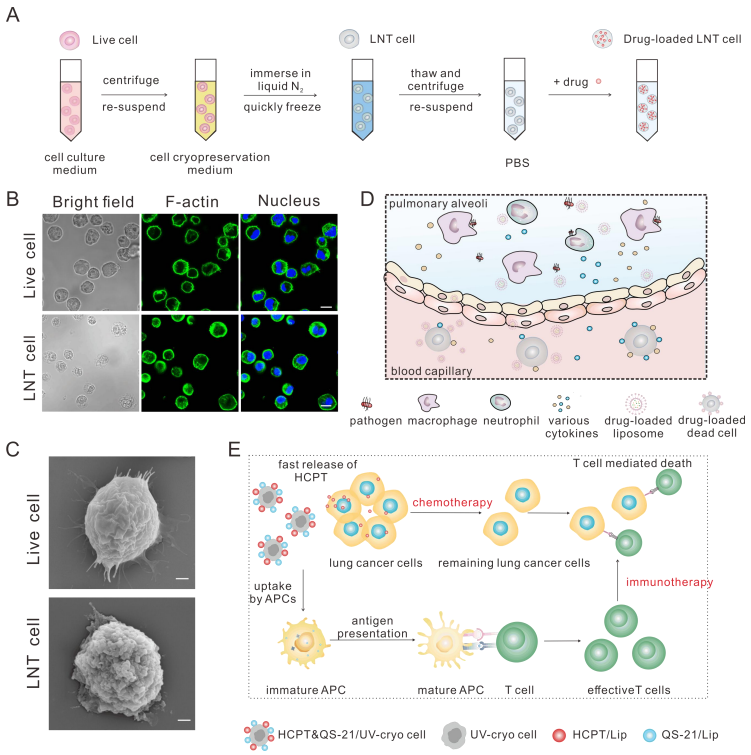

Figure 1. (A) The preparation process of cryo-shocked cells. The cellular structure of cryo-shocked cells evaluated by confocal microscopy (B) and scanning electron microscope (C). (D) Immunosuppression capability of cryo-shocked mononuclear macrophages. (E) Chemoimmunotherapy of lung cancer mediated by UV-cryo shocked cancer cells.

Sodium Bicarbonate Nanoparticles for Amplified Cancer Immunotherapy by Inducing Pyroptosis and Regulating Lactic Acid Metabolism

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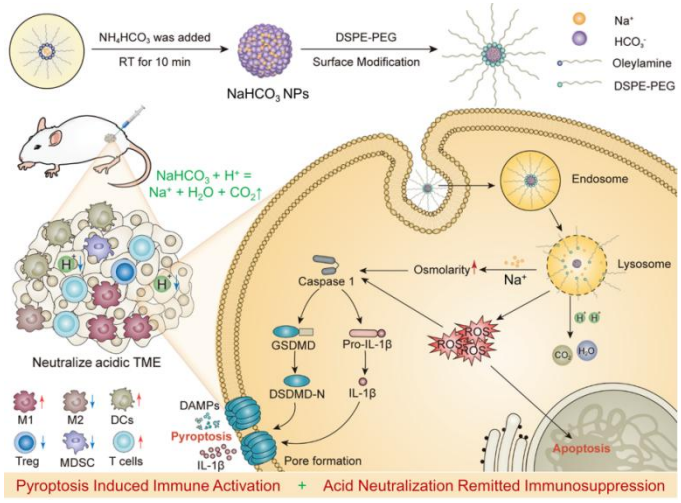
Abstract: Although immunotherapy has a broad clinical application prospect, it is still hindered by low immune responses and immunosuppressive tumor microenvironment (TME). Herein, a simple and drug-free inorganic nanomaterial, alkalescent sodium bicarbonate nanoparticles ($NaHCO_3$ NPs) were prepared via a fast microemulsion method for amplified cancer immunotherapy. The obtained alkalescent $NaHCO_3$ regulates lactic acid metabolism through acid-base neutralization, so as to reverse the immunosuppressive tumor mildly acidic environment. Additionally, it can further release high amounts of Na^+ ions inside tumor cells and induce a surge in intracellular osmolarity, and thus to activate the pyroptosis pathway and immunogenic cell death (ICD), release a mass of damage-associated molecular patterns (DAMPs) and inflammatory factors, and improve immune responses. Collectively, $NaHCO_3$ NPs observably inhibited primary/distal tumor growth and tumor metastasis through acid neutralization remitted immunosuppression and pyroptosis induced immune activation, showing an enhanced antitumor immunity efficiency. This work provides a new paradigm for lactic acid metabolism and pyroptosis mediated tumor treatment, and has a great potential to be applied in clinical tumor immunotherapy.

Keywords: $NaHCO_3$ nanoparticle; lactic acid metabolism; pyroptosis; immunotherapy; immunosuppressive tumor microenvironment



Scheme 1. Schematic illustration of the fabrication and mechanism of sodium bicarbonate nanoparticles ($NaHCO_3$ NPs) for amplified cancer immunotherapy.

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Organic-Inorganic Hybrid Nanoplatforms for Methicillin-Resistant Staphylococcus Aureus Infection Therapy

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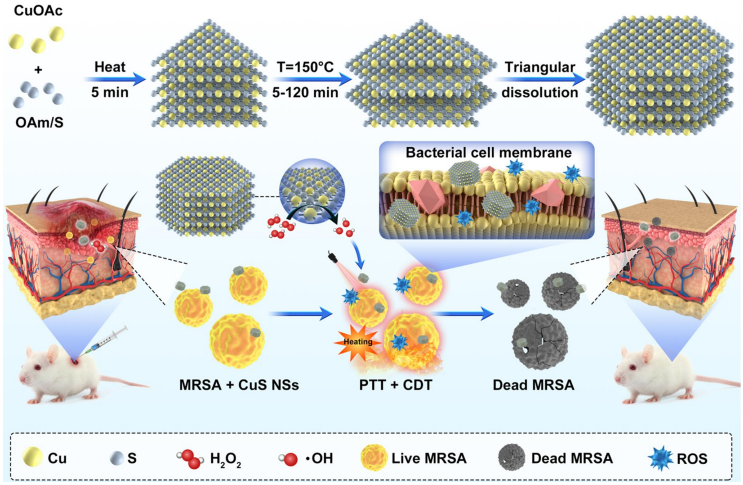
Abstract: One form of bacteria that is extremely resistant to conventional antibiotics and renders a variety of serious infections is the methicillin-resistant *Staphylococcus aureus* (MRSA). Artificial nanozymes that do not require antibiotics can generate enough reactive oxygen species to kill bacteria. Therefore, new broad-spectrum antibiotics with intrinsic enzyme-like activity found in copper-based nanomaterials have shown promising potential. Nevertheless, due to their intricate material design and poor catalytic activity, their viability remains unfathomable. Thus, we synthesized hexagonal copper sulfide nanosheets (CuS NSs) by a modified one-pot method. The CuS NSs demonstrated photothermal stability and superior photothermal conversion efficiency because of their large surface area, existence in the second near-infrared window (1270 nm), and also showed excellent peroxidase-like activity. Upon NIR-II irradiation, CuS NSs displayed an excellent biocatalytic antibacterial role in vitro, accelerated abscess resolution and enhanced the recovery of MRSA-infected wounds in vivo, and most importantly demonstrated negligible toxicity following an amplifying peroxidase-like activity through hyperthermia. Overall, CuS NSs provide a feasible strategy for using the synergistic therapeutic platform for effective therapy of deep-seated MRSA-infected wounds.

Keywords: CuS; Peroxidase-like activity; Photothermal therapy; Antibacterial; Anti-infection therapy



Scheme 1. The description of the synthesis procedure of hexagonal CuS NSs and the efficacy of 1270 nm laser irradiation enhancement of peroxidase activity of CuS NSs against MRSA-infected abscesses *in vivo*.

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A word of caution on using 3-amino-succinimide based fluorescent probe for formaldehyde detection in living system

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Abstract: Exposure to the high level of formaldehyde plays a key role in the development of many cancers, hence its monitoring in living system is very important.[1] In recent years, analyte regenerating strategy for formaldehyde detection is developed. By utilizing 3-amino-succinimide moiety as sensing part, the probes demonstrate fast detection time, excellent detection limit and potential application in formaldehyde homeostasis and function study with minimum perturbation to biological system.[2-3] However, extra care should be taken for the structure of the fluorescent probe due to the risk of self-hydrolysis. Herein, we report a formaldehyde regenerating fluorescent probe, which also been used to test the water stability of 3-amino-succinimide moiety. Although the probe shows a selective response towards formaldehyde, a second emission peak emerge upon storage in PBS buffer solution/ 1% DMSO which could adversely affect the accuracy and reproducibility of formaldehyde detection. From the UPLC-MS analysis, probe hydrolysate is found which can confirm that it undergoes self-hydrolysis in presence of water under neutral pH. The risk of hydrolysis of probe employing this strategy haven’t been investigated previously. This would largely limit the biological application of analyte regenerate strategy.

Keywords: functional fluorescent probe; formaldehyde detection; stability

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The strategy of drug delivery from microneedles in a controlled/sustained release manner

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Abstract: Constructing a novel, safe and effective drug delivery system has important theoretical and practical values for pharmaceutical development and disease treatment. As a convenient, safe, painless, and low-cost transdermal drug delivery system, microneedles have received considerable attention due to the unique advantages. Currently, research on microneedles mainly focuses on the rapid dissolution of microneedles and the bolus release of loaded drugs (such as small chemical drugs, DNA, peptides, or proteins) after entering the skin. However, due to technical difficulties, such as poor stability of drugs, long time needed for microneedles to separate under the skin, and difficulty in implantation of insoluble microneedles, there is few research on separating and implanting drug-loaded microneedles under the skin quickly and achieving slow release of drugs from microneedles under the skin. Therefore, we have developed slowly degraded drug-loaded microneedles by combining drug crystallization technology with biocompatible materials that have been approved by the US FDA, and by using innovative engineering technology (constructing bubble structure and effervescence formulation) to enable the efficient penetration of drug-loaded microneedles into the skin and achieve rapid and effective separation of drug-loaded microneedles (**Figure 1**). In this way, the drug-loaded microneedles can be quickly implanted into the skin by the patient, followed by slow degradation and gradual release of drugs for a long time under the skin.

Keywords: microneedles; sustained release; biodegradation; transdermal drug delivery

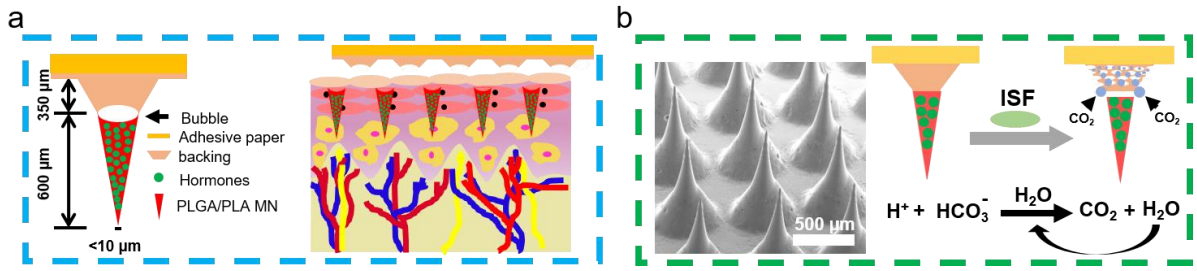

Figure 1. The schematic illustration of microneedles with bubble structure (a) or effervescence formulation (b) for rapid separation of the drug-loaded microneedles in skin.

Multifunctional nano-herb based on tumor microenvironment for enhanced tumor therapy of gambogic acid

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Abstract: Multifunctional drug delivery systems (DDSs) have shown great prospects in overcoming the heterogeneous barrier of targeted delivery drugs to the complex tumor microenvironment (TME). This is mainly because of the ability of these DDSs to actively target and respond to the TME. Therefore, in this study, multifunctional microgels AS/Ge-pNAB with dual-active targeting, triple environment responsiveness, and fluorescence imaging capability were prepared through a straightforward one-step free radical precipitation polymerization procedure. This was aimed to improve the antitumor therapeutic application of gambogic acid (GA) based on the biological characteristics of TME. The microgels have a uniform double-layer structure with aptamer in the outer layer which helps in recognizing receptors on the tumor cells. The microgels loaded GA with high encapsulation efficiency (~86%) to obtain multifunctional nano-herb (AS/Ge-pNAB@GA). The nano-herb exhibited environment-responsive drug release profiles under acidic pH, reductant and high temperature (40 °C). Moreover, it depicted minimal drug leakage under normal physiological conditions. The nano-herb significantly improved the accumulation of GA in tumor sites through the synergistic combination of the enhanced permeability and retention (EPR) effect and dual-ligand mediated internalization. Then, it accelerated intracellular drug release and killed tumor cells. Therefore, the nano-herb had specific therapeutic effects on the tumor *in vitro* and *in vivo* as they remarkably inhibited tumor growth while depicting optimal biosafety. The nano-herb also caused lower levels of off-target toxicity as compared to free GA. Overall, these findings demonstrate the great potential of the multifunctional AS/Ge-pNAB microgels for precisely targeted GA delivery and open a new avenue for the facile preparation of multifunctional DDSs.

Keywords: tumor microenvironment; microgels; dual-active targeting; triple environment responsiveness; gambogic acid

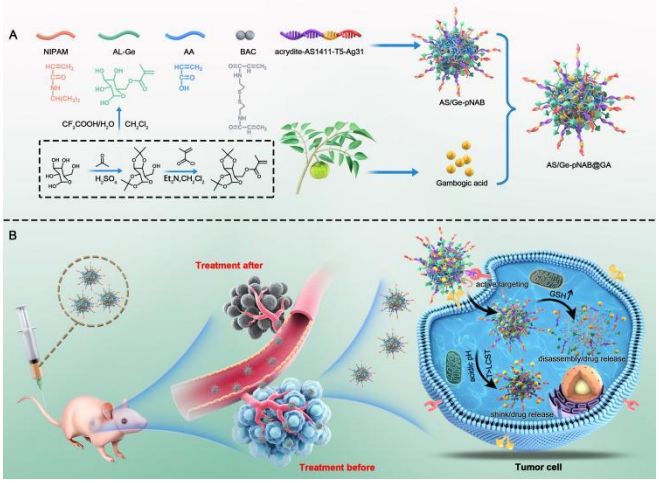

Figure. 1 Schematic overview of the preparation and application of multifunctional nano-herb for precisely targeted delivery of gambogic acid *in vitro* and *in vivo.*

Reference:

[1] X. Y. Wan, H. Zhong, W. Pan, Y. H. Li, Y. Y. Chen, N. Li, B. Tang, Angew. Chem. Int. Ed.[J], 2019, 58, 14134-14139.

Supramolecular nanoassemblies-mediated GSH depletion boosts synergistic chemo- and photodynamic therapy for immunogenicity enhancement

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Abstract: O_2-dependent photodynamic therapy (PDT) generally suffers from compromised therapeutic efficiency due to a hypoxic tumor microenvironment. The therapeutic efficiency enhancement of PDT in a hypoxic tumor microenvironment usually requires sophisticated chemical design and multistep preparation and purification procedures. The development of a facile yet robust strategy to improve the therapeutic efficiency of PDT is thus highly desirable for clinical translations, but remains a significant challenge. For this purpose, we reported herein the use of Azobenzene (Azo) not only as conjugation sites for facile construction of multicomponent supramolecular nanomedicine based on a guest homopolymer poly(Azobenzene) (PAzo) and three β-CD-decorated host moieties, *i.e.*, β-CD-modified photosensitizer chlorin e6 (β-CD-Ce6), chemotherapeutic drug cisplatin (β-CD-Pt(IV)), and hydrophilic poly(oligo ethylene glycol) methacrylate (β-CD-POEGMA) via host-guest interactions, but also for glutathione (GSH) depletion-enhanced synergistic chemo- and photodynamic therapy via hypoxia-triggered cleavage of Azo. Notably, the resulting self-assembled supramolecular nanoparticles (NPs) with a Ce6, platinum(IV), and POEGMA molar ratio of 8:8:2 ($NP_{Ce6/Pt}$) mediated greater cytotoxicity with a half maximal inhibitory concentration (IC_{50}) value 6-fold lower than that of free Ce6 under a hypoxia condition with 660 nm laser irradiation because Azo cleavage-induced GSH depletion boosts synergistic chemo- and photodynamic therapy, which further led to immunogenicity enhancement with a tumor inhibition rate of 93.1% in a murine 4T1 transplantation tumor model. The modularized supramolecular nanoplatform developed herein provides a facile yet robust strategy for advanced combinatory cancer therapy with great potential for clinical translations.

Keywords: Supramolecular nanomedicine, GSH depletion, chemotherapy, photodynamic therapy, immunogenicity enhancement

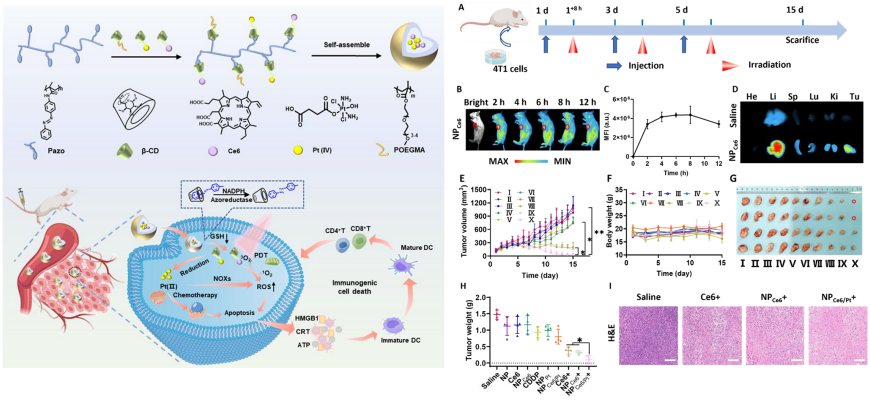

Figure 1. Schematic illustration of the synthesis of supramolecular prodrug nanoassemblies and the enhanced immunotherapy via the combination of photodynamic therapy and chemotherapy (Left); and in vivo therapeutic efficiency of various formulations in a murine 4T1 transplantation tumor model (Right).

Reference:

[1] Peng JL, Zuo C, Xiao Q, Deng KC, Meng C, Liu YP, Zhang M, Ma LW, Pun SH, **Wei H***. Synthesis of stimuli-responsive nanosized ring-like colloids and cyclic polymers via a dual-template approach. **Chem. Sci.** 2019, 10, 3943-3948.

Engineering extracellular vesicles for synergistic cancer immunotherapy

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Abstract: Immunotherapy has revolutionized the treatment of tumor malignancies. However, single cancer immunotherapy frequently leads to treatment failure due to adaptive immune resistance. Herein, a synergistic cancer immunotherapy modality was established by synergizing P21-activated kinases 4 (PAK4) silencing with immunogenic phototherapy in engineered extracellular vesicles. PAK4 is known as a driver for the proliferation and progression of tumors. More recently, it is identified as a tumor-cell-intrinsic “guard” associated with immune exclusion. Therefore, PAK4 silencing can not only directly inhibit the survival of cancer, but also is able to boost intratumoral immune infiltration. To trigger potent antitumor immunity, siRNA against PAK4 (siPAK4) was complexed with the Ce6-conjugated, thioketal-linked polyethyleneimine (TPC) to obtain the photoactivatable nanocomplex (TPCS). Subsequently, TPCS was encapsulated by M1 macrophage-derived extracellular vesicles (EVs) to generate the engineered EVs (TPCS@EV). The results confirmed that TPCS@EV induced potent PAK4 silencing and robust immunogenic phototherapy, thus contributing to effective immune activation and intratumoral immune infiltration for enhanced antitumor effects. Moreover, the antitumor synergism of the combined treatment was quantitatively demonstrated by using the Compusyn approach. Together, this study presents a synergistically potentiated cancer immunotherapy by synergizing PAK4 silencing with immunogenic phototherapy in engineered EVs, which is promising for boosting the antitumor efficacy.

Keywords: engineered extracellular vesicles; synergistic cancer immunotherapy; PAK4; phototherapy

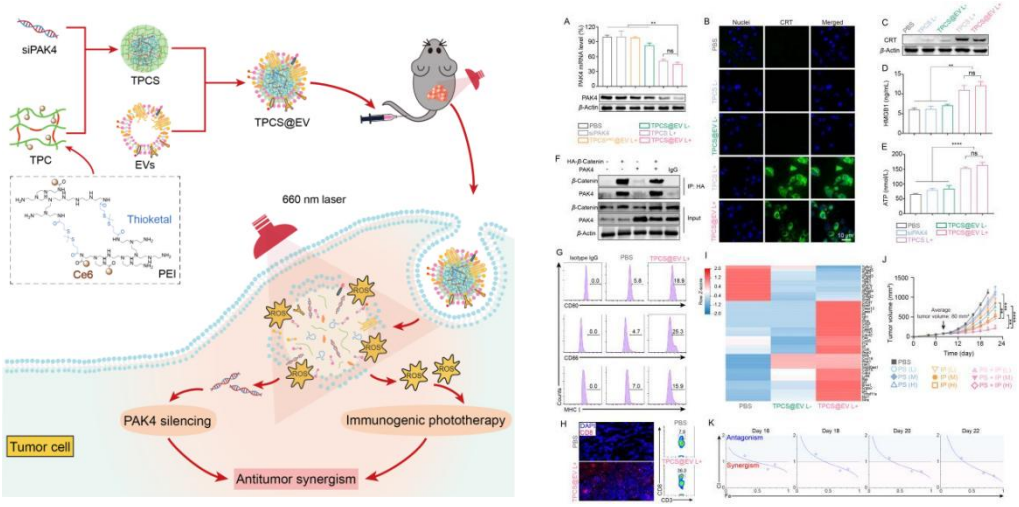

Figure. 1 Schematic illustration of the engineered extracellular vesicles to synergize PAK4 silencing and immunogenic phototherapy, which simultaneously boosts immune activation and intratumoral immune infiltration to synergistically enhance the antitumor effect.

Reference:

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基于纳米载体-蛋白互作的抗感染策略

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摘要：耐药细菌和高变异病毒入侵机体引发的感染性疾病严重威胁人类生命健康。我们围绕内/外源性蛋白与纳米疫苗/药物递送系统的相互作用及对其体内性能的调控开展研究，开发基于纳米载体-蛋白互作的抗感染策略：①开发“载体诱捕”策略，调控纳米载体表面病原蛋白结合吸附，并设计多价类毒素疫苗实现“超级细菌”感染强免疫保护，构建诱捕载体阻断高变异病毒不同毒株感染；②改良纳米载体本征性质，主动调控抗感染药物递送系统表面功能蛋白吸附，实现基于吸附蛋白生物学功能的体内安全高效靶向递送，为抗感染靶向药物递送系统的设计提供新策略。

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