中国颗粒学会第十一届学术年会

暨海峡两岸颗粒技术研讨会

会议摘要集

第

十

分

会

场

中国·厦门

二〇二〇年十月

目 录

论文编号：10–001

仿生疫苗颗粒

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摘要正文：

基因工程疫苗、肿瘤多肽疫苗等新型疫苗和传统灭活疫苗相比，安全性大幅度提高，但存在着免疫原性弱等因素，无法产生足够的免疫应答，打破免疫耐受，难以达到理想的预防和治疗效果。因此，新型疫苗的研发成功和重大疾病免疫治疗的成功越来越依赖于疫苗制剂工程。新冠疫情的爆发也给我们提出了挑战。

本研究提出用颗粒模仿病原体的尺寸、性质及递送过程，即仿生颗粒。以仿生颗粒为“底盘”，将抗原及其他组份组装在仿生颗粒上，共同构筑成合成疫苗（即仿生疫苗），该过程称之为合成疫苗工程（Synthetic Vaccine Engineering）。我们采用不同的仿生策略，在流感、乙肝、肿瘤等的预防和治疗应用中获得了可喜的结果。

要实现应用，不能采用复杂的仿生设计，需采用可应用、可转化的材料、可加工的过程进行仿生颗粒制备。首先，我们建立了均一可降解颗粒可控制造平台，我们发展了2种微孔膜乳化法制备粒径均一纳微颗粒，粒径在0.1-数百微米之间可控，已成功制备出了各种生物可降解微球，包括聚乳酸类、多糖类，并实现了形貌可控。采用均一颗粒，提出并系统研究了疫苗体内递送的不同环节的仿生设计和应用效果。

1）颗粒尺寸和形貌的仿生：颗粒和形貌影响免疫细胞（抗原提呈细胞）对抗原的吞噬，是疫苗递送的关键环节，我们系统研究了颗粒粒径和仿生形貌对免疫效果的影响[1]。

2）胞内递送过程的仿生：病毒在细胞内的复制需要在细胞质中进行。而仿生颗粒被免疫细胞吞噬后是在溶酶体内加工提呈，我们提出多种溶酶体逃逸的仿生策略，发现颗粒促进抗原的溶酶体逃逸是提高细胞免疫和治疗性效果的关键，为此设计制备出了多种pH敏感可降解颗粒，分别将肿瘤抗原、H1N1抗原等组装在颗粒上或颗粒内，同时获得了高的体液免疫和细胞免疫应答[2-3]。

3）递送全过程的仿生：在上述基础上，我们提出用可变形的Pickering乳液的仿生策略。用聚（乳酸-乙醇酸）（PLGA）均一纳米颗粒制备Pickering乳液，将抗原装在PLGA纳米颗粒之间构筑仿生疫苗。该仿生颗粒模仿了病原体的表面图案化，吞噬过程中的可变形和抗原可流动的动态特征，不仅大幅度增强了抗原提呈细胞对抗原的吞噬量，而且具有溶酶体逃逸功能。用该仿生颗粒构建了H1N1禽流感预防疫苗和黑色素瘤治疗疫苗，预防和治疗效果均远远优于用非变形性微球和已有市售佐剂（铝佐剂、MF59等）构建的疫苗[4]。

关键词：均一纳微颗粒；仿生颗粒疫苗；底盘；微孔膜乳化；Pickering乳液

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论文编号：10–002

Bioinspired oral delivery of gut microbiota by self-coating with biofilms

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Disorders of the intestinal microbiota are relevant to a multitude of intractable diseases, such as Alzheimer's disease, diabetes, and some cancers (1). Although fecal microbiota transplantation has demonstrated effective, the implementation has been largely restricted by invasive operation and indeterminate composition, which inevitably result in low patient compliance and safety issues (2). Oral delivery of probiotic species to the gut microbiome is an alternative to address these limitations, unfortunately, environmental complexity and a continuous flow within the gastrointestinal (GI) tract result in low oral bioavailability and limited intestinal colonization (3). Hence, methods capable of simultaneously withstanding the GI tract stressors and slowing bowel transit would be of great significance but remain extremely challenging. In nature, to survive in extreme conditions, bacteria produce biofilms to combat physical threats such as displacement by physical forces and removal by environmental attacks. The coating not only acts as an adhesive for attachment, but also defenses external threats by preventing penetration. Inspired by the dual physical adhesion and chemical barrier function of biofilms, we describe a novel strategy for oral delivery of living beneficial bacteria to the gut microbiome by self-coating with biofilms.

Clinical utilized Bacillus subtilis (BS) was grown on solid lysogeny broth (LB) plates. Seed colonies were first cultured in 4 ml LB medium overnight at 37 °C. Then, 100 μl seed culture medium was resuspended and grown in 4 ml solid minimal salts glycerol glutamate (MSgg) medium overnight at 37 °C. The collected cell pellets were resuspended in 1 ml PBS and 10 μl of the resulted solution was spread on solid MSgg plates. Robust BS biofilms were produced after 2 days culture at 30 °C. Individually coated bacteria were prepared by homogenization.

Using clinical BS as a model probiotic bacterium, biofilm-coated probiotics showed superior resistance and adhesion capacity, demonstrating substantially improved GI tract tolerance and mucoadhesion during in vivo studies in mice and swine. In particularly, coated probiotics exhibited a 125-fold higher oral bioavailability and a 17-times greater intestinal colonization than those of uncoated bacteria in the porcine model. With notable ability to survive and reside in the GI tract, coated bacteria further displayed a significantly enhanced decolonization effect in a murine model of intestinal colonization with Staphylococcus aureus.

In summary, self-coating with biofilms suggests a robust platform for oral doses of gut microbiota, which opens a new window for the efficient transplantation of probiotic bacteria to the gut microbiome.

Acknowledgements

This work was financially supported by the National Natural Science Foundation of China (21875135) and the Recruitment Program of Global Youth Experts of China (D1410022).

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论文编号：10–003

黑磷纳米材料的表/界面修饰与生物医学应用

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Recently, black phosphorus nanomaterials (BPs) has attracted increasing interest because of its unique properties and the promising applications in various fields including biomedicine. However, the lack of air- and water-stability of BPs handicaps its practical applications because BP is very reactive to oxygen and water, resulting in compositional and physical changes and consequently degradation in properties. Preventing the reaction between BPs and oxygen is crucial to enhancing the stability but how to accomplish it in reality is a great challenge. In this presentation, surface modification strategies are proposed to enhance the stability of BPs. With regard to different strategies, BPs after certain surface modification not only devote good stability, but also can be utilized as nanoagents for the biomedical applications including photothermal therapy, photoacoustic tomography, drug delivery as well as tissue engineering.

关键词: 黑磷, 表/界面修饰, 生物医学应用

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论文编号：10–004

Self-assembly and amphiphilic polymeric nanoparticles for drug delivery

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The self-assembly through noncovalent interactions from a single molecule to well-organized nanoscale architectures has a great significance in understanding biological self-assembly process, which offers an effective strategy for creating a myriad of sophisticated nanoparticles in applications of diagnosis, prevention and treatment of tumors[1]. Drug delivery can vary depending on the physicochemical properties of nanoparticles, but the interaction between the physicochemical properties, self-assembly mechanism and biological effects of nanoparticles is still unclear [2]. Here, we reported the design and preparation of a series of amphiphilic polymeric nanoparticles, and then reveal the self-assembly mechanism and nanoparticle-biological interaction through main methods such as all-atom molecular dynamics simulation, multi-omics analysis and imaging mass spectrometry, which may provide the optimal design scheme to guide future nanoparticles designs and delivery strategies for tumor diagnosis and treatment.

Keywords: self-assembly, drug delivery, polymeric nanoparticles, tumor diagnosis and treatment

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论文编号：10–005

Hydroxyethyl starch based smart nanomedicine

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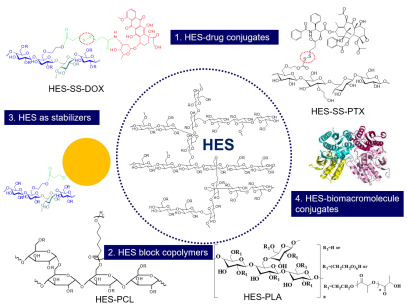
Derived from waxy maize, which contains more than 95% of amylopectin, hydroxyethyl starch (HES) is therefore highly water soluble, keeps the branched structure of amylopectin, and has wide clinical use as plasma volume expander.[1] HES can be categorized into various classes based on its molecular weight, mole substitution of hydroxyethyl, and substitution pattern (C_2/C_6 ratio). These parameters affect the endogenous α-amylase mediated degradation of HES in blood, thus determine the pharmacokinetics of HES, enabling convenient ways to tailor the *in vivo* fates of HES by simply adjusting these parameters.[2] The good manufacturing practice, high water solubility, tailorability, biocompatibility, biodegradability, well defined *in vivo* safeties, and wide clinical applications make HES a promising drug carrier which warrants clinical translation explorations.

In this talk, we will present our progress of HES based smart nanomedicines.[3-8] We prepared a novel redox-sensitive hydroxyethyl starch-doxorubicin conjugate, HES-SS-DOX, with diameter of 19.9 ± 0.4 nm, to alleviate the side effects and improve the antitumor efficacy of DOX.[3] With HES-SS-PTX, we also obtained self-assembled nanoclusters (with diameter of 150 nm), which show dual α-amylase and redox responsive properties for enhanced tumor penetration and therefore improved antitumor efficacy.[4] We conjugated HES with polylactide to afford HES-PLA, which self assembles to nanoparticles with varied sizes. The large sized HES-PLA nanoparticles (with diameter 700 nm) are applied to saturate the MPS system, while the smaller ones (150 nm) are loaded with DOX for enhanced drug delivery efficiency and improved anti-tumor efficacy.[5] Moreover, both cytotoxic drug, for instance DOX, and immunomodulatory, for example TGF-β receptor inhibitor, can be loaded together within HES-PLA for inhibition of insufficient chemotherapy induced metastasis.[6] Our researches collectively corroborate HES would be an excellent candidate for clinical applications[7-8].



Keywords: Hydroxyethyl starch, Smart Nanomedicine, Drug delivery

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论文编号：10–006

Combating New Delhi metallo-β-lactamase (NDM) producing Enterobacteriaceae Superbugs by Engineered Zinc “Nanosponge”

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Carbapenems are recognized as last-resort antimicrobials for curing infections caused by Gram-negative pathogens such as *Enterobacteriaceae*. Unfortunately, widespread of New Delhi metallo-β-lactamases (NDMs) lead to the emergence of carbapenem-resistant *Enterobacteriaceae*, which poses an urgent threat to public health. Herein, inspired by the crucial function of zinc ion in NDMs, an engineered zinc “nanosponge” with pathogen targeting and site-specific drug release properties was developed by cloaking Meropenem loaded PAMAM with platelet membrane for NDM-producing *Enterobacteriaceae* treatment. Our results revealed “nanosponge” PPM effectively reversed carbapenem resistance and cured NDM-producing *Escherichia coli* infections through depleting zinc in NDMs, further proceeding its degradation. Besides, excellent prolonged circulation and targeting ability to pathogens of “nanosponge” were observed in zebrafish and murine pneumonia model. Particularly, “nanosponge” maintains meropenem during circulation, while burst releasing at the infection site, which brings an accurate antibiotic treatment. This study has therefore offered a potential therapeutic platform for NDM-producing *Enterobacteriaceae* treatment.

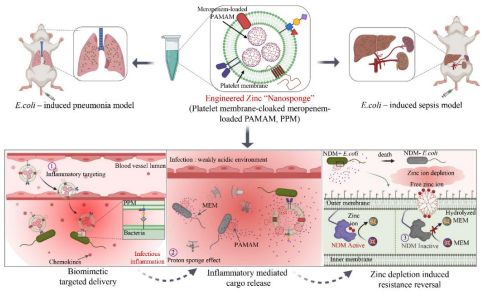

Fig.1 Representative schematic diagram of engineered zinc “Nanosponge” reverse carbapenem resistance for combating New Delhi metallo-β-lactamase (NDM) producing Enterobacteriaceae Superbugs. a, Pneumonia and sepsis models were chosen for evaluating the capability of inflammatory targeting and drug resistance reversal of engineered zinc “nanosponge”. The schemes also showed that engineered zinc “nanosponge” was constructed by using platelet membrane vesicles as shell, coating the meropenem-loaded PAMAM. b, The platelet membrane-cloaked meropenem-loaded PAMAM (PPM) actively reach the infection site after intravenous injection (i.v.) based on chemoattraction, subsequently specifically target activated endothelial cells and adhere pathogens (1), which benefit from the inherent functionality of platelet. The PPM at the local infectious site release PAMAM and meropenem (MEM) owing to the proton sponge effect of PAMAM triggered by local weakly acidification (2). The released PAMAM not only loads a lot of meropenem for local responsive release but also possess high zinc ion chelation ability. Thus PAMAM deprives the zinc ion on NDMs active site and the free zinc ion in the infectious microenvironment, which reduces the availability of zinc ions followed by restoring the sensitivity Enterobacteriaceae to meropenem (3).

Keywords: NDM; Nanosponge; Zinc ions depletion; Pathogen-targeting; Inflammatory controlled release

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论文编号：10–007

Three-dimensional Simulation of Red-blood-cell Particle Sedimentation

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The red-blood-cell particle is important in the researches of blood flow[1] and drug delivery. The biconcave shape makes the motions of the red-blood-cell particle in fluid more complex than sphere or ellipsoid[2,3]. Sedimentation behaviors of a Red-blood-cell particle in long circular tubes are investigated by using the lattice Boltzmann method with the Galilean-invariant momentum exchange method[4]. Different blockage ratios and the particle to fluid density ratios are considered. One periodic and two steady sedimentation modes are discovered. When the blockage ratio groups up, the motion mode of particles changed from horizontal mode to inclined mode. With the increase of the particle to fluid density ratio, sedimentation mode changed from inclined mode to horizontal mode, and the time of the particles reaching the stable state is obviously distinct in different sedimentation modes. Surprisingly, the oscillatory mode is observed in the larger blockage ratio and lower ratio of particle to fluid. This work could make active promotions to the researches of blood circulation of human.

Keywords: particle sedimentation; sedimentation mode; red blood cell; lattice Boltzmann method;

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论文编号：10–008

Rotating Microparticles with Motor Proteins

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Rotary motion is central to macroscale engineering, but much more difficult to achieve by artificial nano-fabrications.[1] Microtubules propelled by surface-adhered motor proteins have been primarily used to generate translational motion, but have also been seen self-assembled circular structures.[2-3] Here, we present a simple method using a microtubule to rotate a microsphere on a kinesin-coated surface.

In this study, biotinylated microtubules are self-assembled with streptavidin-coated 5 micron microspheres with different geometries. Besides rectilinear motions, we observed two typical rotational motions, *in situ* spinning and rolling. In the spinning event, a microtubule is spooling its plus end on the kinesin-coated surface and pushing the microsphere to rotate, with its minus end tightly anchored on the microsphere surface. The rolling motion occurs when the microtubule is perfectly bending on the equator of a microsphere. This microsphere rotation demonstrates a novel approach to realize rotary motion of microscale mechanical components by the microtubule-kinesin system.

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论文编号：10–009

Cellular membrane-derived nanovesicles as a Versatile Drug Delivery System for Imaging-Guided Cancer Therapy

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The development of smart nanoparticles that enable to circumvent biological barriers and transport cargoes to target sites in the body promises safer and more effective drug delivery. Since cell membrane-based nanovesicles have the characteristics of both nano-sized and cell-based drug delivery platforms, they are regarded as promising cancer targeted delivery tools for both endogenous and exogenous cargos. What is perhaps most fascinating about these cell membrane-based drug delivery systems is that the natural targeting ability of those producing cells makes the exogenous engineering of targeting moieties unnecessary. In our laboratory, a variety of bio-inspired nano-biomaterials, such as virus-like nanoparticles and ferritin nanocages, have been studied for drug delivery, cell labeling, and gene therapy. A number of hybrid nanoparticles containing synthetic and biological components have been utilized for achieving sustained release and target-specific delivery. We are particularly interested in cell membrane-based nanoparticles containing bioactive molecules useful for therapeutic and imaging applications in cancer theranostics. In this presentation, an innovative biomimetic nanoparticle platform for delivering therapeutic anticancer agents and imaging-guided cancer therapy will be introduced. In addition, the major hurdles in the clinical translation of cell membrane-based delivery systems will be discussed.

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论文编号：10–010

葡萄糖氧化酶介导仿生矿化磷酸钙纳米颗粒用于癌症诊疗研究

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摘要正文：

葡萄糖氧化酶（GOx）可以专一、高效地催化葡萄糖氧化产生葡萄糖酸和过氧化氢（H2O2）。利用GOx选择性消耗肿瘤内的葡萄糖可以切断肿瘤的能量供给，从而实现饥饿治疗；将GOx介导的饥饿疗法与其他治疗手段相结合，发展多模式协同治疗可以为癌症治疗提供新的解决方案和思路。

然而GOx在体内稳定性差，容易被降解，并且材料复杂的制备过程难以实现临床转化。自然界中的生物体可以利用生物大分子调控生成无机矿物，例如骨骼中的磷酸钙（CaP）。受此启发，我们采用GOx介导仿生矿化合成锰掺杂磷酸钙（MnCaP）纳米颗粒，并通过负载药物阿霉素（DOX），构建一种兼具生物可降解性和肿瘤微环境酸响应性的纳米药物GOx-MnCaP-DOX，用于实现肿瘤MRI示踪的高效协同治疗（Fig. 1）。如图所示，该纳米药物可以响应肿瘤微酸环境快速释放出GOx、Mn2+及DOX，利用GOx催化葡萄糖氧化产生大量H2O2，随后产生的H2O2与Mn2+发生类芬顿反应转化为毒性更强的羟基自由基（•OH）杀伤肿瘤细，通过GOx与Mn2+之间的级联反应可以显著提高治疗效果。与此同时，DOX则通过化疗手段进一步杀伤肿瘤细胞，而释放出来的Mn2+具有顺磁性，可实现MRI诊断成像。通过将值得一提的是，材料降解产物Ca2+、PO43-均可参与人体正常代谢，Mn2+为人体必需微量元素，而GOx在体内会降解成多肽等，因此材料具有很好的生物安全性，具有潜在的临床转应用价值。

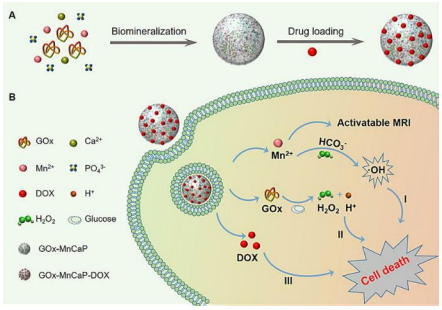

Fig. 1 (A) The preparation process of GOx-MnCaP-DOX, (B) Schematic illustration of GOx-MnCaP-DOX applied for MRI-monitored cooperative cancer therapy. I, Mn2+-mediated Fenton-like reaction for CDT; II, GOx-mediated starvation therapy; III, DOX-induced chemotherapy.

关键词：仿生矿化；葡萄糖氧化酶；磷酸钙纳米颗粒；癌症；诊疗一体化

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论文编号：10–011

仿生纳米药物与肿瘤精准治疗

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摘要正文：

肿瘤的药物高效递送和精准治疗是国际研究的热点和国家重大战略需求，通过仿生纳米技术的确使药物的靶向性和治疗的精准度得到了极大的提高。本课题组受大自然中一些生物的启发，构建了一系列仿生纳米药物，通过模仿生物的结构和功能的策略，实现了药物的高效靶向性和精准治疗的效果。

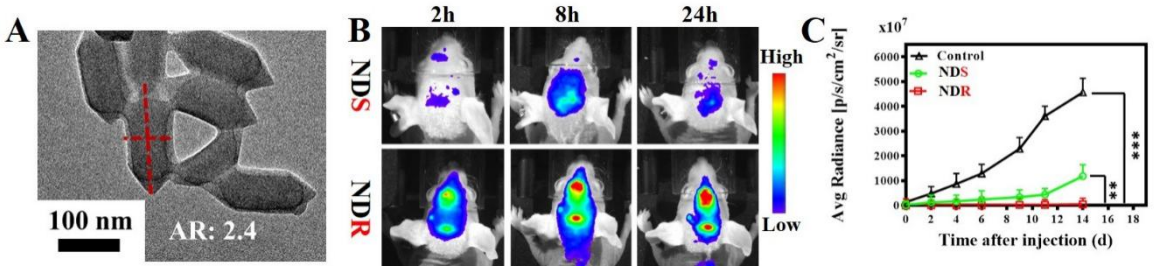

Fig. 1 (A) Structural characterization of probes. (B) Targeted imaging of glial tumors. (C) Chemotherapy of glial tumors

关键词：血脑屏障；仿生；高效靶向；二元协同

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论文编号：10–012

基因编辑递送系统的研究与应用

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摘要正文：

成簇规律间隔短回文重复序列及其关联蛋白 (CRISPR/Cas) 作为一类新型基因编辑工具为疾病的精准治疗提供了重要方案, 并广泛应用于生物学，遗传学，及医学领域。然而，基因编辑递送工具及技术是制约基因编辑技术发展的主要瓶颈。近年来，非病毒载体作为基因编辑元件的递送载体备受关注。此报告将对该领域的发展简单介绍，包括报告人课题组所开展的相关工作，以及对未来治疗遗传性疾病进行展望。

关键词：基因编辑；CRISPR/Cas9；递送载体；基因治疗；非病毒载体

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论文编号：10–013

活性氧物种相关纳米药物的理性构筑与生物医用

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摘要正文：

生物体内，活性氧物种（ROS）在氧气的代谢过程中可以作为副产物持续产生，在细胞信号传导、病原体防御以及生理平衡等过程中，适量的ROS能够作为重要的第二信使发挥功能。然而，高浓度的ROS会对引起正常细胞内的脂质过氧化、蛋白变性或DNA损伤，这些不良反应可能引起包括炎症、肿瘤等在内的疾病。本报告将从ROS相关纳米药物的设计与构筑入手，总结课题组近年来在活性氧物种检测和清除方面的生物应用，并针对ROS相关纳米药物在抗菌和抗肿瘤等医学领域的应用进行系统阐述。

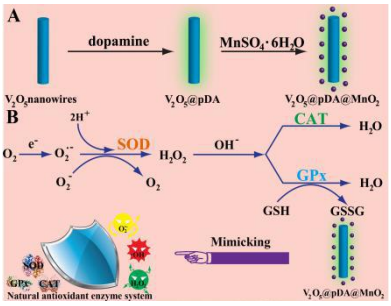

Fig. 1 Synthesis of antioxidant nanomedicines and their use as mimics in intracellular antioxidant defense system.

关键词：活性氧物种；生物剂型工程，纳米药物；生物医用

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论文编号：10–014

异乳清酸-磷酸锌杂化纳米花的合成及其抑菌机理

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摘要正文：

随着纳米颗粒在生物领域研究的兴起，抑菌活性好、低毒性的新材料及其抑菌机理始终是功能材料领域的研究重点。本研究以异乳清酸(5-羧基脲嘧啶)为有机成分，锌离子为无机成分，利用分子自组装首次制备出一种5-羧基脲嘧啶-磷酸锌杂化花状纳米颗粒。X-射线衍射（XRD）、元素分析（EDS）和 傅里叶红外光谱（FTIR）分析证明所制备的纳米花颗粒是异乳清酸和磷酸锌的杂合体。这种磷酸锌基的杂化纳米花通过锌离子与5-羧基脲嘧啶中的氨基形成配合物，这些配合物为磷酸锌晶体成核的提供结合位点，随着磷酸锌晶体的各向异性生长导致形成花状结构。抑菌实验结果表明，这种异乳清酸-磷酸锌杂化纳米花颗粒对革兰氏阳性菌金黄色葡萄球菌及革兰氏阴性菌大肠杆菌具有良好的抑菌效果。在弱酸环境下（pH=5.0）对大肠杆菌抑菌率在90%以上，在弱酸性及中性条件下（pH=5.0和7.0），对于金黄色葡萄球菌的抑菌率也可达90%以上。进一步研究表明，这种异乳清酸-磷酸锌杂化纳米花颗粒优越的抑菌性能是由于花状纳米颗粒大的比表面积更易于吸附并在细胞壁附近溶解释放大量锌离子，锌离子和细胞膜上带负电荷的化合物相互作用导致细胞壁/膜去极化，改变细胞壁/膜的通透性，使细胞内容物泄露，同时释放的锌离子进入细胞后产生的活性氧以及对胞内酶的抑制所产生的协同作用造成细胞死亡。

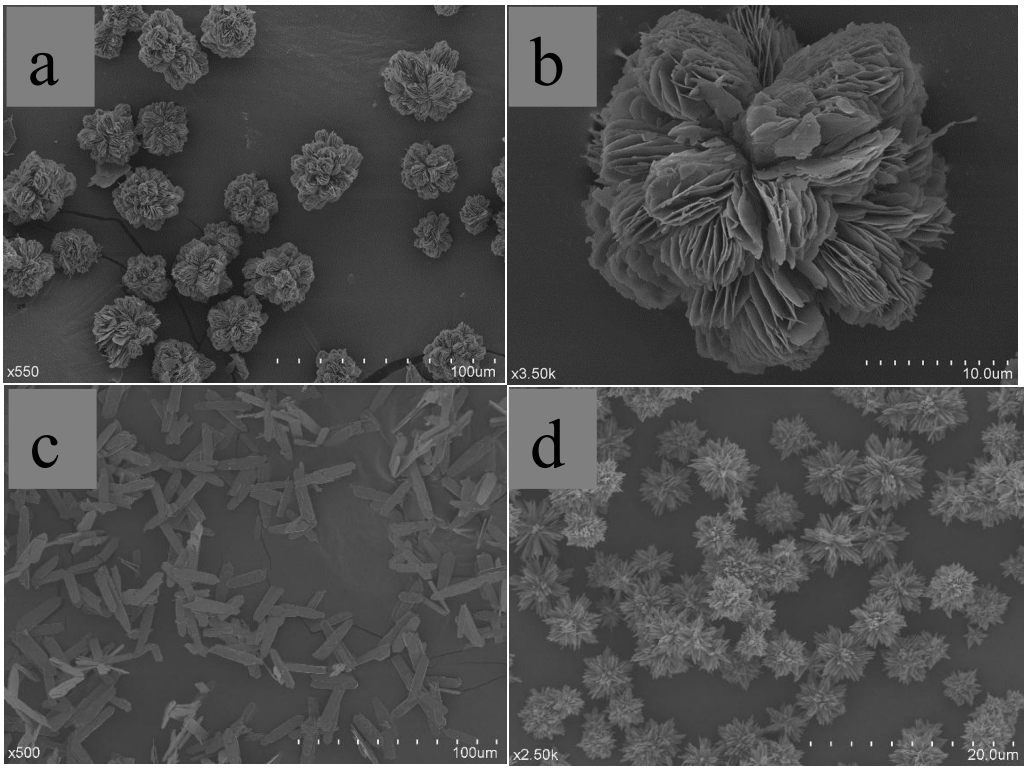

Fig. 1 SEM图：(A,B)　异乳清酸-磷酸锌纳米花; (C) 传统磷酸锌颗粒; (D) 氧化锌颗粒

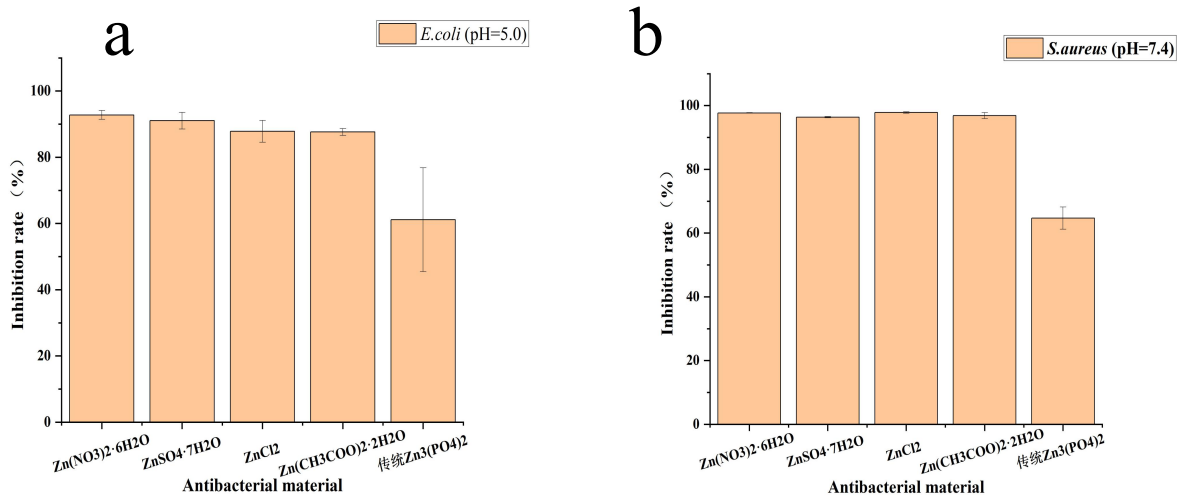

Fig. 2 不同锌盐制备的异乳清酸-磷酸锌纳米花和传统磷酸锌颗粒对不同微生物的抑菌效果

(a) 大肠杆菌; (b) 金黄色葡萄球菌

关键词：异乳清酸；磷酸锌；纳米花颗粒；抑菌机理

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论文编号：10–015

仿生纳米红细胞用于深度乏氧改善的研究

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摘要正文：

氧气是哺乳动物细胞能量代谢的关键成分，炎症部位和实体肿瘤是常见的乏氧区域且乏氧等级随远离血管的程度而逐渐升高。近年来，研究人员多利用携氧载体人为补充氧气以缓解乏氧微环境，但传统载体无法有效深入乏氧组织深部，疗效不佳[1-2]。红细胞是天然的氧气运输载体，独特的双凹盘状结构使其能够通过狭小的毛细血管并借助较大的比表面积实现快速释氧[3]。针对以上问题及红细胞结构仿生的启示，我们设计了以空心盘状介孔氧化硅为核心，外部包被红细胞膜的氧分压敏感型仿生纳米红细胞（PDRs）并通过携载全氟己烷进行氧气递送（Fig. 1 & 2A）。体外氧释放研究结果显示，与天然红细胞类似，盘状PDRs具备良好的氧分压敏感特性，高氧环境下缓慢释氧，低氧环境下迅速释氧，有效改善细胞乏氧状态（Fig. 2B-C）。此外，多粒子追踪结果显示，PDRs利用其纳米尺度小以及盘状侧身运动的特点，能够在生物凝胶屏障如细胞外基质中快速扩散并渗透至组织乏氧深部（Fig. 2D）。在乏氧肿瘤模型中，PDRs展现出良好的长循环特性和组织穿透能力，高效深入肿瘤深度乏氧区域后迅速释氧，显著降低肿瘤内缺氧阳性体积（Fig. 2E-F）。乏氧状态的改善进一步促进细胞周期由G1期向G2期转变，增强肿瘤细胞对化疗药物的敏感性，抑瘤率高达92%，治疗效果显著（Fig. 2G）。因此，本研究中设计的新型仿生纳米红细胞在改善组织深度乏氧领域具有良好的治疗前景。

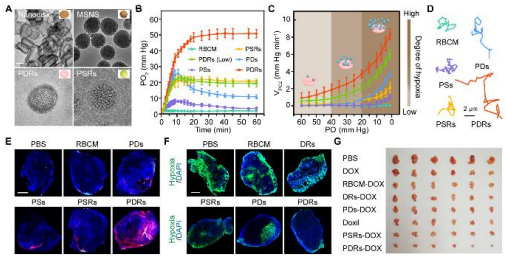

Fig. 1 Illustration of biomimetic oxygen-pressure-sensitive nano-erythrocytes (PDRs) with deep tissue penetration for hypoxia relief.

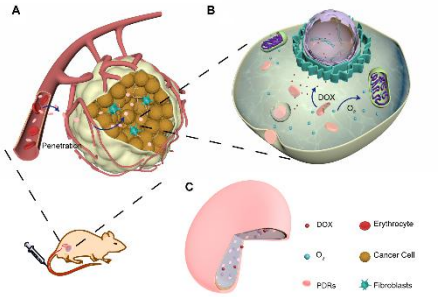

Fig. 2 Characterization (A) and multiple functions of PDRs in oxygen release (B-C), diffusion and tissue penetration (D-E), hypoxia relief (F), and tumor inhibition *in vivo* (G).

关键词：仿生纳米红细胞；氧敏感型释放；深度穿透；氧气递送

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论文编号：10–016

Engineering Cell Membrane Coated Nanoparticles to Target Cancer Autophagy Inhibition and Enhance Antimetastatic Therapy

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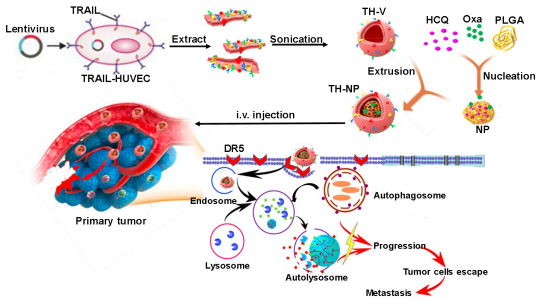
Hepatocellular carcinoma (HCC) is one of the most common cause of cancer-related mortality, and though recent advances in early diagnosis and therapeutics, HCC related morbidity and mortality rate continue to rise. Autophagy is a double-edged sword process that can generate energy and nutrients for HCC cell survival during extreme stress. Autophagy can regulate the migration and invasive ability in HCC, and mediate drug resistance in chemotherapy. Thus, it is of great importance to inhibit autophagy and actively deliver therapeutic agents to TME for the purpose of promoting in situ activity. Herein, we proposed and validated a nanoparticle-based broad-spectrum antitumor strategy for HCC management by fusing TRAIL-anchored cell membranes onto drug-loaded polymeric cores (TH-NPs), which makes them ideal combinational strategy for HCC treatment. Upon intravenous injection of TU-NPs into HCC tumor bearing mice, the fluorescence/photoacoustic dual-modal imaging revealed higher accumulations and longer retention of TU-NPs in TME. In vivo therapeutic evaluations suggested that these nanoparticles could inhibit tumor autophagy, suppress tumor growth, and provide strong protection against HCC metastasis by targeting and deep penetration into the TME. Overall, our work provides a novel strategy to treat HCC with a strong potential for clinical translation.



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论文编号：10–017

纳米限域酶催化过程的多尺度模拟

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摘要正文：

采用纳米材料固定化酶极大地拓展了天然酶催化的应用范畴，全面认识纳米对于酶的结构和催化过程的的影响作用规律对于纳米酶催化剂的设计具有重要的理论指导意义。本团队发展了一种基于分子动力学模拟和Markov状态模型相结合的酶催化过程的多尺度模拟方法。本报告以碳酸酐酶（Carbonic Anhydrase，CA）催化CO_2水合过程为例，介绍采用该方法描述纳米限域对于酶催化过程中底物扩散、底物与酶活性位点结合、产物脱除等步骤的影响规律和作用机制，为纳米酶催化剂的设计和应用提供理论指导。

关键词：固定化酶；纳米限域；分子模拟；Markov状态模型；多尺度

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Multiscale simulation of enzymatic catalysis process in a nanoconfinement

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Recent years have witnessed the rapid of enzyme immobilization on nanomaterials, which has offered numerous ways to enhance enzyme stability and activity under various circumstances and thus paved way to an expanded spectrum of enzyme applications. A global profile, with molecular insight and kinetic details, of the effects of nanoconfinement on the enzyme structure and catalytic process is essential to a rational design of nanostructured enzyme catalysts. We have proposed a new simulation method that combines multi-scale molecular dynamics simulation and Markov state model to describe enzymatic process. Using carbonic anhydrase (CA) as one example, we examined the effects of the nanoconfinement on the diffusion of CO2 from bulk phase to the active site of the confined CA, the binding of CO2 on the active site of CA, and the detachment of HCO3- from CA towards the bulk phase. These finding are helpful in the development of novel nanomaterials for immobilization.

Keywords: Enzyme immobilization, nanoconfinement, molecular simulation, Markov State Model, Multiscale

论文编号：10–018

脱氢酶-辅酶固定化电极构建与应用

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摘要正文：

脱氢酶占氧化还原酶的七成，绝大多数需要辅酶参与反应进行生物电子传递。NAD、NADP等天然辅酶成本较高、稳定性较差、电化学再生电势高，给以脱氢酶催化为基础的酶修饰电极的构建和应用带来了挑战。本团队经过多年研发，开发了一种以脱氢酶-辅酶交联结合为基础的脱氢酶电极制备工艺，通过柔性分子将NAD交联在酶表面，大幅提高辅酶局部浓度，缩短传质和电子传递距离，同时可提高辅酶的稳定性。该技术被应用于生物燃料电池，提高了其输出功率和稳定性；应用于CO2固定产甲酸的生物电化学合成体系，提高了能量转化效率和甲酸的得率；应用于木糖生物传感器，实现了发酵液中木糖的快速灵敏的检测。此外，我们通过仿生纳米颗粒作为辅酶电化学再生的纳米酶催化剂，可以提高生物电化学合成和生物传感器的稳定性和效率，使我们的脱氢酶-辅酶固定化电极具有广阔的应用潜力。

关键词：脱氢酶；辅酶；固定化酶电极；生物电化学；仿生纳米颗粒

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论文编号：10–019

光热-光化学偶联仿生纳米胶囊

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摘要正文：

癌症诊疗药剂的应用通常受到其水溶性差、血液保留时间短、容易引起免疫反应等不利因素的限制。本文制备红细胞（Red blood cell，RBC）膜仿生囊泡，通过红细胞膜囊泡封装光催化剂二氧化钛胶体和光热剂金纳米棒（Au NRs），获得仿生纳米胶囊Au/TiO2@RBC，通过表面细胞膜涂层的光催化降解实现Au NRs的可控释放进而通过近红外（Near infrared，NIR）激光照射产生光热效应，而光催化产生的活性氧物质（reactive oxygen species，ROS）实现光动力治疗（Photodynamic therapy，PDT）。Au/TiO2@RBC具有良好的稳定性。由于天然的RBC涂层，Au/TiO2纳米颗粒的细胞毒性显著降低，同时可以利用RBC涂层的光催化降解实现Au NRs的受控释放，以便在近红外辐射下杀死MCF-7细胞。

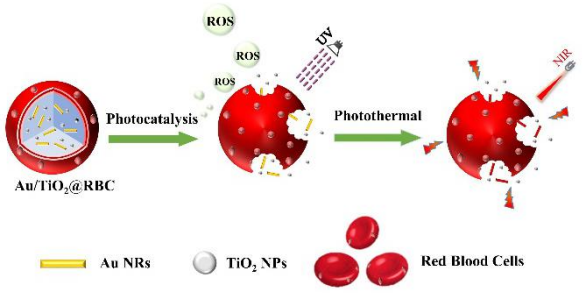

Fig. 1 Design of a biomimetic nanoreactor Au/TiO2@RBC for photothermal therapy by co-encapsulating photothermal agents and photocatalysts in red blood cell membranes.

关键词：红细胞膜；光热治疗；光催化；仿生；可控释放

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论文编号：10–020

酶-纳米材料催化剂的构建及应用

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摘要正文：

酶催化因反应条件温和、绿色高效等优点，在医药、诊断、合成等领域有重要应用。针对天然酶在高温、有机溶剂等严苛条件下的失活问题，本课题组开发了一系列基于纳米材料的酶固定化技术，获得的酶-纳米材料催化剂具有良好的催化活性和稳定性。在传统无机载体固定化酶的基础上，无载体固定化（酶交联聚集体）技术[1]、金属有机框架材料[2]、纤维素纳米晶[3]、聚多巴胺纳米复合物[4]、无机晶体纳米结构[5]、合成型聚合物纳米凝胶材料[6]等新型技术的引入极大地拓展了酶的固定化方法，有效地提高了酶的负载量及固定化酶的催化性能。新型纳米载体的应用范围得到了广泛的开发，可应用于环氧化物水解酶[1]、葡萄糖氧化酶[7]、脂肪酶[6]、蛋白酶[3]等多种酶分子的固定化，制备出高效、稳定、可重复利用的固定化酶制剂。新型酶-纳米材料催化剂具有良好的实际应用价值，可高效催化环氧化合物水解[1]、手性醇不对称合成[8]、葡萄糖快速检测[7]、生物活性物质合成[3-6]等食品、医药、日化领域中的重要反应。同时，该系列催化剂具有优良的操作稳定性和重复利用性，并易于从反应体系中分离，有效节约了生产成本，具有巨大的工业应用潜力。

关键词：纳米材料；固定化酶；生物催化

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论文编号：10–021

固定化生物大分子：高性能酶制剂及生物制剂的创制

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摘要正文：

酶等生物大分子是支撑生命系统运行的功能和分子基础，其在制药、能源、食品、化工等领域具有巨大应用潜力，然而稳定性差、成本高、难以重复利用等自身瓶颈问题限制了生物大分子的工程应用和产业化发展。用载体材料对其进行固定化可解决上述关键瓶颈，并可以重复利用、降低成本，因此，固定化技术是促进酶等生物大分子产业化应用的有效途径和关键环节。载体创新和性能的提升有赖于材料的创新和理性设计，有别于传统固定化载体，晶态多孔材料如金属有机框架（Metal-Organic Frameworks, MOFs）和共价有机框架（Covalent-Organic Frameworks, COFs）材料同时具备高结晶性和多孔性，可以从载体限域空间的尺寸、微环境、排布等多个维度实现设计与调控，为理性设计和精准构筑高性能限域固定化载体提供了结构基础。我们从“构筑适配限域空间”和“固定化策略创制”两方面入手，创建了基于晶态多孔材料的高性能固定化平台，实现酶等生物大分子在理性设计的限域空间内精准高效的可控负载和保护，并从分子水平阐释固定化过程中的重要机理，促进对酶等生物大分子的固定化修饰向复合化、精密化和功能化发展，创建了一系列具有优异性能的功能化酶制剂和生物制剂平台，并实现相关应用转化。

关键词：生物大分子；固定化；生物制剂；酶制剂

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论文编号：10–022

酶-金属复合催化剂的可控合成及应用研究

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摘要正文：

天然酶催化具有高效、高立体选择性、专一等特点。但由于酶催化反应的种类具有局限性，限制了酶在工业催化中的应用。通过改造酶使其拥有催化非天然反应的活性，有利于从分子层面理解酶的构效关系、拓宽酶的应用领域、构建高效的生物/化学级联催化系统。将金属催化剂与天然酶结合，从理论上可以实现酶的非活性位点改造，使其拥有多个活性位点、可同时催化多种不同类型的反应。然而，由于蛋白质的三维构象易变、超小尺寸金属颗粒（<1 nm亚纳米团簇、单原子）易聚集等问题，利用蛋白质等柔性有机物往往难以稳定金属亚纳米团簇（单原子）。针对酶-金属单原子复合催化剂构建的技术瓶颈问题，本研究利用酶-高分子结合物的限域空间，建立了原位还原可控制备酶-金属（团簇、单原子）复合催化剂的方法。利用酶活性位点与相邻金属催化剂之间的协同效应和邻近效应，实现了酶催化和金属催化在温和条件下的高效耦合，并探究了其在生物-化学一锅级联反应合成手性药物分子中的应用。

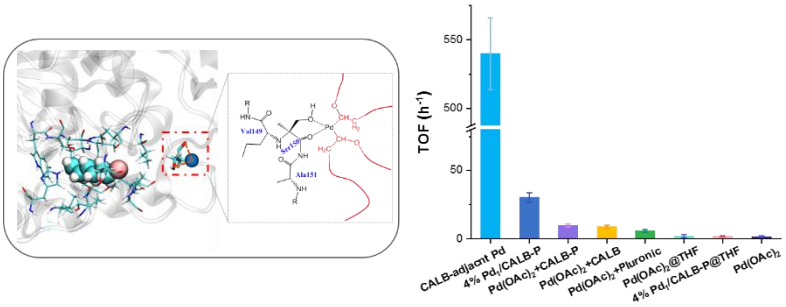

Fig. 1 The configuration and catalytic performance of enzyme-metal nanohybrids

关键词：生物化学催化；协同效应；邻近效应；人工金属酶

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论文编号：10–023

聚电解质复合纳米载体制备与应用

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摘要正文：

聚电解质复合纳米粒子是基于相反电荷链段之间的相互作用而形成的微/纳米结构。其粒子核或壁中含有大量的水和极性官能团，能有效地负载酶、基因等生物分子并保持其（次级）结构和功能。因此，聚离子复合纳米粒子/胶束作为一种“软”纳米载体，广泛应用在药物传输、生物催化等领域。然而，目前聚离子复合纳米载体的制备多依赖组装方式，难以量化制备。且形成的纳米粒子结构和性能调控困难，功能单一，耐盐稳定性差，极大地限制了其应用。针对以上关键问题，本文发展了一种新的配位聚电解质，充分利用其结构、电荷和功能可调性，实现了复合胶束的结构性能调控、耐盐稳定性提升和功能化。(图1) 研究揭示了聚电解质组合的不对称组装特性，以此为理论基础实现了复合粒子的结构调控；利用不同的金属和配体组合，构筑了可控交联的配位聚离子，有效提升了粒子的耐盐稳定性；调控金属配位结构的性质，获得了具有荧光、核磁、催化等不同性质的多功能复合纳米载体。[1-3] 在此基础上，利用静电组装构筑限域环境，实施原位可控聚合，提出了静电组装导向聚合的方法，实现了不同聚电解质纳米粒子的高效、量化制备。该方法利用聚离子-中性嵌段聚合物为模板，引发带相反电荷的单体与交联剂原位共聚，得到分散均一的复合胶束。反应完成后，利用高盐溶液脱除复合胶束中的嵌段聚合物，得到结构和尺寸高度可控的聚电解质纳米凝胶，且分离出的嵌段聚合物可再次作为模板重复循环使用。该方法实现了一系列聚电解质纳米粒子的高效、量化制备，其获得的“软”载体可有效负载酶并提高其催化活性，有望在药物传输和生物催化等领域展现出广泛的应用。[4-5]

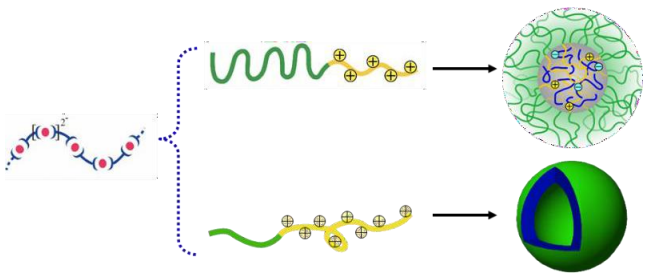

Figure 1 Formation of polyelectrolyte complex nanoparticles based on charge-driven assembly

关键词：软物质；聚电解质；纳米载体；药物传输；酶催化

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论文编号：10–024

抗肿瘤仿生剂型工程

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摘要正文：

由于生物机体的极端复杂性，经过“精心”设计的抗肿瘤纳米剂型在最终临床试验中的表现往往与前期体外实验和动物实验的结果存在较大差异，这些情况无疑会降低研发对象的成药性，从而增加新药开发的风险。因此，对于抗肿瘤纳米剂型，亟需改变传统的研发思路。

为了解决上述问题，我们将生物系统的结构/功能/程序融入纳米剂型的设计中，并发展了新的制备工艺和过程，构建了一系列仿生抗肿瘤纳米剂型：基于笼型蛋白独特的纳米孔道和中空结构，发展了药物的原位限域装载技术，并利用肿瘤细胞表面相应的受体实现药物靶向输送；基于细菌发展了新的水热过程，以此精准调控菌体结构并大量装载肿瘤抗原，通过模拟细菌的感染过程实现高效递送和免疫激活；发展了新的膜乳化过程对纳米颗粒进行细胞膜伪装，以此赋予其体内长循环、肿瘤趋化等优异性能，成功用于肿瘤的多种诊断和治疗。上述仿生抗肿瘤纳米剂型能够遵循体内固有的转运途径，将药物/抗原/探针按照预期准确递送至靶部位，从而产生最小不良反应，获得最佳使用效果，并且有利于降低研发风险，推动临床转化。

关键词：抗肿瘤，仿生，纳米，生物界面

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论文编号：10–025

Cell-derived nanoparticles for Immunotherapy delivery

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Immunotherapy utilizes the patient's own immune system to fight against disease. For example, cancer immunotherapy has been proved successful to treat cancer, remarkably improving the therapy efficacy in clinic. However, some limitations still need to be addressed, such as low response rate and immune-related adverse events (irAEs) caused by off-targeting. Therefore, new target strategy should be developed for improve the immunotherapy.[1] In recent years, a variety of novel biomaterials and strategies have been reported to targeted deliver therapeutics for immunotherapy. Among them, cell and cell-based nanoparticles, such as red blood cells, platelets, cell-derived nanovehicle and exosomes, as a kind of important bio-nanomaterial that has been extensively studied for drug delivery[2-4]. In this talk I will present our recent strategies based on cell-derived nanoparticles for immunotherapy delivery for treatment of cancer and inflammation.

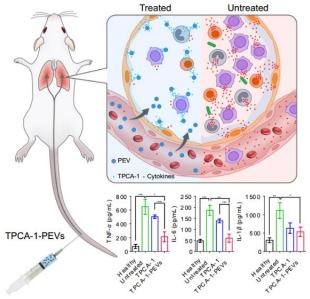

Fig. 1. Calming Cytokine Storm in Pneumonia by Targeted Delivery of TPCA-1 Using Platelet-derived Extracellular Vesicles.

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论文编号：10–026

放射衍生材料与抗肿瘤免疫治疗

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摘要正文：

放射联合免疫治疗，是抗击肿瘤的重要手段。放射治疗从不同方面活化免疫，放射促进肿瘤抗原释放，调节免疫微环境，促进免疫应答[1-3]。临床上存在较多放射治疗不适用的情况，如恶性胸腔积液，恶性腹水等。因此，课题组聚焦于利用放射衍生物进一步扩大放射治疗适应症，为放射联合免疫提供更多可能，为无法实施放射治疗且存在广泛转移的患者提供新策略。

我们的研究发现放射后肿瘤细胞释放的微颗粒可以促进肿瘤细胞发生铁死亡，并促进巨噬细胞向M1型促炎型巨噬重编程，在小鼠恶性胸腔积液模型中，放射后肿瘤细胞释放的微颗粒联合PD-1单抗获得了约40%的治愈率[4]（***Science Advances***，2020）。此外，放射后肿瘤细胞释放的微颗粒可以有效改善肺部微环境，抑制肿瘤细胞定植和形成转移灶。

将放射后肿瘤细胞上清进行超滤，所得超滤液可以活化DC细胞，促进DC细胞提呈抗原，同时促进巨噬细胞向M1亚型重编程，有效改善肿瘤微环境。用该超滤液制备的蜂毒肽水凝胶联合PD-1单抗可以有效治疗对PD-1单抗不敏感的晚期肿瘤。

通过对肿瘤细胞放射衍生物的研究，我们首次提出间接放射治疗的概念，通过获取患者肿瘤组织并提取放射衍生物，可为无法实施放射治疗的肿瘤患者提供个性化治疗手段。

关键词：晚期肿瘤；放射治疗；肿瘤免疫治疗；微颗粒；水凝胶

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论文编号：10–027

仿生纳米粒在神经退行性疾病中的应用策略

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摘要正文：

血脑屏障（BBB）是脑毛细血管壁与神经胶质细胞形成的血浆与脑细胞之间的屏障和由脉络丛形成的血浆和脑脊液之间的屏障，在阻止有害物质由血液进入脑组织的同时，也给中枢神经系统疾病的用药带来了阻碍。葡萄糖是大脑的主要能量来源。研究表明，葡萄糖转运受体1（GLUT1）在脑毛细血管内皮细胞（BCECs）上高表达，降低血糖浓度有助于GLUT1定位在BCECs的腔质膜上，而随时血糖升高， GLUT1又会被内化到BCECs内[1]。因此，我们开发了一种半乳糖修饰的“三重相互作用”稳定的仿生纳米载药系统（Gal-NPs），利用禁食和补充葡萄糖控制血糖变化这一生物策略来触发BCECs上的GLUT1循环，GLUT1特异性识别Gal-NPs，通过GLUT1介导的胞吞作用使Gal-NPs从BCECs腔面迁移到基底面，从而增强了其载带的BACE1 siRNA在神经细胞内的敲低效果，显著抑制了APP/PS1转基因小鼠脑内β淀粉样斑块的沉积，从而有效改善了APP / PS1转基因小鼠的学习记忆及行为认知能力[2]。

关键词：葡萄糖转运受体1；血脑屏障；血糖控制；纳米递送

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论文编号：10–028

治疗COVID-19的抗氧化酶

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摘要正文：

COVID-19大流行给全世界带来了巨大损失，目前还没有专门的抗该病毒的药物或疫苗[1]。本团队开发了一种潜在的治疗方法，针对COVID-19发病过程中活性氧自由基（ROS）诱导的细胞炎症因子风暴，通过原位聚合将过氧化氢酶(CAT)包裹成以磷脂胆碱类聚合物为基础的纳米胶囊 n(CAT)，从而调节ROS达到阻断COVID-19病程的目的。薄壳保护酶，允许过氧化氢快速通过，赋予n（CAT）和天然过氧化氢酶相似的高酶活性、并显著增强稳定性，降低免疫原性。通过与肺上皮细胞、n(CAT) 以及H_2O_2共培养的一系列细胞实验表明n(CAT)不仅可以保护细胞免受氧化损伤的能力，而且具有复苏损伤细胞的能力, 还可以作为炎症反应的免疫调节剂显著下调人白细胞分泌的TNF-α和IL-10的量。而且白细胞、受损肺上皮细胞、n(CAT) 共培养实验结果表明n(CAT)可以保护健康肺泡细胞免受白细胞活化的损伤，显示出一定的抗炎作用。在小鼠的体内实验中，雾化给药后，n(CAT)几乎只滞留于肺部，而在静脉给药后，有效到达肺及其他组织，血清半衰期为8.9h，比天然CAT（0.5h）长16.8倍。值得注意的是，通过对恒河猴进行雾化给药，并通过鼻拭子与咽拭子取样检测，在确定各组织病毒载量的基础上进一步证实n(CAT) 能够抑制SARS-CoV-2在恒河猴体内的复制和侵染。同时，该纳米粒子不仅在人类白细胞、肺泡上皮细胞以及健康小鼠体内未见毒性，而且大剂量静脉注射施用于恒河猴身上，通过组织切片以及血常规，肝肾功能检测均未见任何明显毒性。目前，团队已经完成了n(CAT)的中试规模化制备，这可能为COVID-19或者其他炎症的治疗提供一种有效的治疗手段。

关键词：纳米胶囊；过氧化氢酶；COVID-19；抗炎

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论文编号：10–029

Synthetic organelles for enhanced biosynthesis

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Enzymatic reactions in living cells are highly dynamic but simultaneously tightly regulated. Enzyme engineers seek to construct multienzyme complexes to prevent intermediate diffusion, to improve product yield, and to control the flux of metabolites. Here we choose a pair of short peptide tags (RIAD and RIDD) to create scaffold-free enzyme assemblies, synthetic organelles, to achieve these goals. In vitro, assembling enzymes in the menaquinone biosynthetic pathway through RIAD–RIDD interaction yields protein nanoparticles with varying stoichiometries, sizes, geometries, and catalytic efficiency. In Escherichia coli, assembling the last enzyme of the upstream mevalonate pathway with the first enzyme of the downstream carotenoid pathway leads to the formation of a pathway node, which increases carotenoid production by 5.7 folds. The same strategy results in a 58% increase in lycopene production in engineered Saccharomyces cerevisiae. This work presents a simple strategy to impose metabolic control in biosynthetic microbe factories

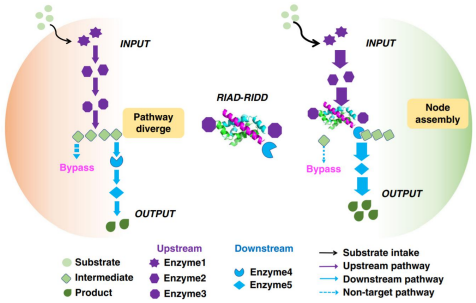

Fig. 1 A synthetic organelle that guides the metabolic flux towards the biosynthesis of target product

Keywords: protein self-assembly, protein protein interaction, multi-enzyme complex.

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论文编号：10–030

基于自愈合大孔微球构建肿瘤精准疫苗

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摘要正文：

肿瘤免疫疗法在2013年被《科学》杂志评为十大科学突破榜首。肿瘤疫苗能够调动机体自身的免疫细胞杀伤肿瘤，临床应用前景广阔，然而传统肿瘤治疗性疫苗忽视了人群间的差异，通用抗原往往不能取得最优的免疫效果；同时单独注射肿瘤抗原也难以激发有效的免疫应答，而疫苗佐剂剂型制备繁琐复杂，面临着需要多次注射、安全性差等一系列难题。

为解决上述难题，本研究利用聚乳酸等FDA批准可注射的生物材料，通过两步乳化法成功制备出了表面多孔、内部贯穿结构的自愈合大孔微球，基于独创的聚乳酸自愈合大孔微球提出了肿瘤精准疫苗治疗新策略：采用基因测序技术和计算机算法预测新生抗原肽，利用微球“差异化装载”的特性实现新生抗原肽和MPLA（单磷酰脂质A）佐剂的共装载，通过合理设计微球的尺寸和结构，实现抗原释放行为与细胞募集行为耦合，并利用微球降解产生的局部酸环境，促进抗原交叉提呈和细胞免疫应答，单次注射后该新生抗原疫苗即可引起持续且强烈的T细胞免疫应答，显著抑制乳腺癌的进展；结合大量临床数据及实验手段筛选出新靶点抗原肽，利用“后包埋”的独特装载方法，实现PD-1抗体和新靶点抗原的共装载，并充分保护了二者的活性，疫苗接种后，微球的缓慢降解不仅形成了有利的局部免疫微环境，而且促进了PD-1抗体向淋巴结的富集，最终实现长效的免疫应答及免疫抑制解除，使得新靶点抗原疫苗在多种白血病模型（包括病人来源白血病异种移植模型）上取得了优于商品化剂型的疗效。

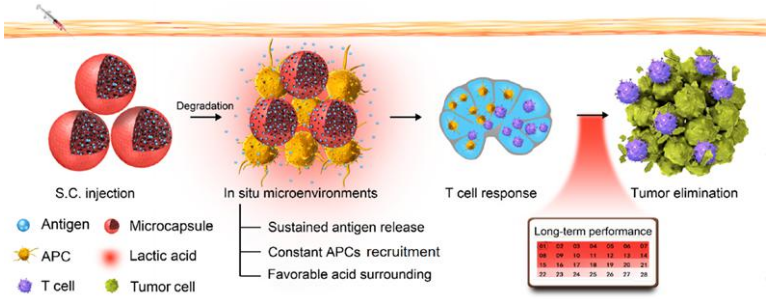

Fig 1. Strategy of utilizing self-healing microcapsules to modulate immunization microenvironments for cancer vaccination.

关键词：自愈合大孔微球；肿瘤个性化治疗；PD-1抗体；白血病疫苗；新生抗原

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论文编号：10–031

Unique properties of the yeast spore wall and their possible applications

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The budding yeast *Saccharomyces cerevisiae* forms a dormant and stress resistant form of cell termed a spore when diploid cells are incubated in starvation conditions. Spores are structurally different from vegetative cells, and distinctive properties are seen in the spore wall. The spore wall consisted of four layers, from the inside to the outside, β-glucan, mannoprotein, chitosan and dityrosine layers. The chitosan and dityrosine layers are unique structures for the spore wall, whereas β-glucan and mannoprotein are common components seen in both the spore and vegetative cell walls. Because of the presence of the chitosan and dityrosine layers, spore exhibits several unique properties. For example, spores can retain soluble proteins in the periplasmic space because the outer two layers work as a diffusion barrier. Although proteins are entrapped in the spore wall, smaller molecules such as sugars can pass through the outer layers. Thus, spores carrying enzymes in the spore wall can be used as enzyme capsules. An advantage of spore-encapsulated enzymes is that immobilized and stress-tolerant enzymes can be produced without purification. As a possible application of this method, we have shown that spores carrying an L-arabinose isomerase are used to produce a rare sugar L-ribulose. As another intriguing property of yeast spores, we have found that they are internalized into mammalian cells. Despite that spores are 2 to 3 μm in diameter, they are internalized even in non-professional phagocytes, such as HEK293T cells. Cellular uptake of spores in HEK293T cells was significantly decreased by washing them with high-salt solution or removal of the dityrosine layer. Thus, a ligand that can induce phagocytosis in non-professional phagocytes is electrostatically attached to the dityrosine layer. Such a molecule may be beneficial to develop cell delivery systems. Currently, we are working on its identification.

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论文编号：10–032

微尺度人工生命系统的构筑

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摘要正文：

创新制造有智能特征的人造生命系统是科学家执着的梦想和追求，力图从不同物理尺度、实现对生物分子机器等的精准控制，以满足多方面的基础科学和应用研究需求。本研究旨在突破自然体系限制，在微尺度下集中于生物大分子和人工细胞两个层次，在体外自下而上重构基本生命转录和翻译过程，融合前沿合成生物学、智能响应材料、电子工程、微流控技术等，构建人工生命系统、并实现在空间和时间上其对物理和化学信号的智能感知和响应。并结合典型应用开展验证，拓展其在生物分子合成制造、传感诊断和医药递送等领域的应用。

关键词：人工细胞；生物大分子；合成生物学

论文编号：10–033

以病毒样颗粒为“底盘”的疫苗仿生合成

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摘要正文：

接种安全、有效的疫苗是预防和控制传染性疾病最有效的手段。然而，病毒的抗原多样性和高度变异性为传统疫苗制备技术带来挑战。报告以典型流感病毒疫苗为研究对象，从疫苗合成生物学的概念出发，以去铁铁蛋白（Apo-ferritin，AFt）和乙肝病毒核心抗原（Hepatitis B core antigen，HBc）病毒样颗粒（Virus-like particles，VLPs）两种蛋白质颗粒为“底盘”，发挥其抗原提呈和免疫刺激的佐剂效应；以流感病毒的重要抗原HA、M2e和NP为“免疫插件”，通过物理、化学和生物法相结合，模拟各“免疫部件”在天然病毒上的空间分布特点，将插件在底盘表面和内部组装，快速构建新一代病毒样颗粒（VLP）流感疫苗。报告将主要介绍如下三个方面的内容：

从颗粒学的角度，借助DLS、TEM、高效液相色谱-多角度激光散射等检测手段，研究AFt和HBc两种蛋白质颗粒的热稳定性，通过温和的加热处理扩充蛋白质颗粒亚基间的孔道，建立了一种在不破坏VLP完整颗粒结构的条件下，将流感病毒抗原NP或M2e组装到底盘颗粒内部的新技术。其中AFt对NP抗原的内部装载效率比文献上的化学酸解法提高5倍，并有效地保持了抗原的活性和VLP的结构。

以天然的AFt为底盘，采用通过上述的加热物理装载与化学偶联相结合，构建了内-外组装流感病毒抗原的新型VLP疫苗。通过小鼠免疫和攻毒实验，表明外部偶联HA抗原，内部装载NP抗原的内-外组装双抗原仿生疫苗可同时激发高水平的HA和NP特异性抗体，对同源和异源H1N1毒株攻毒保护率均达到100%。

以生物合成的HBc蛋白质颗粒为底盘，采用基因编辑和加热装载技术相结合，分别构建了外部组装NP、内部组装M2e的NP_{ext}-HBc+$M2e_{int}$和外部组装M2e、内部组装NP的$M2e_{ext}$-HBc+NP_{int}两种新型VLP疫苗。免疫小鼠后，均可同时激发高水平的M2e和NP特异性抗体，其中NP_{ext}-HBc+$M2e_{int}$对异源H1N1毒株的攻毒保护率仅达到62.5%，而$M2e_{ext}$-HBc+NP_{int}则达到100%。对两种疫苗的免疫保护增强机制进行了分析和比较，并仿生双抗原流感疫苗的高免疫活性机制进行初步阐释。

上述结果表明，以VLPs颗粒为“底盘”，以仿生策略灵活组装和组合抗原“插件”，可以为快速构建更加有效、广谱的流感疫苗。同时为研制针对其他新发、突发传染性疾病的疫苗提供新的策略。

关键词：疫苗合成学，流感疫苗，病毒样颗粒，仿生合成

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论文编号：10–034

酶催化剂工程

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摘要正文：

面向生物化工、生物医药、医学检测等领域对关键生物催化技术的需求，从生物催化与化学催化融合的科学前沿出发，本报告介绍课题组在以“催化剂编辑”为核心的酶催化剂工程研究方向的最新进展。1）针对酶催化和金属催化反应条件不匹配的问题，通过在酶表面原位可控合成金属亚纳米团簇，提高了温和反应条件下金属催化剂的活性，精准构筑了高效耦合的生物-化学复合催化剂。开发了温和条件下高效耦合的酶-金属亚纳米团簇复合催化剂，揭示了酶分子表面官能团对金属亚纳米团簇活性的界面调控机制，为构筑生物-化学复合催化剂，解决生物-化学级联反应效率不高的问题提供了新途径。2）针对生物-化学复合催化剂组成和结构复杂，难以系统探究结构和催化性能间关系的问题，通过研究特征结构对复合催化剂的影响规律并归纳出相应效应，阐述了生物-化学复合催化剂高效耦合催化的关键互作机制。从特征结构对酶、金属催化剂、二者间级联反应的影响规律这三方面阐述了高效耦合催化的关键互作机制：催化剂对酶的限域包埋提高酶的稳定性，载体缺陷提高酶的表观活性—限域效应和缺陷效应；酶分子对金属催化剂表面的配位调控提高其催化活性—界面效应；两种催化剂在载体中的邻近共固定化提高中间产物利用效率—邻近效应。3）针对复合催化剂批式制备效率不高的问题，开发了连续制备技术，并且实现了复合催化剂在药物中间体合成、材料制造和单细胞内代谢物检测中的新应用。开发生物-化学复合催化的产业应用，在液滴快速干燥过程中原位还原制备脂肪酶-Pd亚纳米团簇复合催化剂，实现了连续制备过程，直接得到粉末状催化剂产品。将脂肪酶-Pd亚纳米团簇复合催化剂应用于酯水解和C-C偶联的一锅级联反应，建立了联苯类手性醇药物中间体的合成新路线，可替代原有的多步有机合成过程。利用酶催化和金属催化耦合，为单细胞内代谢物原位检测的难题提供了解决途径。基于该技术开发检测试剂盒及仪器，用于细胞代谢研究，并且探索癌症体外诊断新技术。

关键词：酶催化；酶工程；催化剂设计；催化剂编辑

论文编号：10–035

类囊体启发的酶-光偶联人工光合系统

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摘要正文：

模拟自然界光合作用，将太阳能转化为化学能是化学和化工领域的“圣杯”研究之一。酶-光偶联人工光合系统将半导体材料光吸收能力和生物酶高活性、高特异性特点相结合，为“液态阳光”太阳能燃料的合成提供了一条绿色途径。高效、可控的NADH再生过程是实现太阳能到为化学能高效转化的关键[1]。在绿色植物叶绿体中，光反应合成NADPH主要发生在类囊体膜上。在类囊体膜上限域空间内，光反应中三个模块的竞争协调，即光系统I/II中的电子产生，电子传递链中的电子传递，以及铁氧还蛋白-NADP还原酶中的电子利用，最大程度优化了单一模块的可利用率，使光反应的全局量子效率接近理论值。受类囊体结构和功能启发，本研究制备了“人工类囊体”仿生颗粒，并对仿生颗粒催化NADH再生过程三个关键步骤—电子产生，电子传递和电子利用进行分析[2-3]。通过协调电子产生-电子传递，多步电子传递，以及电子传递-电子利用，实现了NADH再生过程性能强化和酶-光偶联化学品高效合成[4]。

关键词：光催化；酶催化；人工光合系统；类囊体；辅酶再生

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Thylakoid-inspired Photo-Enzyme Coupled Artificial Photosynthesis

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Converting solar energy into chemical energy is one of the “Holy Grail” researches in chemistry and chemical engineering. Photo-enzyme coupled artificial photosynthesis system combines the light absorption ability of semiconductors and the high-activity/specificity of enzymes, offering a green route for “liquid sunshine” fuel production. Nicotinamide adenine dinucleotide (NADH) acts as the “energy currency” to bridge the energy and proton transfer between photocatalysis and enzymatic catalysis. In higher plants, the regeneration of NADPH primarily operates in thylakoid membrane. The competitive coordination of three modules, i.e., electron generation in photosystem I/II, electron transfer in electron transfer chain and electron utilization in ferredoxin-NADP reductase, in the confined space of thylakoid membrane optimizes the modular availability, approaching the quantum efficiency to the theoretical value.

Inspired by this, the three key steps in photocatalytic NADH regeneration, electron generation-transfer-utilization, are optimized to improve the efficiency of NADH regeneration for photo-enzyme coupled chemical synthesis.

论文编号：10–036

载体微环境调控促进酶催化反应

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摘要正文：

酶是契合绿色化学的"催化剂"，已广泛用于精细化学品和药物等的合成，具有选择性佳、条件温和、绿色等优点。工业酶催化剂的挑战是稳定性差，易失活，难以重复使用。构建载体对酶进行固定化可以解决以上问题，但是传统固定化酶载体存在传质限制，酶的负载量低，稳定性提升有限，表观活性低等问题。针对此，本文利用载体工程，通过调控载体的孔结构与和识别位点，模拟细胞内微环境，提高酶的活性和稳定性，同时强化底物传递。

基于细胞对酶的限域效应，采用水凝胶模板扩孔在微孔载体中构建了介孔结构，制备了具有多级孔结构的微介孔载体。通过三聚氰胺和水杨酸之间的氢键驱动形成水凝胶模板，升高温度破坏氢键可以脱除模板，产生介孔结构，介孔孔径为 10-38 nm，比表面积高达1430 m^2/g。通过改变水凝胶前体的浓度可以调控介孔孔径。利用该新型载体固载葡萄糖氧化酶，催化效率比游离酶提高了7.7倍，同时利用介孔结构的限域效应提高了酶的温度和pH稳定性，实现了葡萄糖氧化酶的重复使用。为强化反应过程的底物传递，进一步利用超分子自组装可控构建具有智能响应性能的孔结构，该柔性孔道对CO_2气体底物具有选择性，从而强化CO_2底物传递。同时在载体中引入双键，通过水相原位聚合反应，实现甲酸脱氢酶的限域固定化。基于该新型载体建立了CO_2定向自选择酶催化新方法，最终产物甲酸产量比游离酶提高13.2倍。进一步通过在载体上设计分子印迹选择性识别位点来模拟分子伴侣功能，显著提高了酶的活性和稳定性，酶活比游离酶提高3.5倍，适用pH范围从4.5拓宽到3～8。同时，通过引入外场调控，实现了固定化酶载体的再生利用。

关键词：酶催化；酶的固定化；微环境调控；孔结构；识别位点

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论文编号：10–037

基于颗粒化乳液的新冠疫苗递送系统

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摘要正文：

为快速应对肆虐的新型冠状病毒，基于已有剂型开发安全、高效的疫苗佐剂是一种理想的应对策略。作为最容易获得的佐剂，铝佐剂至今都是大部分发展中国家唯一批准使用的疫苗剂型。然而，由于其片状微凝胶结构，铝佐剂倾向于贴敷在树突状细胞（DC）的表面，而不会其内吞，进而难以影响抗原的内吞、胞内运输和交叉递呈。为解决以上问题，本研究提出颗粒化铝佐剂的策略，通过Pickering乳液将铝佐剂吸附在油水界面上，进而构建颗粒化铝佐剂乳液。（1）利用铝佐剂的微凝胶性质为乳液提供更高的稳定性，制备稳定好、载量高的疫苗剂型。（2）通过铝佐剂紧密排布的油水界面提升DC的亲和性，促进抗原内吞、参与抗原的加工和递呈，引发DC的成熟活化和抗原的交叉递呈；（3）在动物实验中，与商品化佐剂对比，颗粒化乳液显著提升了SARS-CoV-2特异性抗体的分泌水平，并大大强化了T细胞的应答水平，同时具备良好的安全性。并且，基于不同商品化铝佐剂制备的颗粒化乳液均取得了良好的免疫活化效果。本研究的顺利实施将为新冠疫苗提供一种安全、高效的佐剂策略，进而更好地强化新冠疫苗的免疫效果，为全球抗疫提供佐剂策略支持。

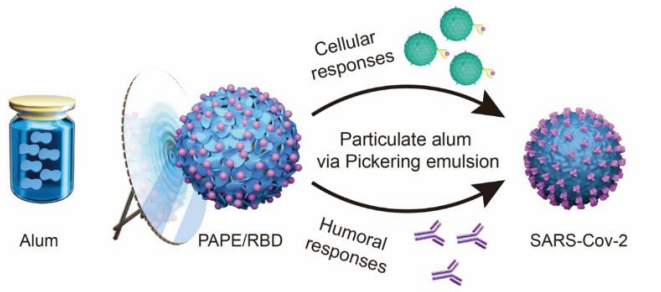

Fig. 1 Potent SARS-CoV-2 vaccine adjuvant based on alum-stabilized Pickering emulsion

关键词：新冠疫苗；颗粒化乳液；铝佐剂；疫苗递送系统

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论文编号：10–038

微流控多相流构筑超分子微胶囊及其功能仿生

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摘要正文：

基于分子间动态化学键作用的超分子壁材赋予了微胶囊材料独特的光、热、化学等刺激响应性以及自适应、自修复、选择透过性等性能，近年来被广泛地应用于药物筛选、基因治疗、人工细胞等领域。本报告将重点介绍如何结合微流控过程强化技术实现基于葫芦脲[8]超分子微胶囊的可控制备，并探讨其在控释、分子识别及生物活体材料等领域的应用。具体涉及：1）基于葫芦脲[8]的超分子微胶囊壁材设计原则、合成方法及生物评价；2）采用微流控多相流技术调控高分子壁材在微液滴受限空间的自组装行为，构筑多层级结构微胶囊囊膜；3）探讨构筑微胶囊材料在控释、分子识别及生物活体材料领域的应用研究。

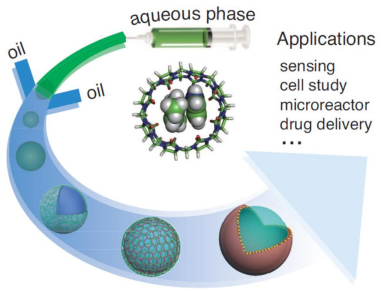

Fig. 1 Schematic illustration of supramolecular polymer microcapsules assembled at the interface of microfluidic droplets

关键词：超分子；微胶囊；微流控；过程强化

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论文编号：10–039

Biomimetic Materials for Heart Regeneration

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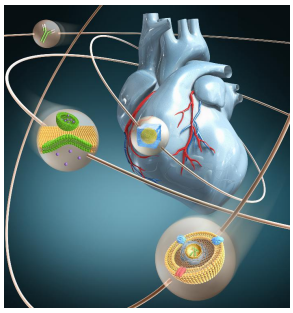
Cardiovascular disease (CVD) is a major health problem worldwide. Since adult cardiomyocytes irreversibly withdraw from the cell cycle soon after birth, it is hard for cardiac cells to proliferate and regenerate after myocardial injury, such as that caused myocardial infarction (MI). Live cell-based therapies, which we term the first generation of therapeutic strategies, have been widely used for the treatment of many diseases, including CVD. However, cellular approaches have the problems of poor retention of the transplanted cells and the significant entrapment of the cells in the lungs when delivered intravenously. Another big problem is the low storage/shipping stability of live cells, which limits the manufacturability of living cell products. Our most recent efforts were synthesizing biomimetic materials such as platelets, exosome with different formulations as novel cardiac cell therapeutic agents.



Keywords: Platelet mimicking materials, Exosomes, Heart regeneration, Stem cell

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论文编号：10–040

仿生纳米粒在神经退行性疾病中的应用策略

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摘要正文：

血脑屏障（BBB）是脑毛细血管壁与神经胶质细胞形成的血浆与脑细胞之间的屏障和由脉络丛形成的血浆和脑脊液之间的屏障，在阻止有害物质由血液进入脑组织的同时，也给中枢神经系统疾病的用药带来了阻碍。葡萄糖是大脑的主要能量来源。研究表明，葡萄糖转运受体1（GLUT1）在脑毛细血管内皮细胞（BCECs）上高表达，降低血糖浓度有助于GLUT1定位在BCECs的腔质膜上，而随时血糖升高， GLUT1又会被内化到BCECs内[1]。因此，我们开发了一种半乳糖修饰的“三重相互作用”稳定的仿生纳米载药系统（Gal-NPs），利用禁食和补充葡萄糖控制血糖变化这一生物策略来触发BCECs上的GLUT1循环，GLUT1特异性识别Gal-NPs，通过GLUT1介导的胞吞作用使Gal-NPs从BCECs腔面迁移到基底面，从而增强了其载带的BACE1 siRNA在神经细胞内的敲低效果，显著抑制了APP/PS1转基因小鼠脑内β淀粉样斑块的沉积，从而有效改善了APP / PS1转基因小鼠的学习记忆及行为认知能力[2]。

关键词：葡萄糖转运受体1；血脑屏障；血糖控制；纳米递送

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论文编号：10–041

Cytosolic delivery of HBsAg and enhanced cellular immunity by pH responsive Liposome

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Priming the cytotoxic T lymphocytes (CTLs) response is a major challenge for the treatment of Hepatitis B virus (HBV) infection. Inspired by an important natural biological behavior, membrane fusion, we constructed a pH-responsive nanocarrier (HBsAg&CpG@Lip) with a membrane fusion capacity for HBsAg intracellular delivery and subsequent process of CTLs. Through the mimic of the intracellular pH environment in a dynamical and quantitative manner (via FRET and FastFLIM), the membrane fusion issue of HBsAg&CpG@Lip was uncovered. This carrier not only achieved cytosolic trafficking of HBsAg successfully, but also tremendously improved the BMDCs cross-presentation activity (MHC-I). After immunization, in a programmatic way, HBsAg&CpG@Lip elevated the Th1-type cytokines (e.g. IFN-γ, IL-2), produced a high ratio of IgG2c/IgG1, facilitated the immune memory, and primed the B cells and cytotoxic T cells. Present results built a bridge between the design of membrane fusion for intelligent carrier and superior performance for antigen specific immune response.

Keywords: membrane fusion, cytosolic delivery, HBV vaccine, pH-responsive nanocarrier

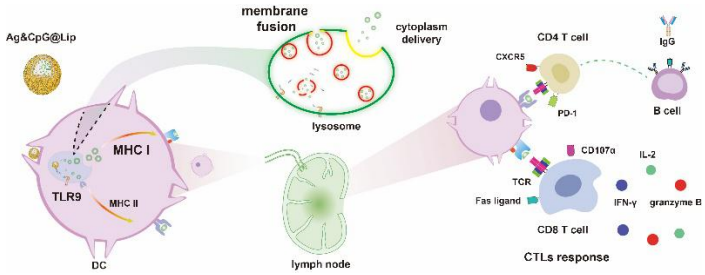

Figure 1. An efficient vaccine delivery via simulating a natural “membrane infusion” behavior

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论文编号：10–042

3D有序磁性大孔金属有机框架物用于固定化酶的研究

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摘要正文：

金属有机框架物（Metal organic frameworks, MOFs）是由有机配体和金属离子配位结合形成的一种纳米复合材料，因其本身比表面积大，孔隙率较高，被广泛地用于酶的固定化[1,2]。然而，大多数的MOFs表面和内部孔径多为微孔和较小的介孔，因此其制备的固定化酶往往表现出固定化效率低以及传质阻力大的现象，严重限制了酶的催化性能。

本研究针对上述问题，以聚苯乙烯微球（PS）为造孔模板，首先制备了一种具有3D有序磁性大孔的ZIF-8金属有机框架物（3NDOM-mZIF-8）[3]，然后利用共沉淀交联的方法将过氧化氢酶固定到载体的表面和内部，得到了CAT/3NDOM-mZIF-8（Fig. 1）。与传统的CAT/ZIF-8相比，固定化效率达到了58%，酶活回收率提高了5倍；并且利用磁力回收，重复使用8次后，仍能保留初始酶活的90%；而CAT/ZIF-8在使用6次后，已基本丧失活性（Fig. 2）。动力学分析表明，CAT/3NDOM-mZIF-8的催化效率是传统CAT/ZIF-8的2倍，这些结果表明，本研究所建立的方法能显著提高传统ZIF-8固定化酶的催化性能。

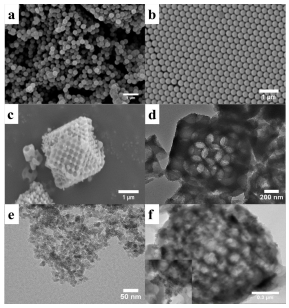

Fig. 1 SEM images of (a) PS, (b) 3DPS and (c) 3DOM-ZIF-8

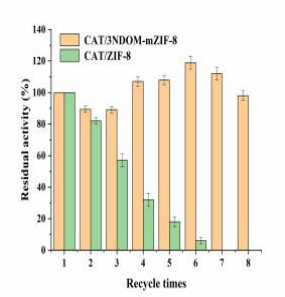

Fig. 2 Reusability of CAT/3NDOM-mZIF-8 and CAT/ZIF-8

关键词：金属有机框架物；聚苯乙烯微球模板；大孔有序结构；固定化酶；固定化效率

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论文编号：10–043

Tea leaf-derived exosome-like nanotherapeutics for orally targeted prevention and alleviation of inflammatory bowel disease and colitis-associated cancer

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The application of conventional nanotherapeutics for the treatment of inflammatory bowel disease (IBD) has significantly improved. However, the unsatisfactory therapeutic outcomes, potential adverse effects, high cost of the mass production, and hazardous environmental effects are challenges to their clinical medical translation. Therefore, novel effective nanotherapeutics are urgently required. Herein, we extracted three specific populations of natural nanoparticles from three different types of green tea leaves. These exosome-like nanotherapeutics (ENs) had average hydrodynamic particle size of around 140.0 nm, narrow size distribution, and negative surface charge. ENs were found to contain high levels of lipids, a few of functional proteins, and abundant of bioactive small molecules. Furthermore, *in vitro* experiments revealed that ENs could be efficiently internalized into RAW 264.7 cells *via* galactose receptor-mediated endocytosis. Strikingly, these ENs could reduce the production of reactive oxygen species, inhibit the expression of the pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, and IL-12), and increase the secreted amount of anti-inflammatory IL-10 in macrophages. Most importantly, oral administration of ENs had the capacities to regulate the overall abundance and diversity of gut microbiota, alleviate the inflammatory reactions, and restore the disrupted colonic epithelial barrier, which resulted in the effective alleviation and prevention of IBD and colitis-associated colon cancer (CAC). Overall, the present study brings a new insight into the exploitation of a facilely, massive, and robust nanoplatform for the prevention and treatment of IBD and CAC.

Keywords: IBD, Orally, exosome-like nanotherapeutics, colon cancer

论文编号：10–044

仿生剂型工程中纳米生物界面的模拟计算

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摘要正文：

纳米剂型药物进入生物系统后，其与生物组分（如细胞、蛋白质、核酸和细胞器等）广泛接触，建立一系列纳米生物界面。这些纳米生物界面包含一系列依赖于时间的动态相互作用，主导着纳米剂型表面与生物组分表面的物理化学相互作用、动力学和热力学交换，进而刺激生物组分的生理应答，介导相应的生理效应，是目前仿生剂型工程的研究热点。但是，受实验方法和精度的限制，无法对纳米生物界面直接进行观测研究；模拟计算作为和实验互补的研究手段，可以克服上述限制因素，广泛应用于纳米生物界面的研究工作。

为了系统阐明纳米生物界面的微观作用机制，我们基于不同的研究背景和体系采用全原子分子动力学模拟和粗粒化方法耦合联用的研究策略，构建了一系列纳米生物界面进行研究：基于二维纳米材料激活体内细胞的研究背景，我们构建了氧化石墨烯/聚乙二醇化氧化石墨烯以水平和竖直作用方式刺激关键膜蛋白（整合素、离子通道蛋白等）的耦合模型，考察了二维材料对细胞膜的作用方式，阐明了膜蛋白激活的信号转导通路；基于细胞外泌体的组分受外界环境调控以及其可以被肿瘤细胞内吞的生理背景，我们根据实验结果构建了不同组分的囊泡和细胞膜，研究了囊泡与细胞膜的纳米生物界面作用，揭示了外界环境调控外泌体的组分，进而介导不同细胞内吞现象的微观机制；基于多成分纳米颗粒的自组装过程，我们研究了不同成分之间的结构信息，阐明了自组装过程的关键调控因素，指导纳米颗粒更好地合成。上述纳米生物界面涉及到仿生剂型工程中颗粒合成、输运、发挥疗效等多个关键环节，阐明其微观作用机制有利于实现靶向调控，降低研发风险，推动临床转化。

关键词：纳米生物界面，模拟计算，仿生

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论文编号：10–045

双靶向型杂化外泌体用于肿瘤免疫治疗

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摘要正文：

恶性肿瘤已成为严重威胁人类健康的重大疾病，肿瘤免疫治疗由于可以激活患者自身免疫系统来诱导机体对肿瘤细胞产生特异性的免疫清除，具有极大的发展潜力和临床应用价值。然而，实体瘤内部存在的免疫抑制性肿瘤微环境，会阻碍效应T细胞浸润入肿瘤内部发挥肿瘤杀伤作用，导致单方面免疫应答激活疗法的治疗效果大打折扣。因此，免疫应答激活和肿瘤微环境改善的双效调节是肿瘤治疗性疫苗发挥高效治疗效果的关键。

本项工作提出了“双靶向”“双效”巨噬细胞杂化外泌体做为肿瘤免疫治疗药物的新型治疗策略。本工作通过对巨噬细胞进行杂化处理而获得的巨噬-肿瘤杂化外泌体，兼具肿瘤细胞和巨噬细胞的杂化性质（肿瘤抗原-MHC分子、肿瘤黏附分子和共刺激分子、免疫激活细胞因子），是一种极有潜力的“双靶向”免疫治疗型药物。一方面，该杂化外泌体可以利用其纳米尺寸粒径靶向到淋巴结内，借助MHC I复合物及共刺激分子激活T细胞，激发肿瘤抗原特异性的细胞免疫应答；另一方面，外泌体膜上表达的肿瘤黏附分子趋化外泌体靶向到肿瘤内部，依靠其免疫激活类细胞分子改善肿瘤免疫抑制微环境，为效应T细胞的浸润杀伤提供合适的“土壤”（图1）。目前，此杂化外泌体良好的双靶向性能及显著的肿瘤治疗效果已在原发肿瘤、转移性肿瘤及术后复发肿瘤等多种模型上获得验证。

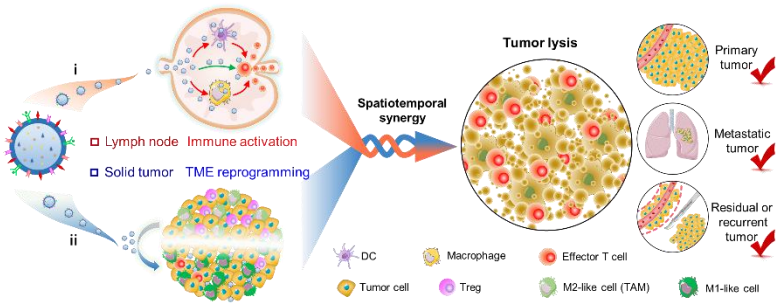

Fig. 1 Tumor inhibition mechanism of macrophage-tumor chimeric exosomes

关键词：肿瘤免疫治疗；外泌体；双靶向；淋巴结；肿瘤微环境

论文编号：10–046

Nanoenabled Disruption of Multiple Barriers in Antigen Cross-Presentation of Dendritic Cells *via* Calcium Interference for Enhanced Chemo-Immunotherapy

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Chemo-immunotherapy holds unique advantage of specific antitumor effects by activating T cell immune response. However, the efficiency of chemo-immunotherapy is restricted to the insufficient antigen presentation of dendritic cells (DCs) in tumor immunosuppression microenvironment. Here, we rationally designed a simple-yet-versatile calcium ion nanogenerator to disrupt the autophagy inhibition condition within DCs, enrich damage associated molecular patterns (DAMPs) and attenuate acidity in tumor microenvironment. After chemotherapy, honeycomb calcium carbonate ($CaCO_3$) nanoparticles (OVA@$CaCO_3$, denoted as HOCN, ovalbumin (OVA) acted as skeleton) could preferentially accumulate in tumor and display a series of benefits for disrupting multiple barriers in antigen cross-presentation of DCs: i) recovering cell viability of DCs by HOCN induced tumor acidity attenuating; ii) disrupting autophagy inhibition condition in DCs by generating Ca^{2+} in cells; iii) improving maturation of DCs by Ca^{2+} overloading-mediated enhanced DAMPs releasing from tumor cells. We believe the regulation of the intratumoral Ca^{2+} offer an alternative strategy for improving cancer chemo-immunotherapy.

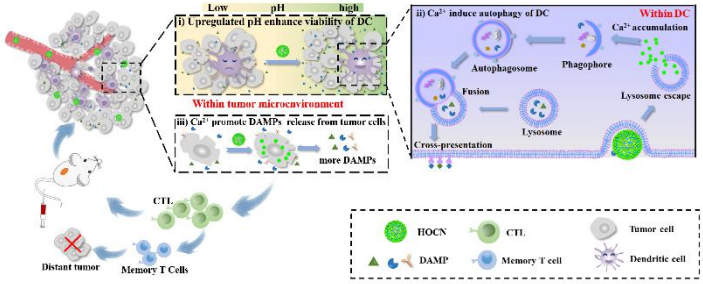

Fig. 1 Schematic diagram of HOCN disruption of multiple barriers in antigen cross-presentation of DCs for enhanced Mitoxantrone (MTX) mediated chemo-immunotherapy: i) the acid-hydrolysis of HOCN improves cell viability of DCs by upregulating the pH of tumor microenvironment; **ii)** the accumulation of Ca^{2+} facilitates the antigen cross-presentation by inducing autophagy in DCs; **iii)** intracellular Ca^{2+} promotes the release of DAMPs from tumor cells into tumor microenvironment.

Keywords: calcium interference; chemo-immunotherapy; dendritic cell; autophagy; antigen presentation

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论文编号：10–047

Rescuing ischemic stroke by biomimetic nanovesicles through sequential enhanced thrombolysis and ischemia-reperfusion protection

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Due to the narrow therapeutic window and excessive dosage of tPA (tissue plasminogen activator) in ischemic stroke, it is easy to cause bleeding and limits clinical application. In addition, the explosion of oxygen and a high level of free radicals after thrombolysis will result in successive injuries to neurocytes. Therefore, to treat ischemic stroke, it is needed to scavenge free radicals for the reperfusion protection, combining rapid and efficient thrombolysis. Here, we report an engineered system (tPA/melanin nanoparticles @ platelet membrane vesicles, tPA/MNP@PMV), which can deliver drugs to the thrombus site efficiently by the natural thrombus targeting property of platelet membrane realizing the accurate and rapid release of tPA under the near-infrared photothermal response of MNP. More importantly, melanin NPs (ultra small particle size＜4.5 nm) cross the blood-brain barrier to remove free radicals for reperfusion protection. The system provides a new idea for the treatment of ischemic stroke.

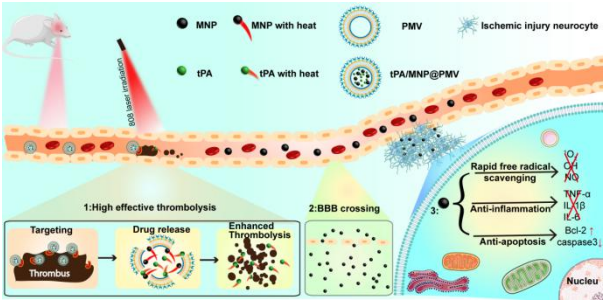

Fig. (1): The system delivers drugs to the thrombus site efficiently with the natural thrombus targeting property of platelet membrane realizing the accurate and rapid release of tPA under the near-infrared photothermal response of MNP. Meanwhile the local temperature can be increased to enhancing thrombolytic effect of tPA at the same time. **(2)**: MNP can successfully cross the BBB (blood brain barrier) with the advantage of small particle size (＜4.5 nm) to the cerebral infarction site. **(3)**: MNP can rapidly scavenge free radicals, inflammatory factors and resist apoptosis.

Keywords： ischemic stroke, thrombolysis, ischemia-reperfusion protection

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论文编号：10–048

Self-responsive co-delivery system for remodeling tumor intracellular microenvironment to promote PTEN-mediated anti-tumor therapy

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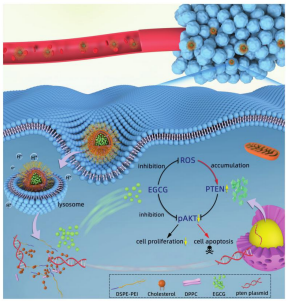
Delivering the pten gene into tumor cells to reacquire PTEN functionality is considered to be an attractive method for cancer treatment. However, the inhibition effect of the tumor intracellular microenvironment (TIME), especially at the high reactive oxygen species (ROS) level, on pten expression and PTEN protein functionality was nearly overlooked. Herein, the development of a potential strategy is described, which enhances PTEN-mediated anti-tumor capability by exhausting the intracellular ROS in TIME. To achieve this, poly(ethyleneimine) (PEI)-modified DSPE was introduced to protect the pten plasmid, and form liposomes for encapsulating the “scavenger” of oxidation homeostasis, epigallocatechin-3-gallate (EGCG). Notably, this was a simple system with improved safety compared which when compared with the use of PEI could accomplish efficient pten transfection and simultaneous disintegration to cause transient release of EGCG responding to the endosome environment through the “proton sponge effect”. In the cytoplasm, EGCG depleted ROS and promoted the expression of the pten gene as well as restoring protein functionality, thus negatively regulating the PI3K–AKT signaling pathway. In vitro and in vivo results revealed that this system significantly inhibited tumor growth via remodeling of the TIME, and provided a promising way to control malignant tumors.



Scheme 1 Illustration of LEPP-mediated intracellular ROS depletion and enhanced PTEN expression for improving anti-tumor efficiency.

Keywords: PTEN; tumor therapy; reactive oxygen species; PI3K–AKT; epigallocatechin-3-gallate

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论文编号：10–049

Localized Fluorescent Imaging of Multiple Proteins on Individual Exosomes Using Rolling Circle Amplification for Cancer Diagnosis

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Exosomes have attracted increasing attention as tumor biomarkers due to their unique biological property. However, conventional methods for exosomes analysis are mainly based on bulk measurements, which masks the exosome-to-exosome heterogeneity in tumor diagnosis and classification. Herein, a localized fluorescent imaging method (termed Digital Profiling of Proteins on Individual Exosomes, DPPIE) was developed for analysis of multiple proteins on individual exosomes. In this assay, an anti-CD9 antibody engineered biochip was used to capture exosomes from clincial plasma sample. Then the captured exosomes were specifically recognized by multiple DNA aptamers (CD63/EpCAM/MUC1), followed by rolling circle amplification to generate localized fluorescent signals. By analyzing the heterogeneity of individual exosomes, we found that the high-dimensional data collected from each individual exosome would provide more precise information than bulk measurement (ELISA) and the percent of CD63/EpCAM/MUC1-triple-positive exosomes in breast cancer patients was significantly higher than that of healthy donors, and this method can achieve an overall accuracy of 91%. Moreover, using DPPIE, we are able to distinguish the exosomes between lung adenocarcinoma and lung squamous carcinoma patients. This individual exosomes heterogeneity analysis strategy provides a new way for digging more information in exosomes to achieve multi-cancer diagnosis and classification.

Keywords: individual exosomes heterogeneity, cancer diagnosis, cancer subtype differentiation, rolling circle amplification, localized fluorescent imaging

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论文编号：10–050

基于狂犬病毒仿生的MOFs用于脑胶质瘤的高效诊疗

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摘要正文：

在中枢神经系统（CNS）类癌症中，脑胶质瘤（GMB）由于其发病占比最大（59.2%），恶性程度最高，同时缺少有效的治疗手段，导致其长期存活率最低。目前脑胶质瘤治疗过程中的首要难题是治疗性药物难以突破血脑屏障（BBB）到达癌变部位发挥作用。狂犬病毒（RBV）是一种典型的可以高效入侵CNS的嗜神经性病毒，这主要得益于其独特的弹状形貌与病毒衣壳中能特异性靶向乙酰胆碱受体的糖蛋白。近些年来，利用“学习自然，道法自然”的仿生理念来模仿生命体中的精妙体系，设计合成更加高效的纳米药物逐渐成为癌症纳米医学的主题之一。基于此，我们取经于RBV，将如何仿生狂犬病毒来构建出可实现脑胶质瘤靶向治疗的纳米药物作为我们的研究目的。RBV可以高效入侵CNS，研究发现这与其独特的弹状形貌及其表面包裹的可特异性靶向中枢神经系统的糖蛋白密不可分。本课题依据仿生的理念，通过模仿RBV可特异性高效入侵CNS的特性，构建出仿生RBV的纳米药物，用于改善治疗药物无法高效地穿越血脑屏障到达癌变部位的窘境。基于此，我们选用结构与性能可调控性强的金属有机框架材料（MOFs）作为纳米载体：一方面调控合成条件控制其尺寸与形状来模仿狂犬病毒的形貌；另一方面对合成的MOFs进行表面功能化修饰连接上由狂犬病毒表面糖蛋白衍生出的嗜神经性多肽RVG29来模仿狂犬病毒由糖蛋白组成的侵染性表面，同时在MOFs的孔道中装载上抗癌药物，最终构建出仿生RBV的纳米药物MILR-RVG29。对仿生纳米药物MILR-RVG29形貌进行表征发现其形貌与狂犬病毒基本相同。为表征MILR-RVG29的性能，同时合成类球状的纳米药物MILS-RVG29作为对比。通过离体细胞靶向性表征，相比与MILS-RVG29，MILR-RVG29针对BBB模型细胞或脑胶质瘤细胞均具有较高的靶向性；而进一步的在体表征发现MILR-RVG在穿越BBB或靶向脑胶质瘤均表现优异，相比与传统的球状纳米载体MILS-RVG29，MILR-RVG在脑胶质瘤额富集量可提高3倍以上，。通过构建脑胶质瘤模型进行疗效评价，仿生纳米药物MILR-RVG显著地抑制了肿瘤的生长，延长了荷瘤小鼠的生存期。本课题基于脑胶质瘤的治疗药物难以跨越BBB到达癌变部位的难题，从仿生的角度出发模仿嗜神经性狂犬病毒构建出仿生纳米药物MILR-RVG29，并且在脑胶质瘤模型中表现出较高的治疗效率，同时有望搭建一个可以高效穿越BBB的纳米药物平台并延伸到其他中枢系统类疾病的治疗中，应用前景宽广。

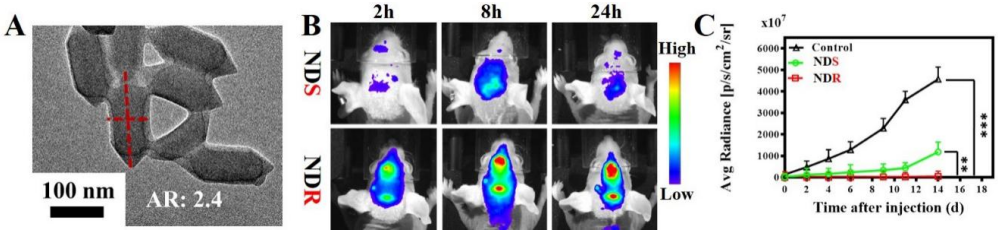

Fig. 1 (A) Structural characterization of probes. (B) Targeted imaging of glial tumors. (C) Chemotherapy of glial tumors

关键词：血脑屏障；仿生；狂犬病毒；二元协同

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论文编号：10–051

Persistent Luminescence Nanocarriers Functionalization with PD-1 Enriched Cell Membrane Enable In Vivo Tumor Targeting and Colorectal Cancer Chemo-immunotherapy

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Colorectal cancer has become one of the malignant tumors with a high rate of morbidity and mortality[1]. Therefore, how to effectively treat colorectal cancer is crucial[2, 3]. Although nano delivery system has been applied to the therapy of colorectal cancer, the majority of existing nano delivery systems still have drawbacks such as low biocompatibility and poor targeting ability. In this work, programmed cell death receptor 1 (PD-1) functionalized cell membrane bioinspired nanoplatform was prepared to enhance the targeting and therapeutic effect for colorectal cancer chemo-immunotherapy. Firstly, hollow long persistence luminescence nanomaterials were synthesized with superior background-free bioimaging effect and high drug-loading content. After loaded with cisplatin, the nanoplatform was camouflaged with erythrocyte and PD-1 expressed 293T hybrid cell membrane. In vivo animal imaging confirmed the nano delivery system with excellent immune escape ability and excellent tumor active targeting ability. In vivo anticancer experiments showed that combined chemotherapy and immunotherapy of this nano delivery system could significantly inhibit tumor growth in tumor-bearing mice. In summary, the PD-1 protein-functionalized cell membrane camouflage produced excellent immune escape ability and cancer active targeting ability, providing a new modality for biomimetic nano delivery systems.

Keywords: Biomimetic, PD-1, Persistent luminescence, Colorectal cancer, Immunotherapy

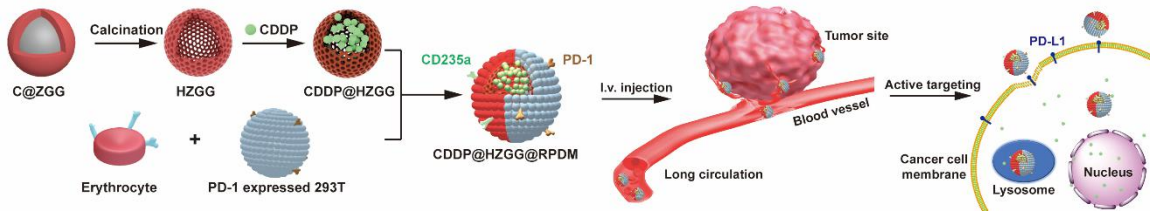

Fig. 1 Schematic diagram of persistent luminescence nanocarriers functionalization with PD-1 enriched cell membrane enable in vivo tumor targeting and colorectal cancer chemo-immunotherapy.

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论文编号：10–052

A MUC-1 recognition and activated drug nanoplatform based on mesoporous silica nanoparticles for precise breast cancer chemotherapy

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Tumor-targeted drug delivery systems with stimuli-response drug release have been increasingly employed to improve the therapeutic efficacy of antitumor drugs. However, drug delivery systems that can selectively sense tumor cells and rapidly sequence activating drug release are desirable because they can be used to selectively kill tumor cells for precise medicine. Here we report a specific molecular recognition activation drug nanoplatform based on specially designed DNA sensor-capped doxorubicin (DOX) loaded mesoporous silica nanoparticles (MSNs). DNA sensor on the targeted nanoparticles (designated as SMRAN) can trigger DOX release through conformational switch induced by MUC-1. The potential of SMRAN for breast cancer therapy was evaluated in vitro and in vivo. In vivo pharmacodynamics experiments showed that the tumor volume of SMRAN treatment group was reduced by ~1.5 times compared with that of DOX group, which revealed that the nanoparticles exhibited a high antitumor efficacy.

Keywords: activated therapy; molecular recognition; drug delivery; DNA sensor

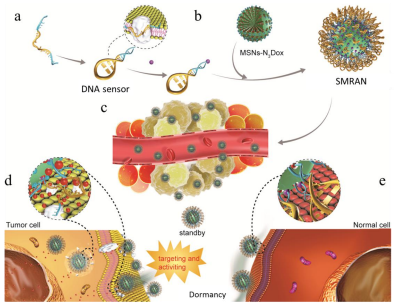

Fig. 1 Preparation and application of the specific molecular recognition activated drug nanoplatform (SMRAN).

论文编号：10–053

Glyco-Gold Nanorods Functionalized by Tailored Sugar Ligands for Sensitive Detection of Tumor Biomarker Galectin-1

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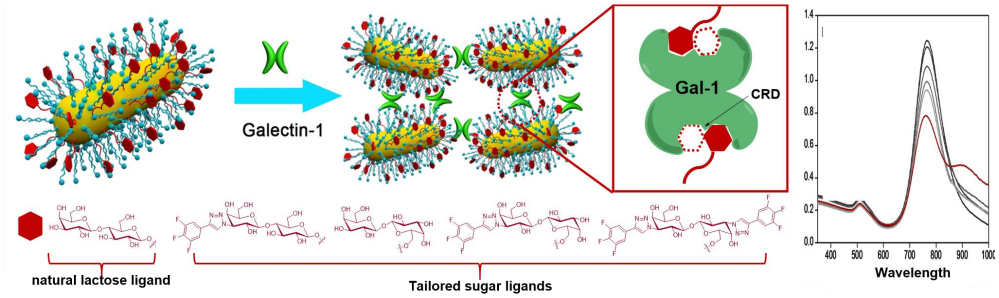
Abundant techniques for the early and confirmed diagnosis of specific cancers have been studied. However, diagnostics for broad-spectrum tumor screening are still lacking, hence should be further developed. Here in our study, a series of glyco-gold nanoprobes functionalized by tailored sugar ligands for Galectin-1 detection were presented. The target Galectin-1 is a universal tumor biomarker for its overexpressed serological level in various tumors[1]. The glyco-gold nanorod probes detect Galectin-1 via aggregation-induced absorption changes from the LSPR effect of gold nanorods[2]. By analysing Galectin-1's carbohydrate recognition domain(CRD) pocket space, a series of Galectin-1's tailored sulfhydryl sugar ligands were designed, synthesized and further applied in the preparation of tailored glyco-gold nanorod probes, which exhibited obvious improvement for Galectin-1 detection sensitivity and specificity than those previously reported lactose glyco-gold nanoprobes[3], thus providing several potential gold nanoprobes for serological Galectin-1 detection for tumor screening.

Keywords: glyco-gold nanoprobe,tailored sugar ligands, galectin-1, tumor biomarker, tumor screening



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论文编号：10–054

Dual Targeting Peptides Modified Ferritin as Mesenchymal Stem Cells Capture and Enhancer for Cartilage Regeneration

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Articular cartilage has no innate ability to mount a sufficient healing response when damage occurs. Currently, stimulating directional differentiation of the bone marrow mesenchymal stem cells (BMSCs) into chondrocytes has paved the way for cartilage repair. [1] However, issues including the lack of a targeting delivery system for BMSCs and low chondrogenic differentiation capacity of exogenous cells are becoming significant obstacles. Herein, we successfully prepared the dual-targeting peptides modified ferritin via genetically engineering tactics. The selected cell-adhesive peptide sequence RGD4C can not only target with integrin Rvβ3 of BMSCs but also promote the proliferation of BMSCs. While another peptide WYRGRL (Col- II) has the appetency for the cartilage matrix component collagen II protein.[2] Together with the stimulating factor kartogenin (KGN) loading into the cavity structure, this kind of double-sided adhesive ferritin could convert the articular cavity from a barrier into a reservoir following intra-articular injection, which has great performance for preventing rapid release and clearance of KGN as well as BMSCs losing from the articular cartilage defect site.[3] Ultimately, this specific ferritin will be an excellent injectable KGN carrier, BMSCs capture and enhancer to troubleshoot the conundrum of cartilage regeneration.

Keywords: Ferritin; bone marrow mesenchymal stem cells (BMSCs); cartilage regeneration;

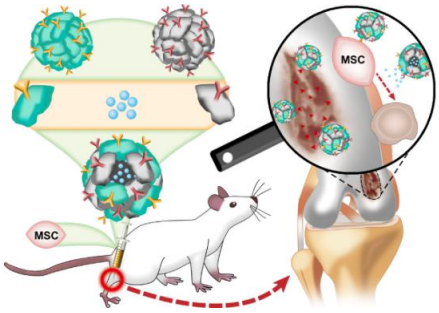

Fig. 1: Schematic presentation of dual targeting peptides modified ferritin as an efficient KGN carrier and BMSCs capture.

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论文编号：10–055

Biomimetic Ca^{2+} nanogenerator based on ions interference strategy for tumor-specific therapy

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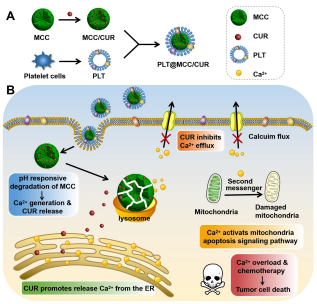
Intracellular Ca^{2+} ions as second messenger played key role in cell behavior,which was often overlooked in traditional antitumor treatment.Disrupting Ca^{2+} ions homeostasis by Ca^{2+} overload might switch ions signal from “regulating” to “destroying”.Inspired by this,we developed a biomimetic Ca^{2+} nanogenerator based on mesoporous calcium carbonate nanoparticles (MCC NPs) by curcumin (CUR) loading and further platelets (PLT) membrane coating. Upon reaching tumor cells by PLT membrane mediated tumor targeting effect,PLT@MCC/CUR would instantaneously decompose in acidic lysosomes,concurrently accompanying with Ca^{2+} generation and CUR release.The CUR could further facilitate Ca^{2+} release from endoplasmic reticulum and inhibit Ca^{2+} efflux, aggravating Ca^{2+} overload to disrupt mitochondrial Ca^{2+} homeostasis for mitochondria apoptosis signaling pathway activation.Based on ions interference strategy,PLT@MCC/CUR herein offered synergistic combination of Ca^{2+} overload therapy and chemotherapy,which would pave the way toward more effective nanotherapeutics.

Keywords: ions interference; biomimetic;calcium overload;calcium carbonate;curcumin



Scheme 1. A) Formulation of PLT@MCC/CUR. B) Schematic mechanism of biomimetic Ca^{2+} nanogenerator mediated synergistic combination of Ca^{2+} overload therapy and chemotherapy based on ions interference strategy.

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论文编号：10–056

Bioengineered Nanocage from HBc Protein for Combination Cancer Immunotherapy

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Protein nanocages are promising multifunctional platforms for nanomedicine owing to the ability to decorate their surfaces with multiple functionalities through genetic and/or chemical modification to achieve desired properties for therapeutic and diagnostic purposes. Here, we describe a model antigen (OVA peptide) that was conjugated to the surface of a naturally occurring hepatitis B core protein nanocage (HBc NC) by genetic modification. The engineered OVA-HBc nanocages (OVA-HBc NCs), displaying high density repetitive array of epitopes in a limited space by self-assembling into symmetrical structure, not only can induce bone marrow derived dendritic cells (BMDC) maturation effectively but also can be enriched in the draining lymph nodes. Naiv̈ e C57BL/6 mice immunized with OVA-HBc NCs are able to generate significant and specific cytotoxic T lymphocyte (CTL) responses. Moreover, OVA-HBc NCs as a robust nanovaccine can trigger preventive antitumor immunity and significantly delay tumor growth. When combined with a low-dose chemotherapy drug (paclitaxel), OVA-HBc NCs could specifically inhibit progression of an established tumor. Our findings support HBc-based nanocages with modularity and scalability as an attractive nanoplatform for combination cancer immunotherapy.

Keywords: Protein nanocage, Hepatitis B core protein, antigen delivery, vaccination, cancer immuotherapy

论文编号：10–057

M13噬菌体作为纳米酶载体实现超灵敏比色检测脱氧雪腐烯醇

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摘要正文：

比色酶联免疫测定技术因其独特的优势在分析检测领域备受关注，然而，传统的比色免疫测定因其检测灵敏度偏低，以及天然酶的性能对使用和存储条件的要求苛刻等因素极大限制了该方法的实际应用和推广。近年来，具有模拟酶活性的纳米材料因其具有高催化活性的、稳定的、可重复利用等特性备受关注。然而纳米酶的催化活性与其表面特性相关，在其作为免疫探针包被蛋白后，催化活性急剧下降。基于此，我们利用硫醇化M13噬菌体pIII蛋白的识别功能和pVIII蛋白的展示功能，在免疫测定中，其既可以作为竞争抗原与DON竞争抗原结合位点，又可以作为纳米酶的载体，使AuNPs通过金硫键在噬菌体表面自组装，之后在AuNPs表面原位还原包裹一层银壳，进一步提高纳米酶活性。通过这种策略检测DON的IC_{50}值是传统ELISA的26倍，是噬菌体ELISA的40倍，并具有良好的特异性和稳定性。

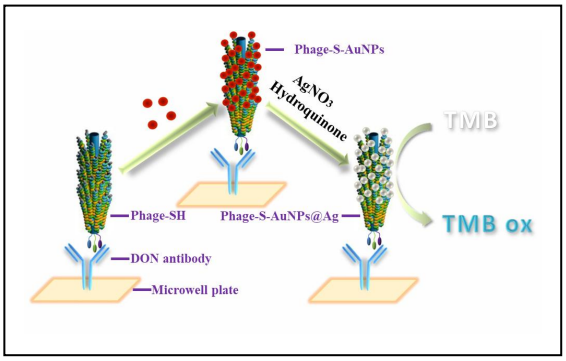

Fig. 1 Chemical Modification of M13 Bacteriophage for Enhanced Detection Sensitivity of colorimetric immunoassay

关键词：M13噬菌体；金纳米粒子；脱氧雪腐镰刀菌烯醇；比色免疫检测

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论文编号：10–058

A biomimetic nanoreactor based on battlefield transfer strategy for tumor therapy

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In this study, we developed an antitumor nanoreactor which replicated the specific killing mechanism in hypoxic red blood cells (RBC). The nanoplatform was formulated based on hollow mesoporous TiO_2 nanoparticles by hemoglobin (Hb) modification, model drug (RRx-001) loading and then cancer cell membrane (CCM) coating. The CCM-Hb-TiO_2/RRx-001 could homologous target the tumor cells and transfer the battlefield from hypoxic RBC to hypoxic tumor cells. Importantly, hemoglobin (Hb) as a natural protein in RBC played a dual role in this nanoreactor. Once the Hb was deoxygenated in the battlefield of hypoxic tumor, the biomimetic nanoreactor was activated and triggered a series of reactions in cascade and specific fashion. The oxygen compensation from Hb enhanced TiO_2 mediated reactive oxygen species (ROS) generation for sonodynamic therapy. Meanwhile, the nitrite reductase activity of deoxy-Hb was potentiated by RRx-001 and drove nitric oxide (NO) generation. Subsequently, the resulted reactive nitrogen species (RNS) were highly active and brought out deleterious consequences in cell damage for tumor therapy. Thus, such biomimetic nanoreactor certainly would bring out the remarkable antitumor effect based on battlefield transfer strategy.

Keywords:TiO_2 nanoparticles, hemoglobin, cancer cell membrane

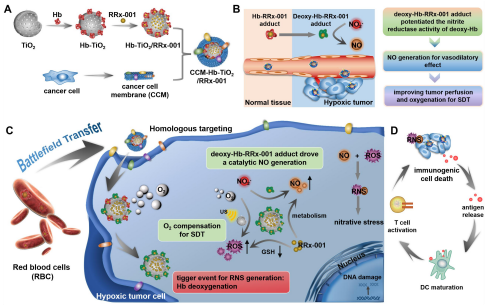

Fig. 1. Schematic of the biomimetic nanoreactor based on battlefield transfer strategy.

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论文编号：10–059

Surface Engineering Antigenic Microparticles Vaccine for Reprogramming Tumor Microenvironment and Enhancing Cancer Immunotherapy

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摘要正文：

免疫疗法作为近年来的热门研究医疗技术，对肿瘤学和人类健康有重大影响。癌症疫苗与免疫检查点阻断疗法、过继T细胞疗法是癌症免疫治疗的三大关键方法。尽管疫苗在癌症免疫治疗方面具有巨大的潜力，但其临床结果迄今仍不理想，这主要是由于无效的肿瘤-免疫微循环和免疫抑制肿瘤微环境(ITME)。在本报告中，我们设计了一种基于生物医学的策略，将肿瘤来源的抗原微颗粒(T-MPs)转化为癌症疫苗，以解决上述难题，并在多种小鼠肿瘤模型中展示了其治疗潜力。T-MPs的内部腔用于贮存纳米Fe_3O_4 (Fe_3O_4/T-MPs)，然后通过温和的表面工程在Fe_3O_4/T-MPs的表面连接致密的装载了佐剂CpG的脂质体(CpG/Lipo)以构建抗肿瘤疫苗(Fe_3O_4/T-MPs-CpG/Lipo)。该疫苗可以共递送Fe_3O_4/T-MPs和CpG/Lipo至抗原呈递细胞(APC)，引起强烈的抗原特异性宿主免疫反应。同时，分布在肿瘤微环境(TME)中的疫苗可以通过纳米Fe_3O_4将浸润的肿瘤相关巨噬细胞(TAMs)逆转为肿瘤抑制的M1表型，惊人地诱导大量的细胞毒性T淋巴细胞浸润，将“冷”肿瘤转化为“热”肿瘤。此外，通过结合Fe_3O_4/T-MPs-CpG/Lipo疫苗和免疫检查点PD-L1阻滞联用，可以实现扩增的抗肿瘤免疫，特异性抑制约83%小鼠的黑色素瘤进展，并将中位生存时间延长至3个月。总的来说，本研究以时空上协同的方式调节TME和宿主抗肿瘤免疫，为我们提示了一种可以针对每个患者的自体癌细胞材料定制个性化疫苗通用的细胞工程策略。

关键词：肿瘤微颗粒；疫苗；免疫治疗；肿瘤微环境

论文编号：10–060

聚离子液体-碳复合材料固定化苯丙氨酸脱氢酶及其性能研究

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摘要正文：

碳材料-高分子复合材料将无机碳材料和高分子有机材料相结合，兼有两者的优点。进而引入离子液体，可与高分子形成聚离子液体，从而获得新型的功能材料用于固定化酶[1]。苯丙氨酸脱氢酶(PheDH)可催化制备天然氨基酸和非天然手性氨基酸，如高苯丙氨酸等，作为重要的药物中间体。氧化石墨烯(GO) 比表面积大，表面官能团丰富。聚乙烯亚胺（PEI）与GO共价接枝获得的GO-PEI具有良好的生物相容性。进一步结合离子液体，获得聚离子液体-碳复合材料用于氧化还原酶固定化。

首先考察不同咪唑基离子液体对游离苯丙氨酸脱氢酶的影响，发现 25 mM [BMIM]Cl酶活有促进作用，其相对酶活为108.0 %。进而利用咪唑基离子液体[BMIM]Cl修饰GO-PEI，分别考察GO，GO-PEI，GO-PEI-[BMIM]Cl固定化苯丙氨酸脱氢酶的性能。GO直接固定化的酶活回收为74.0%，而GO-PEI-[BMIM]Cl固定化的酶活回收可达到92.07%，且高于GO-PEI载体。因此，[BMIM]Cl修饰提高了载体固定化酶性能。

考察不同载体固定化酶的最适温度、最适pH、温度稳定性以及重复利用稳定性。游离酶与固定化酶的最适温度均在65℃，同时GO-PEI -[BMIM]Cl固定化酶的相对酶活高于GO-PEI固定化酶。 GO和GO-PEI 固定化酶的最适pH为9，而GO-PEI-[BMIM]Cl的最适pH为10。GO-PEI-[BMIM]Cl固定化酶经过7次重复利用，仍可保持83.03%的活性，而对照的GO-PEI固定化酶仅有67.74%。聚离子液体-碳复合材料具有良好的生物相容性，且离子液体种类众多，可适用于不同酶的固定化。

关键词：苯丙氨酸脱氢酶；离子液体；碳复合材料

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论文编号：10–061

脑部疾病基因药物递送策略：From nature to “NATURE”

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摘要正文：

实现脑部的有效药物输送必须经过一系列障碍。传统的药物递送体系通常很难满足期望，大自然为设计更有效的药物递送系统提供了广泛的灵感来源[1-3]。基于天然生物颗粒的结构和功能，我们设计了外泌体涂层聚合物杂化递送体系和仿突触小泡递送体系用于帕金森病的治疗。这两种仿生递送体系具有可以满足脑部疾病治疗需求的特性，包括：i）不被血液清除（N），ii）跨越血脑屏障（A），iii）靶向细胞（T），iv）细胞摄取（U），v）可控释放（R），vi）可视化（E）-总结为NATURE，其中如何克服细胞膜屏障和内涵体屏障是长期以来面临的难题，天然纳米载体外泌体和人工制备的仿突触小泡脂质体可以通过膜融合的方式将药物直接释放在细胞质中，有效避免了内涵体导致的药物损失。这两种仿生纳米颗粒能够显著治疗帕金森病，并为其他脑部疾病的治疗提供了平台。

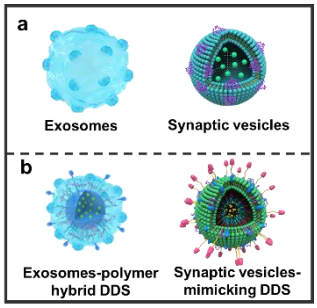

Fig. a) Biomimetic objects: exosomes and synaptic vesicles; **b)** Biomimetic DDS: exosomes-polymer hybrid DDS and Synaptic vesicles-mimicking DDS.

关键词：脑部疾病；仿生递送体系；外泌体；仿突触小泡；膜融合

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Brain disease gene drug delivery strategies: From nature to "NATURE"

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To achieve effective drugs delivery, brain drug delivery systems (DDS) must go through a cascade of barriers. Nature

provides a wide-range source of inspiration for designing more effective DDS. [1-3] Based on the structure and function of natural bio-particles, we designed an exosome-coated polymer hybrid DDS and a synaptic vesicles (SVs)-mimicking DDS for treating Parkinson's disease (PD). These two biomimetic DDS have characteristics that can meet the needs for brain disease treatment, including: i) Non-elimination in blood (N), ii) Across blood-brain barrier (A), iii) Targeting cells (T), iv) Uptake (U), v) Release (R), vi) Eyeable (E)-summarized as NATURE. Especially, how to overcome the cell membrane and endosome barrier is a long-standing problem. Natural exosomes and artificial SVs-mimicking liposomes can directly release drugs into the cytoplasm via membrane fusion, which avoids drug loss caused by endosome/lysosome. These two biomimetic DDS can significantly treat PD and provide a platform for other brain diseases.

论文编号：10–062

Near-infrared Light-triggered Platelet Arsenal for Combined Photothermal-immunotherapy against Cancer

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To address long-standing issues with tumor penetration and targeting among cancer therapeutics, we developed an anticancer platelet-based biomimetic formulation (N-R@PLTs), integrating photothermal nanoparticles (N) and immunostimulator (R) into platelets (PLTs) (Fig. 1). Exploiting the aggregative properties of PLTs and high photothermal capacity, N-R@PLTs functioned as an arsenal by selectively targeting defective tumor vascular endothelial cells, accumulating in a positive feedback aggregation cascade at sites of acute vascular damage induced by N-generated local hyperthermia, and subsequently secreting nanosized proplatelets (nPLTs) to transport active components to deep tumor tissue. The immunostimulator augmented the immunogenicity of antigens released from ablated tumors, inducing a stronger immunological response to attack residual, metastatic and recurrent tumors. Following activation by low-power near-infrared light irradiation, the photothermal and immunological components functioned synergistically to provide exceptionally high therapeutic efficacy across nine murine models that mimicked a range of clinical requirements, and most notably, a sophisticated model based on humanized mouse and patient-derived tumor xenograft.

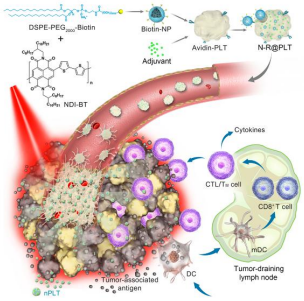

Fig.1 Schematic illustration of N-R@PLTs construction and application in a combined photothermal-immunological therapy.

Keywords: platelet, biomimetic, combined anticancer therapy, near-infrared light

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论文编号：10–063

基于铁蛋白构建白血病靶向制剂的研究

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摘要正文：

三氧化二砷（ATO）是治疗白血病的明星药物，对急性早幼粒细胞白血病的疗效最为显著。然而传统砷制剂仍存在明显的毒副作用，并且对某些类型的白血病敏感度较低。利用靶向修饰的纳米颗粒将负载的ATO准确递送至白血病细胞是解决上述问题的有效方法，但传统精心设计的载体制备过程复杂，生物相容性低，体内外结果差异大，实际疗效不及预期。

铁蛋白是一种内源性的纳米笼形蛋白，其受体较高表达于白血病细胞，因此具有良好的生物安全性和天然的靶向作用。受此启发，本工作开发了一种基于铁蛋白的ATO原位限域装载技术，并通过白血病细胞高表达铁蛋白受体实现砷剂的靶向递送。首先，通过基因工程的方法制备得到靶向性高的全重链人源化铁蛋白，并通过铁辅助成核的方法成功将砷装载至铁蛋白空腔。装砷铁蛋白对白血病细胞具有很高的结合力，并可以显著提高白血病细胞对砷的内吞。内吞进入细胞以后，颗粒主要进入溶酶体中，并释放有效的三价砷。相应地，相比于临床用三氧化二砷注射液，装砷铁蛋白可以显著提高细胞毒性。体内分布结果表明，装砷铁蛋白可以特异性地被白血病细胞内吞，同时减少对其他正常细胞的毒副作用。动物实验进一步证明，该铁蛋白仿生制剂在多种白血病模型中均具有良好的抑制效果。

关键词：白血病，铁蛋白，三氧化二砷，靶向递送

论文编号：10–064

苯丙氨酸脱氢酶的原位分离固定化及其性能研究

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摘要正文：

原位固定化酶的方法无需进行酶的分离纯化，可提高酶活回收，大幅度降低成本并节省操作时间[1,2]。氨基酸脱氢酶可催化制备天然氨基酸和非天然氨基酸，作为合成手性药物、手性农药和手性食品添加剂等精细化学品的关键中间体。还原氧化石墨烯(CRGO)的表面羧基、羟基等含氧基团较少，比表面积大，生物相容性好。聚乙烯亚胺（PEI）表面富含氨基，可以与酶和基底材料形成氢键和静电作用。本研究利用PEI和金属离子修饰CRGO，分别考察载体CRGO，CRGO-PEI， CRCO-Mn，CRGO-PEI-Mn从粗酶液中原位分离固定化苯丙氨酸脱氢酶的性能。基于酶活性和蛋白负载量测定，发现CRCO-Mn原位固定化能达到80.0 %的酶活回收，酶负载量为6.7 mg/mg。Mn离子配位在原位固定化中大幅度提高了载体对目标酶的选择性。CRCO-PEI和CRCO-Mn-PEI在加入PEI后对PheDH负载量降低。进一步考察NaCl浓度对固定化载体的酶负载量影响，在1 M NaCl下分别提高10.7 %和30.6 %。比较了CRCO-Mn原位固定化粗酶与CRCO-Mn固定化纯酶的蛋白吸附曲线，发现二者对苯丙氨酸脱氢酶的吸附曲线接近。原位固定化效率高、成本低，并有利于工业化应用。

关键词：苯丙氨酸脱氢酶；原位固定化；还原氧化石墨烯；金属配位

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论文编号：10–065

氨基酸脱氢酶多肽模块组装及MOF材料固定化酶

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摘要正文：

氨基酸脱氢酶可催化合成系列手性天然氨基酸和非天然氨基酸，也可制备酶电极用于临床诊断、食品安全检测和发酵监控。目前氨基酸脱氢酶的研究主要基于底物结合口袋修饰提高其催化效率、拓展底物谱以及提高其稳定性的报道。多肽具有来源广泛、生物兼容性好、易于修饰等特点，且具有良好的力学和电学性能。ZIF-8型MOF材料具有比表面积大、稳定性高等优点，其中的金属离子可与多肽模块进行配位结合，增强界面相互作用，增大酶的负载量，进而实现在酶在MOF材料上的定向固定化。

主要研究了多肽模块组装对氨基酸脱氢酶的影响，并使用ZIF-8型MOF材料与多肽模块进行配位固定化，提高其在高温下的抗逆性能，和重复利用稳定性。对来源于红球菌的苯丙氨酸脱氢酶（Phenylalanine dehydrogenase，PheDH）进行了多肽模块组装，得到了两种多肽组装酶PheDH_1D01和PheDH_1D02。对改造前和改造后的酶进行了酶学性质的测定和催化动力学的研究。对于氧化脱氨体系，三种酶的最适反应温度均为60°C，最适反应pH值均为11，且两种多肽组装酶PheDH_1D01和PheDH_1D02在pH=12的高碱性条件下能保持79.5%和82.6%相对活性，可适应如此高pH的PheDH较少有报道。还原胺化制备L-高苯丙氨酸的反应体系中，三种酶的最适反应温度均为50°C，原酶的最适反应pH值为9.0，多肽组装酶的最适pH值为10.0，拓展了反应的pH值范围。经酶催化动力学实验测定，两种多肽组装酶分别为较原酶的催化效率1.94和2.16倍。

实验显示Zn^{2+}对多肽组装酶的酶活具有促进作用。选用以Zn为配位金属的ZIF-8型MOF材料作为固定化酶的载体。固定化多肽组装酶PheDH_1D02@ZIF-8的催化活性较未固定的苯丙氨酸脱氢酶，达到了138.7%，且在重复利用6次以后，仍具有81.2%的相对活性。而原酶固定化后得到的PheDH@ZIF-8只剩50%的相对活性。多肽组装酶固定化后，在80°C 的高温条件下，PheDH_1D02@ZIF-8仍具有98.3%的相对活性，说明多肽模块与MOF的配位结合大大提高了酶在高温条件下的稳定性，提升了酶在高温环境下的抗逆性能。

关键词：氨基酸脱氢酶；多肽；固定化；MOF