Supporting Information

Cancer cell membrane camouflaged MOF nanoparticles for a potent Dihydroartemisinin based Hepatocellular carcinoma therapy

Yusha Xiao¹#, W. Huang²#, Daoming Zhu³, Quanxiong Wang¹, Baiyang Chen¹, Zhisu Liu¹, Yang Wang²,*, Quanyan Liu¹,*

¹ Department of General Surgery, Research Center of Digestive Diseases Zhongnan Hospital of Wuhan University, Wuhan, 430071, Hubei, P.R. China.
² School of Chemistry and Chemical Engineering, Yangzhou University, Yangzhou, 225009, Jiangsu, P. R. China.
³ Key Laboratory of Artificial Micro- and Nano-Structures of Ministry of Education, School of Physics and Technology, Wuhan University, Wuhan, 430071, Hubei, P.R. China.
⁴ Department of General Surgery, General Hospital of Tianjin Medical University, Tianjin, 300052, China.

# Both authors contributed equally to this work.

*Author for correspondence: Quanyan Liu, Department of General Surgery, General Hospital of Tianjin Medical University, Tianjin, 300052, China, E-mail: spsslqy@vip.126.com; Yang Wang, School of Chemistry and Chemical Engineering of Yangzhou University, Yangzhou, 225009, Jiangsu, P. R. China, E-mail: wangyzu@126.com.
Experimental Section

**Materials:** Phosphate buffer solution (PBS), fetal bovine serum (FBS) and trypsin were obtained from Thermo-Fisher (USA). Ethylenediaminetetraacetic-acid (EDTA), Indocyanine Green (ICG), DAPI, and Cell Counting Kit-8 (CCK-8) were purchased from Sigma-Aldrich (USA). Tris-HCl (pH = 7.5) and EDTA-free mini protease inhibitor tablets were obtained from Mediatech (USA) and Roche (Switzerland). Sodium dodecyl sulfate (SDS)-polyacrylamide gel and SDS buffer were purchased from Beyotime (China) and Invitrogen (USA). All the aqueous solutions were prepared by using deionized (DI) water purified in an experimental water purification system (Direct-Q3, Millipore, USA). Dihydroartemisinin (DHA), Iron (II) chloride tetrahydrate (FeCl$_2$·4H$_2$O) and 2-Methylimidazole (MeIm) were purchased from Aladdin-Reagent. Zinc nitrate hexahydrate (Zn(NO$_3$)$_2$·6H$_2$O), methanol and other chemicals were purchased from Sinopharm Chemical Reagent and all the chemicals were of analytical grade and used without further purification.

**Preparation and characterization of ferrous ion doped ZIF-8 nanoparticles:** Ferrous ion doped ZIF-8 nanoparticles were obtained based on to the previous report after a minor modification\(^1\). Typically, 810 mg (Zn(NO$_3$)$_2$·6H$_2$O) and 23.8 mg (0.12 mmol) FeCl$_2$·4H$_2$O were dissolved in 40 mL methanol, while 526 mg MeIm was dissolved in 40 mL methanol. After then, the above two solutions were mixed together under vigorous stirring for 10 min. The resulting solution was turned into a Teflon lined autoclave and heated at 100 °C for 12 h. After the reaction cooled to room temperature, the orange product was obtained by centrifugation, and washed for several times with methanol. Subsequently the sample was dried at 80 °C for 12 h in vacuum and defined as Fe/ZIF-8. The DHA loaded Fe/ZIF-8 nanoparticles (DZs) were prepared by incubating the Fe/ZIF-8 (100 μg · mL$^{-1}$) with DHA (10
μg · mL$^{-1}$) under stirring at room temperature for 24 h. The final mixture was centrifuged and washed with PBS to remove the residual free DHA.

To characterize the Fe/ZIF-8, Powder X-ray diffraction (XRD) patterns were collected on a Germany Bruker Co. D8 Advance X-ray diffractometer equipped with Cu Kα radiation over the 20 range of 5-80°. Transmission electron microscopy (TEM) images were obtained on a Philips Tecnai-12 (Netherland) operated at 120 KV. The elements distribution was characterized using a High-angle annular dark-field scanning transmission electron microscopy (HAADF-STEM, FEI Tecnai G2 F30 S-TWIN, USA) with energy dispersive X-ray (EDX) operated at 300 KV. X-ray photoelectron spectroscopy (XPS) on a ESCALAB 250Xi X-ray photoelectron spectrometer (Thermo Scientific, America). N$_2$ adsorption-desorption isotherms were obtained using a Quantachrome Autosorb-iQ Automated Gas Sorption System at 77 K. To determine the loading amounts of DHA, the redundant DHA in the process of drug loading was dissolved in acetonitrile and then analyzed by HPLC. The HPLC analysis system consisted of a reverse-phase C18 column (Waters, USA), with a mobile phase of acetonitrile and purity water (6:4, v/v) pumped at a flow rate of 0.8 mL · min$^{-1}$. The column effluent was detected at 210 nm using an UV-vis detector (2489, Waters, USA) and quantified by comparing the peak areas with the standard curve. The drug loading content (DLC) and drug loading efficiency (DLE) were calculated by using the following formulas: DLC = (weight of feeding drug - weight of redundant drug/weight of drug-loaded nanoparticles) × 100%, DLE = (weight of feeding drug - weight of redundant drug /weight of feeding drug) × 100%.

**Preparation and characterization of CDZs:** To obtain CDZs, an extrusion strategy was used$^2$. First, the G2 cell membrane vesicles (CMVs) as the outer shells were prepared. Briefly, cancer cells were grown in T-175 culture flasks to full confluency and detached with 2 mM EDTA in PBS, and washed in PBS three times by centrifuging at 800 g for 5 min. The cells
were suspended in hypotonic lysing buffer consisting of 20 mM Tris-HCl, 10 mM KCl, 2 mM MgCl₂, and 1 EDTA-free mini protease inhibitor tablet per 10 mL of solution and disrupted using a dounce homogenizer with a tight-fitting pestle. The entire solution was subjected to 20 passes before spinning down at 3,200 g for 5 min. The supernatants were saved, while the pellet was resuspended in hypotonic lysing buffer and subjected to another 20 passes and spun down again. The supernatants were pooled and centrifuged at 20,000 g for 30 min, after which the pellet was discarded and the supernatant was centrifuged again at 80,000 g for 1.5 h using an ultra-speed centrifuge (LE-80K, Beckman Coulter, USA). The pellet containing the plasma membrane material was then washed once with 10 mM Tris-HCl and 1 mM EDTA. The final pellet was collected as purified cancer cell membranes, and then CC-membranes (CMs) were obtained by physically extruding the pellet for 11 passes through a 400-nm polycarbonate porous membrane on a mini extruder (Avanti Polar Lipids, USA). Finally, DZs were mixed with G2 CMs (1 mg) which were quantified by lyophilization and extruded through 200 nm polycarbonate membranes. Then the particle size and zeta potential of CMs, DZs, and CDZs were measured using DLS analyzer (Zetasizer, Malvern, UK). Stability experiments were carried out by measuring CDZs in 1× PBS or 100% FBS for 15 days using DLS. The morphologies of CMs, DZs, and CDZs were characterized by TEM. The cell membrane proteins were further characterized by using sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE). The CMS, DZs, and CDZs were loaded into SDS buffer as measured by the BCA assay kit. Then the samples were heated at 95 °C for 5 min, and 20 μg of each sample was added into each well in a 10% SDS-polyacrylamide gel. Samples were run at 120 V for 2 h, and the obtained gel was stained with Commassie blue, washed with DI water, and imaged.
Figure S1. (A) XPS survey spectrum of Fe/ZIF-8; (B) high resolution XPS spectra of Fe2p of Fe/ZIF-8.

Figure S2. The drug loading content (DLC) and drug loading efficiency (DLE) of DZs.
Figure S3. Stability of CDZs in 1× PBS and 100% FBS over a span of 15 days.

Figure S4. RAW 264.7, U937, HepG2 and L02 cytotoxicities after incubation with CZs at various concentrations.
**Figure S5.** CLSM images of MCF-7 and HCT116 cells after incubation with G2 cell membranes prepared CDZs for 2 h.

**Figure S6.** Immune evasion evaluation. (A) Fluorescence images of U937 cells after incubation with various nanoparticles. The scale bar is 50 μm; (B) Cellular uptake of the different nanoparticles on U937 cells after different incubation time. Error bars: standard deviations (n = 3).
**Table S1** Surface areas, total pore volumes and pore size of Fe/ZIF-8 and Fe/ZIF-8 load DHA.

<table>
<thead>
<tr>
<th>Sample</th>
<th>BET surface area (m² · g⁻¹)</th>
<th>Total pore volume (m³ · g⁻¹)</th>
<th>Pore size (nm)</th>
</tr>
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<tbody>
<tr>
<td>Fe/ZIF-8</td>
<td>1327</td>
<td>0.637</td>
<td>1.2</td>
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<tr>
<td>Fe/ZIF-8 load DHA</td>
<td>987</td>
<td>0.231</td>
<td>0.5</td>
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