**Supporting Information**

**19F MRI-guided** **Flexible Low-intensity Focused Ultrasound for**

**Drug Delivery** **and Molecular** **Targeted Therapy**

Jie Yang1,2,3, Yingbo Li1,2,3, Jiemei Sun1,2,Hongyan Zou1,2,Qian Xie1,2, Rong A1,2, Hongbin Wang1,2, Xiaona Li1,2, Kai Wang1,2, Lili Yang1,2,Lina Wu1,2\* & Xilin Sun1,2\*

1 NHC and CAMS Key Laboratory of Molecular Probe and Targeted Theranostics, Molecular Imaging Research Center (MIRC), Harbin Medical University, 150028 Harbin, Heilongjiang, China.

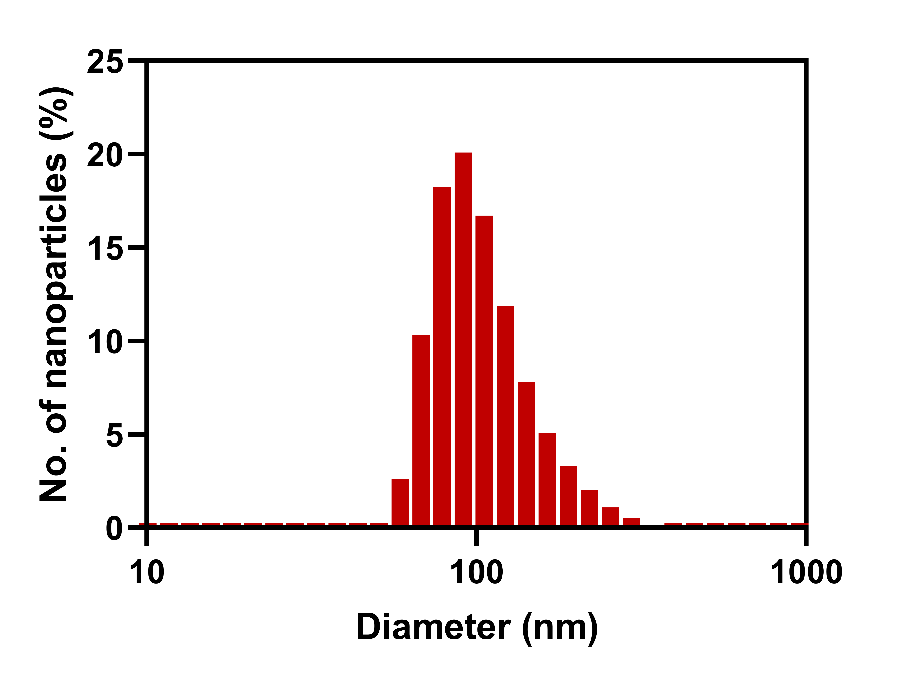
2 Department of Nuclear Medicine, the Fourth Hospital of Harbin Medical University, 150028 Harbin, Heilongjiang, China.

3These authors contributed equally: Jie Yang, Yingbo Li.

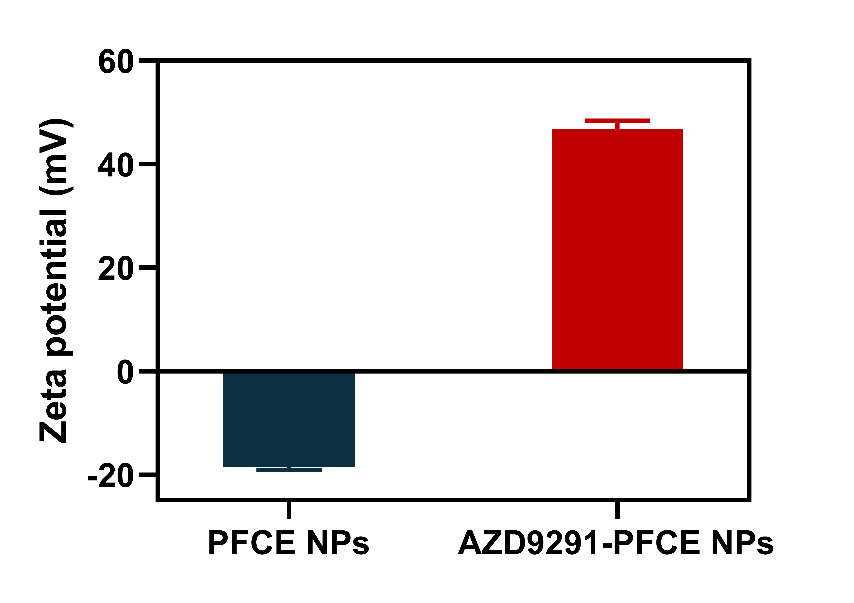
\*email: [sunxl@ems.hrbmu.edu.cn](mailto:sunxl@ems.hrbmu.edu.cn); LinaWu@hrbmu.edu.cn



**Supplementary Figure 1.** Dark-field image of PFCE NPs and the corresponding EDS elemental mapping of carbon (C), oxygen (O) and fluorine (F). Scale bar is 100 nm.



**Supplementary Figure 2.** Average hydrodynamic size of PFCE NPs characterized by dynamic light scattering (DLS).



**Supplementary Figure 3.** Zeta potential of PFCE NPs and AZD9291-PFCE NPs.



**Supplementary Figure 4. a** Fluorescence image (top row) and 19F MR images (bottom row) of reference tubes with various 19F concentrations. **b** Correlation of fluorescence signal and 19F MR signal intensity of AZD9291-PFCE NPs.



**Supplementary Figure 5.** Cell viability of H1975 and H520 cells treated with PFCE NPs for 24h and 48h.



**Supplementary Figure 6.** Cell viability of H1975 and H520 cells treated with free AZD9291 at various concentrations for 24h and 48h.



**Supplementary Figure 7.** 1H MR images of mice injected with 300 μL of PFCE NPs and AZD9291-PFCE NPs at different time points. Four hours after injection of nanoparticles, LIFU (1.1 MHz, 55.8 mW/cm2, 20 min) was applied to trigger the location of the tumor and MRI was performed synchronously.



**Supplementary Figure 8.** Representative ex vivo images of tumors and major organs derived from mice treated with rhodamine-labeled PFCE NPs and AZD9291-PFCE NPs at 48 h post injection (n = 3).



**Supplementary Figure 9.** Rhodamine-labeled PFCE NPs and AZD9291-PFCE NPs distribution in normal tissues. Nuclei were stained by DAPI. Scale bar is 200 µm.



**Supplementary Figure 10.** Photos of H1975 tumor-bearing mice model from each group on day 0, 7 and 14 d after treatment with Control, PFCE NPs (0.1 g/kg), AZD9291 (0.5 mg/kg), AZD9291-PFCE NPs (0.5 mg/kg), Control+LIFU, PFCE NPs+LIFU (0.1 g/kg), AZD9291+LIFU (0.5 mg/kg) and AZD9291-PFCE NPs+LIFU (0.5 mg/kg). Free AZD9291 was given via gavage every day and other groups received intravenous injection every 3 days. LIFU was applied to the tumor site after different administrations for 4 h (1.1 MHz, 55.8 mW/cm2, 20 min).



**Supplementary Figure 11.** **a** The photo of tumors excised from mice after different treatments on day 14. **b** Tumor growth inhibition (TGI) of H1975 tumor-bearing mice after various treatments (n = 5), \*\*\*\* *P* < 0.0001.



**Supplementary Figure 12.** **a** Proliferative index (n = 6) and (**b**) CD31-positive area of tumor tissues in various groups (n = 3). \*\* *P* < 0.01, \*\*\* *P* < 0.001, \*\*\*\* *P* < 0.0001.

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| --- | --- | --- | --- |
| Formulation | Cell | Mean IC50±SD  （24h, μM） | Mean IC50±SD  （48h, μM） |
| AZD9291 | H1975 | 0.018±0.123 | 0.005±0.107 |
| AZD9291-PFCE NPs | 0.025±0.123 | 0.012±0.111 |
| AZD9291 | H520 | 1.03±0.095 | 0.607±0.105 |
| AZD9291-PFCE NPs | 1.468±0.063 | 1.125±0.074 |

**Supplementary Table 1.** The IC50 of H1975 and H520 cells treated with free AZD9291 and AZD9291-PFCE NPs for 24h and 48h. Results are presented as mean ± SD.