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# Enhancing Glioblastoma Immunotherapy with Integrated Chimeric Antigen Receptor T Cells through the Re-Education of Tumor-Associated Microglia and Macrophages

 Nianci Zhu, Sijia Chen, Yu Jin, Meng Wang, Luyao Fang, Lingjing Xue, Dexiang Hua, Ziyao Zhang, Meng Jia, Meixi Hao\*  
 , and Can Zhang\*

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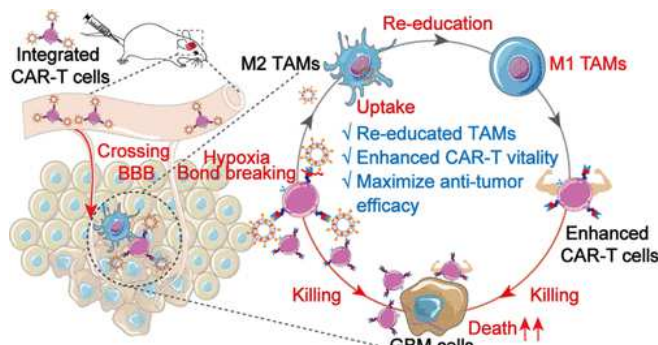
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## Abstract



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cells against GBM. Molecularly targeting drug pexidartinib (PLX) has been reported to re-educate TAMs toward the antitumorigenic M1-like phenotype. Here, we developed a cell–drug integrated technology to reversibly conjugate PLX-containing liposomes (PLX-Lip) to CAR-T cells and establish tumor-responsive integrated CAR-T cells (PLX-Lip/AZO-T cells) as a combination therapy for GBM. We used a mouse model of GBM to show that PLX-Lip was stably maintained on the surface of PLX-Lip/AZO-T cells in circulation and these cells could transmigrate across the blood–brain barrier and deposit PLX-Lip at the tumor site. The uptake of PLX-Lip by TAMs effectively re-educated them into the M1-like phenotype, which in turn boosted the antitumor function of CAR-T cells. GBM tumor growth was completely eradicated in 60% of the mice after receiving PLX-Lip/AZO-T cells and extended their overall survival time beyond 50 days; in comparison, the median survival time of mice in other treatment groups did not exceed 35 days. Overall, we demonstrated the successful fusion of CAR-T cells and small-molecule drugs with the cell–drug integrated technology. These integrated CAR-T cells provided a superior combination strategy for GBM treatment and presented a reference for the construction of integrated cell-based drugs.

**KEYWORDS:** glioblastoma, CAR-T cells, re-educated TAMs, blood–brain barrier 

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## Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsnano.4c00050>.

- Materials and methods including the detailed methods of the synthesis of DSPE-PEG2k-AZO-N<sub>3</sub> and SA<sub>2</sub>-DBCO, preparations and characterization of the liposomes, cell culture, and isolation of the primary cells; synthesis of DSPE-PEG2K-AZO-N<sub>3</sub> and SA<sub>2</sub>-DBCO; <sup>1</sup>H NMR spectra of DSPE-PEG2K-AZO-N<sub>3</sub> and SA<sub>2</sub>-DBCO; UV absorbance of azobenzene bone in DSPE-PEG2K-AZO-N<sub>3</sub> at different time under hypoxic conditions; Figures S4–S5, characteristics of the PLX-Lip; characteristics of GD2 CAR-T cells; optimal preparation conditions of PLX-Lip/AZO-T cells; characteristics of PLX-Lip/AZO-T cells; drug-loading stability of PLX-Lip/AZO-T cells in serum-containing medium; construction of orthotopic GBM-bearing mice model; biodistribution of CAR-T cells and PLX-Lip in vivo; characteristics of integrated CAR-T cells not responsive to hypoxia; release of PLX and PLX-Lip from PLX-Lip/AZO-T cells under hypoxic conditions with time; uptake of PLX-Lip released from PLX-Lip/AZO-T cells by TAMs

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## Associated Microglia and Macrophages

### Supporting Information

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Nianci Zhu<sup>1,2</sup>, Sijia Chen<sup>1,2</sup>, Yu Jin<sup>1,2</sup>, Meng Wang<sup>1,2</sup>, Luyao Fang<sup>1,2</sup>, Lingjing Xue<sup>1,2</sup>, Dexiang Hua<sup>1,2</sup>, Ziyao Zhang<sup>1,2</sup>, Meng Jia<sup>3</sup>, Meixi Hao<sup>1,2</sup>, Can Zhang<sup>1,2</sup>

<sup>1</sup>State Key Laboratory of Natural Medicines, Center of Advanced Pharmaceuticals and Biomaterials, China Pharmaceutical University, Nanjing 211198, China

<sup>2</sup>Chongqing Innovation Institute of China Pharmaceutical University, Chongqing 401135,



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