Tumor-associated macrophage membrane coated biodegradable mesoporous silica nanoparticles for targeted drug delivery of glioblastoma multiforme

Background. Glioblastoma (GBM) is one of the most aggressive human cancer, with median survival of 9-15 months.[1-2] Surgery is the major treatment strategy for GBM, followed by the chemotherapy to remove the residues that can't be removed by resection.[3] However, the formidable blood brain barrier (BBB), poor targeting ability of the drug or drug delivery system, and complex tumor microenvironment usually lead to the failure of the treatment, with high recurrence rate.[4-5] Here we propose to solve this delivery challenge by constructing a glutathione (GSH)-responsive macrophage membrane coated mesoporous silica nanoparticles to fulfill the efficient, targeting drug delivery to GBM tumors. Our hypothesis is that (i) macrophage membrane coating on the nanoparticles not only can efficient cross the BBB and target GBM tumor cells, but also can help the nanoparticle escape the clearance by reticuloendothelial system (RES), [6-7] (ii) the di-thiol bond containing mesoporous silica can release the chemotherapeutic drugs by the specific trigger of GSH in the tumor microenvironment,[8-9] which (iii) will result in efficient GBM chemotherapeutic treatment. This hypothesis is based on our previous works about the development of mesoporous silica nanomaterials,[10-13] as well as the preliminary data demonstrating the GSH-responsive drug release from the nanoparticles. We believe with the success completion of the proposed project, we are on a solid ground to translate this platform into the preclinical setting, which might be extended to other solid tumor treatment rather than just for GBM treatment.

Research Approach. We aim to construct biomimetic nanoparticles for efficient drug delivery, which will prepare, optimize, and characterize the tumor-associated macrophage membrane coated biodegradable mesoporous silica nanoparticles (MSN), especially the following aspects: 1) the ability to cross BBB and targeting GBM in the brain; 2) high drug loading efficiency and tumor microenvironment-triggered precise drug release; 3) biodegradable MSN to eliminate the biotoxicity (Figure 1). We will evaluate the targeting ability and therapeutic efficiency of developed biomimetic nanoparticles in vitro with GBM cell. The first set of experiments will determine the cytotoxicity of the MMSN for two cell lines including U-87 and RAW 264.7 cells using MTT assay.We will also investigate the interaction between MMSN@Cy5 and U-87 cells and RAW 264.7 cells using fluorescence imaging and flow cytometry. The second set of experiments will construct the in vitro BBB transcytosis model to determine the penetration ability of MMSN@Cy5 for BBB in vitro and targeting ability toward cancer cells. Lastly, we will determine the GSH-triggered chemotherapeutic efficiency of the MMSN@TMZ for the U-87 cells in vitro. This will demonstrate the feasibility of our proposed active drug delivery system for GBM targeting therapy.

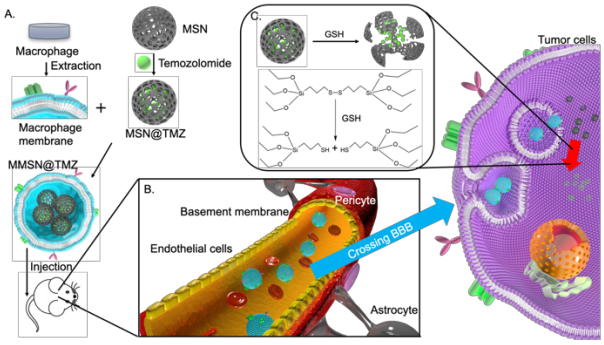

Figure 1. The macrophage membrane coated mesoporous silica nanoparticles (MMSN) will significantly improve the BBB penetration and target delivery the chemotherapeutic drugs into the GBM and will release the drugs upon the high concentration of GSH in the tumor microenvironment.

References

1. Chinot, O. L.; Wick, W.; Mason, W.; Henriksson, R.; Saran, F.; Nishikawa, R.; Carpentier, A. F.; Hoang-Xuan, K.; Kavan, P.; Cernea, D.; Brandes, A. A.; Hilton, M.; Abrey, L.; Cloughesy, T., Bevacizumab plus Radiotherapy–Temozolomide for Newly Diagnosed Glioblastoma. *New England Journal of Medicine* **2014,** *370* (8), 709-722.
2. Wen, L.; Wang, K.; Zhang, F.; Tan, Y.; Shang, X.; Zhu, Y.; Zhou, X.; Yuan, H.; Hu, F., AKT activation by SC79 to transiently re-open pathological blood brain barrier for improved functionalized nanoparticles therapy of glioblastoma. *Biomaterials* **2020,** *237*, 119793.
3. Hanif, F.; Muzaffar, K.; Perveen, K.; Malhi, S. M.; Simjee, S. U., Glioblastoma Multiforme: A Review of its Epidemiology and Pathogenesis through Clinical Presentation and Treatment. *Asian Pac J Cancer Prev* **2017,** *18* (1), 3-9.
4. Jensen, S. A.; Day, E. S.; Ko, C. H.; Hurley, L. A.; Luciano, J. P.; Kouri, F. M.; Merkel, T. J.; Luthi, A. J.; Patel, P. C.; Cutler, J. I.; Daniel, W. L.; Scott, A. W.; Rotz, M. W.; Meade, T. J.; Giljohann, D. A.; Mirkin, C. A.; Stegh, A. H., Spherical Nucleic Acid Nanoparticle Conjugates as an RNAi-Based Therapy for Glioblastoma. *Science Translational Medicine* **2013,** *5* (209), 209ra152.
5. Lombardi, G.; Rumiato, E.; Bertorelle, R.; Saggioro, D.; Farina, P.; Della Puppa, A.; Zustovich, F.; Berti, F.; Sacchetto, V.; Marcato, R.; Amadori, A.; Zagonel, V., Clinical and Genetic Factors Associated With Severe Hematological Toxicity in Glioblastoma Patients During Radiation Plus Temozolomide Treatment: A Prospective Study. *American Journal of Clinical Oncology* **2015,** *38* (5).
6. Zhang, Y.; Cai, K.; Li, C.; Guo, Q.; Chen, Q.; He, X.; Liu, L.; Zhang, Y.; Lu, Y.; Chen, X.; Sun, T.; Huang, Y.; Cheng, J.; Jiang, C., Macrophage-Membrane-Coated Nanoparticles for Tumor-Targeted Chemotherapy. *Nano Letters* **2018,** *18* (3), 1908-1915.
7. Zhen, X.; Cheng, P.; Pu, K., Recent Advances in Cell Membrane–Camouflaged Nanoparticles for Cancer Phototherapy. *Small* **2019,** *15* (1), 1804105.
8. Hadipour Moghaddam, S. P.; Yazdimamaghani, M.; Ghandehari, H., Glutathione-sensitive hollow mesoporous silica nanoparticles for controlled drug delivery. *Journal of Controlled Release* **2018,** *282*, 62-75.
9. Kong, M.; Tang, J.; Qiao, Q.; Wu, T.; Qi, Y.; Tan, S.; Gao, X.; Zhang, Z., Biodegradable Hollow Mesoporous Silica Nanoparticles for Regulating Tumor Microenvironment and Enhancing Antitumor Efficiency. *Theranostics* **2017,** *7* (13), 3276-3292.
10. Chen, J.; Li, X.; Wu, X.; Pierce, J. T.; Fahruddin, N.; Wu, M.; Zhao, J. X., Au–Silica Nanowire Nanohybrid as a Hyperthermia Agent for Photothermal Therapy in the Near-Infrared Region. *Langmuir* **2014,** *30* (31), 9514-9523.
11. Chen, J.; Wu, X.; Hou, X.; Su, X.; Chu, Q.; Fahruddin, N.; Zhao, J. X., Shape-Tunable Hollow Silica Nanomaterials Based on a Soft-Templating Method and Their Application as a Drug Carrier. *ACS Applied Materials & Interfaces* **2014,** *6* (24), 21921-21930.
12. Liang, S.; Zhao, Y.; Xu, S.; Wu, X.; Chen, J.; Wu, M.; Zhao, J. X., A Silica–Gold–Silica Nanocomposite for Photothermal Therapy in the Near-Infrared Region. *ACS Applied Materials & Interfaces* **2015,** *7* (1), 85-93.
13. Liu, X.; Wu, X.; Xing, Y.; Zhang, Y.; Zhang, X.; Pu, Q.; Wu, M.; Zhao, J. X., Reduced Graphene Oxide/Mesoporous Silica Nanocarriers for pH-Triggered Drug Release and Photothermal Therapy. *ACS Applied Bio Materials* **2020,** *3* (5), 2577-2587.