PURDUE UNIVERSITY | Department of Industrial and Physical Pharmacy

Industrial & Molecular Pharmaceutics Seminar

IPPH 69600

Monday, October 30, 2023
3:30 PM in RHPH 164

"Engineer CAR-neutrophils from human pluripotent stem cells for targeted chemoimmunotherapy against glioblastoma"

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Glioblastoma (GBM), the most common type of primary brain tumor, is characterized by high mortality rate, short lifespan, and poor prognosis with a high tendency of recurrence. Functional therapeutics, including PRMT5 inhibitors, radiosensitizers, and emerging chimeric antigen receptor (CAR)-T immunotherapy, have been developed to treat GBM. However, the existence of physiological blood-brain barrier (BBB) or blood-brain-tumor barrier has impeded the efficient delivery of such promising therapeutics into the brain and limited their therapeutic efficacy. Given the native ability of neutrophils to cross BBB and penetrate the brain parenchyma, here we tested the therapeutic concept that neutrophils could be engineered with synthetic CARs to specifically target GBM and effectively deliver chemo-drugs to brain tumor as a novel dual chemoimmunotherapy for the first time. Primary neutrophils are short-lived and resistant to genetic modification. Therefore, we genetically engineered human pluripotent stem cells with different chlorotoxin (CLTX) CARs and differentiated them into functional CAR-neutrophils. Systemically administered hPSC-derived CLTX CAR-neutrophils significantly reduced tumor burden in xenograft mouse models and extended their lifespan, suggesting superior abilities of neutrophils in crossing BBB and penetrating GBM xenograft in mice. We also loaded hypoxia-activated prodrug tirapazamine (TPZ) into CAR-neutrophils using silica nanoparticles with rough surfaces (R-SiO2-TPZ) and demonstrated their enhanced antitumor activities in xenograft mouse models, serving as a novel dual chemoimmunotherapy against GBM. Our results established that CAR neutrophil-mediated drug delivery may provide an effective and universal strategy for specific targeting of solid tumors.