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SEMINAR SERIES

Wednesday, May 3rd, 2023
Seminar Presentation: 11:00am – 12:00pm
SME room 248

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

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Abstract: 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. As compared to CAR-natural killer (NK) cells, 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.

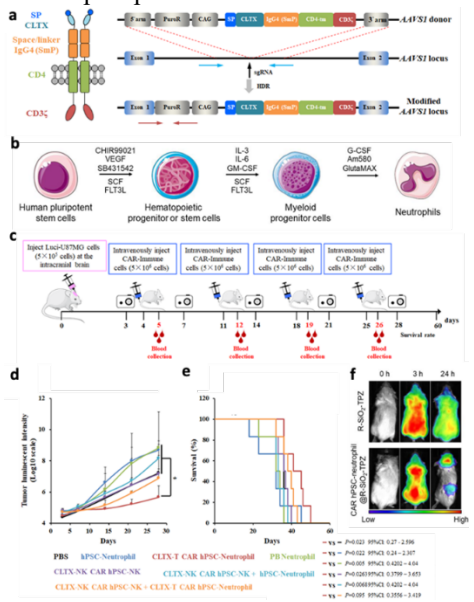

Fig. 1: a) Schematic of chlorotoxin (CLTX) CAR construct and targeted knock-in strategy at the AAVS1 safe harbor locus of human pluripotent stem cells (hPSCs). b) Schematic of optimized neutrophil differentiation from hPSCs under chemically-defined conditions. c) Schematic of intravenous injection of CAR-neutrophils and/or CAR NK cells for in vivo study. d) Time-dependent tumor burden was determined and quantified by bioluminescent imaging. e) Kaplan-Meier curve demonstrating survival of experimental mice. f) Time-dependent biodistribution of Cy5+ neutrophils and nanodrugs in whole body was determined by fluorescence imaging at the indicated hours.

Biosketch: Dr. Bao is currently an assistant professor at the Davidson School of Chemical Engineering and a member of Purdue Institute for Cancer Research. His research program at Purdue focuses on stem cell bioengineering and immunoengineering. Dr. Bao earned his B.S. degree from Tsinghua University in 2011 and his Ph.D. from University of Wisconsin-Madison in 2016. Prior to Purdue, Dr. Bao was a post-doc fellow at the University of California-Berkeley (2016 to 2018). Dr. Bao was recent awardees of Young Investigator Award 2022 of Cells Tissues Organs Journal, 2023 BMES-CMBE Rising Star Junior Faculty Award, NSF CAREER Award, NIH Stephen Katz Early Stage Investigator R01 Research Project Grant, Showalter Research Trust Young Investigator Award, and Purdue Cancer Center Robbers New Investigator Award.