

JOSEPH F. FOSTER MEMORIAL CHEMICAL BIOLOGY AND BIOCHEMISTRY SEMINAR

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3:30 PM, BRWN 4102**

“Use Of A Universal CAR T Cell To Simultaneously Kill Cancer Cells And Cancer-Associated Fibroblasts”



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Abstract:

Chimeric antigen receptor (CAR) T cell therapies have shown significant efficacy in treating hematologic cancers, but their ability to eliminate solid tumors has been limited. One potential reason for this difference could be the immunological and physical barriers presented by cancer-associated fibroblasts (CAFs). These CAFs, constituting a substantial portion (15-85%) of non-tumor cells in a tumor mass, have been correlated with poor patient survival. CAFs hinder CAR T cell efficacy by releasing immunosuppressive cytokines, promoting tumor cell growth, and creating fibrotic obstacles that prevent CAR T cell penetration into tumors. Unsurprisingly, numerous researchers are actively exploring strategies to suppress or remove CAF-related activities within the tumor microenvironment (TME). An interesting target for CAR T cell therapy is fibroblast activation protein (FAP), which is uniquely present on CAF surfaces. In this study, we developed an innovative, highly specific small molecule that targets FAP to guide our universal CAR T cells towards CAFs. For this purpose, we utilized a previously designed CAR incorporating a classical structure except for the extracellular single-chain variable fragment (scFv) that specifically binds to fluorescein instead of a traditional tumor antigen. Through a bispecific adaptor connecting fluorescein to our FAP ligand (FAPL), an interaction forms between the anti-fluorescein CAR on the T cell and FAP on the CAF. This then leads to the creation of an immunological synapse between the CAR T cell and CAF, triggering the destruction of CAFs and the proliferation of CAR T cells. Notably, this CAR T cell design also allows for the simultaneous use of a second bispecific adaptor (fluorescein attached to a cancer-specific ligand), enabling the same CAR T cells to eliminate neighboring cancer cells. To validate whether this universal CAR T cell can indeed eliminate both cancer cells and CAFs simultaneously, we implanted KB cells (a cell line representing an immunologically "cold" solid tumor expressing folate receptor (FR)) into NSG mice. We then assessed the toxicity of CAR T cells in the presence of one or both bispecific adaptors. While administering universal CAR T cells followed by intravenous injection of an FR-targeting bispecific adaptor achieved significant anti-tumor effects, co-administration of a FAP-targeted bispecific adapter notably enhanced this efficacy without observable toxicity. Examination of tumor masses during treatment revealed that the FAP-targeted bispecific adapter not only facilitated CAF elimination but also improved CAR T cell infiltration and activation. In summary, the use of bispecific adaptors in conjunction with universal CAR T cells presents a unique avenue to simultaneously eradicate cancer cells and CAFs, thereby enhancing the overall performance of CAR T cells in treating solid tumors.



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