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POINT OF VIEW

Commentary: IL-12-secreting tumor-targeted chimeric antigen receptor T cells: An unaddressed concern on Koneru et al. (2015)

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ABSTRACT

To date, chimeric antigen receptor (CAR) T cells have shown remarkable responses in patients with certain hematological malignancies particularly acute lymphocytic leukemia (ALL), but have led to more limited success with solid tumors probably due to immunosuppressive networks in the tumor environment. To overcome this issue, Koneru et al. have recently demonstrated IL-12-producing CAR T cells, also known as armored CAR T cells, to simultaneously target both ovarian tumor cells and their microenvironment. This commentary challenges the study design of Koneru et al. study and highlights the importance of choosing the most appropriate experimental animal model in preclinical cancer studies.

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For years, the cornerstones of cancer treatment have been surgery, chemotherapy, and radiation therapy. Over the last decade, targeted therapies have also emerged as standard treatments for a number of cancers. And now, despite years of starts and stutter steps, excitement is growing for therapies that harness the power of a patient's immune system to combat their disease. One approach to immunotherapy involves engineering patients' own T cells, known as CAR T cells, to recognize and attack their tumors. Although this approach has been restricted to small clinical trials so far, treatments using these engineered immune cells have made some remarkable strides in treatment of patients with advanced cancers like relapsed or refractory acute lymphoblastic leukemia (ALL) and lymphoma.[1,2] Recently, Koneru et al. have demonstrated anti-ovarian cancer effect of IL-12-producing CAR T cells both *in vitro* and *in vivo*.[3] However, we have concern about the study design used by the authors. In fact, the aim of the study was to design and generate CAR T cells not only target MUC-16^{ecto}-expressing human ovarian tumor cells but also secrete IL-12 to modulate/diminish immunosuppressive effects of ovarian tumor microenvironment which is generated and/or induced by the tumor cells and is mainly accumulated by immunosuppressive cells including regulatory T cells (Tregs), myeloid derived-suppressor cells (MDSCs), M2 tumor-associated macrophages (TAMs) and a wide spectrum of soluble/insoluble immunosuppressive molecules such as TGF-β, IL-10, IDO, PG-E2, FasL, PD-L1, and etc.[4,5] The authors supposed that IL-12-producing CAR T cells could overcome immunosuppressive effects of tumor microenvironment, thereby enhancing antitumor effect of immunotherapy through multiple mechanisms including reversing anergy in tumor-infiltrating cells (TILs), stimulation of IFNγ and TNF-α production from T cells and NK cells, inhibition of Treg-mediated suppression of antitumor effector functions of T cells, enhancement of the cytotoxic activity of NK cells and CD8$^+$ cytotoxic T lymphocytes and their recruitment to the tumor site, inhibition of the production of immunosuppressive cytokines such as IL-10 and TGF-b by tumor associated myeloid cells.[6] To verify the expression of the IL-12 by IL-12-expressing CAR T cells *in vivo*, authors measured the secretion of human IL-12 (p70) by MUC-16^{ecto}-specific CAR T cells (4H11–28z) and armored MUC-16^{ecto}-specific CAR T cells (4H11–28z/IL-12) in serum of CAR T cell treated -SCID-Beige mice (with impaired lymphoid development and reduced NK cell activity but normal macrophage and dendritic cells) with established ovarian tumors using a luminex assay.[7] However, the authors did not pay attention to an important point where SCID-Beige mice have normal macrophages and dendritic cell populations and these cells are endogenous sources of IL-12 production (mouse IL-12, mIL-12) upon tumor challenge. In fact, after tumor challenge and tumor antigen recognition, these cells could produce mIL-12. Therefore, concentration of indicated serum IL-12 might be consisted of both endogenous and exogenous IL-12 and it does not solely reflect IL-12 produced by armored CAR T cells. Moreover, since mIL-12 (but not human IL-12) acts on both mouse and human cells therefore the authors should have ruled out endogenous sources of IL-12 using SCID-Beige IL-12$^{-/-}$ mice to gain more reliable data. We believe that the experiments should be performed to measure IL-12 and its consequent effects on IFNγ production in a more reliable *in vivo* context such as SCID-Beige IL-12-knockout mice. In conclusion, advanced preclinical mouse models have a central role in linking basic discovery research with the translational development of novel therapeutic strategies, and the findings can be extrapolated to cancer disease in humans as well as to prevent experimental artifact and to avoid misinterpretation of results, investigators

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must carefully consider the focus of study and experimental design when choosing an animal model to ensure that the species is the most appropriate model.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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