M & I
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University of North Carolina at Chapel Hill

DISSERTATION SEMINAR

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"CD30-Redirected Chimeric Antigen Receptor T Cells Target Embryonal Carcinoma Via Antigen-Dependent and Fas/Fasl Interactions"

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2004 Marsico Hall

Dissertation Advisor: Dr. Gianpietro Dotti

Presented in partial fulfillment of the requirements for the degree of Doctor of Philosophy

Abstract

Lee K. Hong: : CD30-Redirected Chimeric Antigen Receptor T Cells Target Embryonal Carcinoma via Antigen-dependent and Fas/FasL Interactions
(Under the direction of Drs. Gianpietro and Savoldo)

Embryonal carcinomas (ECs) and mixed testicular germ cell tumors (TGCTs) containing EC express CD30 and are the most aggressive TGCT subtypes. Chimeric antigen receptor T cells (CAR-Ts) combine the cytotoxic properties of T cells with the antigen specificity of monoclonal antibodies to target antigen-expressing cells, such as infected or cancerous cells. CAR-Ts targeting CD30 (CD30.CAR-Ts) have shown robust anti-tumor activity against Hodgkin's lymphoma, but have not been tested against solid tumors. We tested whether CD30.CAR-Ts could also target ECs using *in vitro* and *in vivo* models. CD30.CAR-Ts exhibited anti-tumor activity *in vitro* against the human EC cell lines Tera-1, Tera-2 and NCCIT, and putative EC stem cells identified by Hoechst dye staining. Cytolytic activity of CD30.CAR-Ts was complemented by sustained proliferation and pro-inflammatory cytokine production. CD30.CAR-Ts also demonstrated anti-tumor activity in an in vivo xenograft NSG mouse model of metastatic EC. Remarkably, we observed that CD30.CAR-Ts, while targeting $CD30^+$ EC tumor cells through the CAR (i.e. antigen-dependent targeting), also eliminated surrounding $CD30^-$ EC cells in an antigen-independent manner via cell-cell contact-dependent Fas/FasL interaction. In addition, inducing Fas (CD95) expression in $CD30^+$ but Fas^- EC was sufficient to improve CD30.CAR-T anti-tumor activity. Overall, these data suggest that CD30.CAR-Ts can be used as a novel immunotherapy for ECs. Additionally, Fas/FasL interaction between tumor cells and CAR-Ts can be exploited to reduce tumor escape due to heterogeneous antigen expression or to improve CAR-T anti-tumor activity.