Novel Immunotherapies targeting BAFF-receptor for drug-resistant B-cell lymphoma and leukemia.

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I. Abstract

Monoclonal antibody (mAb) and chimeric antigen receptor (CAR) T-cell therapies have demonstrated promising clinical outcomes treating hematological malignancies. However, disease relapse remains problematic and likely caused by loss of therapeutic targets on tumors.[1] Thus, novel immunotherapies against alternative targets are urgently needed. We developed a new therapeutic mAb against B-cell activating factor receptor (BAFF-R), a tumor necrosis factor primarily expressed on B cells and B-cell lymphoma and leukemia.[2] The mAb induced antibody-dependent cellular cytotoxicity against a panel of human B-cell tumor lines and primary tumors including samples from relapse after rituximab treatment. Potent *in vivo* antitumor effects were observed on two drug-resistant human lymphoma models (rituximab- and ibrutinib-resistant lymphomas) resulting in eradication of implanted tumors and long-term, tumor-free survival (P<0.001).[3] Adapting the antibody binding domain, we developed a BAFF-R CAR containing CD3ζ and 4-1BB intracellular signaling domains. BAFF-R CAR-T cells had significant activation and killing against various malignant B-cell lines and primary tumors (NHLs, acute lymphoblastic leukemias, and chronic lymphocytic leukemias), *in vitro*. Tumor eradication and tumor-free survival was repeatedly observed in human lymphoma xenograft models including mantle cell (JeKo-1, Z-138) and Burkitt (Raji) lymphomas in NSG mice (P<0.01). Moreover, our BAFF-R CAR-T therapy eradicated CD19KO Z-138 tumors that is resistant to CD19-CAR treatment in NSG mice (*P<0.01 Figure). Altogether, our results strongly support the translational significance of our novel BAFF-R targeting immunotherapies, particularly for the major unmet clinical need of drug-resistant relapses in B-cell lymphoma and leukemia.

II. Image:

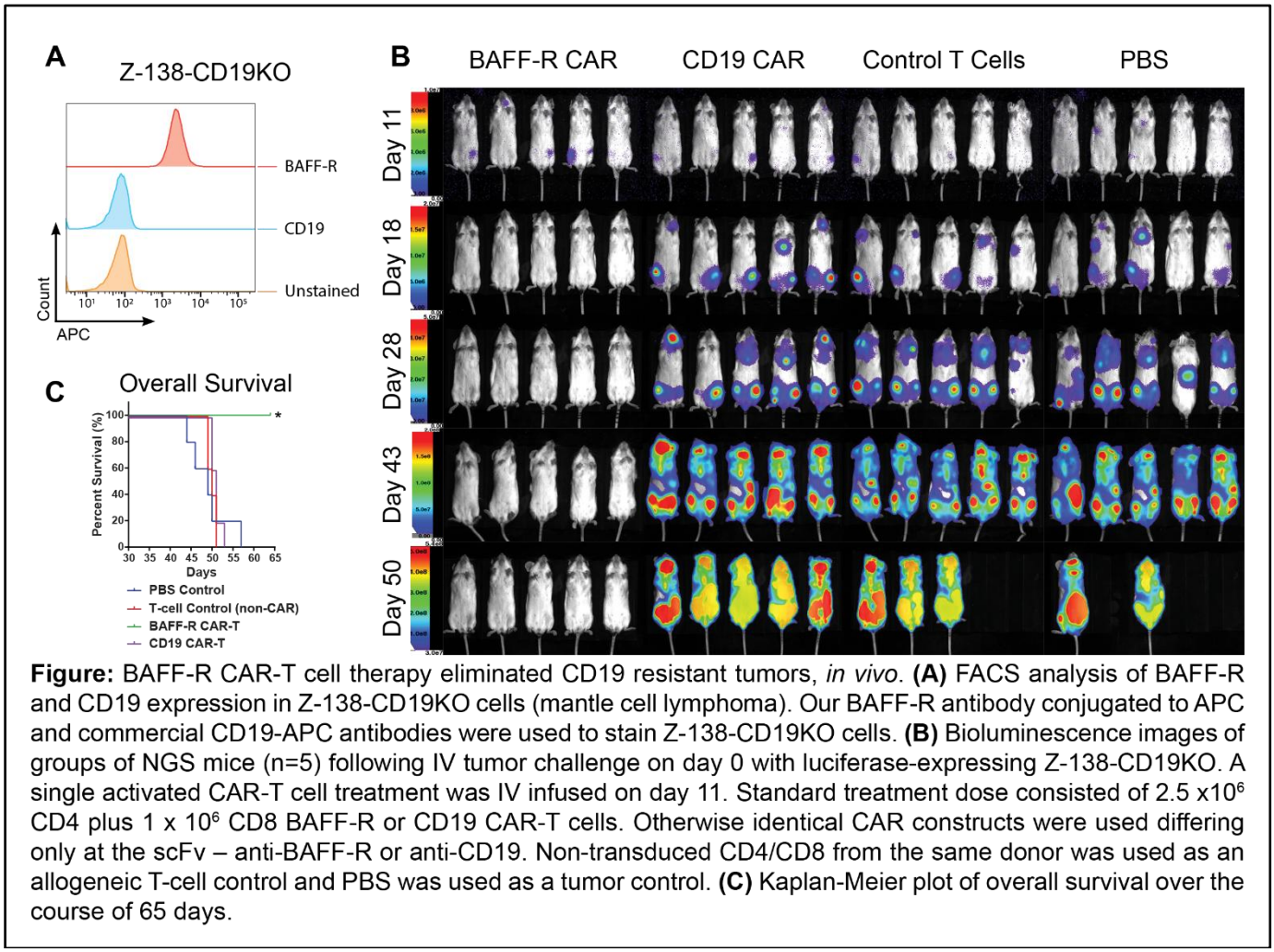


Figure: BAFF-R CAR-T cell therapy eliminated CD19 resistant tumors, *in vivo*. **(A)** FACS analysis of BAFF-R and CD19 expression in Z-138-CD19KO cells (mantle cell lymphoma). Our BAFF-R antibody conjugated to APC and commercial CD19-APC antibodies were used to stain Z-138-CD19KO cells. **(B)** Bioluminescence images of groups of NGS mice (n=5) following IV tumor challenge on day 0 with luciferase-expressing Z-138-CD19KO. A single activated CAR-T cell treatment was IV infused on day 11. Standard treatment dose consisted of 2.5 x10^6 CD4 plus 1 x 10^6 CD8 BAFF-R or CD19 CAR-T cells. Otherwise identical CAR constructs were used differing only at the scFv – anti-BAFF-R or anti-CD19. Non-transduced CD4/CD8 from the same donor was used as an allogeneic T-cell control and PBS was used as a tumor control. **(C)** Kaplan-Meier plot of overall survival over the course of 65 days.

III. References:

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IV. Biography:

Dr. Hong Qin currently serves as Associate Professor in the Toni Stephenson Lymphoma Center at City of Hope in Duarte, California and he has been developing novel immunotherapies for over 15 years. Since completing his PhD in 2003 at the University of Western Ontario, Canada and post-doctoral fellowship in 2008 at MD Anderson Cancer Center in Huston, Texas, Dr. Qin has demonstrated his broad experience in immunology by developing cancer vaccine, monoclonal antibody, and CAR-T cell therapies.

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