DNA vaccine co-expressing *Her2/ErbB2* antigen, fused with LAMP, elicits strong antitumor effects *in vivo* by increasing tumor infiltration with CD8⁺ T cells

Renhuan Xu, Anthony Marketon, Greg Wilson, Yoshimi Johnson, Juliete Macauley and Teri Heiland
Immunomic Therapeutics, 15010 Broschart Road, Rockville, MD 20850

Abstract

DNA vaccine has emerged as an attractive immunotherapeutic approach against infectious diseases and cancer due to their fast, efficient design and validation. It remains, however, a challenge in clinical settings due to historically low levels of immunogenicity in humans.

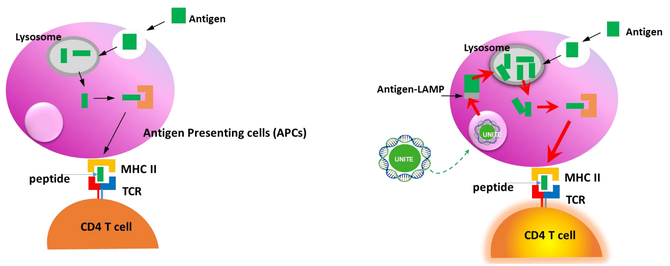
In order to enhance the immunogenicity of DNA vaccines used as a cancer therapy, we have developed a nucleic acid platform, UNITE™ (UNiversal Intracellular Targeted Expression), which combines novel delivery methods and adjuvants that complement our lysosomal targeting technology. Fusing a tumor associated antigen (TAA) with the Lysosomal Associated Membrane Protein 1 (LAMP-1), we can activate Ag specific CD4+ T cells by targeting the major histocompatibility complex II compartment. In this study, we selected ErbB2/Her2 as the cancer target because it is a broadly overexpressed and well-characterized oncoantigen.

Mice vaccinated with Her2-LAMP DNA demonstrate robust Her2-specific CD4+ and CD8+ T cells, in addition to antibody responses, which in turn have significant antitumor effect in murine breast and bladder tumor models. Moreover, we demonstrate that the Her2-LAMP vaccine promotes CD8+ T cell tumor infiltration to a greater degree than when compared to a traditional DNA vaccine without LAMP. In summary, we demonstrate that a UNITE™ nucleic acid vaccine can enhance antitumor immunity in vivo.

Introduction

- The platform of UNITE™-VAX utilizes a plasmid DNA expressing TAAs and LAMP to deliver TAAs to the MHC II compartment, which potentially enhances both antibody generation and CD4⁺ T cell response.
- Based on our previous studies, we hypothesize that LAMP can rapidly prime and activate antigen-specific CD4⁺ T cells and these activated CD4⁺ T cells play an essential role for the function and infiltration of CD8⁺ T cells into tumor sites.

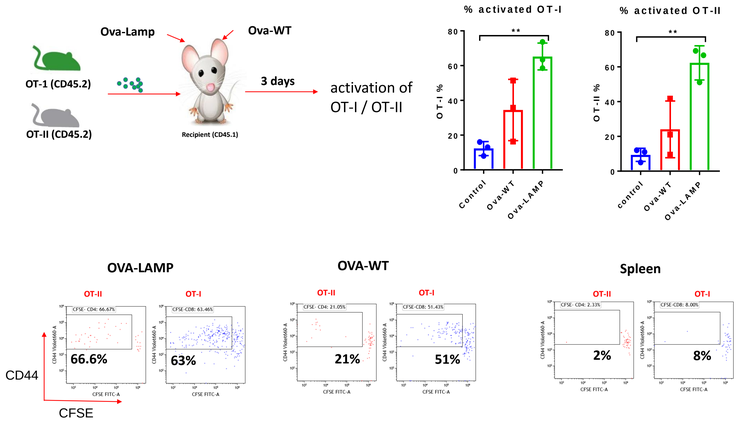
UNITE™ platform: Unique Mechanism of Action



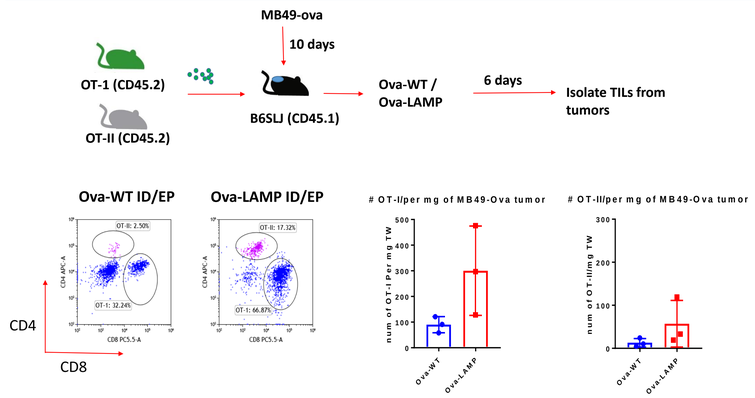
A classic activation of CD4 T cells is initiated by APC cells to present Ag to MHC II molecule after taking up and processing extracellular Ag.

LAMP-DNA mediated activation of CD4 T cell can be achieved by APC cell processing **endogenous Ag**

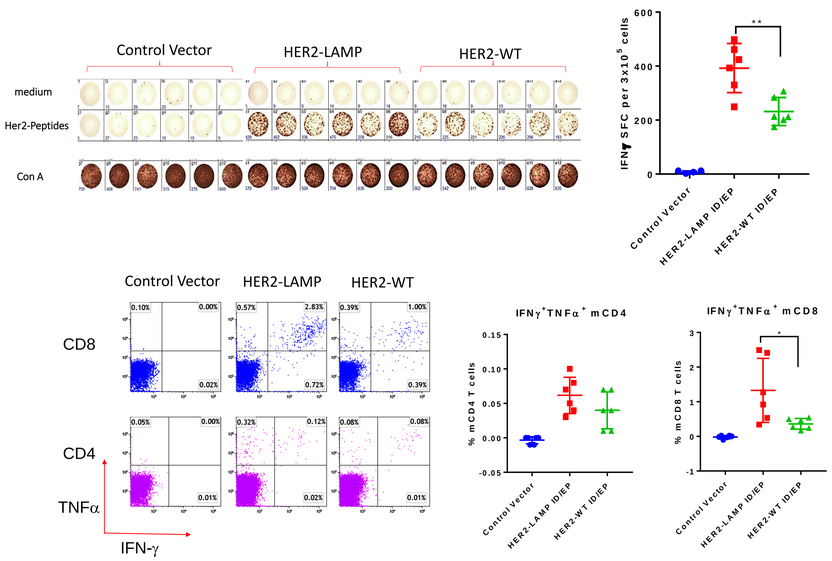
OVA-LAMP DNA vaccine rapidly activates Ag-specific CD4⁺ and CD8⁺ T cells in the draining LNs



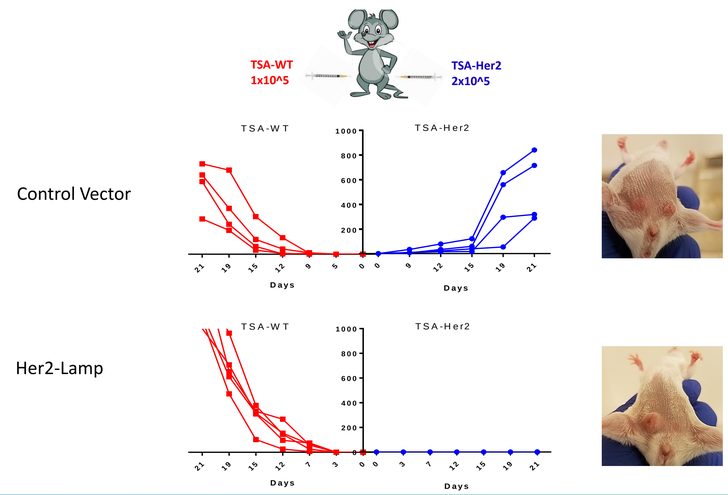
LAMP DNA vaccine promotes tumor infiltration with antigen-specific CD8⁺ T cells



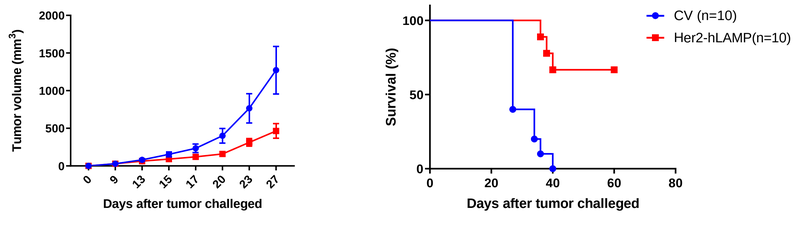
In vivo immunogenicity study demonstrates that HER2-LAMP DNA elicits robust Her2-specific T cell



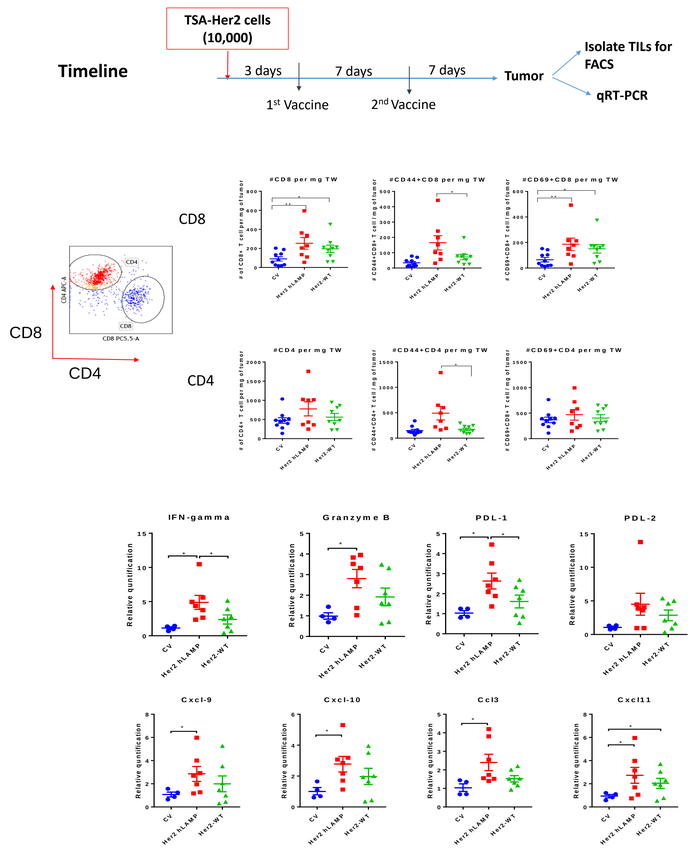
Prophylactic study: HER2-LAMP DNA efficiently protected mice from Her2-expressing breast tumor with Her2-specific T cells



Therapeutic study: HER2-LAMP DNA vaccine significantly suppressed HER2-expressing breast tumor growth and improved survival



HER2-LAMP significantly promotes tumor infiltration with activated CD8⁺ T cells, upregulates T cell recruiting chemokines but also increases the expression of PDL1



Conclusions

- HER2-LAMP DNA vaccine elicits robust Her2-specific CD4+ and CD8+ T cell responses in vivo, which in turn have significant antitumor effect in murine breast tumor model.
- Her2-LAMP DNA vaccine significantly promotes tumor infiltration with activated CD8+ T cells suggesting LAMP benefits CD8 T cell infiltration.
- The expression of PDL1 in tumor microenvironment (TME) is upregulated with HER2-LAMP vaccine suggesting combination Her2-LAMP with PD1/L1 blockage could have the potential to increase the therapeutic effect.

Contact

Name: Renhuan Xu
Immunomic Therapeutics
Email: rxu@immunomix.com
Website: www.immunomix.com

References

- Ahrends T, Spanjaard A, Pilzecker B, Bąbała N, Bovens A, Xiao Y, Jacobs H, Borst J. CD4(+) T Cell Help Confers a Cytotoxic T Cell Effector Program Including Coinhibitory Receptor Downregulation and Increased Tissue Invasiveness. Immunity. 2017 Nov 21;47(5):848-861.e5.
- Spitzer MH, Carmi Y, Reticker-Flynn NE, Kwek SS, Madhireddy D, Martins MM, Gherardini PF, Prestwood TR, Chabon J, Bendall SC, Fong L, Nolan GP, Engleman EG. Systemic Immunity Is Required for Effective Cancer Immunotherapy. Cell. 2017 Jan 26;168(3):487-502.e15.

Acknowledgments

We would like to acknowledge Dr. Zachary C. Hartman and Alan Chen (Department of Surgery, Duke University Medical Center) for their scientific consultation and for various reagents.