Finding the Best Dosing Ratio to Predict Optimal Anti-Tumor Response

A. d28/d0

B. Generation of Memory and Effector T-cell Populations

Vikas Tahiliani, Jayalakshmi Miriyala, Patrick Dillon, Jason Rose, Louise Giffin, Jeff Hutchins, Matthew M Seavey*

Poster# 5744

Heat Biologics’ technology is focused on developing a next generation cellular vaccine that incorporates a tumor antigen chaperoned (gp96-Ig) with T-cell costimulation (HS-110-Ig) into a single tumor vaccine. Vaccination with HS-110-Ig (d0) and gp96-Ig (d28) in a human and allogeneic cell line, stably transfected to express gp96, is being tested in a Phase 2 clinical trial (NCT02439450) with checkpoint inhibition for NSCLC. A similar line is being generated with checkpoint inhibition (d0) and complementary HS-110-Ig (d28). To model how the addition of human gp96-Ig to HS-110-Ig may impact and tumor rejection, we adapted Nicchitta’s system (Nature Rev Immunol 2003; Vol 3, May) to include a new generation of tumor-bearing mice and a novel analysis system that treats tumor-bearing animals with mouse-matched irradiated mouse cancer cell lines (melanoma: B16F10) expressing gp96-Ig (mHS-110) and OX40L-Ig (mHS-130) both expressing adalimumab (ADA), in our model tumor-humans-associated antigens.

Single dose vaccination with escalating doses of 300 ng to 3000 ng of secreted gp96-Ig provided sufficient anti-tumor CD8+ T-cell expansion, with the greatest expansion observed on day 1, post-infection. To identify the best ratio of mHS-110 to mHS-130, a dose ratio study was performed. Fixed numbers of mHS-110 (300 ng secreted gp96-Ig) were matched with different ratios of mHS-130 (gp96-Ig). Similar to our single dose vaccination with escalating doses of 300 ng to 3000 ng of secreted gp96-Ig, we observed the greatest expansion of CD8+ T cells on day 1, post-infection, and that the addition of mHS-110 further boosted anti-tumor CD8+ T-cell expansion by 3-fold when the ratio of mHS-110 to mHS-130 was at a 1 to 0.5 ratio (300 ng secreted gp96-Ig to 150 ng secreted OX40L-Ig). These ratios were subsequently boostied at days post-infection, and we clearly found that the 1 to 4.5 ratio of mHS-110 to mHS-130 gave the maximum expansion of CD8+ T-cell responses, peaking on day 28 and contracting thereafter. Importantly, these ratios led to higher frequencies of antigen-specific CD8+ T cells at both priming and boosting, which enhanced rejection of established lethal tumors and increased overall animal survival.

**p<0.01, ***p<0.001, 'ns' p>0.05, not significant.