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INHIBIGEN™ ADMINISTRATION PROMOTES ABERRANT T CELL RESPONSES IN CANCER BUT MAY BE BENEFICIAL FOR AMELIORATION OF AUTOIMMUNE DISEASE

Victoria DeVault*, Hanna Starobinets, Julie Arnold, Stephanie Rinaldi, Charley Hubbard, Osaruese Odeh, Cindy Nguyen, Laura Apolloni, Dmitry Lineker, Jessica Flechtner, Hubert Lam. *Genocea Biosciences, Cambridge, MA, United States*

Background Selecting neoantigens that generate robust anti-tumor T cell responses remains a challenge for cancer immunotherapy design. The ATLAS™ platform, a functional recall assay using patient autologous cells, identifies both stimulatory and inhibitory (Inhibigen) neoantigens via up- or downregulation of T cell cytokine secretion.¹ We propose that stimulatory neoantigens are ideal targets for cancer vaccines and T cell therapies. In contrast, data suggest that Inhibigens be excluded, due to their association with accelerated tumor growth and dampened immunity in a murine melanoma model.² While detrimental to cancer immunotherapy, the Inhibigen-associated downregulation of cytokine production may be beneficial in the context of autoimmunity.

Methods ATLAS screens were performed as previously described.^{1,2} Peptide vaccines containing tumor-specific neoantigens ± Inhibigens were evaluated in prophylactic and therapeutic B16F10 melanoma tumor models for immunogenicity and efficacy. RNAseq analysis was performed on T cells sorted from draining lymph nodes of vaccinated tumor-bearing mice. For experimental autoimmune encephalomyelitis (EAE) studies, mice were administered a vaccine containing MOG peptide ± the melanoma MMP9_{FS} Inhibigen. Immune responses and phenotypic analyses for both models were measured by flow cytometry, ELISPOT, and immunohistochemistry.

Results In the melanoma model, inclusion of the Inhibigen MMP9_{FS} accelerated tumor growth in a non-dose dependent manner and abrogated immune responses. RNAseq of T cells from tumor-bearing mice vaccinated with MMP9_{FS} showed a higher level of differentially expressed genes (adjusted P value of <0.05) in TCR-signaling regulation and suppressor GO pathways (>5 distinct pathways/gene) as compared to stimulatory controls, indicating Inhibigen-specific effects on T cells. In the EAE model of autoimmunity, animals treated with MOG peptide + MMP9_{FS} exhibited dampened anti-MOG immune responses, delayed disease onset, reduced disease incidence and scoring (average 1 vs. 3) and decreased spinal cord immune infiltration as compared to control vaccination. These data indicate that Inhibigen administration has the potential to ameliorate autoimmune sequelae, independent of cognate antigen expression.

Conclusions Functional identification and exclusion of Inhibigens from cancer immunotherapies may be critical to protective immunity since their inclusion can result in quelling of otherwise beneficial immune responses. Conversely, Inhibigen-specific responses can dampen destructive autoimmune sequelae. Mechanistic studies show altered T cell signaling pathways in the context of therapeutic Inhibigen vaccination. These data suggest that Inhibigen-specific responses, while detrimental for the treatment of cancer, may have a therapeutic benefit in other disease contexts.

REFERENCES

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Ethics Approval All animal studies were undertaken in conformity with the Cambridge, MA Ordinance 1086 of the city's Municipal Code and in accordance with the policies and protocols approved by Genocea's Institutional Animal Care and Use Committee (IACUC).

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