749 A NOVEL TRANSLATIONAL MOUSE MODEL FOR ASSESSMENT OF HUMAN STING-TARGETING THERAPIES

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Background Although Immune checkpoint inhibitors (ICI)-targeting therapies have revolutionized the treatment of cancer, several tumors do not respond to those therapies. Preclinical and clinical evidences suggest that STING is a promising target to improve the immunogenicity of tumors, turning them responsive to ICI, and enhancing anti-tumor response. DMXAA failed to show efficacy in clinical trials, despite its encouraging anti-tumor response in preclinical phase, highlighting the need of accurate translational preclinical models. On top of the specificity barrier reported for STING-targeting agents, the heterogeneity of STING variants and their variability in the response to STING-targeting therapies, brings another level of complexity in preclinical evaluation of anti-STING therapies. Here, we report the generation of STING humanized (hSTING) mouse models enabling the in vivo assessment of STING-targeting agents.

Methods Human STING variants show a high heterogenicity and population stratification. Different variants, and isoforms, respond differently to STING agonists. We developed mouse models expressing the main human STING variants and isoforms found in the population to recapitulate this complexity. Human STING was inserted by knock-in at the endogenous locus to enable a physiological expression pattern of STING while invalidating the mouse gene. Herein, we will focus on the human STING full length H323 model.

Results T and B lymphocytes, NK, DCs and monocytes frequence in the spleen, bone marrow and blood were found to be similar in hSTING and WT mice, suggesting that the humanization of STING did not alter the immune cell distribution in these compartments. These cells express human STING, while no expression of mouse STING was observed. Splenocytes isolated from hSTING and WT mice produced IL-6 and IFN-γ upon activation with 2'3'-cGAMP, a cyclic dinucleotide with activity towards both mouse and human STING. Similarly, a mouse and human STING agonist induced the activation of DCs in both hSTING and WT mice, as observed by the increased expression of CD80/CD86 on DCs ex vivo and in vivo. Moreover, systemic production of IL-6, IFN-γ and TNF-α in response to this STING agonist was observed and suggest that human STING is functional in hSTING mice. As expected, hSTING mice did not respond to activation with DMXAA in vivo, whereas this agonist induced the systemic production of cytokines and activation of DCs in WT mice.

Conclusions The novel hSTING model described here supports the assessment of human STING-targeting agents in immuno-oncology and inflammation. Intercrosses of this model with ICI humanized models could support the assessment of combination therapies

http://dx.doi.org/10.1136/jitc-2021-SITC2021.749