T cells by anti-CD8 mAbs from day 29 onwards, and maintained weekly, as in this model CD8+ T cells are the main hapten responder population. Samples were collected for histochemistry and analyzed by flow cytometry.

Results Our data indicate that despite the depletion of circulating T cells, anti-PD-1 recipients mount a higher initial recall response to contact agents. Higher ear swelling was observed with increased inflammation in these mice. Our data suggest anti-PD-1 can liberate local T cell responses in the absence of a contribution from blood, and may offer a model to test therapeutic interventions to alleviate peripheral immune toxicities.

Conclusions Our results suggest that this murine model of contact hypersensitivity represents a potential model for skin immune checkpoint toxicities. This model of locally-mediated inflammatory recall may advance the goal of uncoupling toxicity from efficacy in patients with immune-related adverse events.

Ethics Approval The animal study was approved by Weill Cornell Medicine's IACUC; approval number D16-00186.

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http://dx.doi.org/10.1136/jitc-2020-SITC2020.0646

647 EVALUATION OF EFFICACY AND TOXICITY OF CD137 IMMUNOTHERAPY WITH URELUMAB-MIGG1 CHIMERIC ANTIBODY IN CD137 HUGEMM™

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Background CD137 (4-1BB) is a powerful T cell co-stimulatory molecule belonging to the TNF receptor superfamily, which promotes cytotoxic T cell survival and memory formation upon CD137L ligation. CD137 has become an attractive immuno-oncology therapeutic target with multiple agonistic antibodies in clinical trials, including urelumab and utomilumab, with promising response in combination with anti-PD1 immunotherapies such as nivolumab. Clinical applications of CD137 agonistic antibodies are hampered, however, by dose-limiting off-tumor liver toxicity (urelumab) or lower efficacy (utomilumab). The cause of liver toxicity is reported primarily to be due to Fcγ receptor mediated cross linking;[1–3] CD137 agonistic antibodies may also trigger hepatotoxicity through activation of IL-27 secreting liver Kupffer cells and monocytes.[4] The remaining challenge in decoupling efficacy from liver toxicity is the lack of preclinical mouse models which can be used to assess both efficacy and the immune-related adverse events (irAE) of human CD137 agonistic antibodies.

Methods To mimic the clinical outcomes of urelumab, we utilized humanized CD137 knock-in mice in Balb/c background (Balb/c CD137 HuGEMM) to evaluate its efficacy with CT26.WT syngeneic tumors. Liver toxicity was analyzed by monitoring fasting serum ALT/AST levels at different time points.

Results Urelumab showed moderate anti-tumor response at the dose level of 5 mg/kg, while serum ALT/AST levels showed no difference compared to isotype control suggesting that, due to the different binding capacity of the human IgG4 Fc domain to mouse FcγR, the human version of the agonistic antibody cannot fully recapitulate its effect on HuGEMM mice. Therefore, a chimeric antibody with mouse IgG1 Fc domain (urelumab-mIgG1) was created to dissect the potential role of FcγR mediated cross linking on both efficacy and liver toxicity; an urelumab-mIgG1-DANA variant with D265A/N297A mutation to abolish Fc effector function was also included as a dominant negative control. We found that urelumab-mIgG1 showed further enhanced efficacy compared to urelumab alone through FcγR mediated cross linking, while urelumab-mIgG-DANA showed compromised anti-tumor response. With regards to liver toxicity, urelumab-mIgG1 caused chronic liver inflammation and hepatocyte damage indicated by immune cell infiltration in the liver and significantly elevated serum ALT levels, which was abolished by the urelumab-mIgG1-DANA variant. The study also compared urelumab treatment in CD137 HuGEMM head-to-head with the mouse surrogate agonistic antibody (3H3) in wild-type BALB/c mice. 3H3 showed robust tumor growth inhibition as well as dramatic ALT elevation.

Conclusions We faithfully recapitulated the clinically observed tumor growth inhibition and liver toxicity of urelumab by using a chimeric version of urelumab in CD137 HuGEMM, indicating the importance of both the mouse model and antibody version in evaluation of efficacy and irAE.

Ethics Approval Animal experiments were conducted in accordance with animal welfare law, approved by local authorities, and in accordance with the ethical guidelines of CrownBio (Taicang).

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