18 GENERATION AND VALIDATION OF HUMANIZED GARP/TGFB1 MICE FOR TESTING NOVEL ANTI-HUMAN GARP ANTIBODIES

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Background Checkpoint inhibitors targeting PD-1 or PD-L1 are at the forefront of cancer immunotherapy, however, treating tumors that have primary or acquired resistance to PD-1/PD-L1 blockade therapy remains a challenge. In an effort to overcome drug resistance to anti-PD-1 therapy, studies have derived an anti-mouse GARP:TGF-β1 monoclonal antibody that inhibits the release of active TGF-β1 by mouse regulatory T cells (Tregs), which ultimately reduced mouse tumor growth via selective inhibition of Treg function.[1] Tregs play an immunosuppressive role in the tumor microenvironment (TME), such that altering or depleting Treg function has emerged as an important anti-tumor strategy. Collectively, this suggests a need for preclinical models that support Treg-targeted therapies.

Methods To address this, Biocytogen developed a double humanized (B-hGARP/hTGFB1) mouse model to evaluate *in vivo* efficacy of combination therapies. In this model, using gene editing technology, the full-length coding sequences of human GARP and human TGFB1 replaced murine Garp and murine Tgfb1. GARP and TGFB1 protein expression was analyzed in B-hGARP/hTGFB1 mice by flow cytometry. We also analyzed the distribution of leukocyte subpopulations in B-hGARP/hTGFB1 mice compared to wild-type mice by flow cytometry. Lastly, we used an MC38 tumor model to assess the efficacy of an anti-human GARP/latent-TGFβ1 antibody.

Results Flow cytometry confirmed human GARP and TGFB1 protein expression in B-hGARP/hTGFB1 mice. Additionally, the distribution of basal leukocyte subpopulations of blood, spleen, and lymph nodes in humanized B-hGARP/hTGFB1 mice was similar and comparable to those in wild-type C57BL/6 mice as assessed by flow cytometry. Finally, combination therapy using anti-human GARP/latent-TGFβ1 and anti-mouse PD-1 antibodies was effective in controlling MC38 tumor growth in B-hGARP/hTGFB1 mice.

Conclusions This line provides a powerful preclinical model for *in vivo* anti-human GARP/latent-TGFβ1 therapeutic antibody evaluation.

REFERENCE

1. de Streel G, Bertrand C, Chalon N, Liénart S, Bricard O, Lecomte S, Devreux J, Gaignage M, De Boeck G, Mariën L, Van De Walle I, van der Woning B, Saunders M, de Haard H, Vermeersch E, Maes W, Deckmyn H, Coulie PG, van Baren N, Lucas S. Selective inhibition of TGF-β1 produced by GARP-expressing Tregs overcomes resistance to PD-1/PD-L1 blockade in cancer. *Nat Comm*. 2020;**11**: 4545.

Ethics Approval All animal studies were reviewed and approved by the Institutional Animal Care and Use Committee (IACUC) of Biocytogen Beijing Co., Ltd.

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