

A NOVEL B2M-DEFICIENT IMMUNODEFICIENT MODEL EXPRESSING HUMAN IL15 FOR PRECLINICAL EVALUATION OF T CELL AND NK CELL-BASED THERAPIES

¹Yanhui Nie, ²Xiaofei Zhou, ²Sujata Nerle*, ¹Qiang Liu, ¹Jiangfeng Yuan, ¹Yuelei Shen.
¹Biocytogen Pharmaceuticals (Beijing) Co., Ltd., Beijing, China; ²Biocytogen Boston Corp., Boston, MA, USA

Background Natural killer (NK) cells and T cells are important therapeutic populations that can target and eliminate cancer cells. Although human NK/T cell populations can be reconstituted in immunodeficient mice to test novel NK and/or T cell modulators, the time window for experimentation is often limited due to GvHD (graft-versus-host disease) complications. Moreover, human NK cell development and maturation is limited in such models due to the lack of human IL15. Previously, we disrupted the murine B2m allele in immunodeficient (B-NDG) mice and fused the FcRn coding region to the modified allele to ensure normal IgG metabolism, thereby generating B-NDG B2m KO mice plus. Here, we generated B-NDG B2m KO mice plus expressing human IL15 for improved NK cell engraftment and survival following human PBMC reconstitution.

Methods We introduced the human IL15 coding sequence into the murine IL15 locus, and crossed the mice with B-NDG B2m KO mice plus to generate B-NDG B2m plus/hIL15 mice. Expression of B2m and IL15 protein in B-NDG B2m plus/hIL15 mice was evaluated using flow cytometry and ELISA, respectively. To assess human T cell and NK cell reconstitution, B-NDG B2m plus/hIL15 mice and B-NDG mice were engrafted with human PBMCs. To examine the engraftment capacity of hematopoietic stem cells (HSCs), B-NDG B2m plus/hIL15 or B-NDG hIL15 neonates were injected with human CD34+ cells (3E4) from mixed donors via the facial vein. Blood from engrafted mice was sampled for flow cytometric analysis. Survival and weight were recorded to monitor GvHD and incidence of other health-related effects.

Results ELISA confirmed expression of human IL15, but not murine IL15 in B-NDG B2m plus/hIL15 mice. PBMC engraftment did not induce GvHD in B-NDG B2m plus/hIL15 mice over the 4 week study, while the survival rate of B-NDG mice was 20% after 2 weeks. Importantly, human T and NK cells were successfully reconstituted after PBMC engraftment. In newborn mice engrafted with CD34+ HSCs, higher levels of NK and myeloid cell reconstitution were observed in B-NDG B2m plus/hIL15 mice compared to B-NDG hIL15 mice. While all engrafted B-NDG hIL15 mice survived to 20 weeks, survival of B-NDG B2m KO/hIL15 mice dropped to 80% past week 12, and below 70% past week 18.

Conclusions We established an immunodeficient humanized IL15 model that lacks B2m to reduce GvHD incidence upon PBMC engraftment. B-NDG B2m plus/hIL15 mice provide an ample therapeutic window for testing novel NK cell or T cell modulators *in vivo*.

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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