Background IL-15 is a four α-helix bundle cytokine produced by dendritic cells, monocytes, and epithelial cells. IL-15 is necessary for the development, survival, and activation of natural killer (NK) cells.

Methods Human IL-15 (hIL-15) was knocked into NCG mice to create a model (NCG-hIL15) that can assist the reconstitution of human NK cells.

Results Compared with NCG, hIL-15 expression was significantly increased in NCG-hIL15het and NCG-hIL15homo. The development and function of human NK cells were evaluated in the NCG-hIL15 mouse reconstituted with three different types of human cell sources: (1) purified NK from human PBMC, (2) human PBMC, and (3) human CD34+ hematopoietic stem cells (HSC). In PBMC and CD34+ HSC-reconstituted mice, NK cell development was evident, with approximately 20% of hCD45+hCD56+ NK cells detected in the peripheral blood within weeks of engraftment. The level of hCD45+hCD3+ T cells reached 10 to 30% within 12 weeks of HSC reconstitution, while it reached greater than 80% within 2 weeks of PBMC reconstitution. In the purified NK engrafted cohort, the hCD45+hCD56+ NK cell numbers increased by at least two-fold within the first 3 weeks. Human NK cells were detected in multiple tissues and organs of all reconstituted NCG-hIL15 mice regardless of source of engraftment, except the colon, in the hPBMC-reconstituted NCG-IL15 mice. It was also noted that the level of NK cells post-engraftment varied depending on the donor of the PBMC.

To determine whether the reconstituted NK cells remain functional, purified NK cells from CD34+ HSC engrafted NCG-IL15 were isolated. Data showed that the NK cells could exert cell cytotoxicity when tested in vitro with leukemia cells, Raji, and Rituximab. Similarly, in vivo tumor growth inhibition (TGI= 49%) was observed with Raji.

Conclusions Overall, the addition of human IL-15, via genetic engineering in immunodeficient NCG mice provides excellent support for NK cell development. The NCG-hIL15 is a valuable tool for NK cell research and preclinical agent evaluation that requires NK and T cell activity.