22 HUMANIZED NOG-EXL MICE EXHIBIT IMPROVED OVERALL SURVIVAL AND LESS SEVERE MYELOID CELL ACTIVATION RELATIVE TO HUMANIZED NSG-SGM3 MICE

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Background Engraftment efficiency of human immune cell lineages in super immunodeficient mice varies, and numerous strains have been developed to improve reconstitution of humanized immune system mice. NSG-SGM3 and NOG-EXL mice combine severe immunodeficiency with transgenic expression of human myeloid stimulatory cytokines, resulting in improved expansion of myeloid populations. However, humanized NSG-SGM3 (huNSG-SGM3) mice develop a lethal macrophage activation syndrome (MAS) and mast cell hyperplasia that limit their use in long-term studies, especially those requiring humanization followed by tumor xenotransplantation. It is currently unclear to what extent humanized NOG-EXL (huNOG-EXL) mice suffer from the same conditions observed in huNSG-SGM3 mice. In this study, we aimed to compare the effects of human CD34+ hematopoietic stem cell engraftment in these two mouse strains in an orthotopic glioblastoma patient-derived organoid xenograft model.

Methods NSG-SGM3 mice (n=10) humanized in-house were compared to both NOG-EXL mice (n=10) humanized in-house and to commercially available huNOG-EXL mice (n=12). Mice were euthanized at humane or study endpoints, and a complete pathological assessment was performed. A semiquantitative multiparametric clinicopathological scoring system was developed to characterize the myeloid proliferative disorder.

Results Both the NOG-EXL mice humanized in-house and commercially available huNOG-EXL mice survived longer (to experimental endpoint) than huNSG-SGM3 mice (22 vs 17 weeks post engraftment), with significantly less severe MAS and lack of mastocytic proliferation. Major findings included mast cell infiltration of the pancreas and liver (huNSG-SGM3 only), increased eosinophilopoiesis, anemia, and histiocytic infiltration of the spleen (both strains). Engraftment of human lymphocytes, assessed by immunohistochemistry, was similar in the two strains. The longer survival and decreased MAS severity in NOG-EXL mice enabled their use in a patient-derived xenograft transplantation study.

Conclusions Humanized NOG-EXL mice develop a milder myeloid activation syndrome and do not develop mast cell hyperplasia relative to humanized NSG-SGM3 mice. Thus, the NOG-EXL model may be better suited than the NSG-SGM3 model for immuno-oncology studies requiring long-term survival post humanization. Future directions include further assessment of the lymphocyte populations in both strains and application of the humanized NOG-EXL for patient-derived xenograft models.

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Ethics Approval All the mice included in this study were maintained by the Stem Cell and Xenograft Core at the University of Pennsylvania under the protocol #803506 which has been reviewed and approved by the Institutional Animal Care and Use Committee (IACUC). The participant gave informed consent for use of glioblastoma patient-derived organoids, under protocol #832366, approved by the University of Pennsylvania Institutional Review Board (IRB).

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