154 GENERATION OF HUMANIZED MOUSE MODELS FOR THE PRECLINICAL EVALUATION OF NOVEL IMMUNE CHECKPOINT INHIBITORS, IMMUNE CELL ENGAGERS AND CELL THERAPIES

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Background The preclinical evaluation of many novel immune therapies requires the use mouse models with a functional human immune system. In previous studies we have demonstrated that either peripheral blood mononuclear cells (PBMCs) or subpopulations of PBMCs such as T- and NK-cells or hematopoietic stem cells (HSC) can be used to establish a humanized immune system in immunodeficient mice system with functional T-, B-, and NK cells as well as monocytes and dendritic cells. By transplanting either cell-line or patient-derived tumor xenografts into humanized mice, we successfully generated a fully human tumor-immune-cell model for several tumor entities. Finally, we validated the functionality of these models using either immune-checkpoint inhibitors, cell therapies, or immune cell engagers.

Methods HSC-humanized mice were generated by i.v. injection of CD34+ stem cells into immunodeficient NOG mice. PBMCs or enriched T- or NK-cell populations from a curated set of blood donors were used to humanize mice by either single or multiple i.v. injections. CDX and PDX models from different entities (i.e. lymphoma, neuroblastoma, and breast cancer) were transplanted into these humanized mice which were used to evaluate novel immune therapy options. The presence of immune cells and their activation status was analyzed by flow cytometry in blood and tumor samples

Results Injected HSCs successfully engrafted and established a functional human immune system with proliferating and differentiating immune cell populations. Fourteen weeks after injection, up to 20% of the human immune cells in the blood were functional T-cells. Several CDX and PDX models successfully engrafted in these humanized mice without significant differences regarding tumor growth compared to non-humanized mice. Checkpoint inhibitor treatment led to tumor growth delay in selected models and flow cytometry analysis of tumor samples revealed a high number of tumor infiltrating T-cells. A comparison of checkpoint inhibitor activity in a pancreatic cancer PDX model using four different humanized mouse models in parallel (HSC, PBMC, T-or NK cell humanized) revealed most convincing results in terms of tumor growth inhibition for the HSC humanized model.

Conclusions We have established fully human tumor-immune-cell models for different tumor entities in combination with different donor derived immune cell subsets as effector cells and have demonstrated successful long term engraftment of HSCs. All models have been used for the evaluation of either novel checkpoint inhibitors, cell therapies or immune cell engagers and will allow preclinical and translational studies for the identification of novel therapy options, drug combinations and biomarkers.

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