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Preclinical models of humanized mice for immuno-oncology research

Short Title: Humanized immune-oncology mouse models

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The recent clinical success of immune checkpoint modulators has stimulated immune-oncology research leading to the identification of new tumor immunology targets. However both, target validation and drug development need better preclinical immune oncology models. Translational research further urgently needs such models for identification of clinically relevant biomarkers and defining rational combination strategies.

In previous experiments, we have demonstrated, that hematopoietic stem cells (HSC) can proliferate and differentiate in vivo to form a functional humanized immune system including T cells, B cells, NK cells, monocytes and dendritic cells in these mice. Further we have shown engraftment of patient- (PDX) and cell-line-derived xenografts (CDX) on these humanized mice. All CDX and most of the PDX showed no difference in tumor growth compared to non-humanized mice (= fully immune resistant). However other PDX showed a delayed growth on the humanized mice (= partly immune resistant), whereas only one model did not grow at all (= immune sensitive), demonstrating a high sensitivity to the innate immune response of this PDX. In the next step, we determined PD-L1 expression as a target for immunotherapy on different CDX and PDX on RNA level and on protein. Engraftment delay seems to be dependent on PD-L1 expression of PDX (the higher PD-L1, then the higher growth delay).

At least functionality of the humanized mice was evaluated by the treatment with the checkpoint inhibitors and in initial experiments in combination therapy with radiation. So far we treated over 20 PDX and CDX models (lung, colon, melanoma, mammary, ovarian, lymphoma) with ipilimumab or nivolumab alone or in combination. In most case we observed a slight tumor growth delay and an increased percentage of T cells in the blood and in the tumor. Better response to checkpoint inhibitors showed a correlation to innate immune response and PD-L1 expression of PDX and CDX.

Summary:

Our humanized PDX models enable appropriate preclinical studies on tumor immune biology, evaluation of new immune therapies and combinations, as well as the identification and validation of biomarkers for tumor immune therapy.