Humanized mouse models for preclinical evaluation of novel immune cell therapies, check point inhibitors, and immune cell engagers

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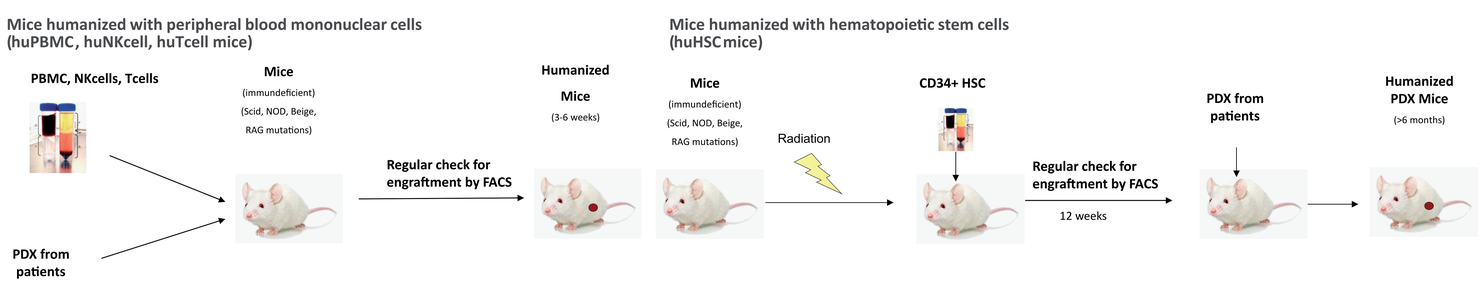
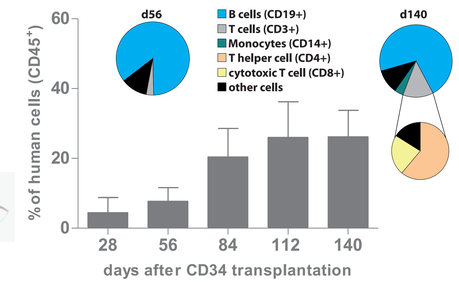
Background and Aim

- preclinical evaluation of novel immune checkpoint modulators require models with functional immune cells
- in previous experiments, we have demonstrated, that we can use hematopetic stem cells (HSC), peripheral blood mononuclear cells (PBMCs) or subtypes of PBMCs like T or NK cells to establish a humanized immune system on highly immunodeficient mice with functional T, B or NK cells
- by co-transplantation of CDX and PDX, we s uccessfully generated a fully human tumor-immune-cell model in mice
- for orthotopic models of l ymphoma or leukemia models, we generated luciferase labeled cell lines to use bioluminescence to follow up tumor growth during the study
- model have been experimentally validated in preclinical studies with checkpoint inhibitors
- humanized models will contineous improved by using new mouse strains or optimized cell numbers

Humanized mouse models with immune cells and PDX - schematic overview



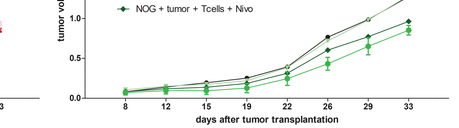


huPBMC, huNKcell and huTcell mice

- PBMCs, NK or Tcells can be isolated from buffy coats and whole blood samples
- cohort of HLA analyzed donors available from whole blood samples to match with suitable PDX models
- NK and T cells can be expaned in vitro for in vivo studies
- improvement of models with 2nd generation NOG mouse strains (IL15, IL6 and IL2)

huHSC mice

- HSC could reconstitue a humanized immune system in mice
- long-term engraftment could be observed over 14 weeks
- functionality of T cells was determined by inhibition of PD-1 expression through treatment with Nivolumab
- improvement of model with 2nd generation NOG mouse strains (NOG-EXL, NOG-IL6 and supplementation of cytokines



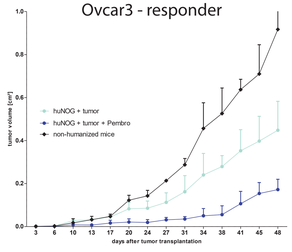
Summary and Outlook

- we successfully established a fully humanized mouse models for immuno-onocology by co-transplantation of CDX or PDX and human HSC or immun cells from whole blood (PBMCs, T, or NK cells)
- we observed engraftment of CDX and PDX on most humanized mice, however in some cases it was delayed and seems to be dependent on HLA matching and PD-L1 expression
- we see different therapeutic effects of checkpoint inhibitors like Nivolumab, Pembrolizumabm or Ipilimumab with strong, to minor responders, or non responders
- several CDX and PDX have been investigated in humanized HSC mice, huPBMC, huNK cells and huT cell mice
- comparing tumor growth and checkpoint inhibitor activity in the pancreatic cancer PDX Panc12975 on four different humanized mouse models, humanization with HSC provided best results in comparison to single immune cells
- we successfully established an orthotopic model of lymphoma model Karpas299 using for immuno-onocology research tumor growth can be measured with bioluminescene during the experiment
- we demonstrated in our preclinical studies eligibility of the humanized models for peclinical research in tumor immunology, evaluation of new therapiesand combinations, as well as the identification and validation of biomarkers for immune therapy
- combination therapies with radiation and using mouse strains improving engraftment of HSC (NOG-EXL mice) and immune cells (NOG-IL-15 mice) are under investigation
- furthermore, these novel models have been successful used for the preclinical evaluation of new bispecific immune cell engagers (BITE) and cell therapies (CAR T cells)

Evaluation of immun therapies with CDX models on humanized mouse models

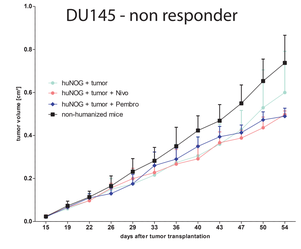
human HSC mice

Ovcar3 - responder



- delayed growth of Ovcar3 CDX on humanized HSC mice, distinct efficacy of checkpoint inhibitor Nivolumab could be shown

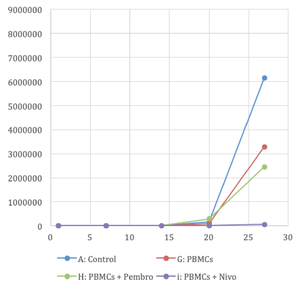
DU145 - non responder



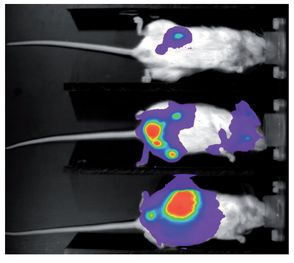
- comparable growth of DU145 CDX on humanized HSC mice, no effects of checkpoint inhibitor Nivolumab and Pembrolizumab could be shown

human PBMC mice

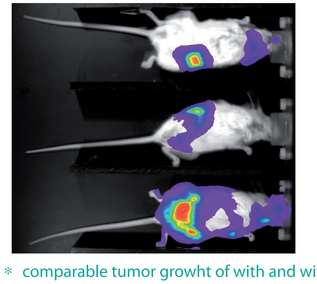
Karpas299/Luc - responder



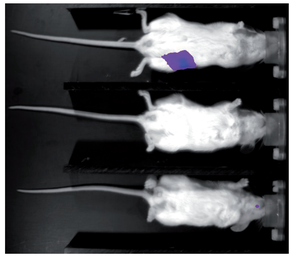
PBMCs only



PBMCs + Pembrolizumab



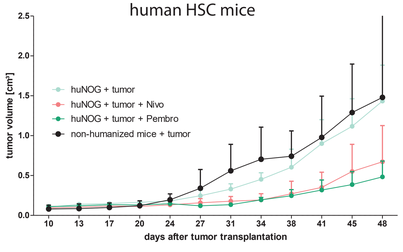
PBMCs + Nivolumab



- comparable tumor growht of with and without PBMCs
- tumor growth delay can be induced by treatment with checkpoint inhibitors
- Nivolumab induced significant tumor growth reduction in comparison to Pembrolizumab

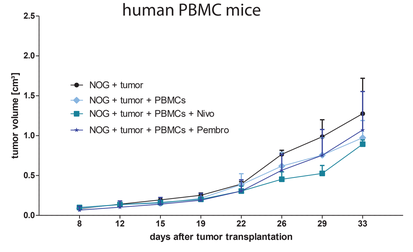
Evaluation of immuno therapies with PDX model Panc12975 on four different humanized mouse models

human HSC mice



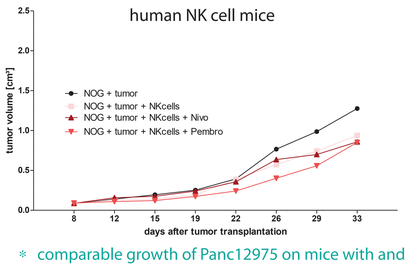
- comparable engraftment of Panc12975 on huHSC and non-humanized mice, efficacy of checkpoint inhibitors Nivolumab and Pembrolizumab could be shown in Panc12975 PDX model

human PBMC mice



- comparable grwoth of Panc12975 on mice with and without PBMC humanization, no effects of checkpoint inhibitors

human NK cell mice



- comparable growth of Panc12975 on mice with and without NK cell humanization, no effects of checkpoint inhibitors

human T cell mice

- comparable growth of Panc12975 on mice with and without T cell humanization, no effects of checkpoint inhibitors

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