Preclinical models for translational immuno-oncology research - rare patient-derived xenografts on humanized mice -

#5204

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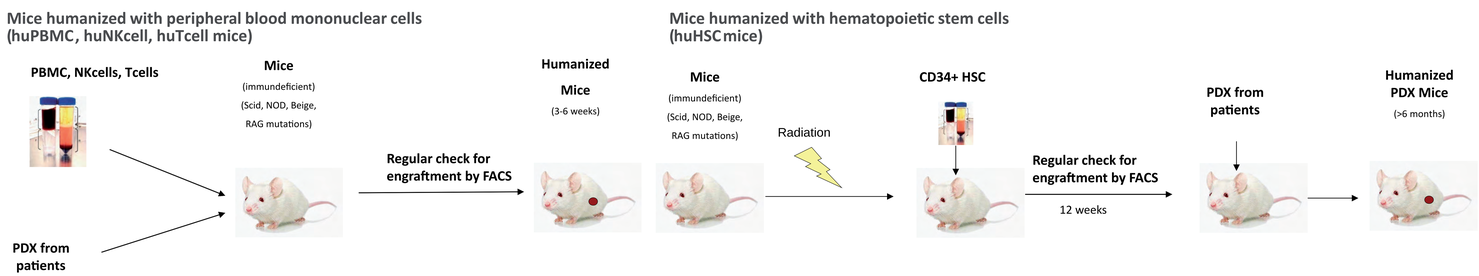
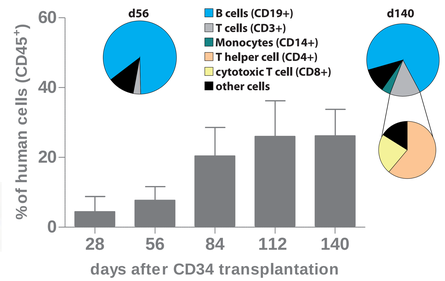
Background and Aim

- 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
- we successfully generated rare and challenging patient-derived xenografts (PDX) for in vivo studies and detailed characterization: leukema, lymphoma, sacroma and glioblastoma models as well as pancreatic and NUT carinoma PDX
- model have been experimentally validated in preclinical studies with checkpoint inhibitors on humanized mice

Humanized mice models with immune cells and PDX - schematic overview



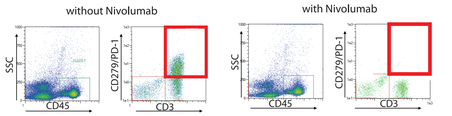


huPBMC, huNKcell and huTcell mice

- 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

huHSC mice

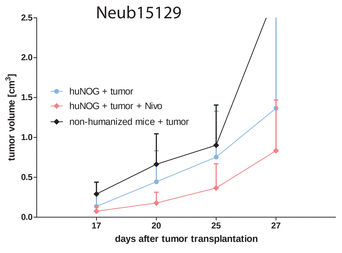
- HSC could reconstitue a humanized immune system in mice
- long-term engraftment could be observed over 14 weeks
- functionality of T cells was determined by inhibition of PD-1 expression through treatment with Nivolumab



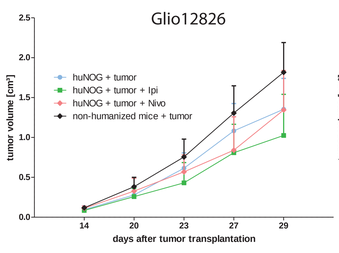
Summary and Outlook

- we successfully established a fully humanized mouse models for immuno-onoclogy by co-transplantation of PDX and human HSC or immun cells from whole blood (PBMCs, T, or NK cells)
- we observed engraftment of PDX on most humanized mice, however in some cases it was delayed and seems to be dependent on HLA matching
- we see different therapeutic effects of checkpoint inhibitors like Nivolumab, Pembrolizumabm or Ipilimumab with strong, to minor responders, or non responders
- several rare and difficult to establish tumor models have been investigated in humanized HSC 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 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 identicifaction 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)

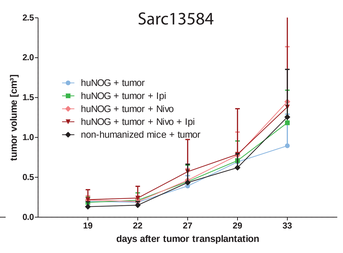
Generation of humanized PDX models from rare indications and evaluation of immuno therapies



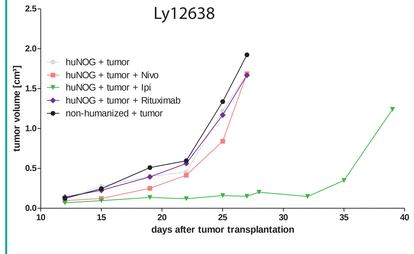
- delayed growth of neuroblastoma PDX on humanized HSC mice, minor efficacy of checkpoint inhibitor Nivolumab



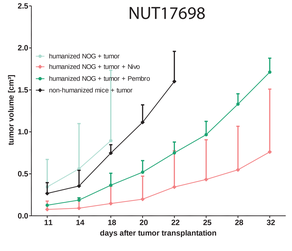
- delayed growth of glioma PDX on humanized HSC mice, no efficacy of checkpoint inhibitors



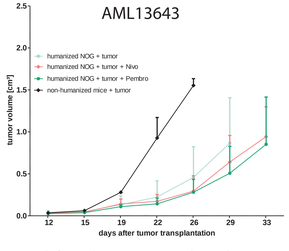
- comparable growth of sarcoma PDX model on huHSC mice, no tumor growth inhibition by treatment with checkpoint inhibitors



- comparable growth of lymphoma PDX on humanized HSC mice, strong efficacy of checkpoint inhibitor Ipilimumab in this Rituximab resistant model

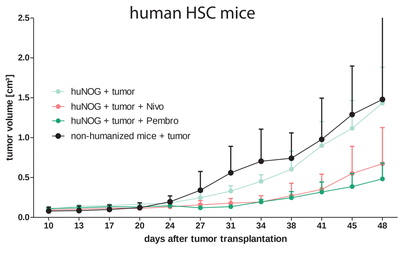


- comparable tumor growht of NUT PDX on humanized mice, efficacy of check point inhibitor of Nivolumab and Pembrolizumab could be shown

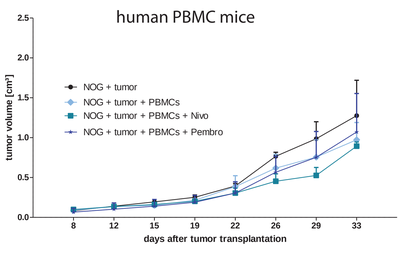


- delayed tumor growth on humanized HSC mice, minor effects of checkpoint inhibitors could be shown for AML PDX

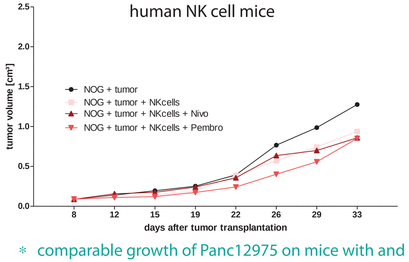
Evaluation of immuno therapies with PDX model Panc12975 on four different humanized mouse models



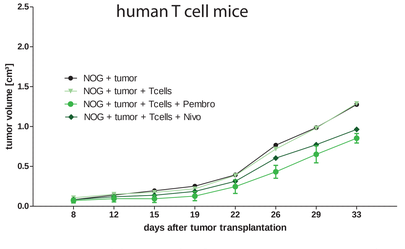
- comparable engraftment of Panc12975 on huHSC and non-humanized mice, efficacy of checkpoint inhibitors Nivolumab and Pembrolizumab could be shown in Panc12975 PDX model



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



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



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

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