Humanized mouse models for preclinical evaluation of novel immune cell therapies, checkpoint inhibitors, and immune cell engangers

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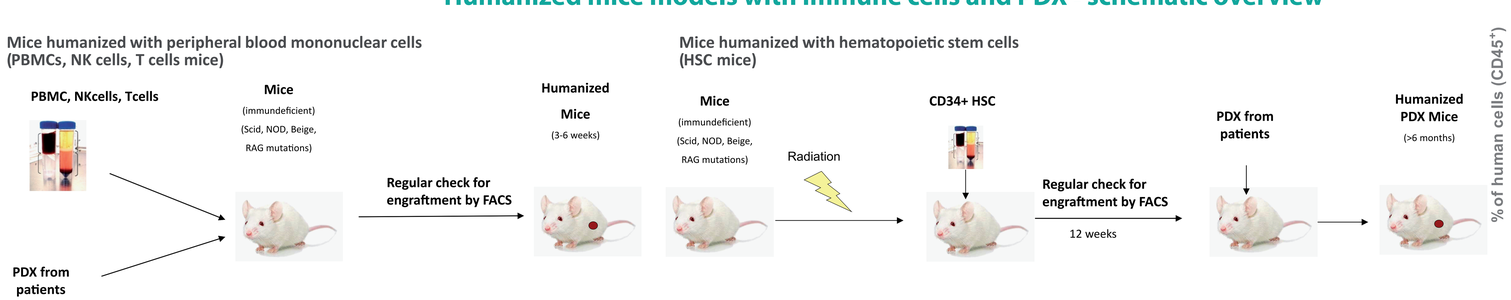
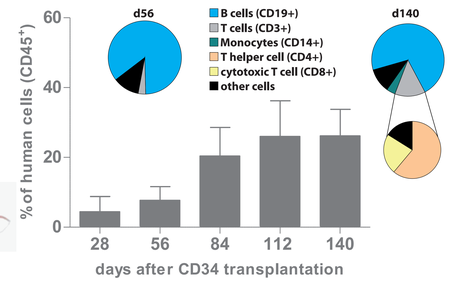
Background and Aim

- preclinical evaluation of novel immune checkpoint modulators require models with functional immune cells
- in previous expĕriments, 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 immuno-deficient mice with functional T, B or NK cells
- we demonstrated funtionality of T, B or NK cells and checked growth of co-transplantation with PDX tumors
- models were experimentally validated in preclinical studies with checkpoint inhibitors

Humanized mice models with immune cells and PDX - schematic overview



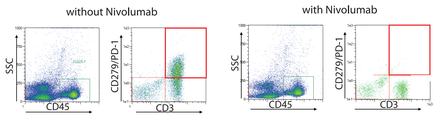


humanized mice with PBMC, NK cells or T cells

- PBMCs, NK or Tc ells 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

humanized mice with HSC

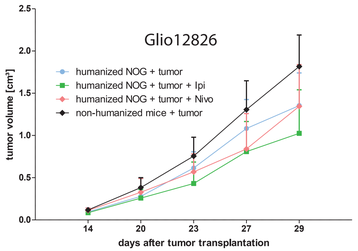
- HSC could reconstitue a humanized immune system in mice
- long-term engraftment could be observed over 14 weeks
- functionality of T cells was determined by inhibition of PD-1 expression through treatment with Nivolumab



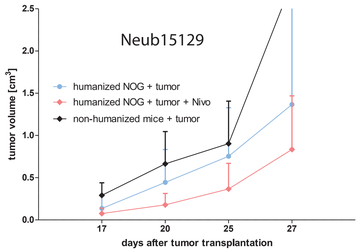
Summary and Outlook

- we successfully established a fully humanized mouse model for immuno oncology by co-transplantation of PDX and human HSC or immune cells (PBMCs, NK or T 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, Pembrolizumab, or Ipilimumab with strong to minor responders or resistant tumors
- 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 research in tumor immunology, evaluation of new therapies and 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 inverstigation

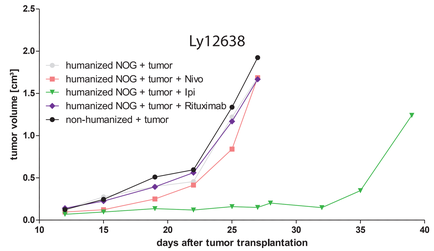
Evaluation of immuno therapies in human HSC - PDX models



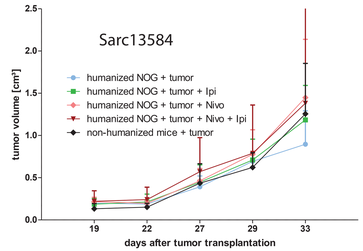
- delayed engraftment of glioma PDX on humanized mice with HSC, minor efficacy of checkpoint inhibitor Ipilimumab



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

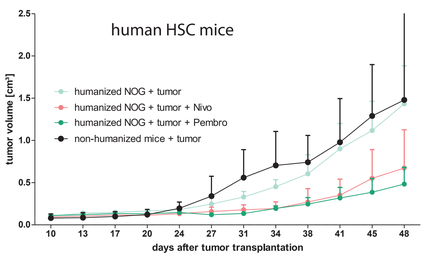


- efficacy of checkpoint inhibitor Ipilimumab could be shown in Rituximab resistant Lymphoma model

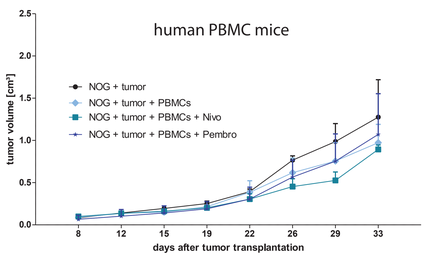


- immune checkpoint inhibitor resistant sarcoma PDX model on humanized mice with HSC

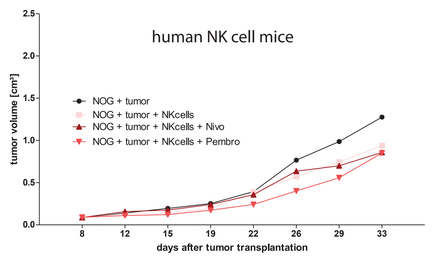
Evaluation of immuno therapies with PDX model Panc12975 on four different humanized mouse models



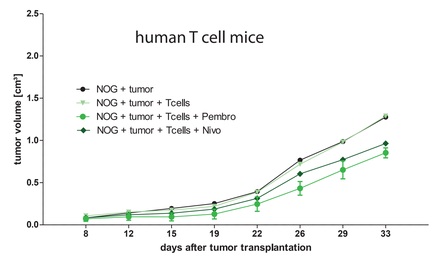
- comparable engraftment of Panc12975 on HSC-humanized and non-humanized mice, efficacy of checkpoint inhibitors Nivolumab and Pembrolizumab could be shown in Panc12975 PDX model



- treatment with checkpoint inhibitor Nivolumab or Pembrolizumab in PBMC-humanized mice showed only a minor effect on tumor growth in Panc12975 PDX model



- treatment with checkpoint inhibitor Nivolumab or Pembrolizumab on NK-cell humanized mice showed no effect on tumor growth in Panc12975 PDX model



- treatment with checkpoint inhibitor Nivolumab or Pembrolizumab could be shown in combination with T cells in Panc12975 PDX model

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