Preclinical Case Study: Patient-derived head and neck cancer xenograft on mice humanized with autologous immune cells - a model for personalized immuno-oncology research -

#360

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Background and Aim

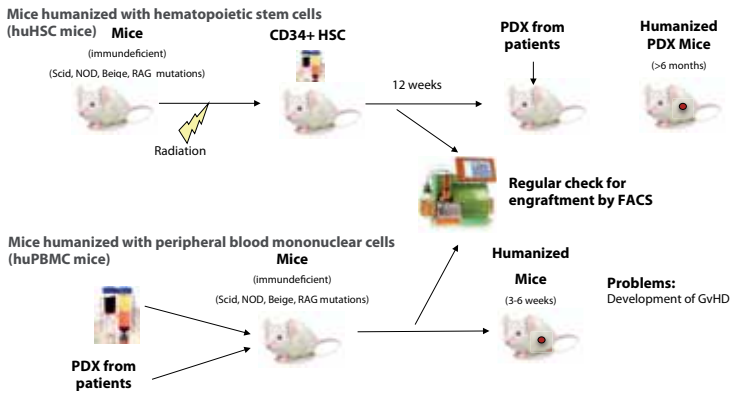
The preclinical evaluation of novel immune checkpoint modulators for cancer treatment remains a challenge, as models require both, engraftment of human tumor cells and a compatible human immune cell population. In previous experiments, we have demonstrated, that we can use either peripheral blood mononuclear cells (PBMCs) or hematopoetic stem cells (HSC) to establish a humanized imme system with functional T-, B-, and NK cells, monocyztes, and dendritic cells on highly immundeficient mice. However, these models are limited by rarely matching HLA isotypes between tumor and immune cells.

In this case study, we established a patient-derived xenograft (PDX) model from a patient with Head and Neck squamous cell cancer (HNSCC). Furthermore, we collected blood samples and isolated PBMCs from this patient (autologous system). In addition, we isolated PBMC from other donors (allogeneic system). Beside, we used our humanized mice (HSC based) to investigate this model under immunotherapy.

Summary and Outlook

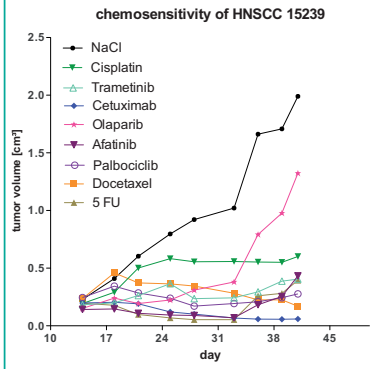
We developed a humanized immune PDX model enabling appropriate preclinical translational research on tumor immune biology and the evaluation of new therapies and combination, as well as the identification and validation of biomarkers for immune therapy. Furthermore, results showed a correlation between immune therapy effect and HLA matching in preclinical models, especially using PBMCs as cell source for humanization. Humanized mice based on HSC transplantation have to be further characterized and the correlation with the HLA-match has to be investigated in detail.

Humanized mice models with immune cells and CDX/PDX - schematic overview



Establishment and characterization of HN15239

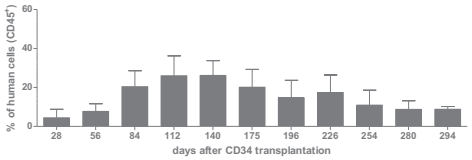
- PDX of HNSCC was established by directly transplanting surgical material to immunodeficient mice
- xenografts are passaged in vivo and stored as stock in liquid nitrogen



- HN15239 is chemosenitive to Cetuximab, Docetaxel, Palbociclib, Trametinib and Cisplatin
- Olaparib induced no tumor growth inhibition compared to the other treatments

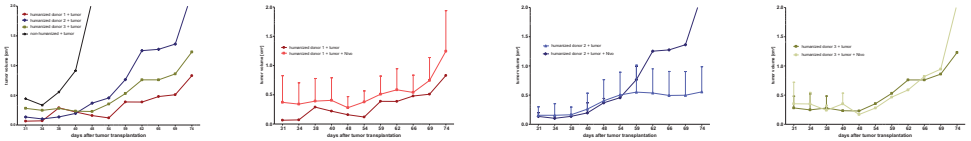
Patient-derived xenograft models on huHSC mice

Humanization of immunodeficient mice with CD34+ stem cells from cord blood (HSC)



- humanized immune system in mice could be established with HSC
- long time engraftment could be observed over 400 days
- engraftment donor depend when using single donors instead of mixed donors

HN15239 PDX on huHSC mice



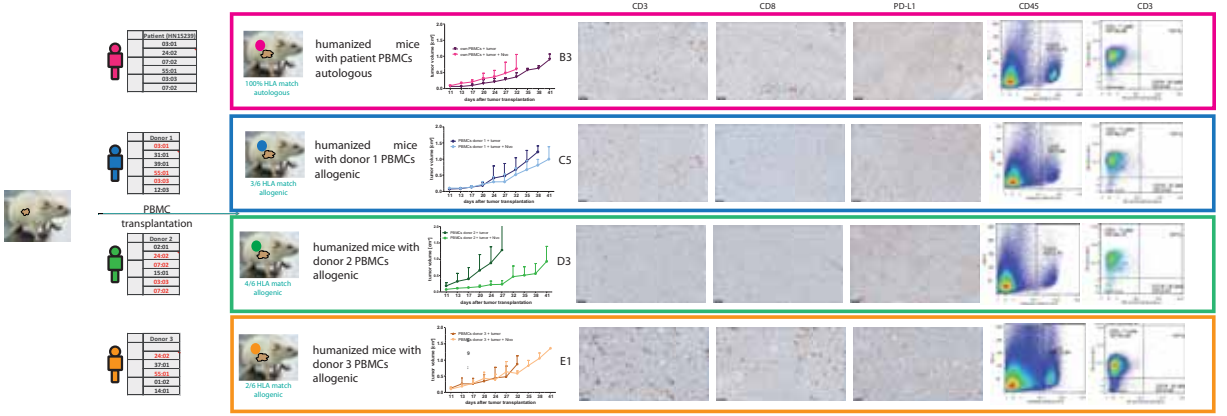
- 3 cohorts of humanzed from single donors were established
- PDX HN15239 was s.c. transplanted after humanization (12- 14 weeks); control group - non-humanized mice
- treatment start with Nivolumab was started >TV 0,1cm³

- between donors distinct differences of tumor growth could be seen
- under Nivolumab treatment a donor dependent effect could be observed
- correlations between HLA-match or other reasons of tumor growth delay are under investigation

Patient-derived xenograft models on huPBMC mice

HN15239 PDX on huPBMC mice

- 4 treatment groups (B - autologous PBMCs; C - E allogenic PBMCs with different HLA match)
- i.v. transplantation of PBMCs 3 of 5 mice per group were treated with Nivolumab
- Tumor samples of HN15239 were formalin fixed and embedded in paraffin (FFPE) and stained for CD3 (Ventana), CD8 (DAKO) and PD-L1 (Cell Signaling)
- FACS analysis: cell suspension were stained with 8-color-Immunophenotyping Kit (Miltenyi).



- PDX model HN15239 showed a donor dependend tumor growth
- PBMCs with a high HLA match ‚support' tumor growth compared to non-humanized mice and to PBMCs with a lower HLA match
- treatment with Nivolumab induced a strong growth inhibiton compared to non-treated mice in group with high HLA-match

- no treatment effects could be observed in combination with autologous PBMCs (patient of PDX is still under Nivolumab treatment in the clinic)
- IHC staining and FACS analysis showed infiltration of immune cells in autolgous and allogenic settings

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