Human leukocyte antigen (HLA) matching of cancer patient-derived xenografts (PDX) models with immune cell-humanized mice

Theresia Conrad[1], Simone Rhein[1], Annika Wulf-Goldenberg[1], Maria Stecklum[1], Michael Becker[1], Konrad Klinghammer[2], Jens Hoffmann[1]

[1] Experimental Pharmacology and Oncology (EPO) GmbH, Robert-Roessle-Str. 10, 13125 Berlin, Germany

[2] Charité University Medicine, Berlin, Germany

Background

In immuno-oncology research, matching of human leukocyte antigen (HLA) profiles of patient-derived xenografts (PDX) and compatible human immune cell populations is an important factor to enable personalized, preclinical studies. With this objective, we determined individual HLA profiles of a broad panel of PDX models from 18 different tumor entities and performed comprehensive HLA matching analyses of all models and peripheral blood mononuclear cell (PBMC) donors.

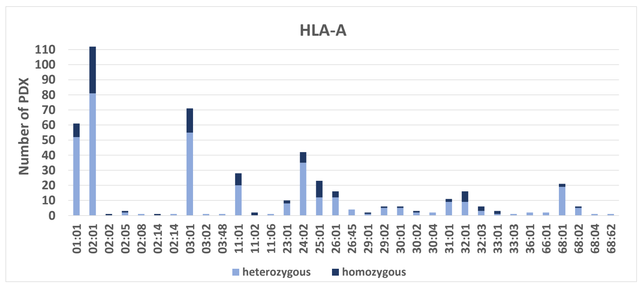
Methods

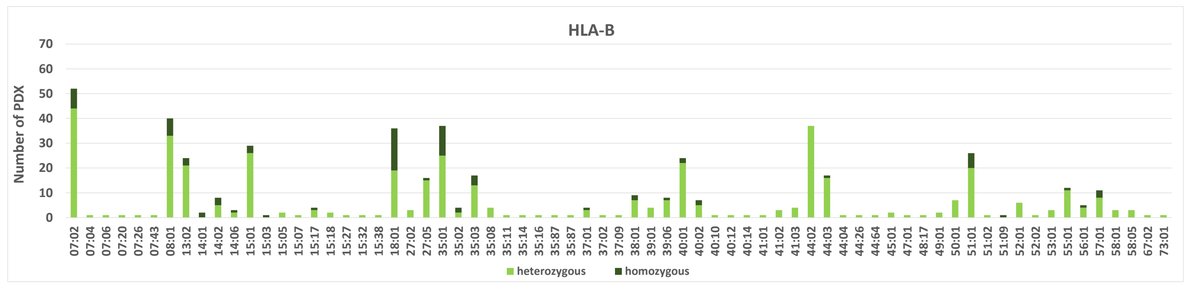
- ❖ Based on RNA-sequencing data, HLA class I, II and non-class types of 291 established PDX models were determined in 4-digit resolution.
- ❖ For comparative analyses, HLA allele and haplotype frequencies of 8862 German stem cell donors (GSCD) provided by The Allele Frequency Net Database were used (*Gonzalez-Galarza et al. (2020), DOI: 10.1093/nar/gkz1029*).
- ❖ According to donor-recipient HLA matching criteria recommended by the Blood and Marrow Transplant Clinical Trials Network, matching analyses of all PDX and PBMC donor HLA profiles were performed (*Howard et al. (2015), DOI: 10.1016/j.bbmt.2014.09.017; Fürst D et al. (2019), doi: 10.1159/000502263).*

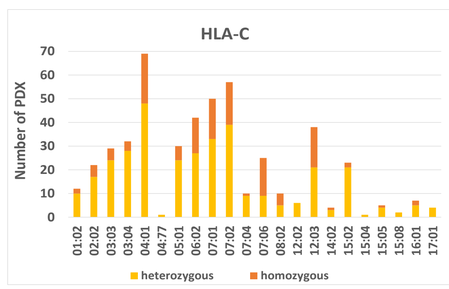
Results

HLA typing and analysis of 291 established PDX models

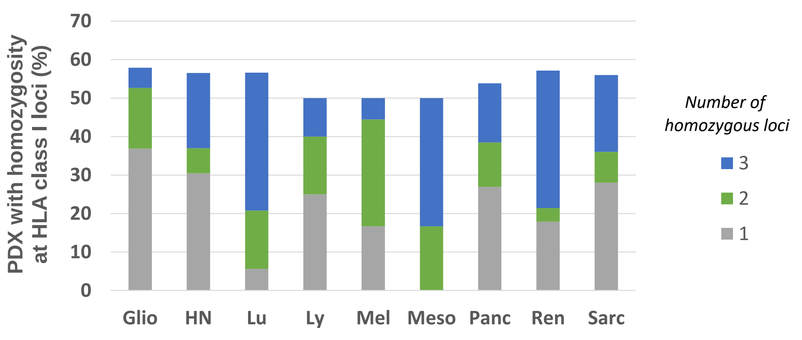
- ❖ Individual HLA profiles were generated comprising HLA-A, -B and -C (class I), HLA-DQA1, -DQB1, -DRB1, -DPA1 and -DPB1 (class II) as well as HLA-H (non-class) types of all PDX models. HLA class I types are shown.



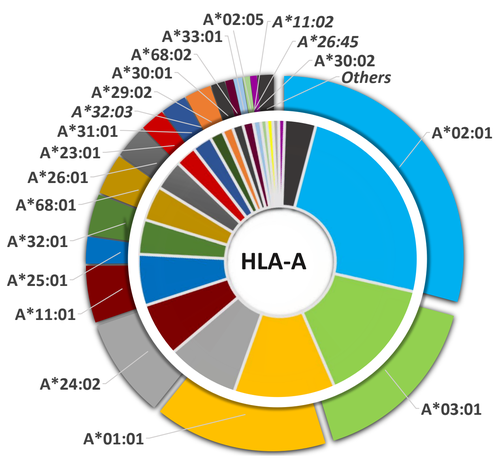


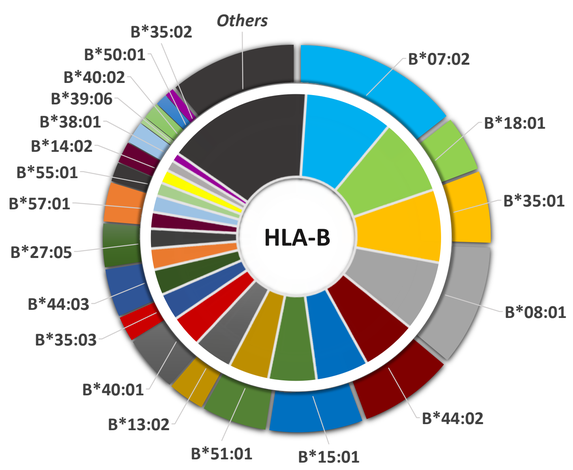


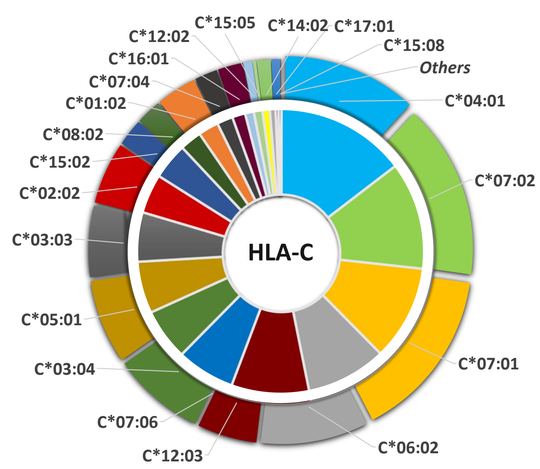
- ❖ More than 50 % of the determined HLA profiles show allele homozygosity at ≥ 1 HLA class I loci of PDX models from lung, renal cell, head and neck carcinoma as well as from pancreatic cancer, glioma, lymphoma, melanoma, mesothelioma and sarcoma.



- ❖ Comparisons of PDX models (inner ring) and GSCD (outer ring) HLA profiles resulted in comparable frequencies of most of the alleles and haplotypes but also in certain variations.







- ❖ The obtained high proportions of homozygosity and specific HLA haplotypes were likewise reported in the literature and may serve as prognostic markers for risk and progression of cancer.

Table 1: Comparison of class I~DRB1 haplotype frequencies (> 1%) of PDX models and GSCD

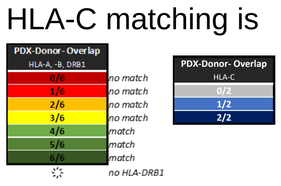
PDX HLA haplotypes	PDX haplotype frequency (%)	GSCD HLA haplotypes	GSCD haplotype frequency (%)
A*01:01~B*08:01~C*07:01~DRB1*03:01	**2.647**	**A*01:01-B*08:01-C*07:01-DRB1*03:01**	**5.826**
A*02:01~B*07:02~C*07:02~DRB1*15:01	**2.572**	A*03:01-B*07:02-C*07:02-DRB1*15:01	3.843
A*03:01~B*35:01~C*04:01~DRB1*01:01	**1.852**	**A*02:01-B*07:02-C*07:02-DRB1*15:01**	**2.181**
A*01:01~B*08:01~C*07:06~DRB1*03:01	1.411	**A*03:01-B*35:01-C*04:01-DRB1*01:01**	**1.540**
A*25:01~B*18:01~C*12:03~DRB1*15:01	1.183	A*02:01-B*15:01-C*03:04-DRB1*04:01	1.286
		A*02:01-B*44:02-C*05:01-DRB1*04:01	1.207
		A*29:02-B*44:03-C*16:01-DRB1*07:01	1.005

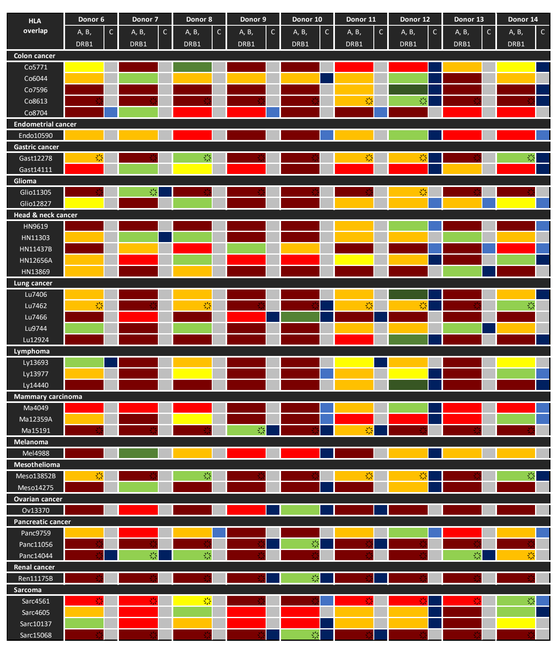
Table 2: Selected findings as potential prognostic markers

Description	Frequency in PDX models	Reported association
high proportion of homozygosity at ≥ 1 HLA class I loci	***52.23%***	Short survival in patients with non-small cell lung cancer treated with single agent immunotherapy *Abed et al. (2020), DOI: 10.1136/jitc-2020-001620*
*DQB1*03:02~DRB1*04*	***6.25%*** in top 5 of DQB1~DRB1 haplotypes	Metastatic progression of melanoma *Luongo et al. (2004), DOI: 10.1111/j.0001-2815.2004.00250.x*
*DQB1*05:01~DRB1*01*	***5.83%*** in top 5 of DQB1~DRB1 haplotypes	Metastatic progression of melanoma *Luongo et al. (2004), DOI: 10.1111/j.0001-2815.2004.00250.x*
*A*01:01~B*08:01~C*07:01 ~DQA1*05:01~DQB1*02:01 ~DRB1*03:01*	***2.78%*** in top 3 of class I~II haplotypes	Increased risk for squamous cell carcinoma *Ferreiro-Iglesias et al. (2018), DOI: 10.1038/s41467-018-05890-2*

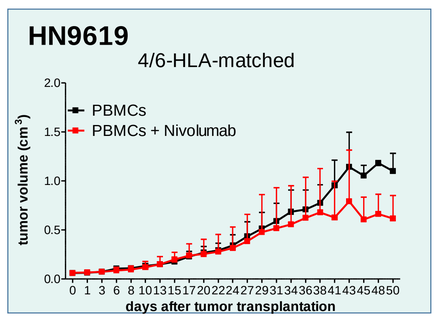
Immune checkpoint inibition in HLA-matched PBMCs-PDX tumor models

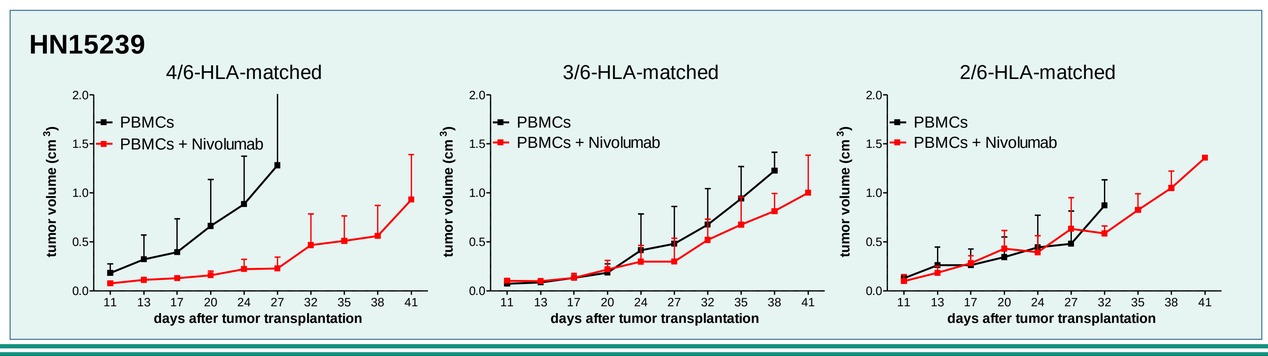
- ❖ HLA profile matching analyses revealed PDX-donor matches from 14 tumor entities. For a match, PDX and donor should be ≥ 4/6 match at HLA-A (2-digit resolution), -B (2-digit res.) and -DRB1 (4-digit res.). Loci with unidirectional mismatches where the PDX is homozygous and the non-shared HLA type is only present on the donor site were considered as completely matched loci.
- ❖ In addition, HLA-C matching is indicated.





- ❖ Immune check point inhibition in head and neck squamous cell cancer (HNSCC) PDX tumor models humanized with PBMCs from HLA-matched or non-matched blood donors shows powerful tumor growth inhibition in matched HLA settings. Strength of tumor inhibition is model / donor dependent.





Conclusion

The generated comprehensive HLA profile portfolio containing matching information on a broad panel of PDX models and PBMC donors supports the investigation of prognostic markers and enables personalized, preclinical immune-oncology studies to encourage the development of novel immune-therapeutic strategies.

Corresponding address: simone.rhein@epo-berlin.com

www.epo-berlin.com