Patient-derived xenograft models from hematological malignancies for preclinical drug development and biomarker research

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Background and Aim

Acute leukemias and lymphomas encompass a diverse group of hematologic malignancies, posing significant challenges in clinical practice. They often exhibit resistance to standard-of-care (SoC) treatments and have a high recurrence rate. Recent advancements in molecular profiling have identified potential drivers for various leukemia and lymphoma subtypes, offering new therapeutic targets.
However, the validation of these targets and the development of drugs rely heavily on preclinical models that faithfully represent the different clinical subtypes. These models play a crucial role in refining target selection and facilitating drug development projects

Methods

AML- and ALL-PDXs were derived from bone marrow aspirates or peripheral blood samples, from primary or relapsed acute leukemia patients. Purified cells were transplanted either intravenously (i.v.) and/or subcutaneously (s.c.) into immunodeficient mice. Some mice developed a systemic AML, which was monitored by flow cytometric analysis of blood samples. Non-Hodgkin (NHL) - or Hodgkin lymphoma (HL)-PDX were derived from peripheral blood, lymph node extirpations or core needle biopsies, and were usually transplanted subcutaneously into immunodeficient mice.

Results

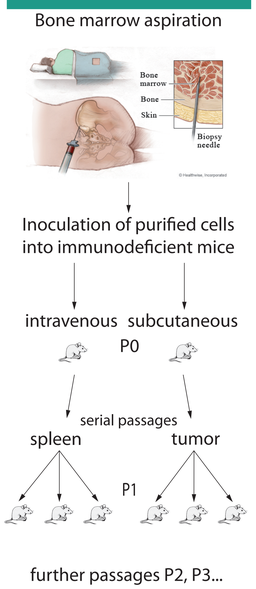
More than 45 PDX models from AML, ALL, NHL and HL have been successfully established and characterized. Highly individual response rates to SoC and investigational drugs were observed and correlated with mutation and gene expression data. An individual Human Leucocyte Antigen (HLA) profile of each PDX was determined by RNA-seq and a comprehensive HLA matching analysis of the models and peripheral blood mononuclear cell (PBMC) donors was performed to enable personalized, preclinical immuno-oncology studies

Conclusion

Our extensively characterized PDX models derived from hematologic malignancies serve as valuable tools for evaluating novel targeted and immunological therapies. These models provide an exceptional platform for identifying and validating new targets, as well as preclinical screening of compounds and combinations for translational research projects in this field.

Acute Myeloid Leukemia (AML) and Acute Lymphoid Leukemia (ALL)

PDX establishment



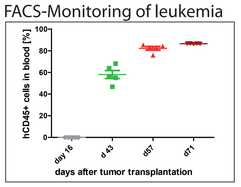
Clinical data of acute leukemias and characteristics of established PDX models

PDX ID	FAB classification	Mutations PDX	Tumor inoculation	Read out	
				Time +/- (days)	Parameter
AML 6252	M4	FLT-3, PTPN-11	s.c.	50	tumor volume
			i.v.	30	spleen weight, survival
AML 6256	M5	TP53, PTPN-11	s.c.	45	tumor volume
AML 6617	M5	ATM, PTPN-11	s.c.	45	tumor volume
AML 6799	M1	APC, HNF1A, RET	s.c.	50	tumor volume
AML 11655	M1	IDH1, NPM1	s.c.	60	tumor volume
			i.v.	80	spleen weight
AML11810	M5b	APC, BRAF	s.c.	30	tumor volume
AML12680	M4	KDR, KIT	s.c.	35	tumor volume
AML12683	M4/M5	KRAS	s.c.	60	tumor volume
AML13643	M5	N/A	s.c.	35	tumor volume
AML13990	M5	N/A	s.c.	40	tumor volume
ALL-SCID 2	c-ALL	N/A	i.v.	45	spleen weight
ALL-SCID 3	T-ALL	N/A	i.p.	40	tumor nodules weight
ALL-SCID 4	T-ALL	NOTCH-1, NRAS	s.c.	50	tumor volume
ALL-SCID 5	c-ALL		s.c.	70	tumor volume
ALL-SCID 6	T-ALL	none	s.c.	40	tumor volume
			i.v.	60	spleen weight
ALL-SCID 7	pre-B-ALL	HNF1A, NRAS	i.v.	30	spleen weight, survival
ALL-SCID 19	pro-B-ALL	N/A	s.c.	40	tumor volume
ALL11656	c-ALL	none	s.c.	60	tumor volume
			i.v.	55	spleen weight

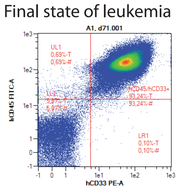
AML11655 i.v. - monitoring by flow

Analyses between day 60-80:
- Leukemic cell load: hCD45
- Specific differentiation marker: hCD11b, hCD14 and hCD15
- time to disease manifestation
- spleen weight

FACS-Monitoring of leukemia

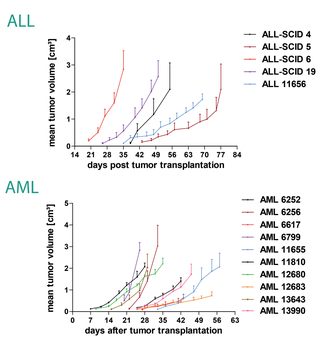


Final state of leukemia

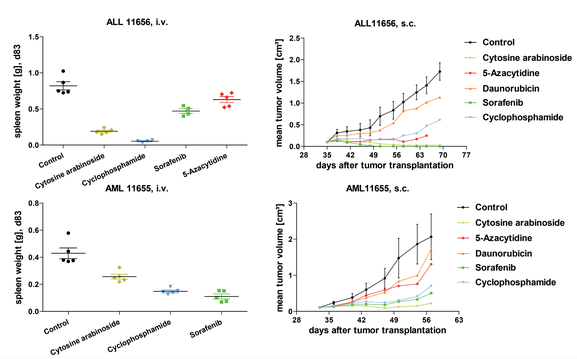


Acute Leukemias

Different growth kinetics of PDX



Similar response to SoC in s.c.- and i.v.- PDX



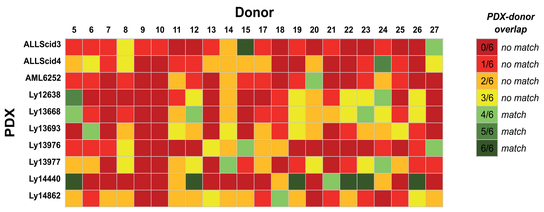
Lymphomas

Clinical data of lymphomas

PDX ID	Histology	COO*	Translocation	Protein expression	CD markers
Ly13005	DLBCL	ABC	UPF3B/GPR34 t(q24;p11.4) KDM6A/DACH2 t(p11.3;q21.2)	BCL2 BCL6 MYC	CD10 CD20 CD30
Ly12318	DLBCL (double hit)	ABC	none	BCL6	CD5 CD10 CD19 CD20 CD38
Ly13136	Anaplastic TCL	intermediate/ unclassified	ALK translocation	ALK	N/A
Ly13802	Angio-immuno-blastic TCL	N/A	N/A	N/A	CD3 CD20
Ly13943	Hodgkin lymphoma	N/A	N/A	BOB1 OCT-2 IRF4 PAX5	CD20 CD30

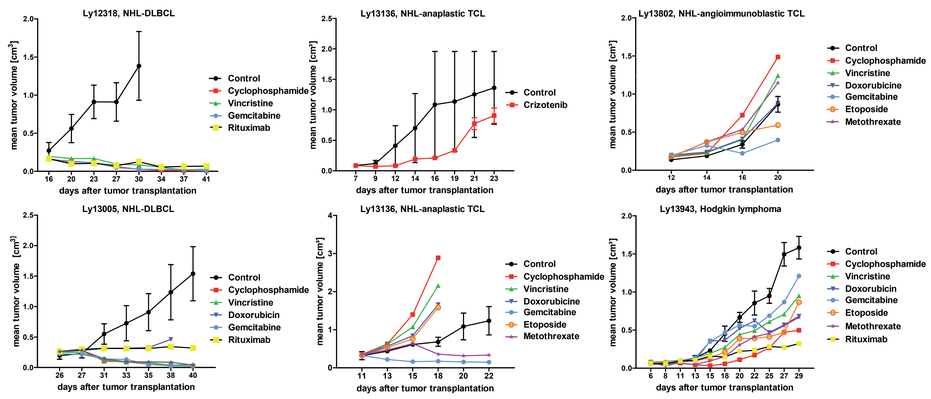
*COO: Cell Of Origin N/A: not yet available

HLA matching: PDXs with PBMC donors



HLA profile matching analyses resulted in 10 PDX-donor matches across all ALL, AML and LY models. For a match, PDX and donor should be ≥ 4/6 match at HLA-A (2-digit resolution), HLA-B (2-digit resolution) and HLA-DRB1 (4-digit resolution)

Lymphomas - individual response to SoC



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