Patient derived xenografts of hematologic malignancies for translational research

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Background and Aim

Acute leukemias and lymphomas represent a very heterogeneous group of hematologic malignancies and pose an important challenge in the clinical routine. They frequently develop resistance to the treatment with standard-of-care (SoC) drugs and have a high incidence of disease recurrence. Recent progress in molecular profiling has helped to identify new potential drivers for the different leukemia and lymphoma subtypes, with some of them being potential therapeutic targets. Further target validation and drug development projects are highly dependent on corresponding preclinical models representing the different clinical subtypes.
Therefore, we started to establish and characterize new patient derived xenografts (PDX) of AML, ALL and lymphomas for drug development and translational research.

Methods

AML- and ALL-PDX 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- or Hodgkin lymphoma-PDX were derived from peripheral blood, lymph node extirpations or core needle biopsies, and were usually transplanted subcutaneously into immunodeficient mice. All samples were obtained after informed consent.
After at least three in vivo passages PDX models were treated with SoC and investigational drugs. Gene expression profiles as well as analyses of gene mutations within the first in vivo passages are under progress.

Results

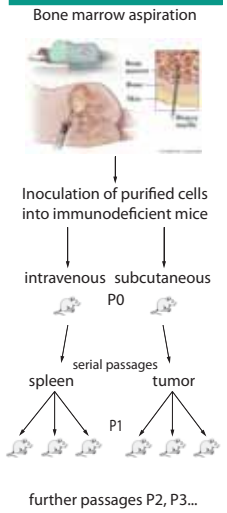
More than 20 new PDX models from AML, ALL, NHL and HL have been successfully established and characterized. Highly individual response to the treatments were observed, correlation analyses with mutations and gene expression are ongoing.
A systemic AML-PDX (AML11655) was established and tracking the leukemic cells in blood allows early evaluation of treatment effects.

Conclusion

These newly and extensively characterized PDX models from hematologic malignancies are suitable tools for preclinical drug development. They provide an exceptional platform for the identification and validation of new targets and allow the preclinical screening of new compounds and combinations for translational research projects.

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

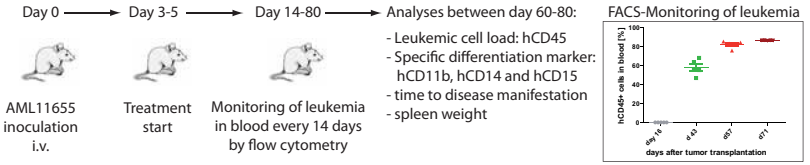
PDX establishment



Clinical data of acute leukemias and characteristics of established PDX models

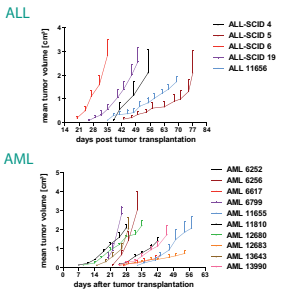
PDX ID	FAB classification	Mutations PDX	Tumor inoculation	Read out	
				Time +/- (days)	Parameter
AML 6252	M4	FLT-3, PTPN-11	s.c.	50	tumor volume
			i.v.	30	spleen weight, survival
AML 6256	M5	TP53, PTPN-11	s.c.	45	tumor volume
AML 6617	M5	ATM, PTPN-11	s.c.	45	tumor volume
AML 6799	M1	APC, HNF1A, RET	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. - adjuvant therapy setting

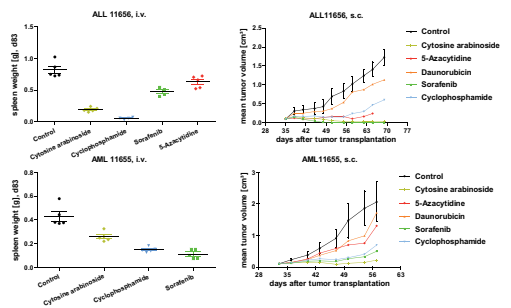


Acute Leukemias

Different growth kinetics of PDX



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



Lymphomas

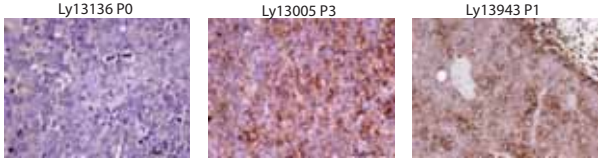
Clinical data of lymphomas

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

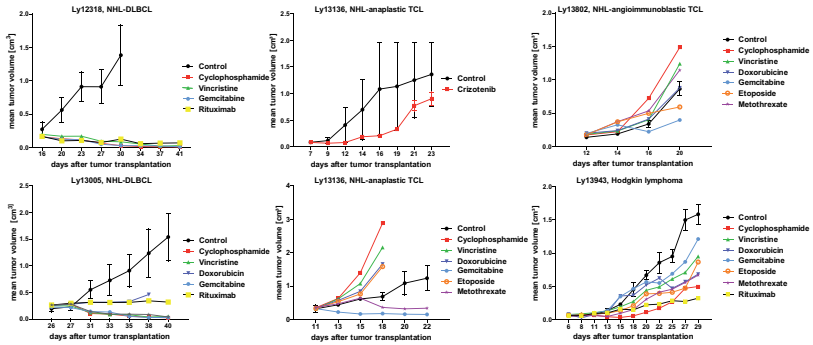
*COO: Cell Of Origin N/A: not yet available

Lymphomas

CD20 staining of Lymphoma-PDX



Lymphomas - individual response to SoC



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