Immune-Avatar humanized models For IO *in vivo* studies

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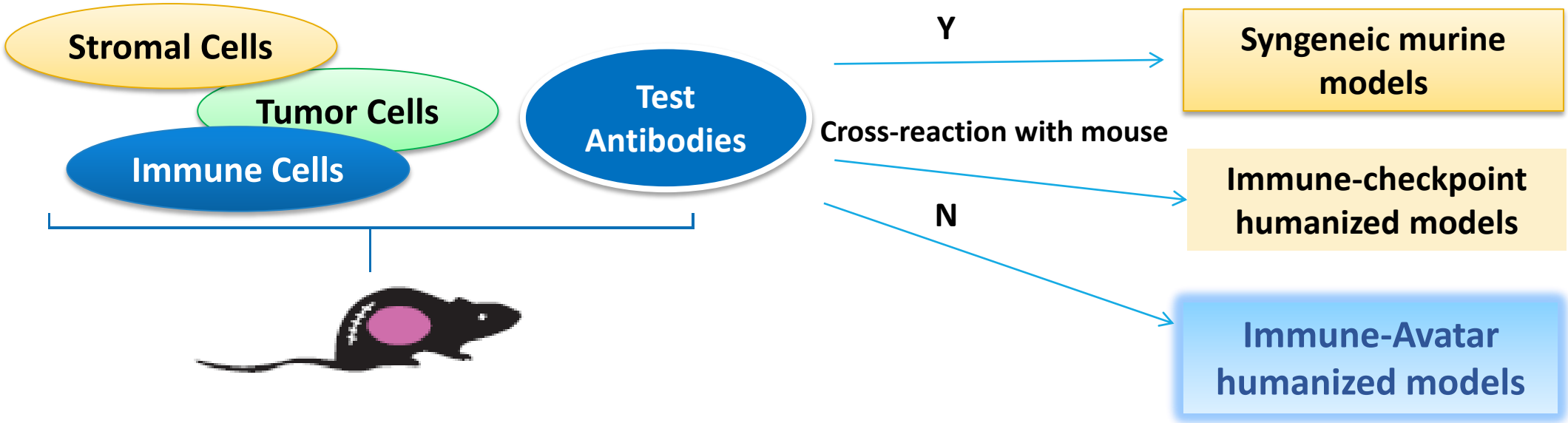
Outline

- WuXi in vivo models in Immuno-Oncology
- WuXi immune-avatar humanized models
  - WuXi PBMC humanized models
  - WuXi hHSC humanized models
- Next generation humanized models

WuXi *in vivo* models in Immuno-Oncology

Background



What are we looking for?

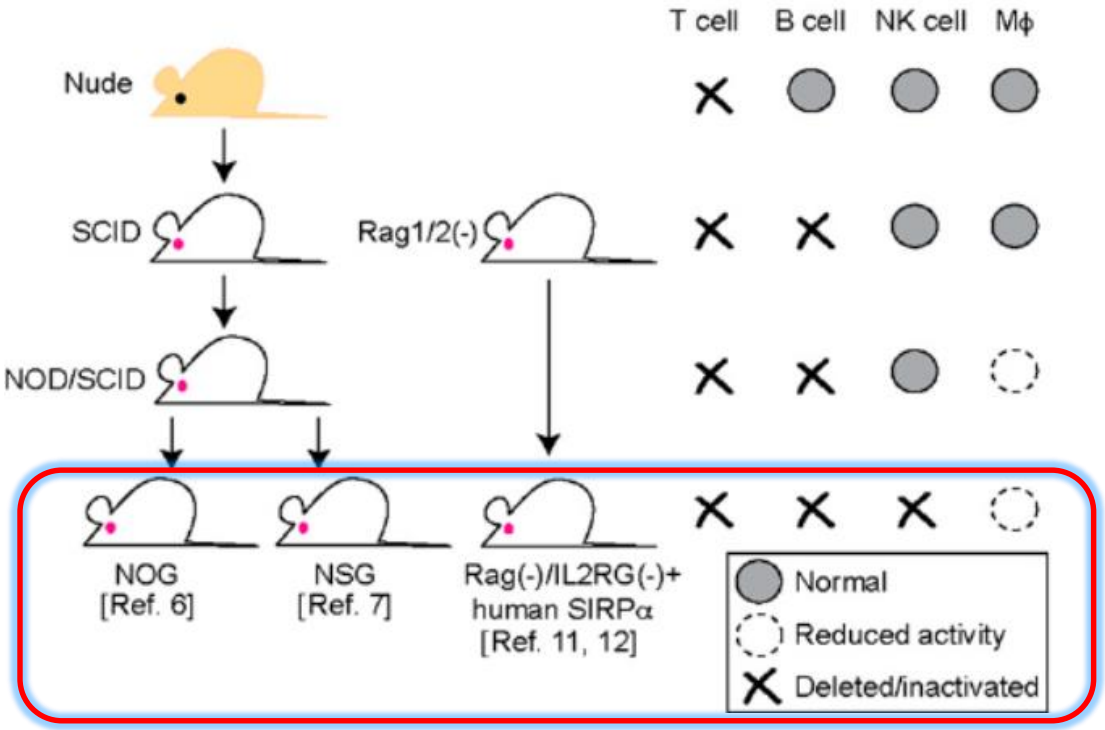
Mouse models harboring human tumor and immune cells to study efficacy and MoA of humanized/fully human antibodies

Immune-Avatar humanized models

Severe immunodeficient mice engrafted with human immune cells (HSCs or PBMCs) and bearing human tumor xenografts

WuXi immune-avatar humanized models

Background



The “NOD SCID Gamma” background recipient mouse has been shown to support greater engraftment of human immune cells
(Goyama, Blood 2015)

hPBMC model

- T cell focused studies, quick and flexible
- 1 wk for re-constitution/3-5 wks of dosing &observation window
- 2 systems for different study purpose
- Combine with WuXi PDX/CDX models

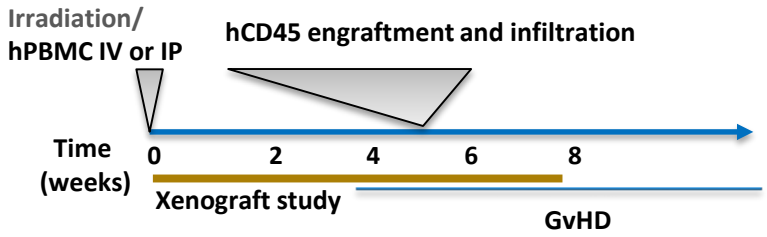
hHSC model

- Multiple lineage re-constitution
- 4-8 months lead time
- Combine with WuXi PDX/CDX models

WuXi PBMC humanized models

Two PBMC delivery systems: i.v. injection or co-inoculation with tumor

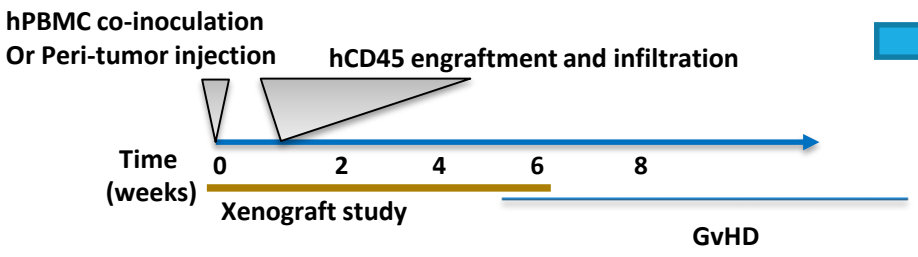
Systemic delivery PBMC (Systemic model)



- **More relevant**: circulation T cells infiltrating in tumors
- Only **3-4 arms** per study (single donor)
- Earlier GvHD

→ **Translational Research**
→ **Drug/Candidate efficacy**

co-inoculation of PBMC with Tumor cells (co-inoculation model)



- **More straight forward**: direct contact between effect cells and target cells
- **8-12 arms** per study(single donor)
- Delayed GvHD
- Multiple injection feasible

→ **MoA study**
→ **Lead screening & Optimization**

Criteria

QC: Immune reconstitution
Donor: single donor for 1 study, HLA typing (optional)
Leading time: 2-3 months

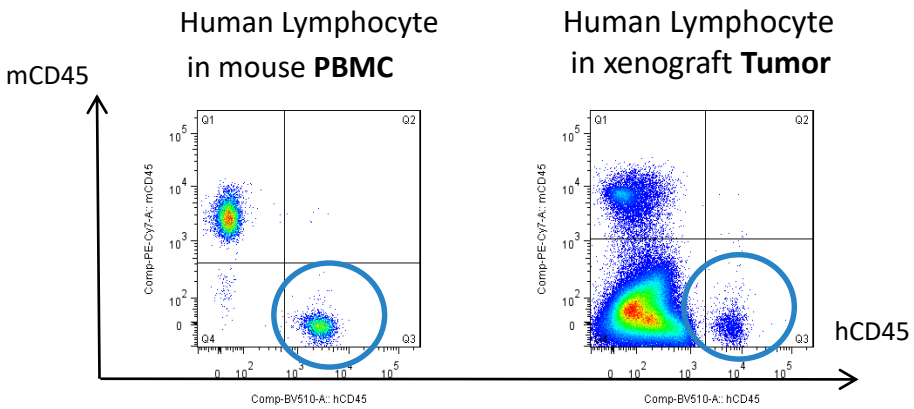
Feasible conditions

Immune cells: PBMC/T cells
Precondition: *in vitro* activation/ co-culture with target cells
Injection: IP/IV/SC; single/multiple injection

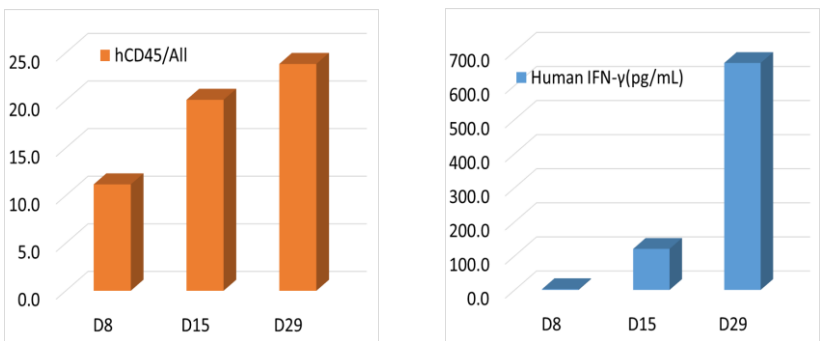
WuXi PBMC humanized models

PBMC engraftment in NOG mice via i.v. injection

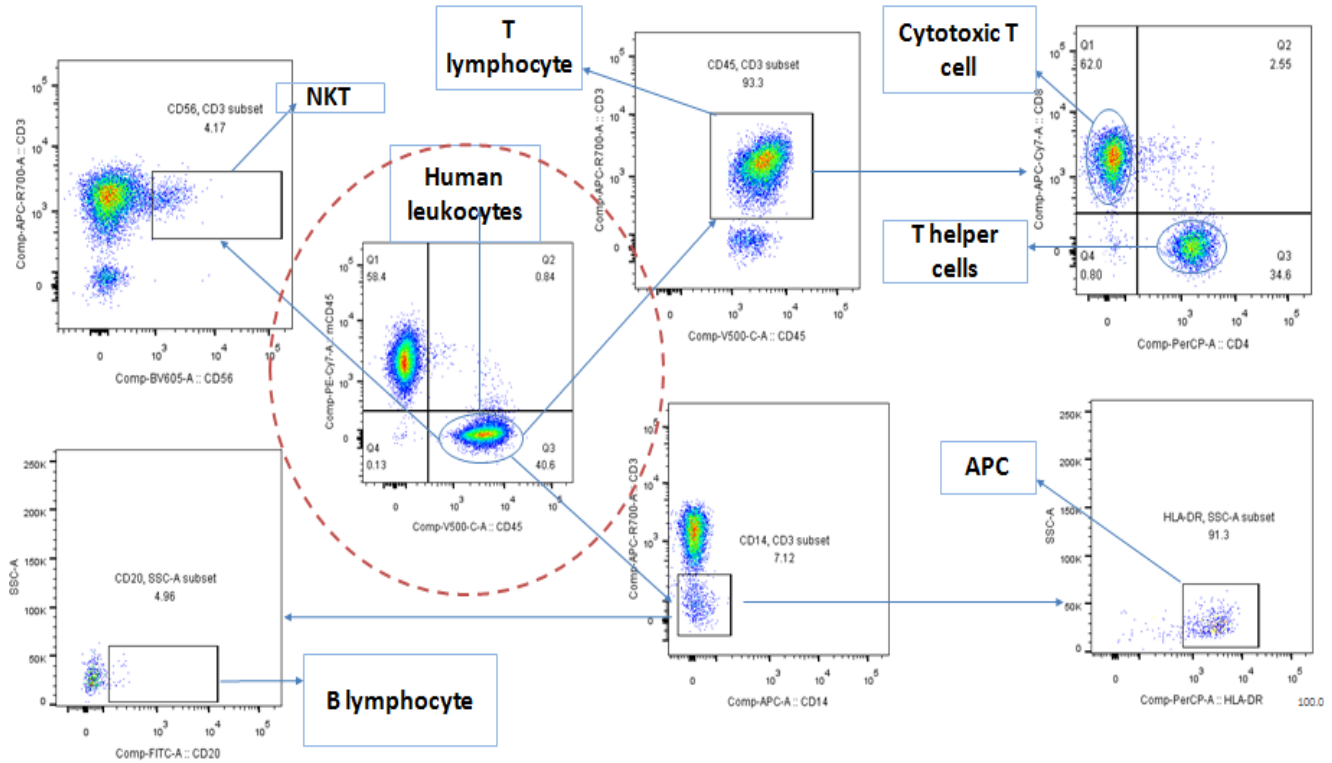
Successful human lymphocyte engraftment



Functional T cell release human cytokine

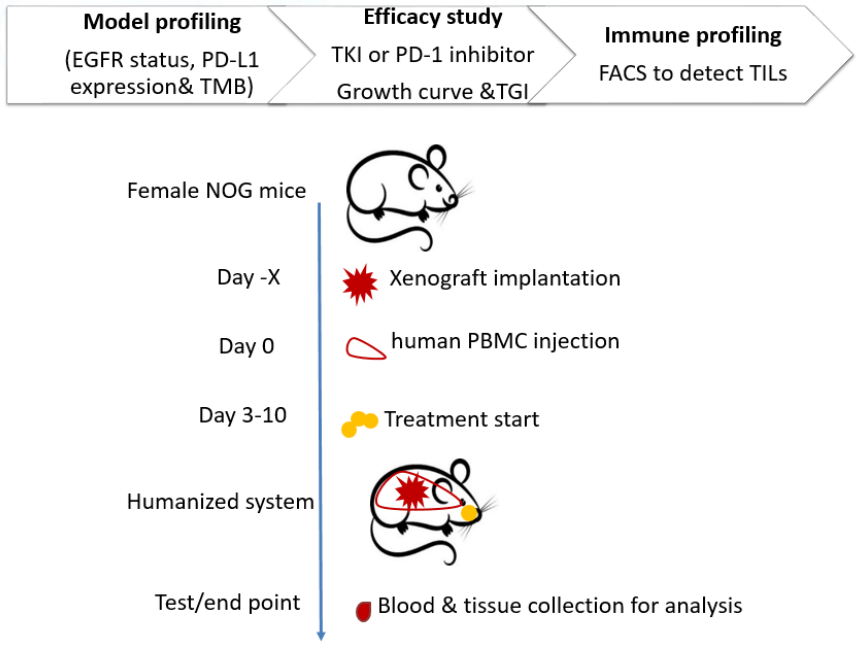


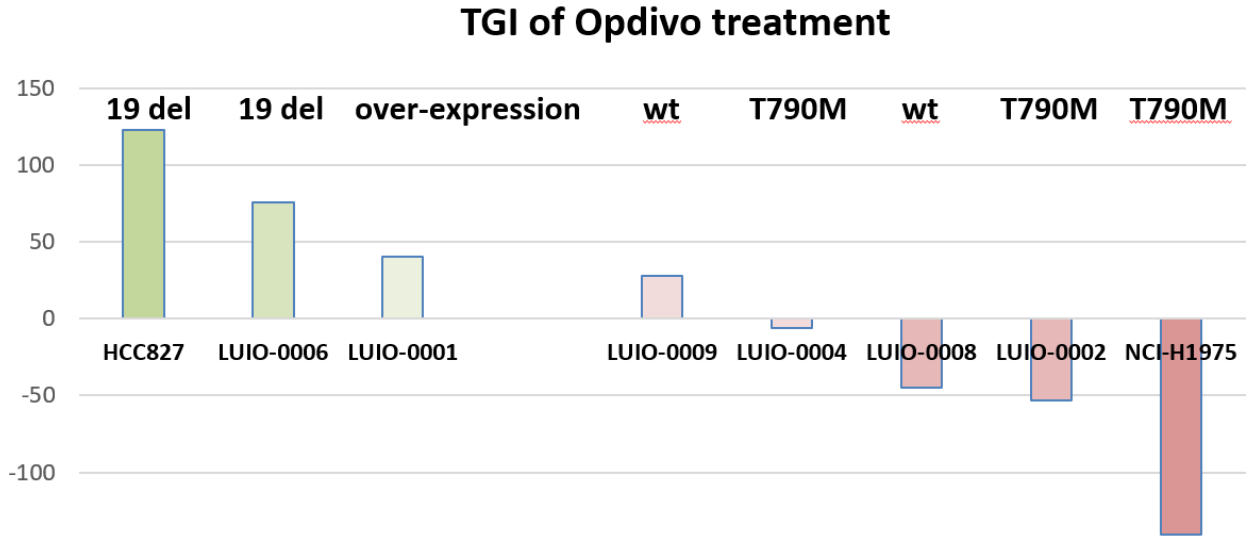
Human Lymphocyte subpopulation

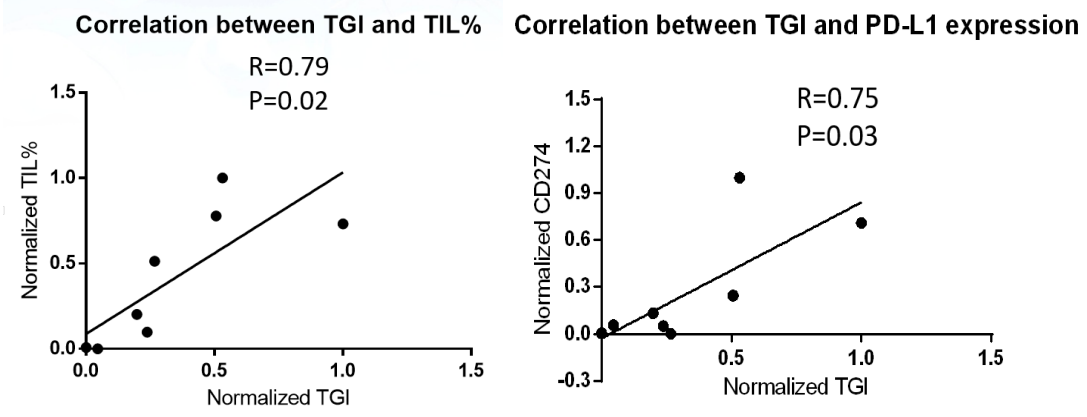


WuXi PBMC humanized models

Mouse trial of PD-1 antibodies in hPBMC-PDX models





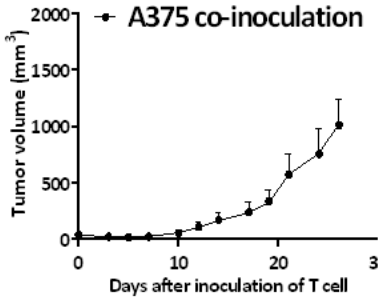


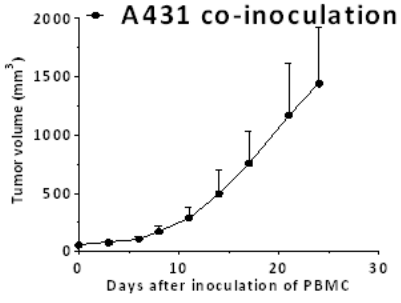
- Only 30% IO-xenograft models can benefit from nivolumab treatment
- Good correlation have been observed
  - a) between tumor lymphocyte infiltration (human-reconstituted) and efficacy of nivolumab
  - b) between PD-L1 expression and efficacy of nivolumab

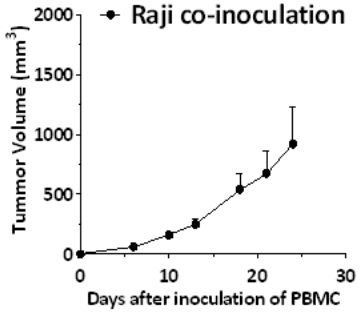
WuXi Immune-avatar humanized models

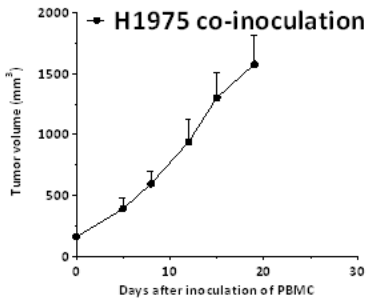
Growth kinetics and TILs analysis

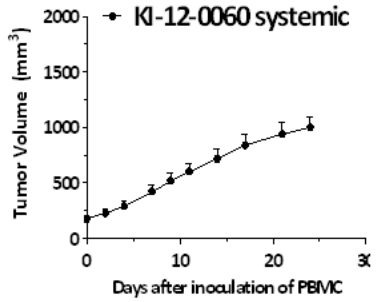
Growth curve of 6 xenografts on PBMC humanized models

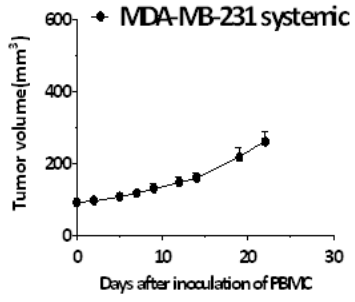




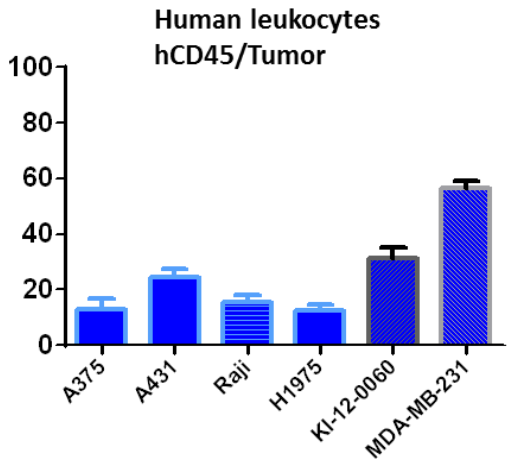


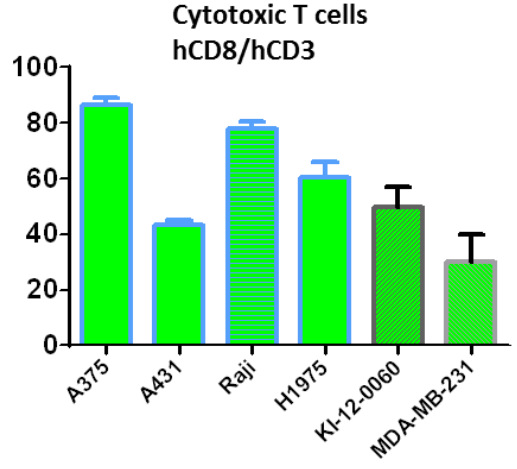


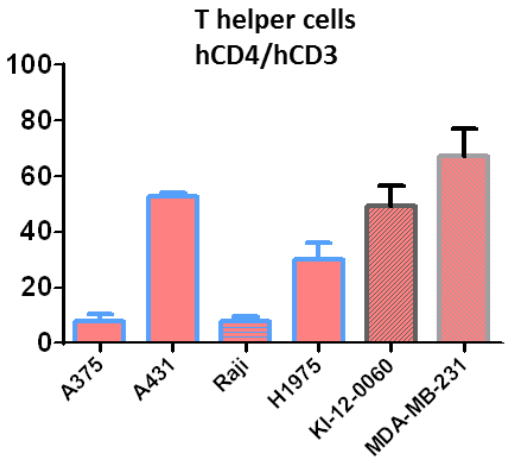




Tumor infiltrating leukocytes in 6 xenograft on PBMC humanized models







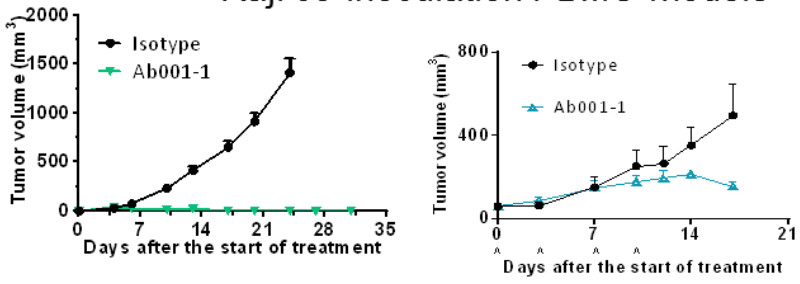
WuXi Immune-avatar humanized models

Reproducibility and variation

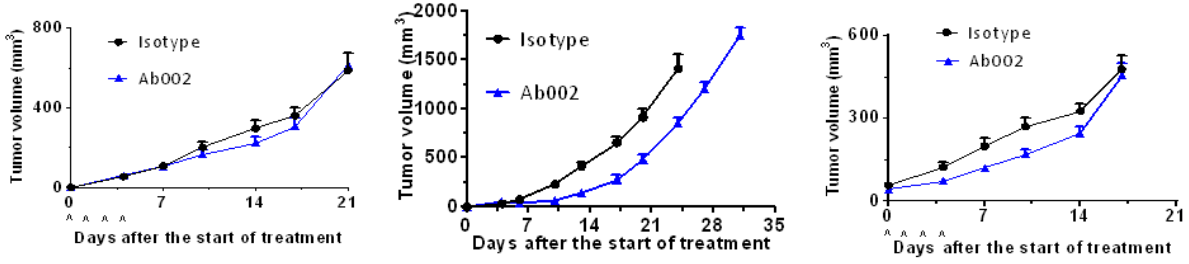
Reproducibility of drug response

Raji co-inoculation PBMC models

Ab001



Ab002



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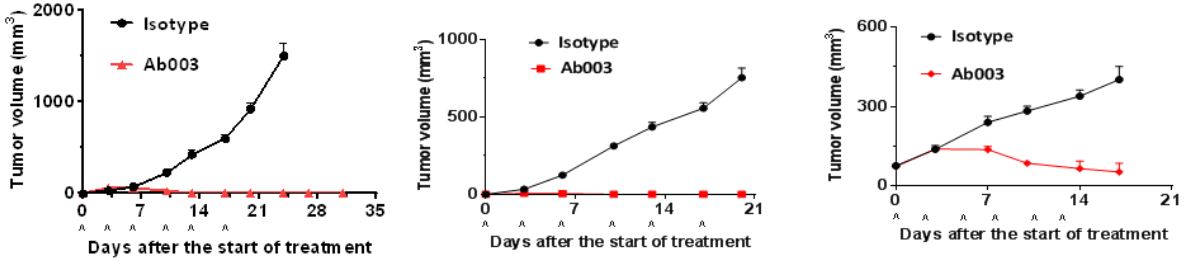
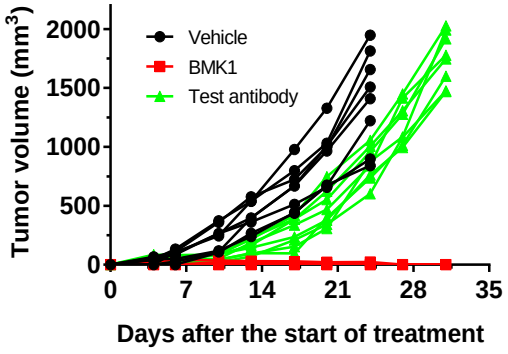
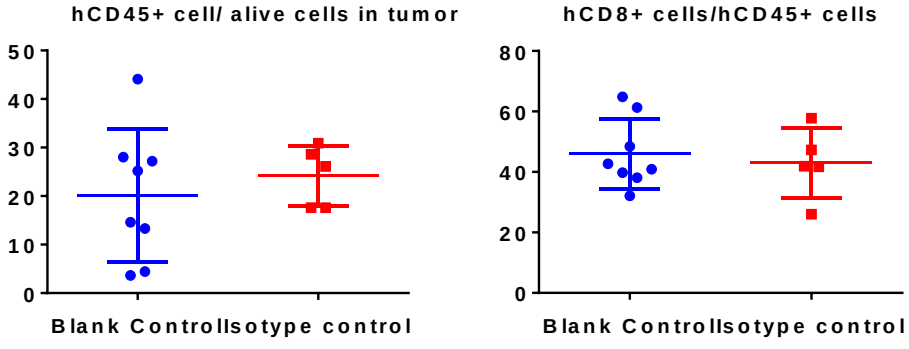


Individual tumor growth kinetics

Raji co-inoculation PBMC model



Individual tumor infiltration lymphocytes



The growth curve may varies among different donors, but the response trend are consistent.

WuXi PBMC humanized models-Systemic (25)

Model ID	Cancer type	Target	Efficacy
PDX (14)			
LU-01-0737	Lung Cancer	EGFR, PD-1	Yes
LU-01-1004	Lung Cancer	EGFR, PD-1	Yes
LU-01-1013	Lung Cancer	EGFR, PD-1	Yes
LU-01-1008	Lung Cancer	EGFR, PD-1	Yes
LU-01-1017	Lung Cancer	EGFR, PD-1	Yes
LU-01-1030	Lung Cancer	EGFR, PD-1	Yes
LU-01-1033	Lung Cancer	PD-1	Yes
LU-01-1038	Lung Cancer	PD-1	Yes
LU-01-1056	Lung Cancer	PD-1	Yes
LU-01-1113	Lung Cancer	PD-1	Yes
LU-01-1114	Lung Cancer	PD-1	Yes
KI-12-0060	Renal Cancer	PD-1	Yes
KI-12-0062	Renal Cancer	PD-1	Yes
CO-04-0284	CRC	TRK; PD-1	Yes

Model ID	Cancer type	Target	Efficacy
CDX (11)			
BT-474	Breast Cancer	HER2, CD3	
HCC827	Lung Cancer	PD-1, EGFR	Yes
Daudi	Lymphoma	CD19, CD3	
K562	Leukemia	CD19, CD3	
Nalm-6	Leukemia	CD19, CD3	
NCI-N87	Gastric Cancer	HER2, VEGF, CD3	
MKN-45	Gastric Cancer	-	
A375	Melanoma	VEGFR2	Yes
A431	Skin Cancer	EGFR/CD3	Yes
MDA-MB-231	Breast Cancer	PD-1	Yes
PC-3	Prostate Cancer	CD3, CD155, PSMA	

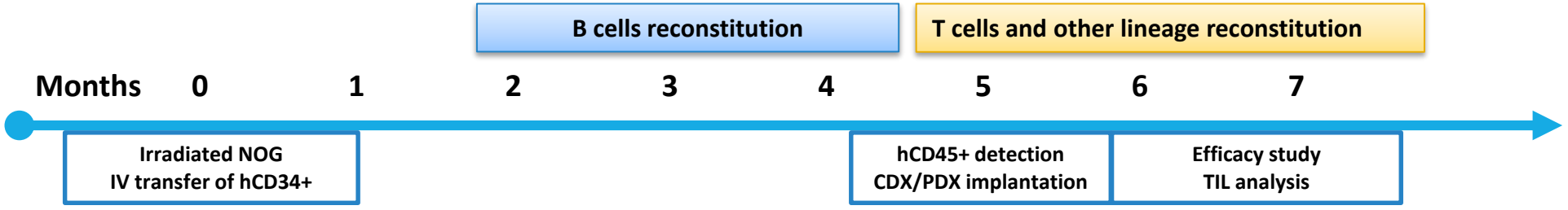
WuXi PBMC humanized models- co-inoculation or peri-tumor (26)

Model ID	Cancer type	Target	Efficacy
PDX (5)			
LU-01-0737*	Lung Cancer	EGFR, PD-1	Yes
LU-01-1004	Lung Cancer	EGFR, PD-1	Yes
LU-01-1013	Lung Cancer	EGFR, PD-1	Yes
LU-01-1008	Lung Cancer	EGFR, PD-1	Yes
CO-04-0284	CRC	TRK; PD-1	Yes

Model ID	Cancer type	Target	Efficacy
CDX (20)			
NCI-H1975*	Lung Cancer	EpCAM/CD3; EGFR/CD3	Yes
HCC827	Lung Cancer	PD-1; EGFR	Yes
K562	Leukemia	CD19, CD3	
Nalm-6	Leukemia	CD19, CD3	
Raji*	Lymphoma	CD19/CD3; CD20/CD3	Yes
Ramos	Lymphoma	CD19/CD3	
Jeko-1	Lymphoma	CD19/CD3; CD20/CD3	
Hep3B	Liver cancer	CD3, CD133	
Huh-7	Liver cancer	*EpCAM, CD3*	
BT-474	Breast Cancer	*HER2, CD3*	
MDA-MB-231	Breast	PD-1	Yes
LoVo	CRC	VEGFR/CD3	
HT29	CRC	VEGF165, PD-1	
SNU-16	Gastric Cancer	-	
PC-3	Prostate Cancer	CD3, CD155, PSMA	
A431*	Skin Cancer	EGFR/CD3	Yes
U266B1	Multiple Myeloma	NY-ESO-1	Yes
A375*	Melanoma	VEGFR2	Yes
SK-OV-3	Ovarian	HER2/CD3	
HT-1080	Sarcoma	-	

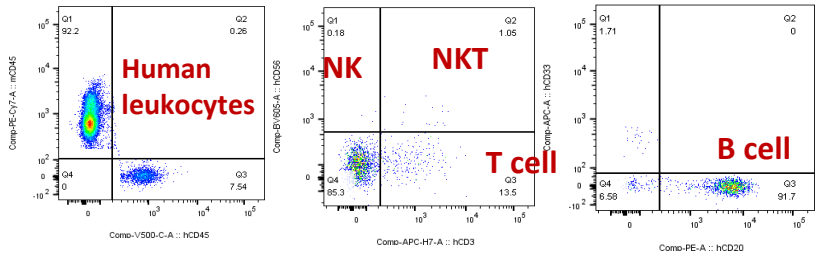
WuXi Immune-avatar humanized models-HSC models

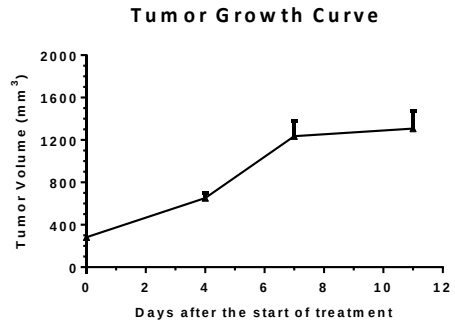
HSC humanized models introduction



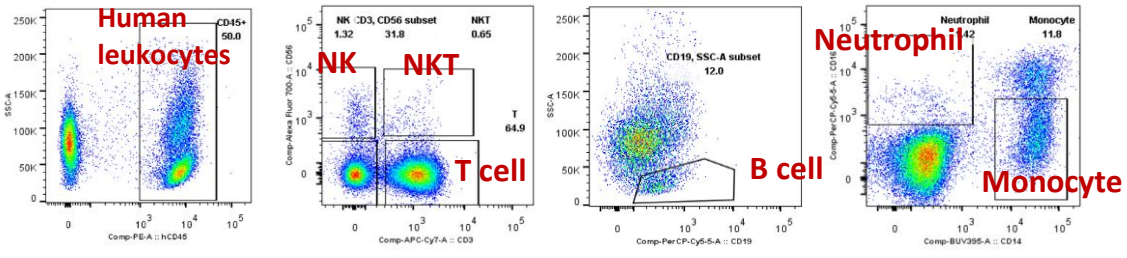
In blood

2 months



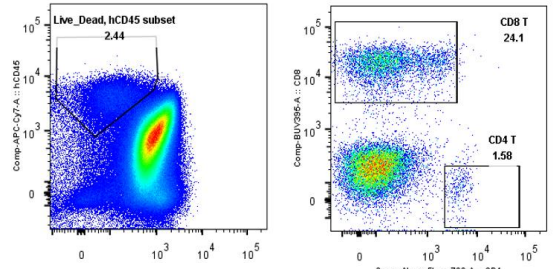


6 months



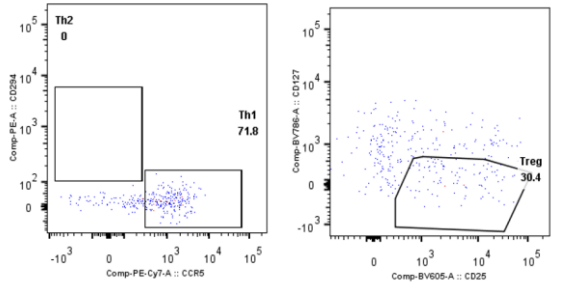
Tumor infiltrating lymphocytes

Human leukocytes



T helper and Cytotoxic T

Th1 and Th2

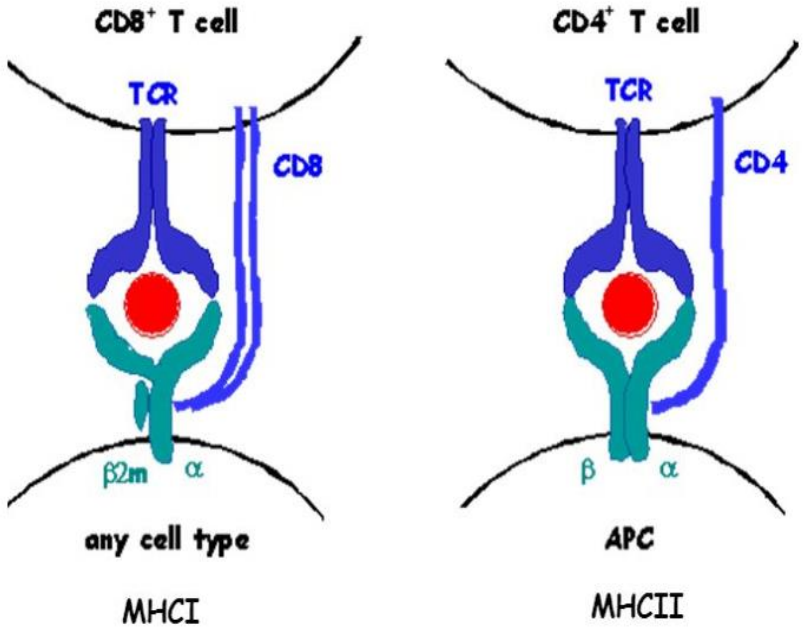


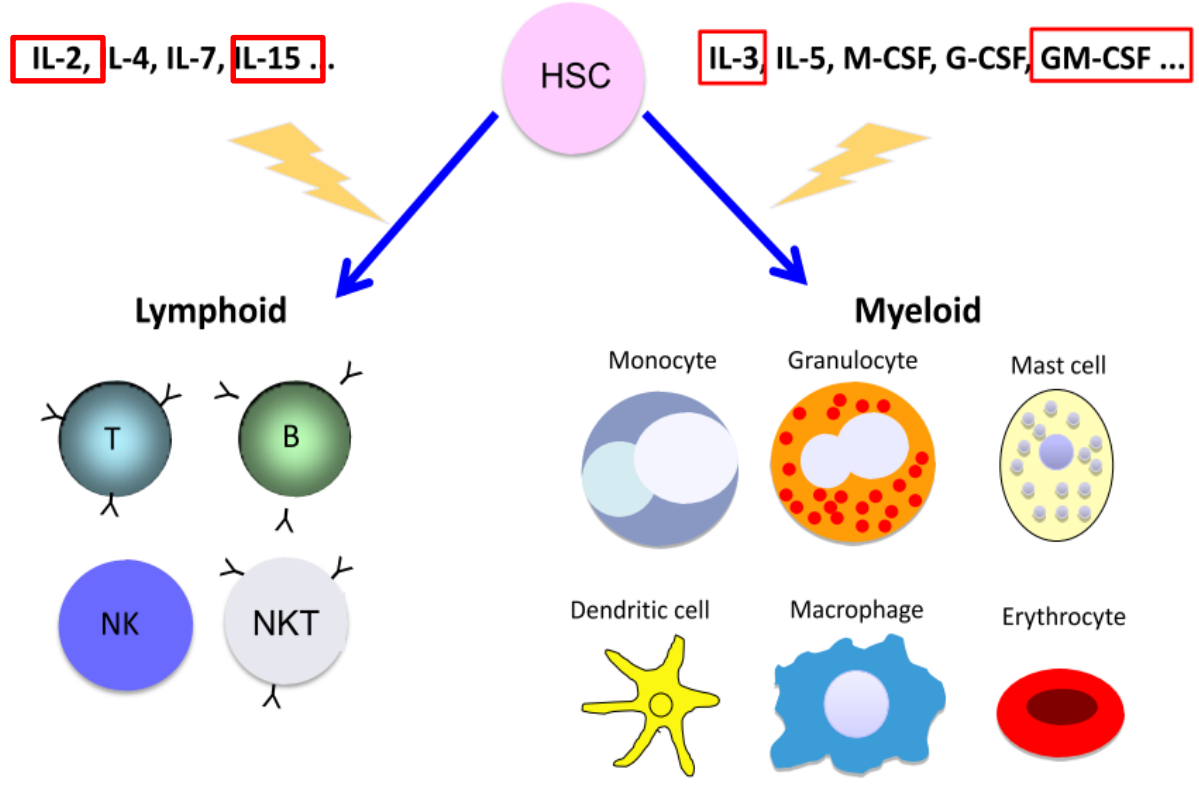
Treg

- CD8+ T cells (cytotoxic T cell) predominated in TILs
- Th1 (cellular immunity) and Treg (suppressor T cells) were detected in TILs while Th2 (humoral immunity) was not

Next generation humanized models

Design





Transgenic HLA expression or elimination of mouse H2

Reduce xeno-reactivity, delay GvHD
Increase study window of PBMC humanized models

Transgenic Human cytokine expression

Promote myeloid cell engraftment/NK cell engraftment for hHSC humanized models

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