Humanized mouse models for evaluation of cancer therapies

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Generation of human immune system reconstituted mice

INTRODUCTION

Mice with a humanized immune system **(HIS)**, so called "humanized" mouse models, can be used to study the complex interactions between the human immune system and tumor cells. In order to assess compounds efficiency in immune-oncology, the *in vivo* model should recapitulate the biological characteristics of the human tumor and the related immune microenvironment.

Human immune system is reconstituted in **immunodeficient mice** using either **human PBMCs or hematopoietic stem cells (HSCs) as well as specific human immune cells such as Dendritic Cells (DCs), T cells, subset of T cells (e.g. gamma9 delta2 T cells) and NK cells.** We also developed mouse humanization models using **combinations of immune subpopulations such as co-transfer of autologous T cells and DCs.**

Humanized mice bearing human target tumor cells constitute relevant models for **evaluation of cancer therapeutics** such as **bispecific antibodies, immune cell targeting antibodies.**

A comprehensive offer with solid experience and know-how

Immune system with hPBMCs	Immune system with hHSCs	Immune system with specific cells
Mouse Host SCID, NOD-SCID, SCID-Beige NSG, NOG	Mouse Host NSG, NSG-SGM3 NOG, NOG-IL2, NOG-IL15 NOG-EXL, BRGS	Mouse Host NSG, NOG
1st study in 2002 at ODS	1st study in 2008 at ODS	1st study in 2017 at ODS
● Tumor free - GvHD - Antigen recall response	● Tumor free - Cytokine secretion assay	● Immune cells - Gamma delta T cells - Gamma delta T cells + iNKT cells - T cells - Autologous T + moDCs
● Tumor bearing - Ab targeting tumor antigen - Immune retargeting compounds - Engineered T cells - Immune checkpoint modulators	● Tumor bearing - Ab targeting tumor antigen - Engineered T cells - Immune checkpoint modulators	● Tumor free - Immune cell residence time in blood ● Tumor bearing - Ab targeting tumor antigen

Humanized mouse platform

RESULTS

Tumor cells drive the immune infiltration

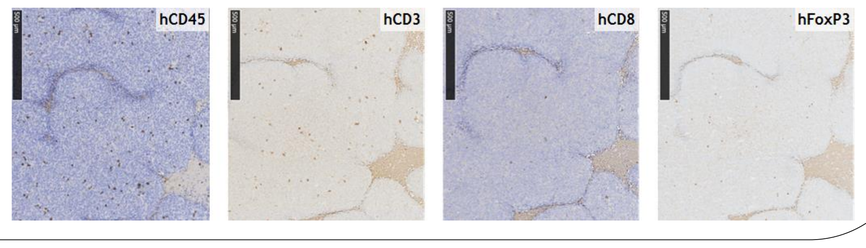
ID# PDX	Patient Infiltrat	NOG–PBMC	NOG-EXL (HSCs)
OD-BRE-589	+/-	-	-
IM-BRE-044	+++	++	+++
IM-OVA-512	+/-	+/-	+/-
IM-OVA-535	+++	+/-	+

Interactions between tumor cells and immunomodulators inside the tumor microenvironment play a key role in success of immunotherapy.

ID# PDX	Mouse model	hCD45	hCD3	hCD8	hFoxP3	hPD-L1
OD-BRE-589 (TNBC, poorly infiltrated in patient)	NOG-PBMC	-	-	-	-	-
	NOG-EXL (HSCs)	-	-	-	-	-
IM-BRE-044 (TNBC, highly infiltrated in patient)	NOG-PBMC	++	++	++	+	++
	NOG-EXL (HSCs)	+++	+++	+++	+++	++

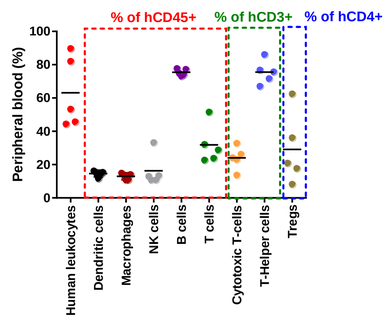
Level of TILs in PDX xenografted into humanized mice is correlated with immune cell infiltration in originating patient tumor

IM-BRE-044 tumor bearing NOG-EXL (HSCs) mice



Selecting the best HIS model to address a specific question

NOG-EXL(HSCs) mice

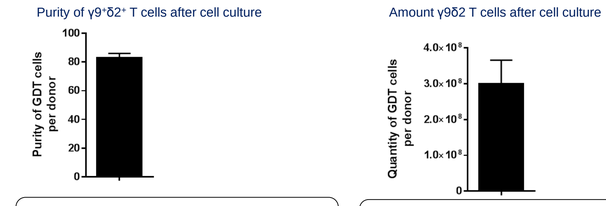


Abundant T cells & B-cells, as well as macrophages, DC and NK cells are detected in blood in huNOG-EXL mice

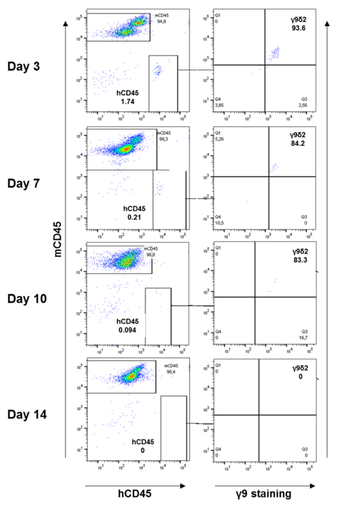
Parameters to consider for HIS model selection:

- **MOA of test molecule**
- **Mouse host**
- **Type of human cells engrafted and supported**
- **Advantages/limitations of each HIS model**

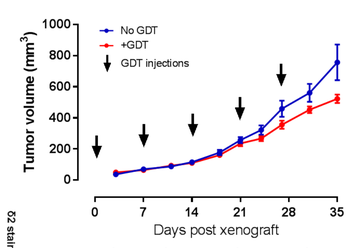
γ9δ2 T cell culture setting



Proportion of γ9δ2 T cell in mouse blood over time



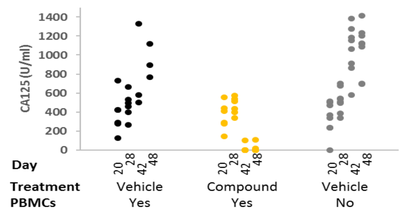
Impact of γ9δ2 T cell humanization on LoVo tumor growth



A protocol to culture and expand pure γ9δ2 T cell was set up. After injection in mice, γ9δ2 T cells could be detected up to 3 days, became rare events after 7 days and were undetectable after 10-14 days. Weekly injection of γ9δ2 T cells in NSG mice bearing LoVo tumors show that γ9δ2 T cells slightly decrease tumor progression.

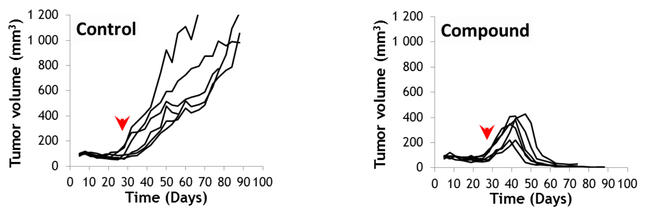
In vivo pharmacology studies using humanized mice

Circulating biomarker



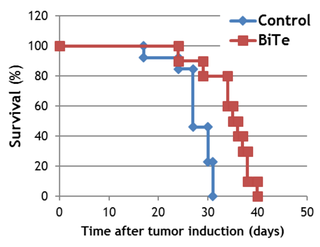
A bispecific antibody recruting human effector cells led to a significant reduction of CA125 biomarker in an ascitic NIH:OVCAR-3 ovarian tumor humanized mouse model

Tumor volume

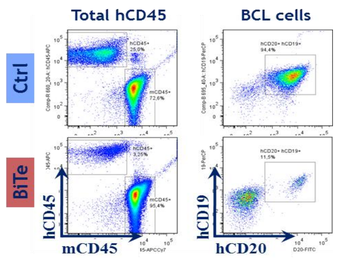


A bispecific antibody cured human breast BT-474 tumor in PBMC-reconstituted mice.

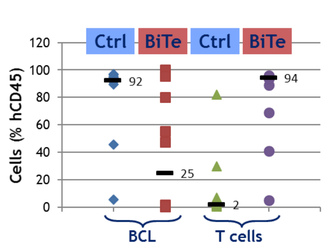
Survival increase



Tumor cell depletion

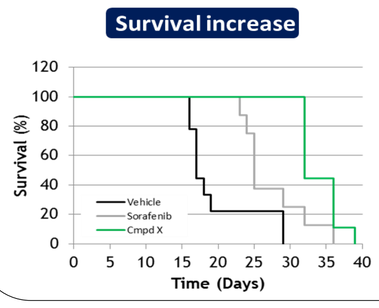


Immune cell recruitment

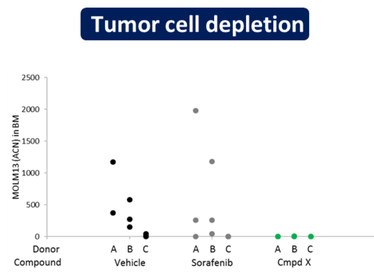


A BiTe therapy increased survival of hematological tumor bearing PBMC-engrafted mice. This improved survival was correlated with a tumor burden reduction and a T-cell recruitment

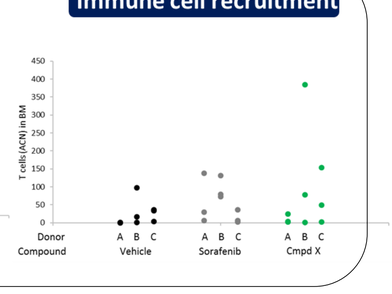
Survival increase



Tumor cell depletion



Immune cell recruitment



Survival of disseminated human AML in T-cell reconstituted mice was significantly increased and associated with tumor burden reduction and immune cell recruitment

CONCLUSIONS

- Simultaneous implantation of human immune cells and tumor results in a humanized mouse model that recapitulates the development of human TILs and allows an assessment of tumor and immune system interaction.
- Humanized mouse models constitute **preclinical tools for studying immunologic process** and evaluating immunomodulating agents in complement of our syngeneic mouse model platform.
- **A large panel of humanized mouse models is available to address specific immune cancer cell questions**

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