Humanized Mouse Models for Evaluation of Cancer Therapies

5196

O. Duchamp[1], F. Bichat[1], C. Mignard[1], F. Ghiringhelli[2], J.-F. Mirjolet[1]

[1] Oncodesign, Dijon, [2] Center Georges Francois Leclerc, Dijon (FRANCE)

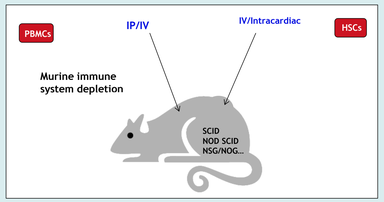
For more information: contact@oncodesign.com

INTRODUCTION

Generation of human immune system reconstituted mice

Mice with a **humanized immune system**, so called **"humanized" mouse models**, have been established to study the complex interaction of the human immune system during human disorders. In case of cancer research, the ***in-vivo* model** ideally should recapitulate the biological characteristics of the human tumor and of the related tumor microenvironment in patient such as immune system.

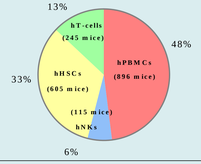
Human immune system is reconstituted in **immunodeficient mice** using either **human PBMCs or hematopoietic stem cells (HSCs)**. Humanized mice bearing human target tumor cells constitute relevant models for **evaluation of cancer therapeutics** such as **bispecific antibodies**, **immune cell targeting antibodies**.



➢ **POC studies with hPBMCs reconstituted mice**
- Injection of human PBMC in irradiated NOG mice
- IV injection of B-cell lymphoma or SC injection of plasma cell myeloma
- Tumor volume monitoring with caliper for SC tumor, mice termination when hind leg paralysis for IV tumor
- Quantification of immune cell populations and tumor cells in blood bone marrow and spleen samples using flow cytometry analysis (IV tumor model)

➢ **POC studies with hHSCs reconstituted mice**
- Injection of human HSC in BRGS mice
- SC xenograft of lung and ovarian PDX tumor samples
- Tumor volume monitoring with caliper
- Mice termination for collection of blood, spleen, bone marrow and tumor
- Quantification of immune cell populations using flow cytometry and immunohistochemistry analysis

Immune system reconstituted mice



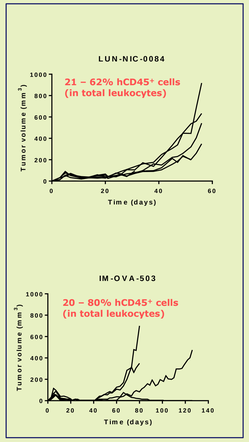
A large panel of humanized mouse models to address specific immune cancer cell questions

Oncodesign has a large experience with immune system reconstituted mice xenografted with solid tumors (BT474, FaDu, HCT-116, LoVo, PDX...) as well as hematological tumors (Daudi, Karpas-299, Ramos...)

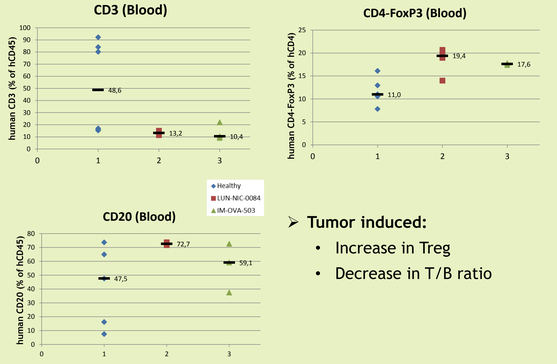
RESULTS

hHSCs reconstituted mice

PDX tumor growth is not affected by humanization in BRGS mice



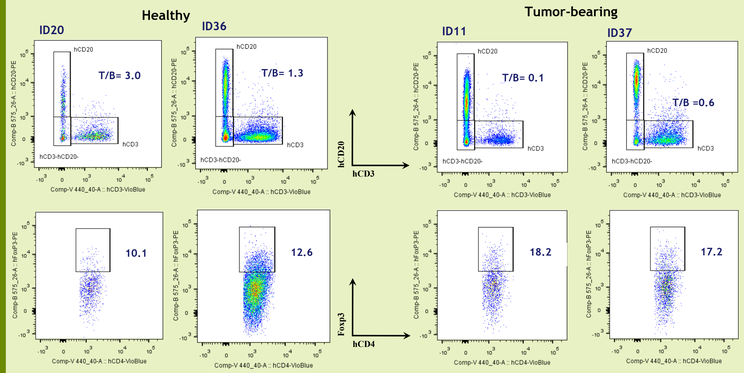
Tumor growth modifies the composition of central lymphoïd and myeloïd cells in blood of humanized BRGS mice (Flow cytometry)



➢ **Tumor induced:**
- Increase in Treg
- Decrease in T/B ratio

➢ **Model of interest for further evaluation of compounds targeting Tregs or interfering with CD8/CD4 populations** (ipilimumab, nivolumab...)

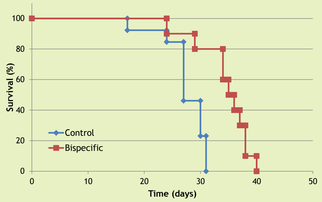
Spleen : non-tumor bearing mice vs tumor bearing mice



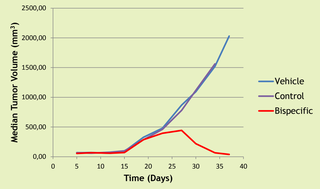
Representative flow cytometry pictures showing human T & B cells population (top panel), Treg population (bottom) in healthy (left) and tumor bearing mice (right).

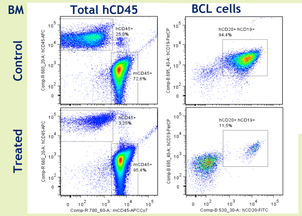
hPBMCs reconstituted NOG mice

IV B cell lymphoma



SC plasma cell lymphoma





➢ **Humanization did not modify tumor progression**

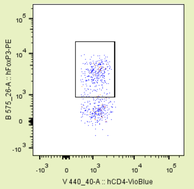
➢ **Death of mice is related to tumor development**

➢ **Efficacy of the compound**
- Increased survival and tumor regression
- Spleen: no remaining B cells
- Bone marrow: significant decrease in BCL cells

➢ **hPBMC humanized and tumor bearing mouse model are of interest to evaluate T cell** recruiting compounds such as bispecific antibody or to evaluate engineered immune cell based therapy such as CAR-T cells.

Tumor infiltration by human immune cells

Treg identified within the tumor (n=2)



➢ **Tumor Lymphoid cells & Myeloid cells (Flow cytometry analysis)**
- T cells: ~55%
- B cells: ~4%
- NK cells: ~6%
- Monocytes: ~3%
- Other myeloid cells: ~5%

Conclusions

➢ **Humanization of immune system of mice** with either hPBMCs of hHSCs **permits the growth of human tumors** either SC *vs* IV xenografted,

➢ **Lymphoid and myeloid cells**, in particular Treg, **are detected in blood and tumors from humanized mice**,

➢ Humanized mouse models constitute **preclinical tools for studying immunologic process** and evaluating immunomodulating agents in complement of our syngeneic mouse model platform.

American Association for Cancer Research (AACR) Annual Meeting / *New Orleans, LA. USA. April 16-20, 2016*

This work was partly supported by a grant from bpifrance *and the French Government*