

Introduction

Immune cells within the tumor microenvironment are now well recognized as targets of interest for cancer treatment.

Many findings from conventional animal models do not apply to humans due to intrinsic differences between species. This fact would explain the great need for humanized mouse models that will accurately support the preclinical development of such therapeutic approaches.

Human immune system should be reconstituted in immunodeficient mice using either human PBMCs, hematopoietic stem cells (HSCs) or other differentiated cells such as T and NK cells. So called "Humanized Immune System" (HIS) mouse models, have been established to study the complex interaction of the human immune system during human disorders, when the syngeneic mouse model cannot constitute the test model.

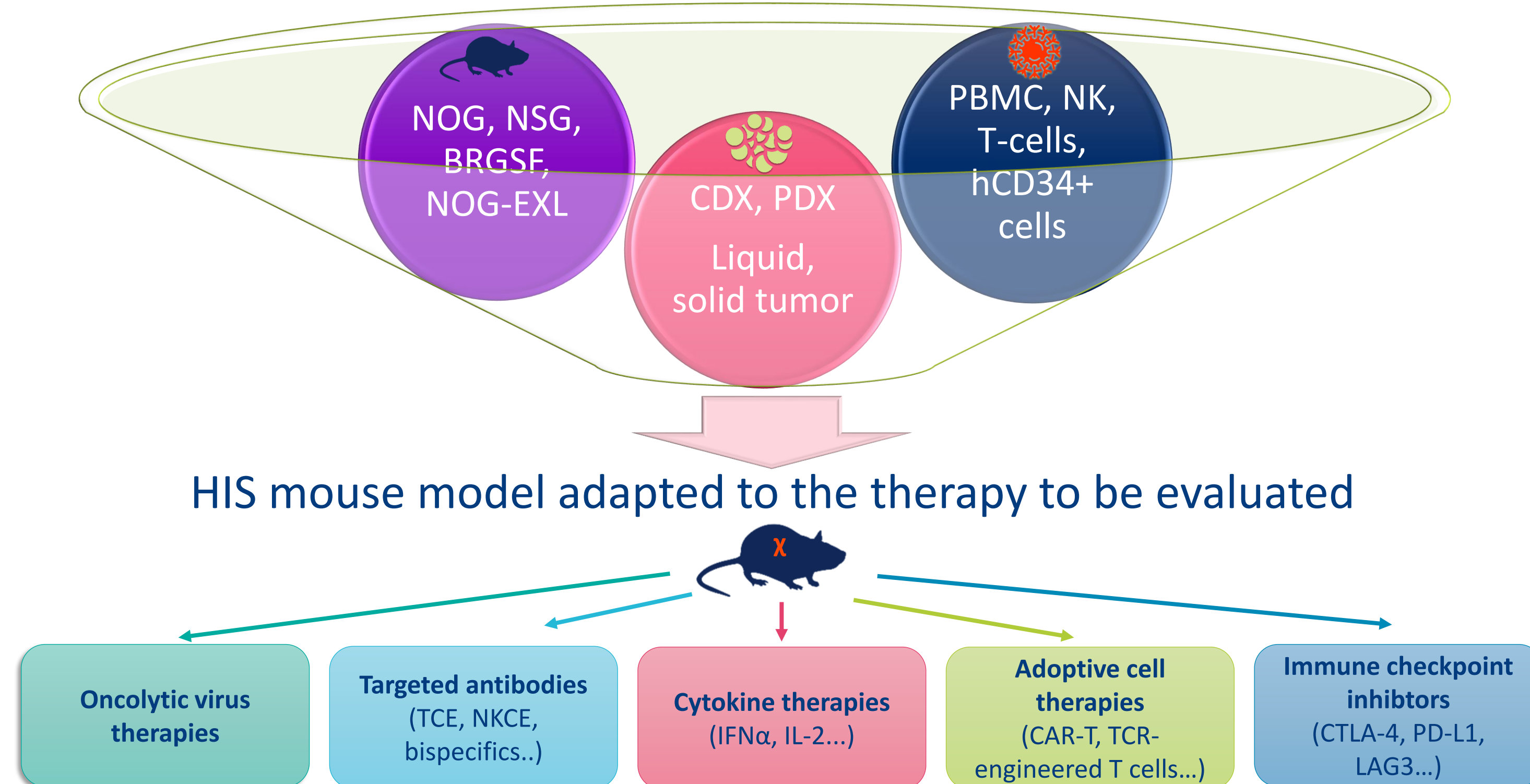
Humanized immunodeficient mice, bearing human immune cells with human target tumor cells, are relevant models to test various therapeutic strategies (e.g. adoptive cell transfer, immune checkpoint inhibitors, oncolytic viruses...) in oncology.

Therapeutic efficiency was assessed by monitoring mice survival and tumor growth using caliper or imaging. The impact of therapeutics on tumors and immune cells was also assessed by flow cytometry and immunohistochemistry analyses.

Model selection: Draw on our experience to build your tailor-made solution

Parameters to consider for HIS model selection:

- MOA of test molecule
- Mouse host
- Tumor molecular and growth characteristics
- Type of human cells engrafted and supported
- Advantages/limitations of each HIS model

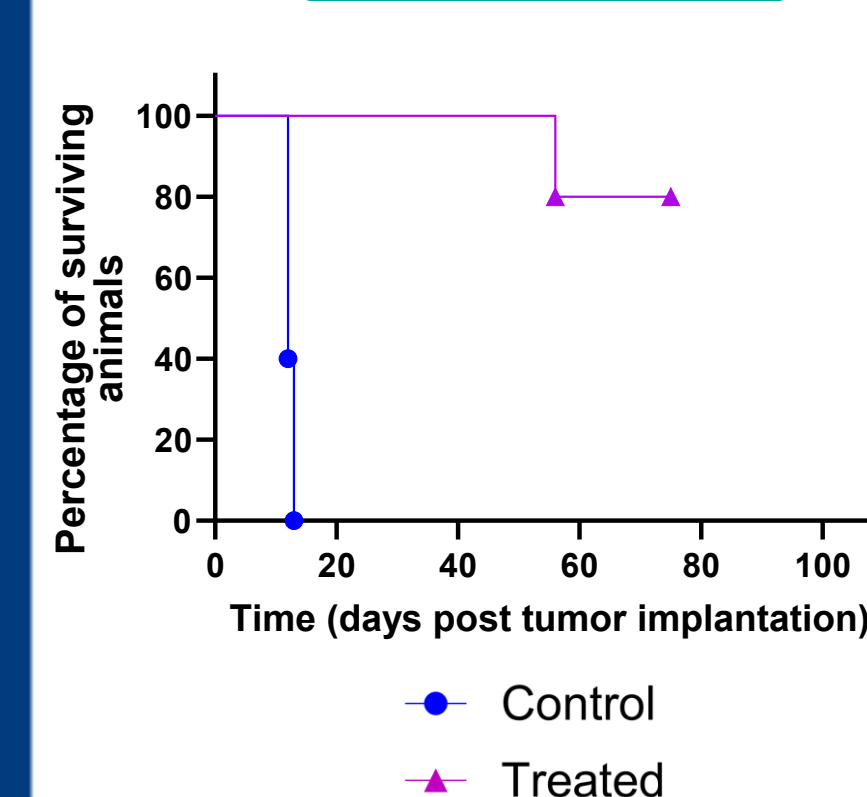


Experiments

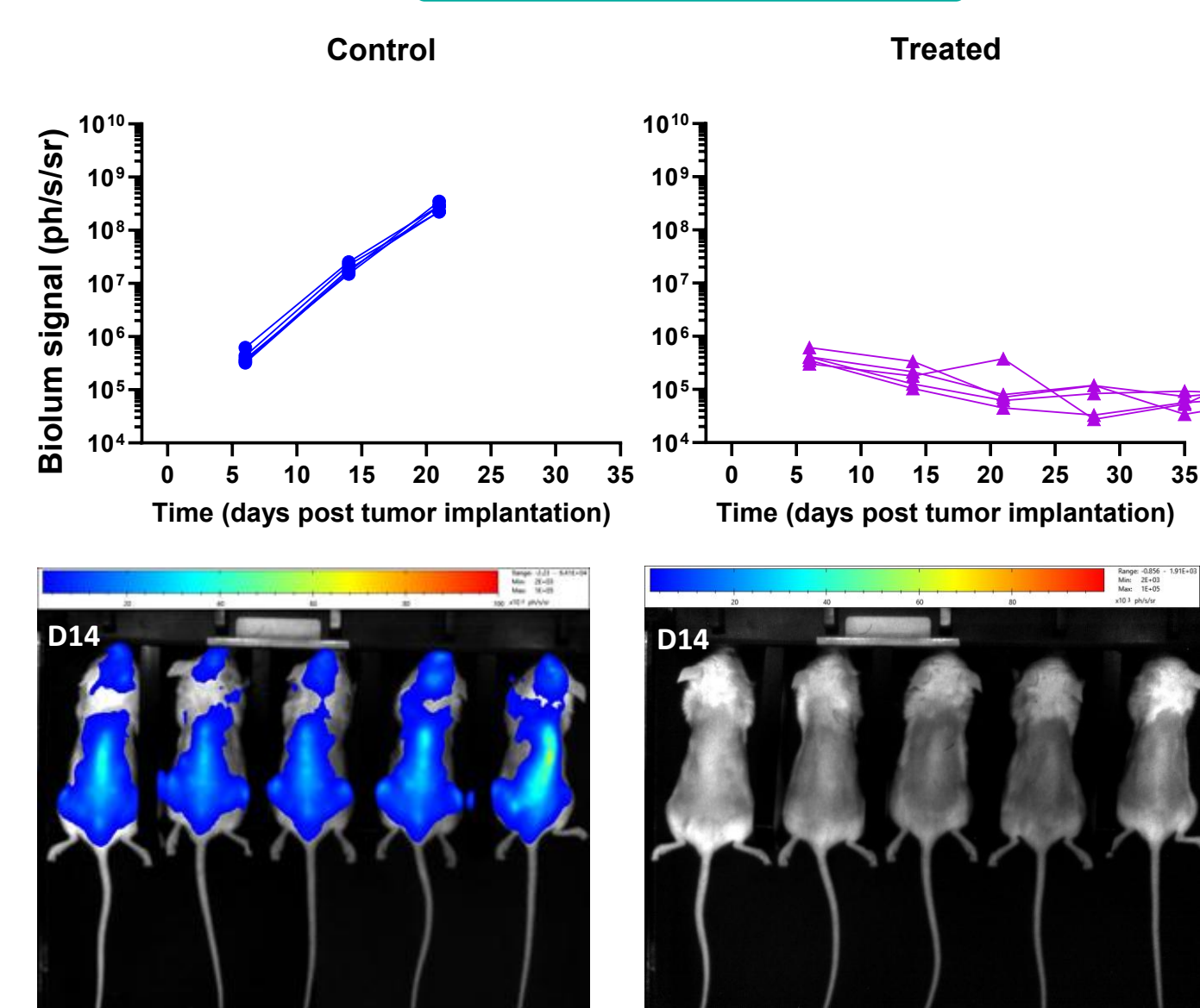
In vivo evaluation of engineered T cells

- CAR-T cells reduced bioluminescence signal in disseminated blood tumor bearing mice, resulting in an increased survival time.

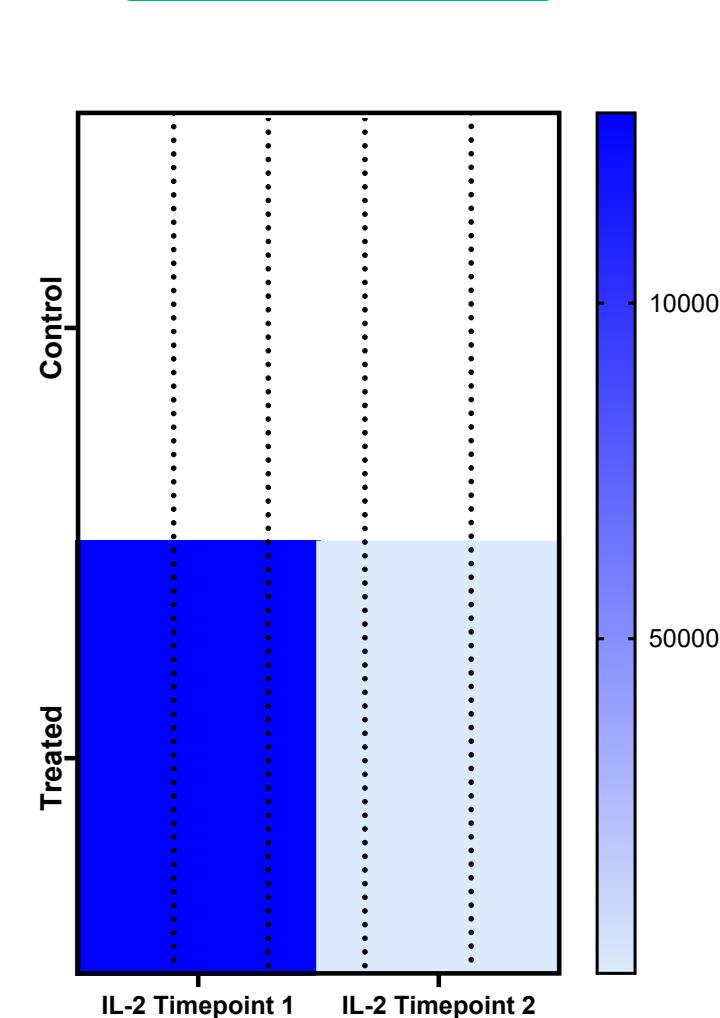
Survival increase



Bioluminescence imaging



Cytokine profile



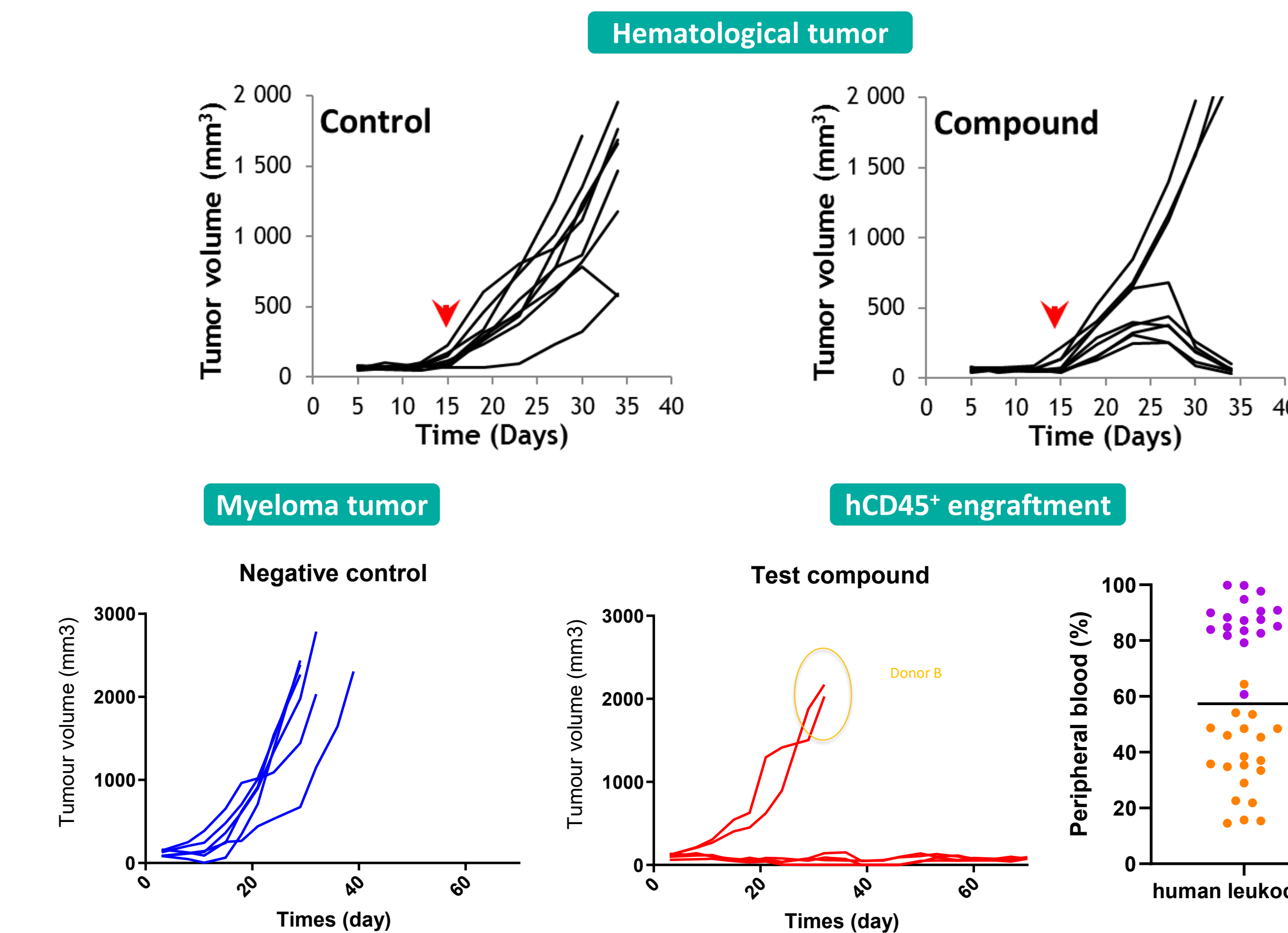
Humanized mice in Immuno-Oncology : A game-changer for preclinical research

Caroline Mignard, Charlotte Dejucq, Estelle Verronese, Damien France, Vincent Faugeron, Emilie Heckel
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Experiments

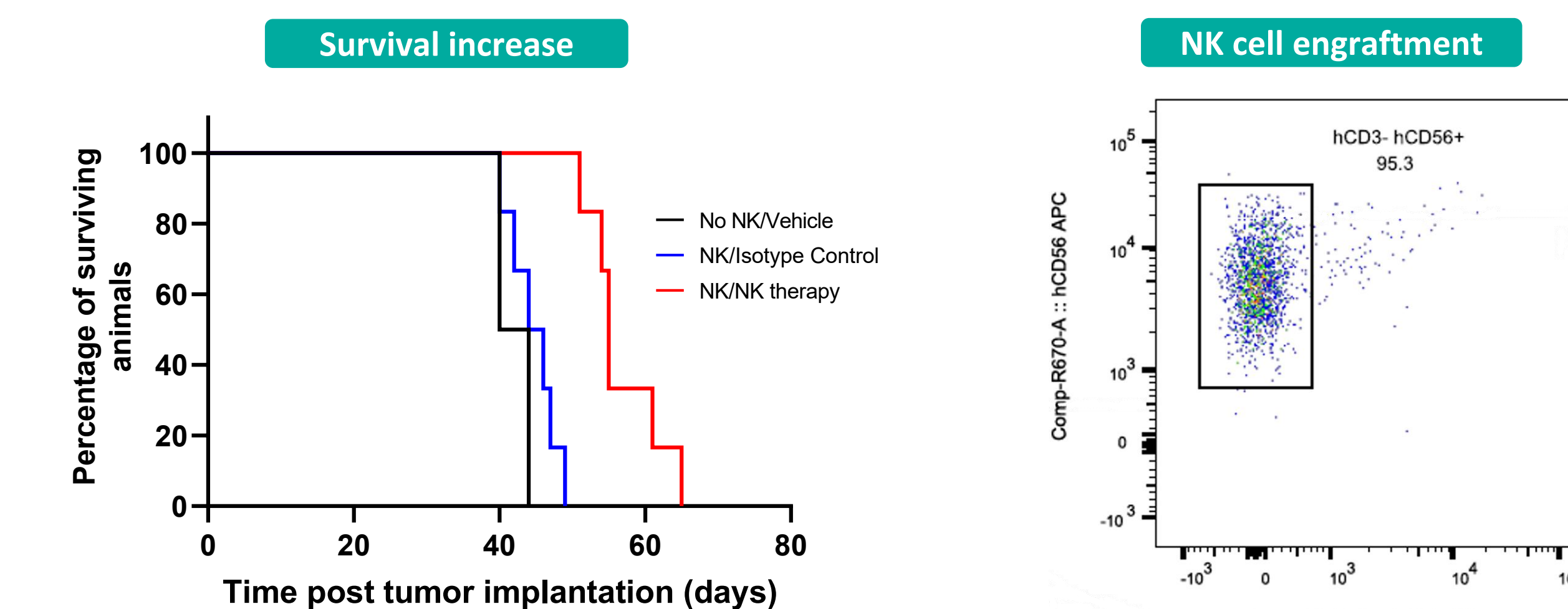
In vivo evaluation of T-cell engager antibodies

- PBMC or hCD34⁺ engrafted immunodeficient mice
- TCE treatment induced a marked tumor regression in humanized mice implanted with solid tumor



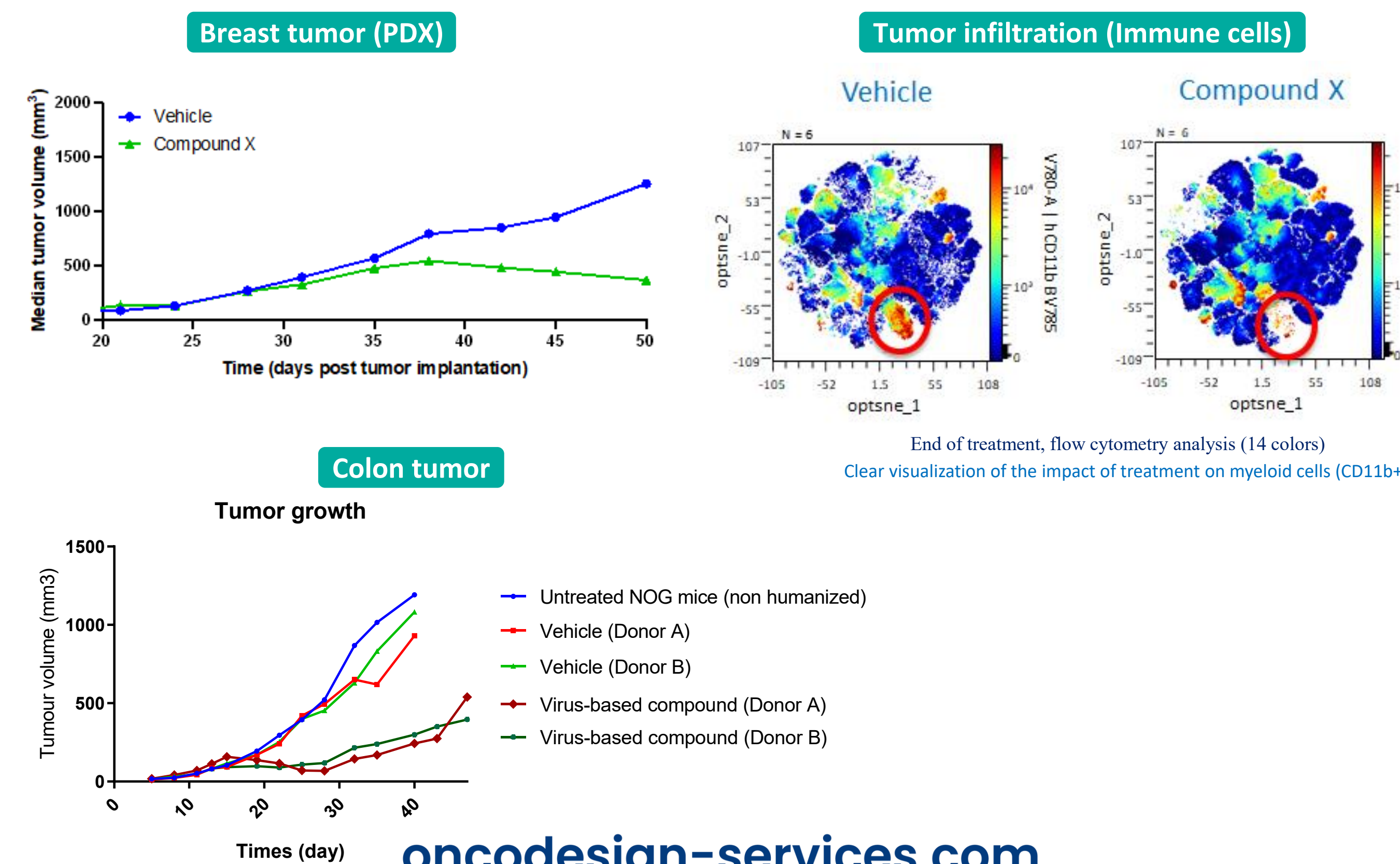
In vivo evaluation of NK-cell targeting compounds

- NK-engrafted super immunodeficient mice.
- NK therapy demonstrated a highly increased survival time in humanized mice intravenously implanted with human multiple myeloma



In vivo evaluation of myeloid or multiple cell-targeting therapies.

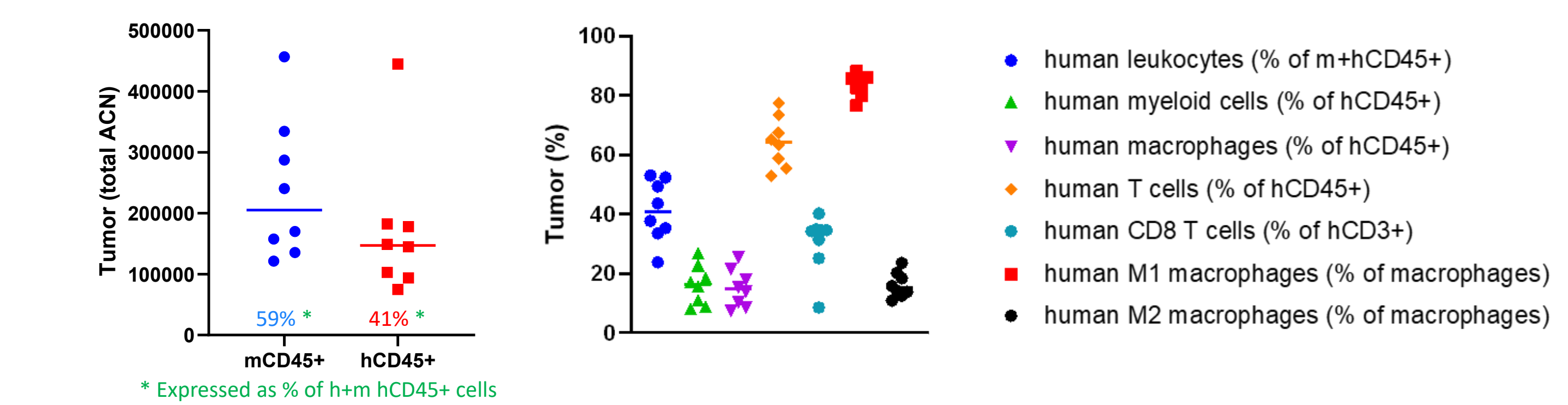
- hCD34⁺ engrafted super immunodeficient mice
- Myeloid cell-targeting therapy delayed the growth of breast PDX or colon tumor implanted in humanized mice



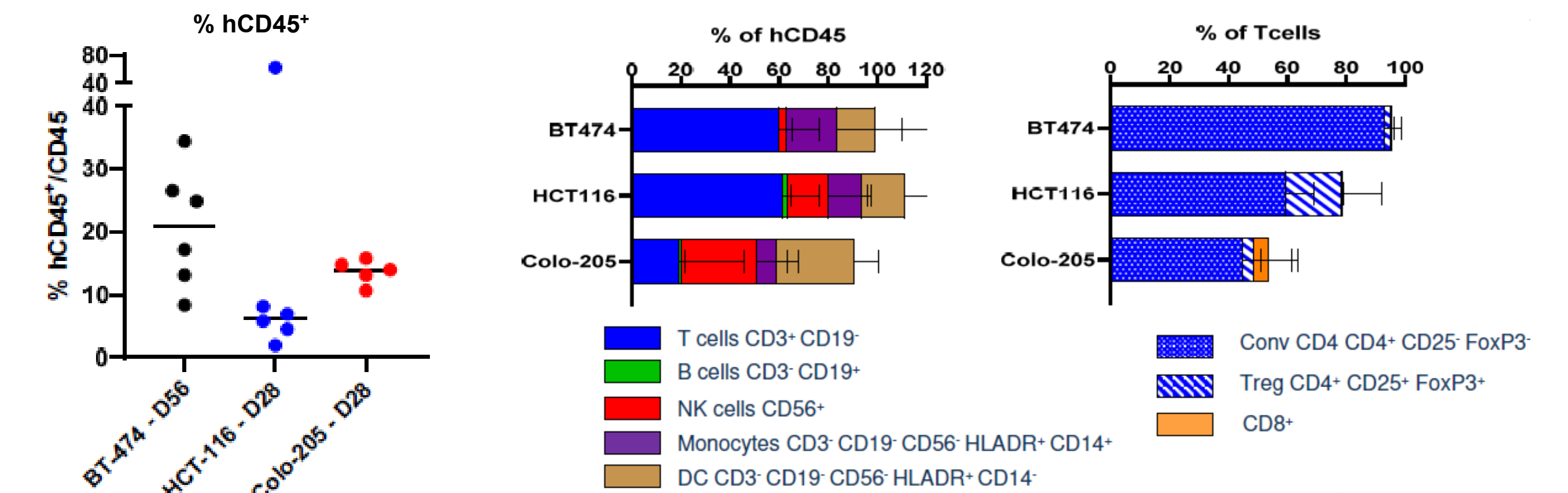
Immune cell engraftment and immune cell composition in TME vary among mouse strains and among tumors

- Cytokine expression drives immune cell engraftment, therefore the use of transgenic mice expressing human cytokines is helpful to increase the differentiation of myeloid lineages and NK cells
- The immune cell profile is dependent on the tumor model and several models are identified as phenotypically "inflamed" tumor models
- This characterization can provide guidance for the rational selection of models to evaluate new drug candidates.

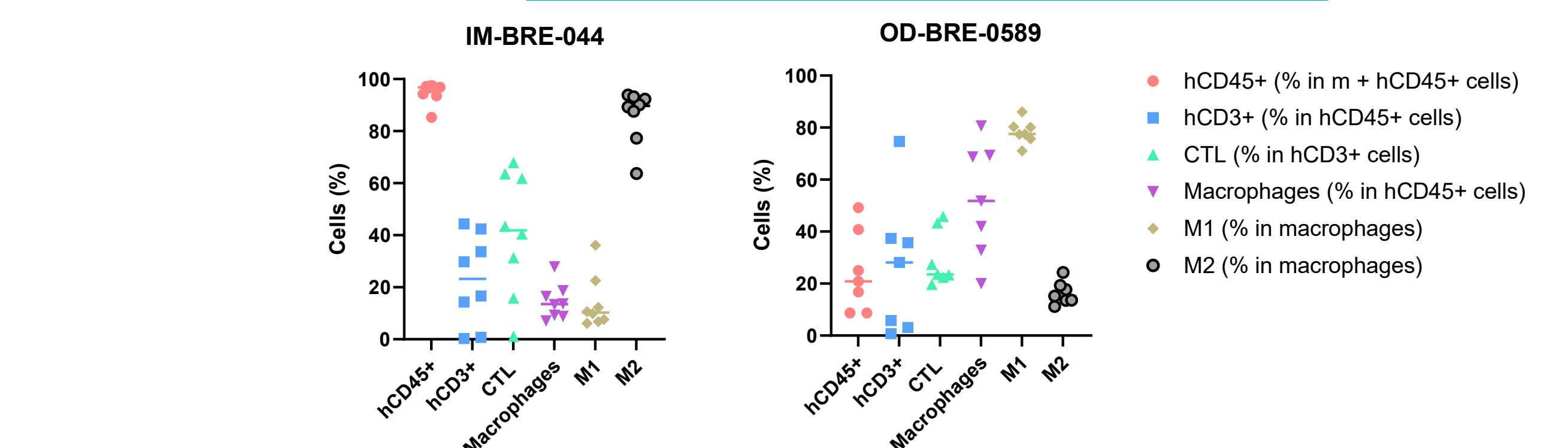
Immune profile (MDA-MB-231 tumor, hCD34+ NOG-EXL mice)



Immune profile (human CDX tumors, hCD34+ BRGSE mice)



Immune profile (breast PDX tumors, hCD34+ NOG-EXL mice)



Patient Tumor	Sub-Type	CD45	CD3	CD8	FOXP3
OD-BRE-589	TNBC	sparse	+	sparse	0
IM-BRE-044	TNBC	++	+++	+++	++

Tumor infiltration in humanized mice is correlated with immune cell infiltrate in originating patient tumor

Conclusion

- There is no unique HIS tumor model that mirrors the tumor in patient and the complexity of the cancer microenvironment, implying the most appropriate model to be considered and selected to answer a specific question.
- Selection of the most appropriate mouse model: essential consideration to optimize the translational potential of studies with humanized mice.
- Limitations of each specific model need to be considered to ensure an effective study as much as possible.
- Recommendations:
 - Use of multiple donors (donor-to-donor variation)
 - Pilot validation experiment with the selected mouse model to confirm that is appropriate
- Immunocompetent syngeneic models exhibiting physiological, human-like target expression constitute also useful tools.

An animal model remains an experimental model which cannot always answer all questions at once
We must be critical when searching for the right animal model

