Graft Versus Host Disease (GVHD)

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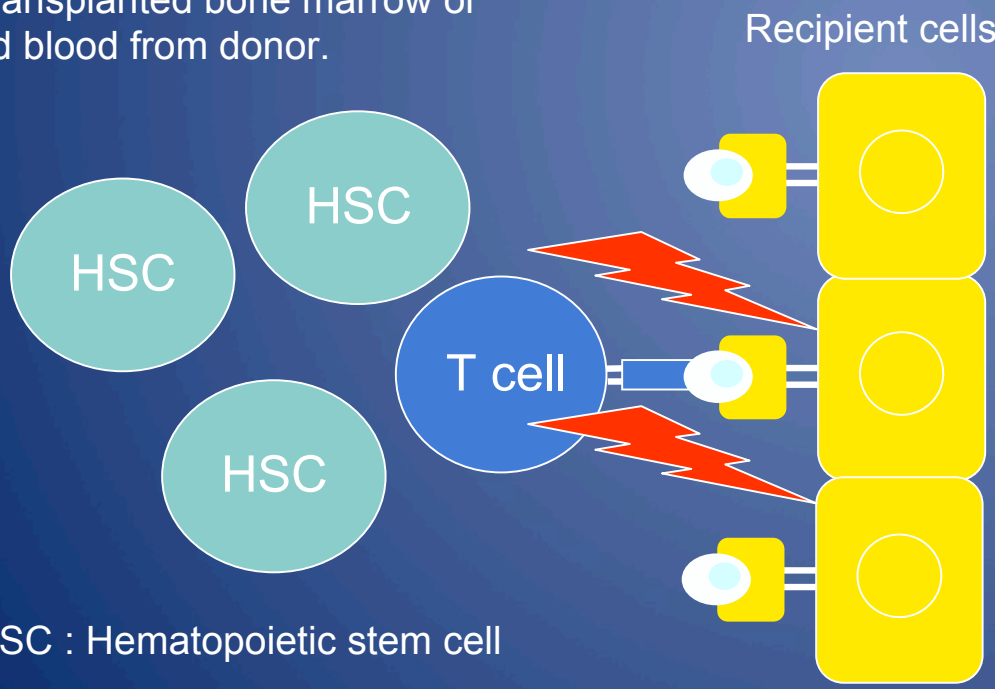
Graft versus host disease (GVHD) is known as a major complication in allogenic bone marrow or cord blood transplantation for therapy of several diseases such as acute/chronic leukemia, aplastic anemia and congenital immunodeficiency, and is characterized by immediate and high mortality after onset.

Allo-reactive T cells are contained in transplanted bone marrow or cord blood from donor.



* HSC : Hematopoietic stem cell

<u>Symptoms</u>

Severe damage by donor lymphocyte infusion is observed in various organs including skin, lung, liver and gut in HLA-mismatched recipient.

<u>Treatment</u>

There are only symptomatic therapies such as administration of immunosuppressive agents and corticosteroid.

GVHD model mouse

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・Allogenic GVHD model --- Transplantation of murine lymphocytes into mice with allogenic-MHC.

・Xenogenic GVHD model --- Transplantation of human lymphocytes into immunodeficient mice.

Previous xeno-GVHD models

Immunodeficient mice	Cell no. of lymphocyte neccesary for GVHD induction	Transfer route
C.B.17 scid	＞1x10e8	I.P. -- Yes
		I.V. -- No
NOD-scid	>3x10e7	I.P. -- Yes
		I.V. -- No
NOD-scid β2m null	>1x10e7	R.O. -- Yes
		I.V. -- No
BALB/c-RAG2null IL2RγCnull (dKO)	>1x10e7	I.P. -- Unknown
		I.V. -- Yes

Previous xeno-GVHD models are disadvantage because large number of human lymphocytes and total body irradiation are required to induce GVHD.

Appropriate route for induction of xeno-GVHD in NOG mice

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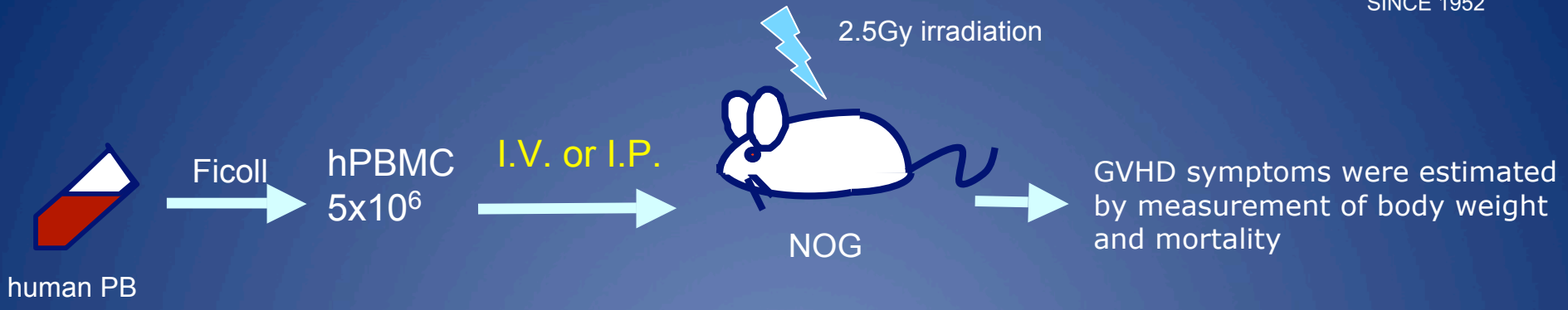
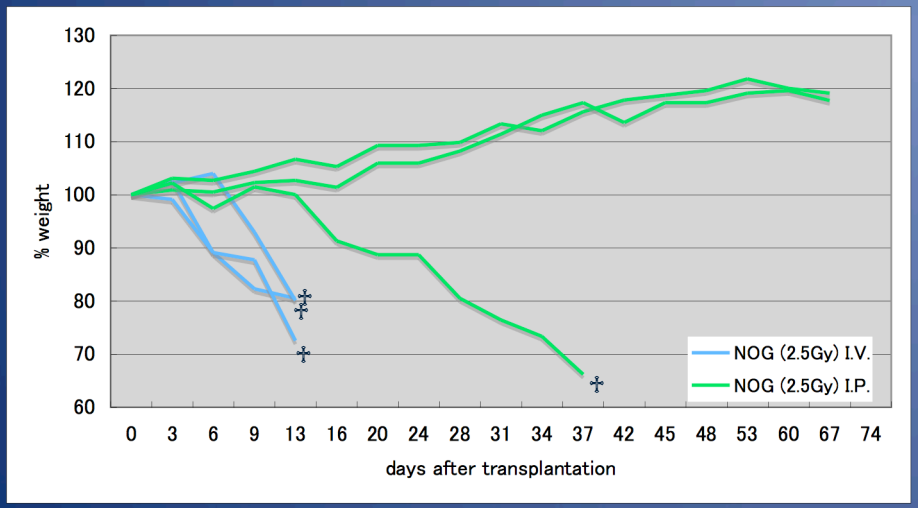


1st



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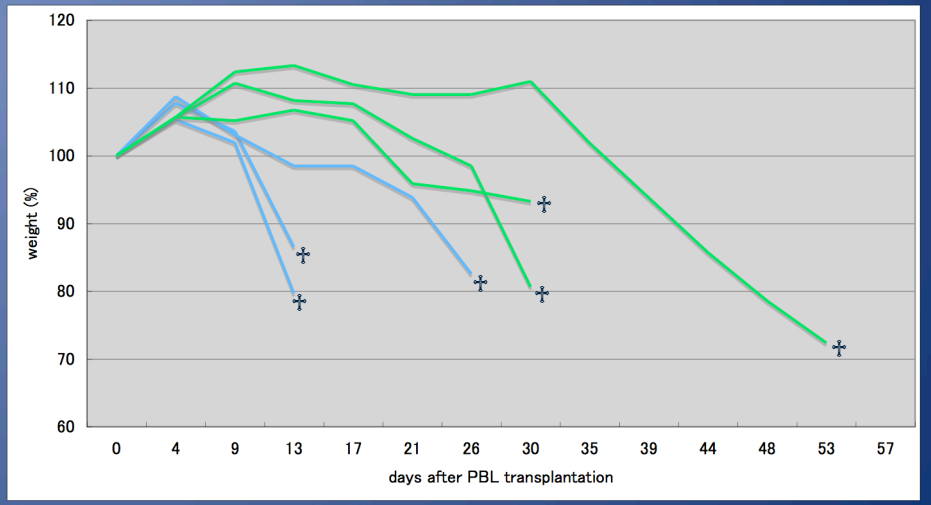

R Ito et al. 2009 *Transplantation*

Minimum cell numbers for induction of xeno-GVHD

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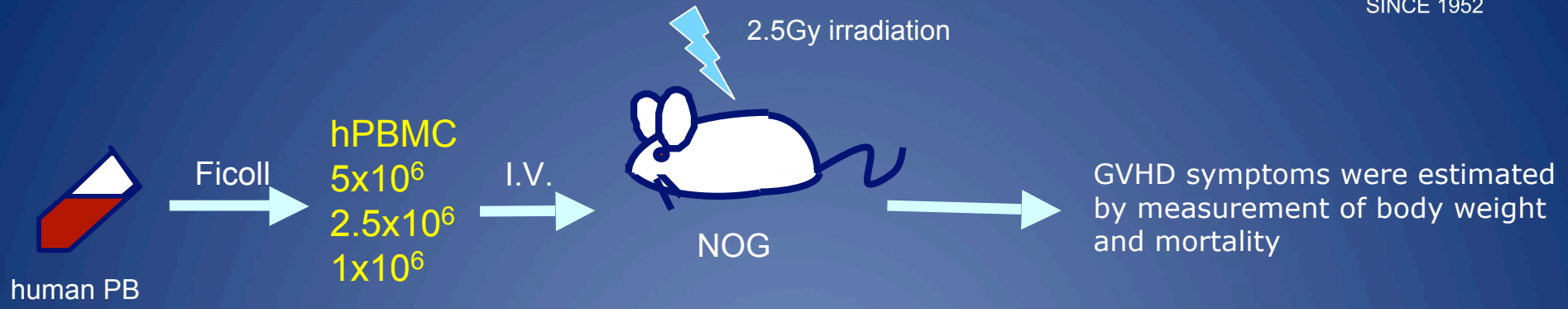

Cell numbers of PBMC transferred	Numbers of mice dying from GVHD	Mean days until death
5×10^6	3/3	34.7±6.7
2.5×10^6	3/3	46.3±14.3
1×10^6	0/3	–

Induction of xeno-GVHD in NOG, dKO and NOD-scid mice

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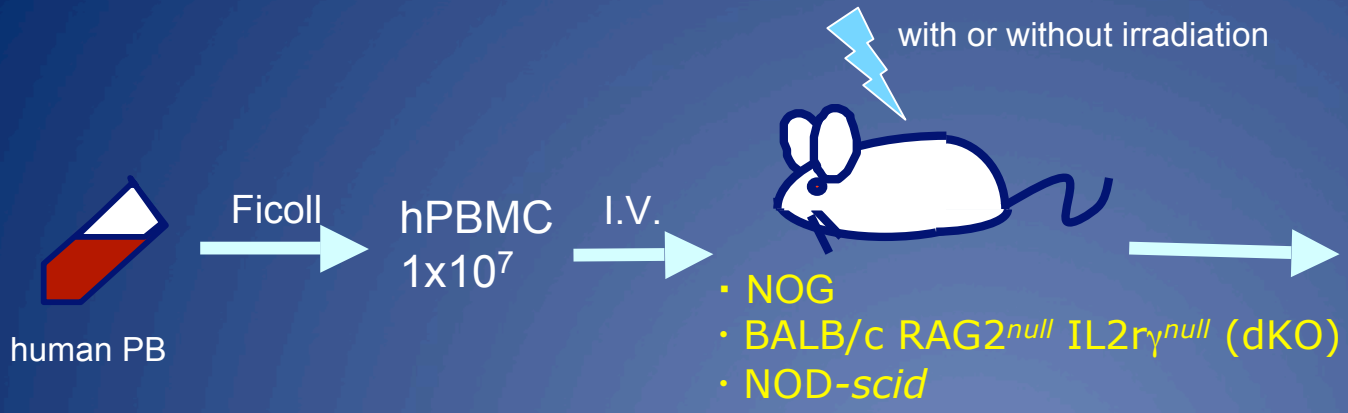
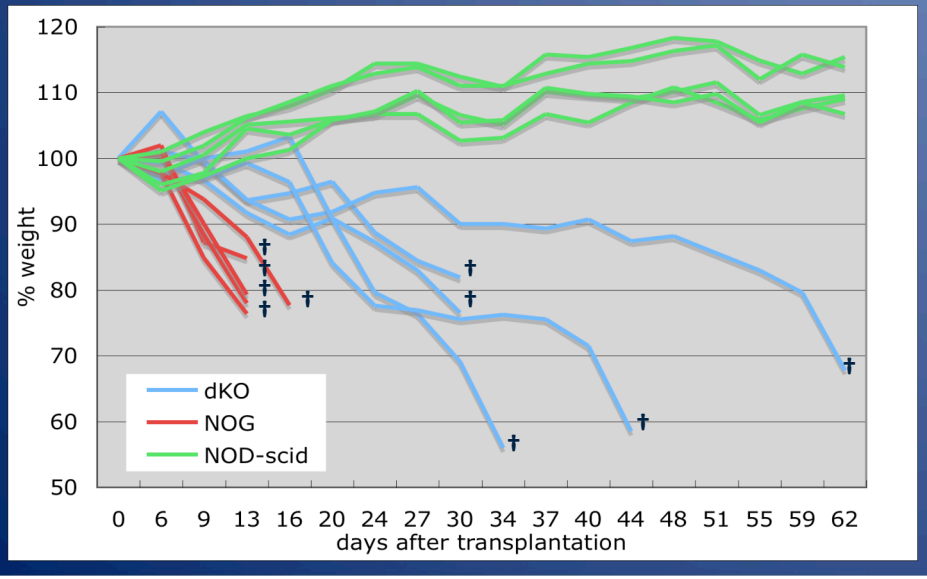
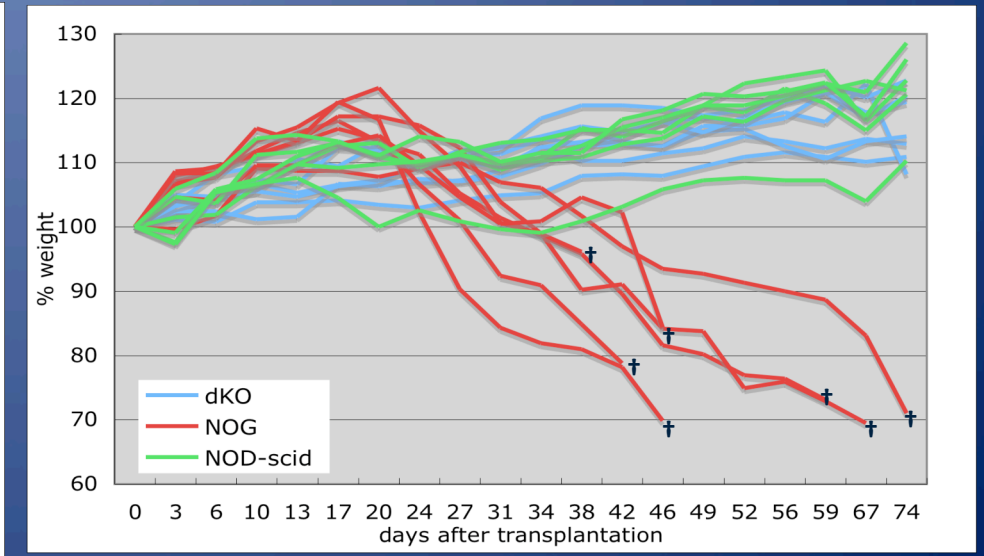


GVHD symptoms were estimated by measurement of body weight and mortality

With irradiation
- dKO: 3.5Gy
- NOG: 2.5Gy
- NOD-*scid*: 3.5Gy



Without irradiation



Engraftment of human cells in GVHD induced immunodeficient mice

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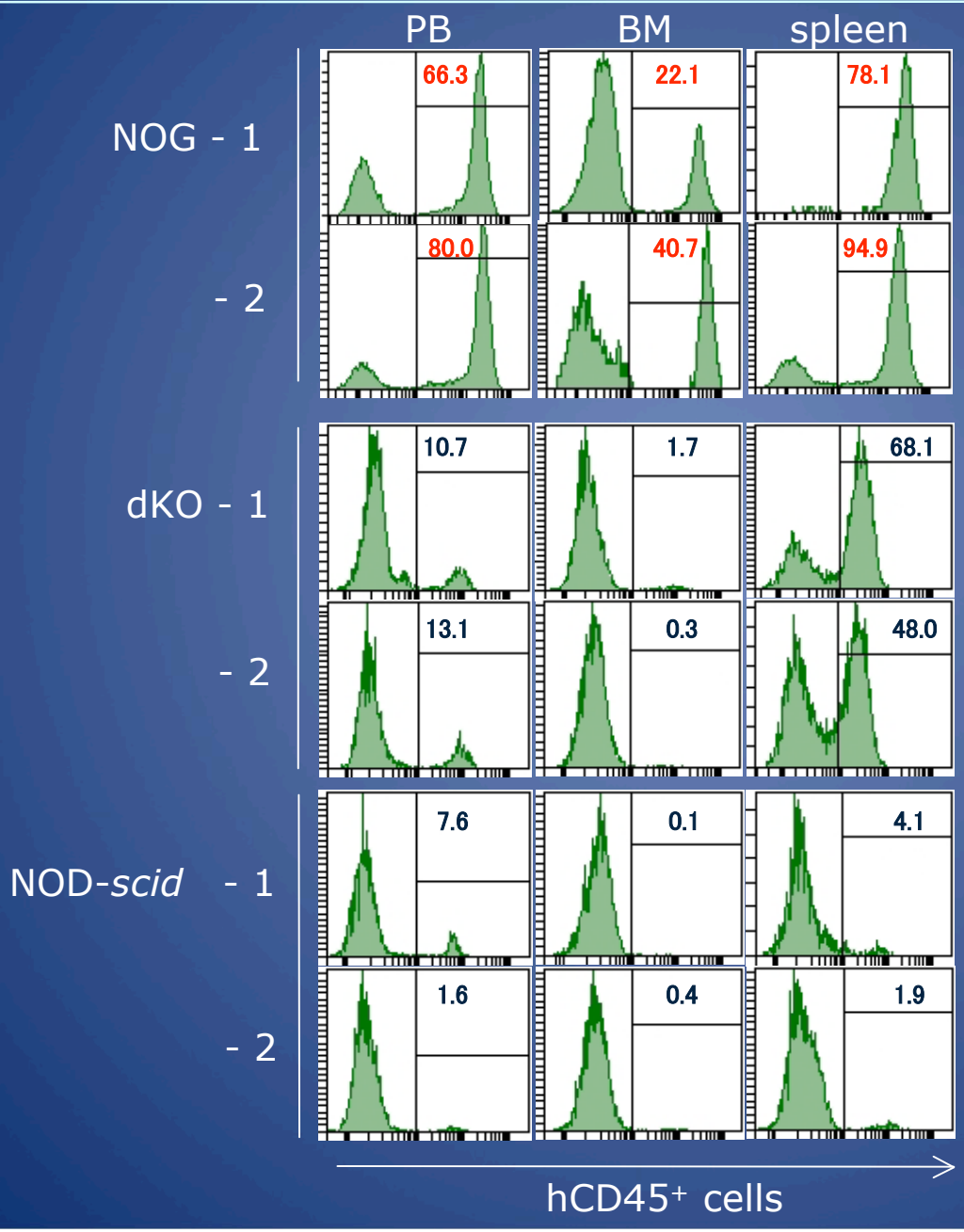

Infiltration into non-lymphoid organs in GVHD induced immunodeficient mice

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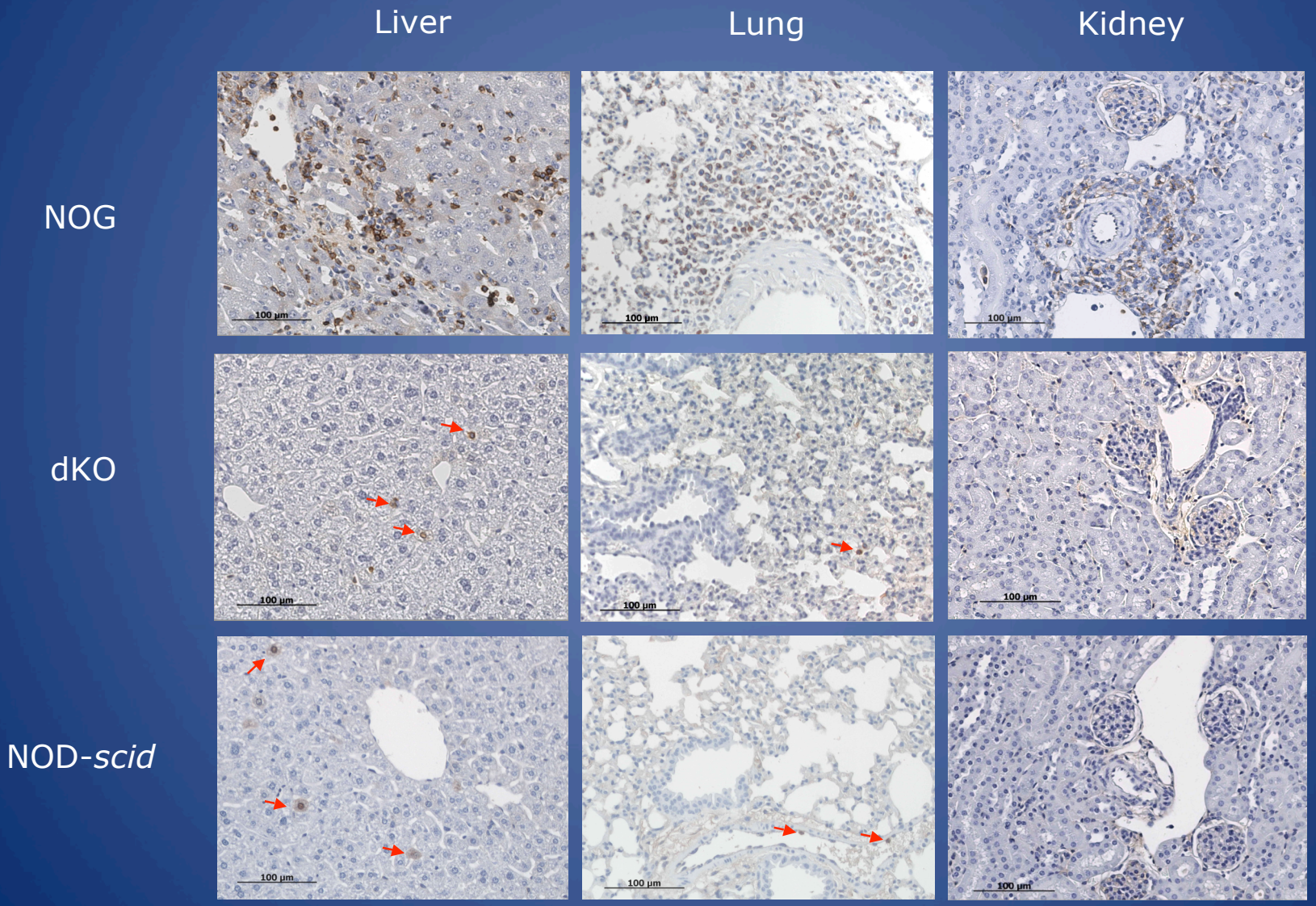

Conclusion

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NOG mice showed higher sensitivity to xeno-GVHD than other immunodeficient mice, and they have the following advantages :

- Intravenous transplantation was possible.
- A small number of hPBMCs was sufficient to induce xeno-GVHD.
- Total body irradiation was not always necessary.

From these results, NOG mice are considered to be a useful tool for studying GVHD and further studies will be needed for clinical applications.