# Humanized mouse model: A preclinical platform feasible for antibody-based therapy

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## INTRODUCTION

The selection of appropriate preclinical models based on similarity to human biology and disease genotype and phenotype carries considerable potential to ensure higher predictability of preclinical trials. The design and interpretation of first-in-man trials remains a major challenge in the development of novel anti-cancer agents. Key study design elements such as schedule, escalation strategy, targeted patient population, etc. rely heavily on preclinical (usually in vivo) data. It is especially difficult to model for preclinical assessment of cancer immunotherapy, the most actively developing area in oncology.

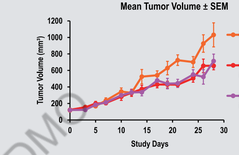
To build a preclinical mouse platform to evaluate immunotherapies for human cancer, we have established a tumor and immune system double-humanized mouse model, "Ideal Immune", by implanting tumor tissue from patients into HuNPI mice (NPI, NOD-Prkdc$^{scid}$-Il2rg$^{em1IDMO}$). The Ideal Immune model can mimic the interaction between the human immune system and primary tumor, which allows scientists to evaluate cancer immunotherapies together with better understanding of tumor microenvironment.

## RESULTS

Fig. 1 Schematic diagram of in vivo validation using HuNPI tumor models

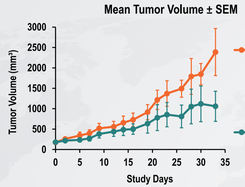
Fig. 2 Case study-anti-PD1 or anti-PDL1 antibodies:

Female HuNPI mice, reconstituted for 16~20 weeks, were implanted with MDA-MB-231 or PDX tumor tissues subcutaneously in the right flank. Dosing began on Day0 in mice with established tumors (group mean 120mm^3). The study endpoint was a tumor volume of 1500mm^3 in the control group. Mean tumor growth and HLA typing results are shown using (A) MDA-MB-231 tumor model, (B) CRC PDX model- CRC-17052, and (C) NSCLC PDX model- LC-3328



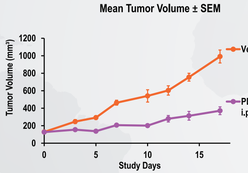

(A)

| Sample Name | HLA typing | | |
|---|---|---|---|
| | A | B | DR |
| MDA-MB-231 | A* 02 | B* 40 | DRB1*07 |
| | A* 02 | B* 41 | DRB1*13 |
| HuNPI | A* 02 | B* 56 | DRB1*12 |
| | A* 31 | B*57 | DRB1*12 |




(B)

| Sample Name | HLA typing | | |
|---|---|---|---|
| | A | B | DR |
| CRC-17052 | A* 02 | B* 15 | DRB1*04 |
| | A* 02 | B* 15 | DRB1*09 |
| HuNPI | A* 02 | B* 38 | DRB1*11 |
| | A* 31 | B*51 | DRB1*15 |

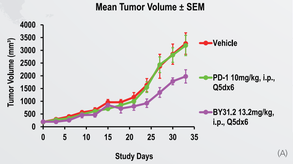



(C)

| Sample Name | HLA typing | | |
|---|---|---|---|
| | A | B | DR |
| LC-3328 | A* 02 | B* 27 | DRB1*08 |
| | A* 11 | B* 27 | DRB1*08 |
| HuNPI | A* 02 | B* 13 | DRB1*15 |
| | A* 31 | B*40 | DRB1*15 |

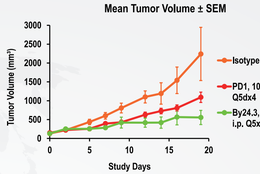
Fig. 3 Case study-anti-PD1 bispecific antibodies:

Female Hu-CD34 NPI mice, reconstituted for 16~20 weeks, were implanted with PDX tumor tissues subcutaneously in the right flank. Dosing began on Day0 in mice with established tumors (group mean 120mm^3). The study endpoint was a tumor volume of 1500~3000mm^3 in the control group. Mean tumor growth and HLA typing results are shown using (A) NSCLC PDX model-LC3104, and (B) NSCLC PDX model-LT3020.




(A)

| Sample Name | HLA typing | | |
|---|---|---|---|
| | A | B | DR |
| LC3104 | A* 03 | B* 15 | DRB1*04 |
| | A* 11 | B* 44 | DRB1*13 |
| HuNPI | A* 02 | B* 40 | DRB1*04 |
| | A* 24 | B*54 | DRB1*09 |



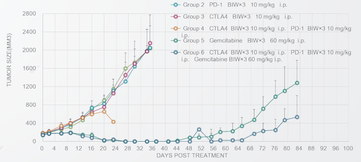

(B)

| Sample Name | HLA typing | | |
|---|---|---|---|
| | A | B | DR |
| LT3020 | A* 02 | B* 15 | DRB1*04 |
| | A* 02 | B* 40 | DRB1*15 |
| HuNPI | A* 02 | B* 40 | DRB1*04 |
| | A* 03 | B* 48 | DRB1*15 |

Fig. 4 Case study-anti-PD1 antibody combo therapy:

Female HuNPI mice, reconstituted for 16~20 weeks, were implanted with NSCLC PDX tumor tissues subcutaneously in the right flank. Dosing began on Day0 in mice with established tumors (group mean 120mm^3). The study endpoint was a tumor volume of 1500~3000mm^3 in the control group. Mean tumor growth (A) and bodyweight change (B) are shown. The significant tumor growth inhibition in a PD-1 and CTLA-4 combo-antibodies treatment group, together with dramatic toxicity. However, combo with chemotherapy prolonged tumor-free phase.

(A)




(B)

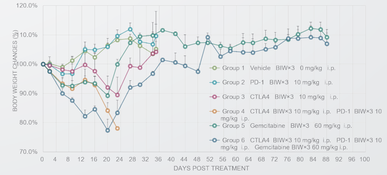
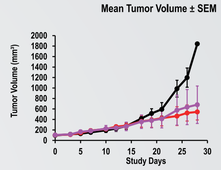



Fig. 5 Case study-toxicity of anti-CD47 antibody:

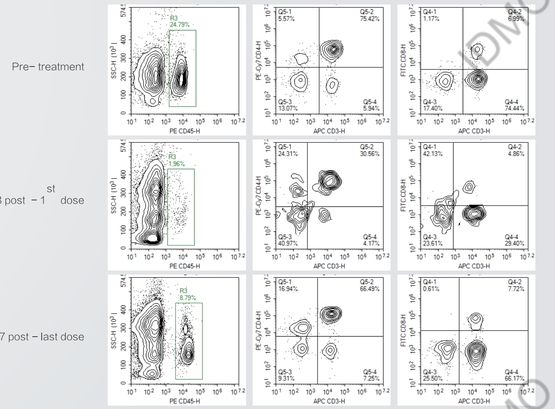
Female HuNPI mice, reconstituted for 16~20 weeks, were implanted with MDA-MB-231 cell line subcutaneously in the right flank. Dosing began on Day0 in mice with established tumors (group mean 100mm^3). Mean tumor growth (A) and CD45+ % change in peripheral blood (B) are shown.




(A)

| Sample Name | HLA typing | | |
|---|---|---|---|
| | A | B | DR |
| MDA-MB-231 | A* 02 | B* 40 | DRB1*07 |
| | A* 02 | B* 41 | DRB1*13 |
| HuNPI | A* 02 | B* 56 | DRB1*12 |
| | A* 31 | B* 57 | DRB1*12 |

Gated on CD45+




(B)