Humanized mouse model: A preclinical platform feasible for immunotherapy

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INTRODUCTION

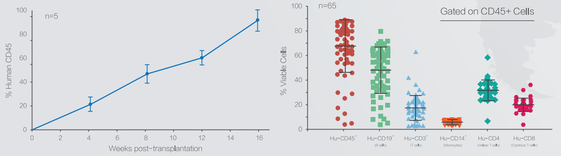
The selection of appropriate preclinical models based on similarity to human biology and disease genotype and phenotype carries considerable potential to ensure higher predictability of preclinical trials. The design and interpretation of first-in-man trials remains a major challenge in the development 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 Engraftment of Human Immune System:

CD34+ hematopoietic stem cells (HSCs) purified from umbilical cord blood were implanted into NPI mice to establish the HuNPI mouse model.(A) After HSC transplantation, reconstitution was determined by FACS analysis of peripheral blood from 4 to 16 weeks post-implantation, which showed a steady increase of reconstituted human lymphocytes in Hu-NPI mice. (B) After 16 weeks reconstitution, human CD45+ cells remained stable at 60-90%. All the compartments can be detected in peripheral blood. All the data shown was collected from HuNPI mice reconstituted from the same donor. (C) Various subsets of immune cells were detected in spleen, bone marrow and peripheral blood in HuNPI after 24 weeks reconstitution.



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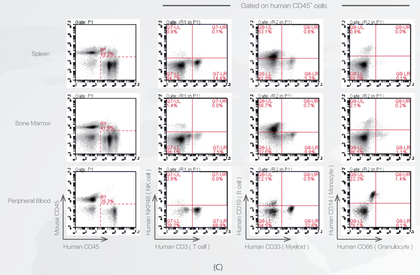
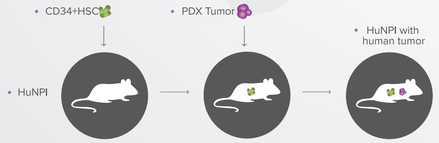


(C)

Fig. 2 Establishment and characterization of Patient derived xenografts (PDXs) in HuNPI mouse model:

(A) Schematic diagram of establishment of HuNPI PDX models; (B) Immunoprofiling of lymphocytes in peripheral blood of PDX-Hu-CD34 NPI by FACS analysis; (C) Lymphocyte infiltration in PDX tumor tissues (colon cancer) was determined by FACS analysis and IHC staining; (D) Immunoprofiling of tumor infiltrated lymphocytes (TILs) by FACS analysis



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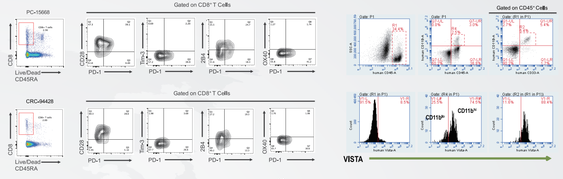

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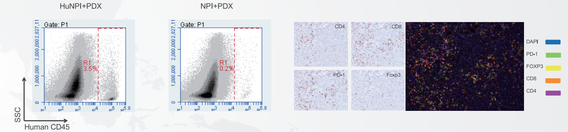

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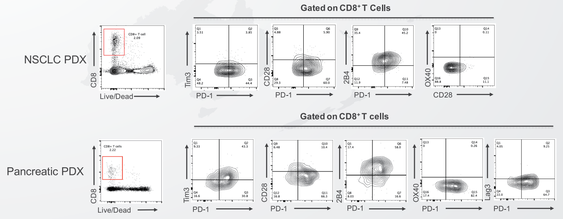
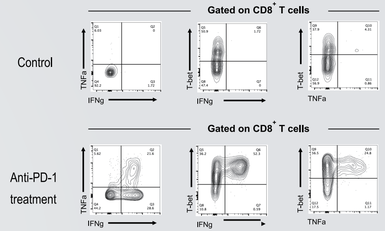


(D)

Fig. 3 Functional validation of TILs in HuNPI PDX mouse model:

Female HuNPI mice, reconstituted for 16 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 1500mm^3 in the control group. (A) Perbrolizumab was administrated i.p. at 10mg/kg， BIW. The function of CD8 cells in tumor were determined by intracellular cytokine staining. (B) Ipilimumab was administrated i.p. at 10mg/kg, BIW. Depletion of Treg cells was analyzed by FACS.



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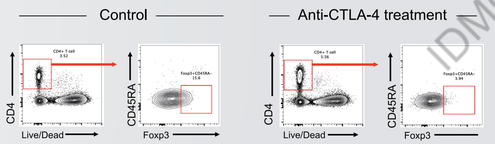

(B)

CONCLUSIONS

1. Various subsets of immune cells were detected in spleen, bone marrow and peripheral blood in HuNPI after 24 weeks reconstitution.
2. HuNPI PDX mouse model can be used to determine the immuno-profiling of tumor infiltrated lymphocytes, such as expression of immune checkpoints (PD1, Ox40, Tim3, Lag3 et al) on CD8 T cells.
3. CD8 cells in tumor are not activated, while turned into killing mode by IFNY and TNFα release after anti-PD1 treatment.
4. Treg cells in tumor can be depleted after anit-CTLA4 treatment through ADCC (antibody-dependent cell-mediated cytotoxicity).
5. HuNPI PDX mouse model is a suitable preclinical in vivo model for immunotherapy.