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Letter to the Editor

Empowering Cancer Immunotherapy: Actionable Guidance and Strategies Towards Optimal Humanized Mouse Models

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Dear editors,

The development of cancer immunotherapies has marked a significant milestone in oncology, offering new hope and therapeutic avenues for patients with various malignancies. The advent of immune checkpoint inhibitors, chimeric antigen receptor T-cell therapy, and other immune-modulating strategies has shifted the paradigm of cancer treatment. However, preclinical development of these therapies has been hindered by the lack of clinically relevant models that accurately mimic human immune responses and tumor interactions. A recent study by Li *et al*., published in *International Immunopharmacology*, addresses this critical gap by presenting a comprehensive evaluation of humanized immune system (HIS) models,[1] which are essential for *in vivo* efficacy testing and understanding the mechanisms of action (MOA) of immuno-oncology (IO) drugs. This editorial aimed to highlight the strengths and innovations of this study, particularly the establishment and optimization of a suite of humanized mouse tumor models—including humanized genetically engineered mouse models (GEMMs), hematopoietic stem cell (HSC) HIS, peripheral blood mononuclear cell (PBMC) HIS, natural killer (NK) HIS, and monocyte HIS—with a specific focus on the NK-HIS platform and its implications for future cancer research.

The study is notable for its comprehensive evaluation of humanized immune system models, methodological rigor, and the introduction of the novel NK-HIS platform. The authors examine various HIS models, including target-humanized GEMMs with competent immune systems, as well as diverse xenograft tumor models reconstituted with HSCs, PBMCs, NK cells, or myeloid cells. These models provide unique niches, allowing researchers to investigate specific aspects of human immune responses in a controlled environment.

The study employs rigorous methodologies for immunophenotypic analysis, ensuring the accuracy and reliability of results. These methods include flow cytometry, immunohistochemistry, and molecular assays to characterize immune cell populations and their functional states. The efficacy of various IO drugs is evaluated using standardized protocols, including tumor growth inhibition assays, survival studies, and cytokine profiling. This comprehensive approach ensures that the findings are robust and reproducible.

This paper provides an extensive analysis of different HIS models, such as humanized GEMMs reconstituted with human immune components, offering unique niches for studying human immune responses in a controlled environment. The authors also explore models reconstituted with human HSCs, PBMCs, and NK cells, which include multiple human immune cell types, thereby mimicking the complex interactions within the tumor microenvironment (TME). This holistic approach is crucial for understanding the multifaceted nature of tumor-immune interactions and for evaluating the efficacy of IO therapies.

The study's methodological rigor is evident in its thorough immunophenotypic analysis, employing techniques like flow cytometry, immunohistochemistry, and molecular assays. These methods ensure accurate characterization of immune cell populations and their functional states. Moreover, IO drugs' efficacy is evaluated using standardized protocols, such as tumor growth inhibition assays, survival studies, and cytokine profiling. This comprehensive approach guarantees the robustness and reproducibility of the findings, providing a reliable foundation for further research.

NK cells play a crucial role in the innate immune response against tumors, and their inclusion in HIS models enhances the ability to evaluate these cells' antitumor effects. Humanized tumor models based on innate immune cells represent a significant demand in the field due to the emergence of numerous novel molecular and therapeutic modalities targeting innate immunity. Among innate immune cells, NK-HIS models face challenges due to the characteristics of NK cell proliferation and activation.[2] A significant innovation introduced in this study is the NK-HIS platform, which offers high and durable reconstitution of human NK cells within the TME. This optimized NK-HIS platform utilizes both primary and expanded NK cells, which maintain functionality within the TME, ensuring a robust and sustained NK cell presence. This development is at the frontier of humanized mouse model research for reconstituting sub-lineage human blood cells, such as monocytes and granulocytes, or red blood cells.[3,4]

The key findings of the study by Li *et al*.[1] have important implications for cancer immunotherapy. The NK-HIS platform demonstrated superior NK cell reconstitution compared to traditional models, achieved using primary and expanded NK cells. Harnessing innate immunity alongside adaptive immunity could open new avenues for cancer treatment. The enhanced reconstitution of NK

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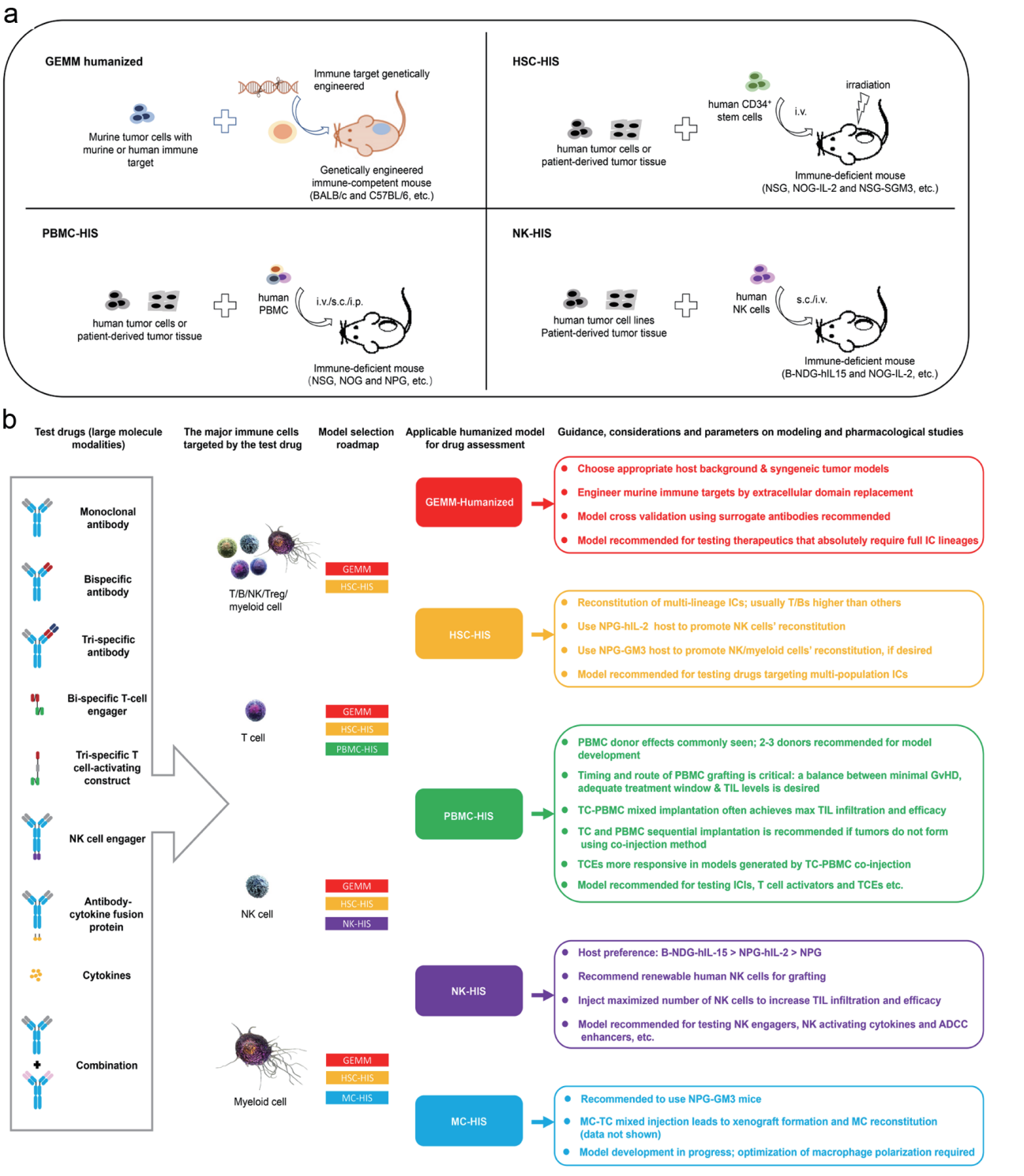

Fig. 1. Schematic representation of strategies for developing humanized immune system (HIS) models, along with recommended guidance on model selection, application, and key parameters for testing various large-molecule therapeutics in immuno-oncology. (a) Graphic strategies for generating GEMM humanized, HSC-HIS, PBMC-HIS, and NK-HIS systems. Key components, steps, and experimental processes of GEMM humanized, HSC-HIS, PBMC-HIS, and NK-HIS models are shown. (b) Roadmap for selecting and applying humanized tumor models, detailing test article categories, targeted immune cells, model preferences, and key considerations for IO translational research. The model selection process should be guided by various factors, including drug type, drug mechanism of action (MOA), targeted immune cell populations, and other parameters. GEMM, genetically engineered mouse model; HIS, humanized immune system; HSC, hematopoietic stem cell.; IC, immune cell; MC, myeloid cell; NK, natural killer cell; PBMC, peripheral blood mononuclear cell; TC, tumor cell; TCE, T-cell engager.

cells in the NK-HIS platform has significant implications for developing NK cell-based therapies, which have shown promise in preclinical and early clinical studies.

The study provides actionable guidance on selecting appropriate HIS models based on the MOA and target immune cell populations of investigational drugs. This tailored approach can significantly improve the predictive power of preclinical studies and accelerate the translation of promising therapies to clinical trials. A decision tree for model selection is introduced (illustrated in Fig. 1), helping researchers navigate the complex landscape of HIS models and choose the most suitable model for their specific experimental needs.

The study by Li *et al*.[1] represents a significant advancement in cancer immunotherapy research. By providing a comprehensive evaluation of HIS models and introducing the novel NK-HIS platform, the authors address critical gaps in current preclinical models. This work enhances the predictive power of preclinical data, facilitating the development of effective cancer immunotherapies and potentially advancing personalized medicine by tailoring therapies to individual patients' immune profiles.

The integration of HIS models with advanced technologies, such as single-cell sequencing and imaging techniques, can provide deeper insights into immune-tumor interaction dynamics, enhancing our understanding of the complex mechanisms driving cancer progression and therapeutic response. Developing new HIS models that incorporate additional human immune cell types could further improve these models' relevance for studying the TME, informing combination therapy development, and optimizing therapeutic outcomes.

The enhanced predictive power of HIS models can lead to more reliable preclinical data, reducing IO drugs' attrition rate in clinical trials, accelerating therapy development, and improving clinical success rates. HIS models can also help identify biomarkers of IO therapy response, providing valuable insights into the mechanisms underlying treatment efficacy and resistance and guiding patient selection for specific therapies.

As with all experimental studies, Li *et al*. extensively discussed the limitations of HIS models for translational projects.[1] The potential influence of tumor heterogeneity should be considered when using such models to profile compounds or elucidate drug candidates' MOA targeting immuno-oncology.

The comprehensive study provided by Li *et al*.[1] serves as a valuable reference, highlighting the decision-making process for selecting the most suitable HIS model for specific IO studies. The decision tree illustrated in Figure 1 is a practical tool, offering researchers a clear, concise guide for model selection, emphasizing its role as both a visionary summary and practical selection guide for HIS models based on specific experimental needs.

The development of cancer immunotherapies has revolutionized oncology; however, the translational field faces challenges due to the lack of *in vivo* models that accurately represent human immune responses and tumor interactions. The study by Li *et al*.[1] is a noteworthy methodological contribution to the field of cancer immunotherapy. By providing a detailed evaluation of a wide range of HIS models, the authors offer actionable and practical approaches for translational immuno-oncology research. The introduction and optimization of the novel NK-HIS platform demonstrate durable and meaningful reconstitution of NK cells within the human cancer xenograft system, representing a significant advancement in preclinical modeling. Additionally, the study offers practical guidance on developing appropriate HIS models based on the MOA and immune targets of investigational drugs. Finally, the study presents a visual and concise decision tree (Fig. 1) for strategically selecting HIS models based on the specific needs of each researcher.

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Conflict of interest

Prof. WenQing Yang is an employee of Nanjing ClinBridge Biotechnology Co., Nanjing, Jiangsu, China, and has been an editorial board member of *Journal of Exploratory Research in Pharmacology* since November 2021. The author has no other conflict of interests related to this publication.

Author contributions

WY is the sole author of this manuscript.

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