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# Mapping the cell therapy landscape: insights into clinical trials and regulatory advances in China

Xin Du<sup>1</sup>, Xingxian Luo<sup>2</sup>, Lanqiu Liu<sup>3</sup>, Yanlin Cao<sup>4</sup>, Yajuan Zhang<sup>5,6\*</sup> and Yi Zhang<sup>1\*</sup>

## Abstract

In recent years, cell therapy research and commercialization have significantly accelerated, especially after the US FDA approved CAR-T therapy. While cell therapy now leads immuno-oncology in clinical trials, challenges such as redundant R&D, target clustering, and unmet clinical need remain. Since 2017, China has established a dual-track regulatory framework, facilitating rapid growth in its cell therapy pipeline, making it the second largest in the world. Despite this progress, China faces similar global challenges. Our study covers 2,794 registered cell therapy clinical trials in China, including 2,045 for immune cell, 683 for stem cell, and 66 for other somatic cell. It compares cell therapy products approved in China, the US, EU, and Japan, analyzes the evolving clinical trials landscape, and highlights the characteristics of investigator-initiated trials (IITs) and industry-sponsored trials (ISTs) in China. Our findings indicate that despite the high disease burden and unmet clinical needs for solid tumors in China, over 38% of trials between 2021 and 2023 focused on hematologic malignancies with established targets like CD19 and BCMA. Over 90% of trials are IITs, which show notable clinical differences from ISTs. We recommend that Chinese regulators establish specific guidelines to promote clinical-value-driven research. Stricter regulatory standards should also be implemented to minimize redundant R&D. Additionally, a value-based reimbursement system for within-class targeted cell therapy products may further reduce duplicated R&D efforts. Given the prevalence of IITs, specifying requirements for IITs could create a new pathway to accelerate product development and better address unmet clinical needs in China.

**Keywords** Cell therapy, Dual-track regulatory framework, Investigator-initiated trials, Industry-sponsored trials

## To the Editor

In recent years, cell therapy research and commercialization have significantly accelerated [1]. Recognizing the complexity and higher risks, the US, EU, and Japan have established specific regulatory frameworks for cell therapy (eTable1). By August 1, 2024, 27, 13 and 18 cell therapy products were approved in the US, EU and Japan, respectively (Fig. 1, eFigure2). Since 2017, China has established a dual-track regulatory framework for cell therapy, clarifying the requirements for cell therapy and facilitating the growth of both investigator-initiated trials (IITs) and industry-sponsored trials (ISTs) [2].

\*Correspondence:

Yajuan Zhang

zhangyajuan@mail.tsinghua.edu.cn

Yi Zhang

yi\_zhang@mail.tsinghua.edu.cn

<sup>1</sup>Vanke School of Public Health, Tsinghua University, Beijing, China

<sup>2</sup>Department of Pharmacy, Peking University People's Hospital, Beijing, China

<sup>3</sup>School of Medical Humanities, Capital Medical University, Beijing, China

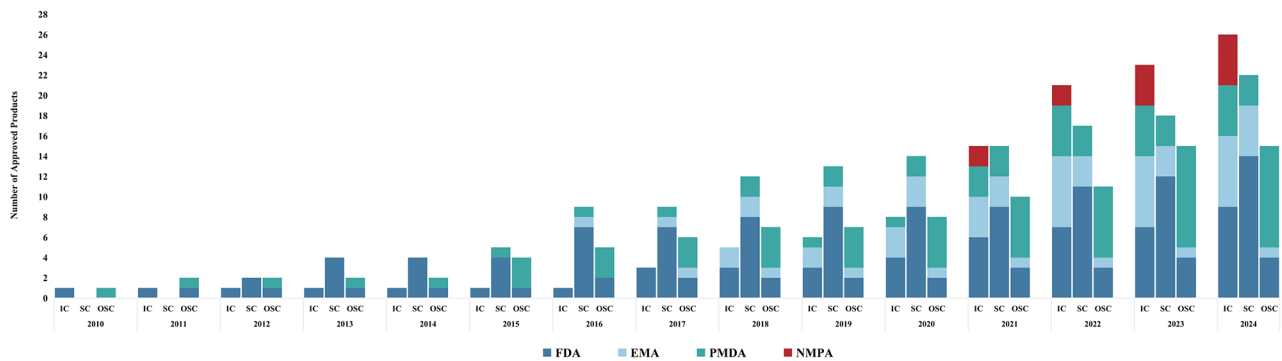
<sup>4</sup>Institute of Medical Information, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

<sup>5</sup>School of Pharmaceutical Sciences, Tsinghua University, Beijing, China

<sup>6</sup>Key Laboratory of Innovative Drug Research and Evaluation, National Medical Products Administration, Beijing, China



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**Fig. 1** Cumulative Number of Cell Therapy Products Approved for Marketing by the NMPA, FDA, EMA and PMDA (2010–2024). Abbreviations: FDA, Food and Drug Administration; EMA, European Medicines Agency; PMDA, Pharmaceuticals and Medical Devices Agency; NMPA, National Medical Products Administration. IC, Immune Cell; SC, Stem Cell; OSC, Other Somatic Cell. Note: The cut-off date was August 1, 2024

Consequently, China's cell therapy pipeline has grown rapidly to the world's second largest. However, challenges such as redundant R&D, target clustering, and unmet clinical needs persist both in China and globally [3]. This study examines China's evolving clinical trial landscape, comparing it to global trends, while highlighting differences between IITs and ISTs, and proposing potential solutions for unmet clinical needs.

### Overview of cell therapy clinical trials in China: types and phases

This study analyzed cell therapy clinical trials from January 1, 2005 to August 1, 2024, with classifications consistent with previous research (eAppendix, eFigure 1) [2, 4]. It encompassed 2,794 registered trials: 2,045 for immune cell (73.2%), 683 for stem cell (24.4%), and 66 for other somatic cell (2.4%). The most common immune cell therapies were CAR-T cells (46.9%). For stem cells, mesenchymal stem cells (18.3%) dominated. Other somatic cells mainly included cardiomyocytes (0.4%). Over half of the trials were in Phase I (40.5%) or Phase I/II (21.2%) (Fig. 2a, eFigure 4, eTable 3).

### Characteristics of indications and targets

The majority of cell therapy clinical trials in China target cancer, comprising 69.0% of all trials (Fig. 2d, eTable 4). From 2005 to 2024, over 37.5% of the trials focused on hematologic malignancies. Beyond oncology, clinical trials increasingly focus on other areas, including infections (4.0%) and immune disorders (5.5%) (Fig. 2d). The most prominent targets were hematological malignancies, with CD19 leading at 416 trials (26.7%), of which 388 (93.3%) being CAR-T (Fig. 2b and d, eTable 5, eFigure 7, eFigure 8). Notably, between 2021 and 2023, there was an increase in trials for less common targets in solid tumors, such as CLDN18.2, HER2 and MSLN.

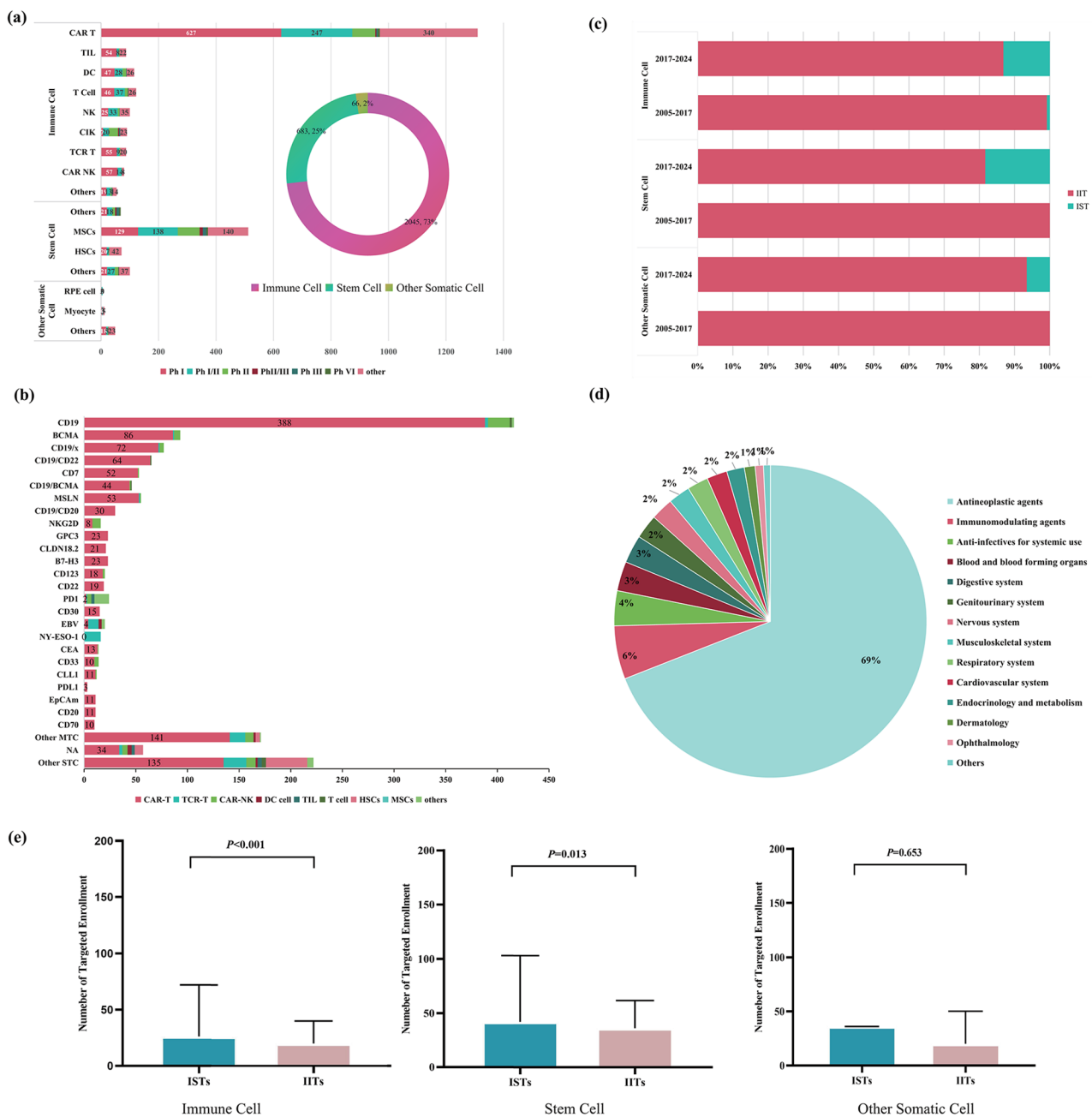
### Characteristics of IITs and ISTs

As of August 1, 2024, IITs ( $n=2,519$ , 90.2%) far exceeds ISTs ( $n=275$ , 9.8%). Since the 2017 National Medical Products Administration (NMPA) guidelines clarified regulatory requirements for cell therapy products, ISTs in stem cell and somatic cell therapy increased significantly from zero. In immune cell therapy, ISTs generally had higher target enrollments than IITs (26 vs. 20,  $P<0.001$ ). Stem cells had more target enrollment in IITs than in ISTs (36 vs. 27,  $P=0.013$ ), with no significant difference in somatic cells (Fig. 2e, eTable6, eTable7, eTable8).

### Outlook

Advancements in cellular technology have diversified cell therapy products [5]. Currently, nine solid tumors products have approved globally; but in China, the scope of approved products remains limited and relatively homogeneous, despite solid tumors making up over 90% of cancer cases (eTable 2) [6]. To address unmet clinical needs, we recommend that the NMPA establish specific guidelines to promote clinical-value-driven research [7].

Limited R&D resources in China hinder the exploration of new targets in cell therapy trials, leading to redundant R&D and target clustering. While global trials investigate new targets like CLDN18 (+400%), KRAS (+125%), Chinese trials remain focused on established targets, with over 38.0% targeting CD19 and BCMA, compared to 36.2% globally.<sup>3</sup> This trend implies a preference for proven targets to reduce costs and shorten development cycles. The FDA recently issued guidance on CAR T-cell therapy, encouraging concurrent companion diagnostic tool development to improve trial accuracy [8]. We thereby recommend stricter regulatory standards to minimize redundant R&D. Furthermore, as specific cell therapy indications are included in China's reimbursement list, establishing a value-based reimbursement system could help lower costs for within-class targeted cell therapy products and reduce market clustering [9, 10].



**Fig. 2** Scope and Distribution of Clinical Trials for Cell Therapy in China. **(a)** Cell therapy across various therapy types by different development phases in China from 2005 to 2024. **(b)** Molecular target distribution of clinical trials for cell therapy in China from 2005 to 2024. **(c)** Comparison of ISTs and IITs of all three categories of cell therapies initiated between 2000–2017 and 2017–2024. **(d)** Distribution of indications in clinical trials for cell therapy from 2005 to 2024. **(e)** A comparison of the targeted enrollment numbers between IITs and ISTs from 2005 to 2024 of all three categories of cell therapy. Abbreviations: ISTs, industry-sponsored trials; IITs, investigator-initiated trials. Note: The cut-off date was August 1, 2024

IITs offer more flexibility in trial design and generate substantial early exploratory data. Although NMPA guidelines since 2017 allow IIT data to support IND applications, challenges persist in research quality and cell production management [11]. We recommend that the NMPA specify regulatory and technical requirements for using IIT data for IND applications to establish

a new pathway that accelerates cell therapy research and address unmet clinical needs.

**Abbreviations**

- IITs Investigator-initiated trials
- ISTs Industry-sponsored trials
- US United States
- EU European Union

R&D	Research and development
IND	Investigational New Drug
NMPA	National Medical Products Administration
CAR	Chimeric antigen receptor
DC	Dendritic cell
NK	Natural killer
NKT	Natural killer T cell
MSC	Mesenchymal stem cell
HSC	Hematopoietic stem cell
RPE	Retinal pigment epithelium
TCR	T cell receptor
TIL	Tumor-infiltrating lymphocyte
CD	Cluster of differentiation (such as CD19)
BCMA	B-cell maturation antigen
MSLN	Mesothelin
PD1	Programmed cell death protein 1
B7-H3	B7 Homolog 3
GPC3	Glypican 3
CLDN18.2	Claudin 18.2
EBV	Epstein-Barr Virus
NY-ESO-1	New York esophageal squamous cell carcinoma 1
NKG2D	Natural killer group 2 member D
CEA	Carcinoembryonic antigen
CLL1	C-type lectin-like molecule-1
EpCAM	Epithelial cell adhesion molecule
PDL1	Programmed death ligand 1.

## Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13045-024-01616-8>.

Supplementary Material 1

## Author contributions

XD and XXL were involved in the conception and design of the study. XD contributed to framework planning, data analysis, interpretation, and draft writing. XXL contributed to framework planning and data interpretation. LL was responsible for framework planning and data analysis. YC handled data cleansing and processing. YZ and YZ led the overall framework planning and provided guidance for data interpretation. All authors read and approved the final manuscript.

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## Data availability

Cell therapy clinical trial data were retrieved from the China Drug Trials Registry established by the National Medical Products Administration ([www.chinadrugtrials.org.cn](http://www.chinadrugtrials.org.cn)), Chinese Clinical Trial Registry ([www.chictr.org.cn/](http://www.chictr.org.cn/)), and ClinicalTrials.gov ([clinicaltrials.gov](http://clinicaltrials.gov)) established by the U.S. Clinical trials conducted or registered in China up until August 1, 2024 were retrieved and analyzed. The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

## Declarations

### Ethics approval

Not applicable.

### Competing interests

The authors declare no competing interests.

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