

## ORIGINAL RESEARCH ARTICLE

# Progress and challenges of mesenchymal stem cells as oncolytic virus delivery systems: A bibliometric analysis of the top 100 most-cited papers in the past ten years

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## Abstract

Oncolytic virotherapy has emerged as a promising approach to cancer treatment, and mesenchymal stem cells (MSCs) are increasingly recognized as effective carriers to enhance the delivery and efficacy of oncolytic viruses (OVs). This study explores the potential use of MSCs as carriers for OVs in targeted cancer therapy. MSCs are considered ideal delivery vehicles for OVs due to their immunomodulatory properties, inherent tumor-homing ability, and capacity to protect and transport therapeutic agents. Advances in genetic engineering have enhanced the interaction between MSCs and OVs, improving delivery efficiency and therapeutic outcomes in cancer treatment. This study conducted a bibliometric analysis of the 100 most-cited articles on both MSCs and OVs, using data from the Web of Science Core Collection database. It identified major trends, challenges, and research hotspots, highlighting significant progress in preclinical studies while noting ongoing issues related to delivery efficiency, virus modification, and tumor microenvironment optimization. The findings underscore the promise of MSCs as effective delivery systems for OVs and outline emerging research areas, such as precise delivery methods and clinical applications, alongside current obstacles. As this field advances, it is expected to play a crucial role in the future of cancer immunotherapy.

**Keywords:** Mesenchymal stem cells; Oncolytic viruses; Drug delivery systems; Cancer immunotherapy; Bibliometric analysis

## 1. Introduction

Mesenchymal stem cells (MSCs) are multipotent stem cells with the ability to self-renew and differentiate into various cell types, including components of tissues, such as fat,

bone, and cartilage.<sup>1-4</sup> In the 1960s, Caplan<sup>5</sup> was the first to discover the potential of adult stem cells and later defined MSCs and described their multipotent properties and applications in tissue repair.<sup>5,6</sup> Due to their availability from various tissues (bone marrow, fat, umbilical cord, placenta, etc.), high immunotolerance and immunomodulatory abilities, ease of expansion, and demonstrated safety with low oncogenicity in numerous current clinical studies, MSCs are widely regarded as ideal carriers for clinical cell therapy and translational research.<sup>7,8</sup> Over the past few decades, the immunomodulatory functions of MSCs and their potential for treating various diseases have been extensively studied, including autoimmune diseases,<sup>9,10</sup> cardiovascular diseases,<sup>11</sup> and neurodegenerative diseases.<sup>12,13</sup> Recent advances in viral transfection and genetic engineering have enabled the use of MSCs as efficient carriers for a variety of therapeutic payloads. These include therapeutic proteins, microRNAs, prodrugs, chemotherapeutic drugs, suicide genes, and oncolytic viruses (OVs).<sup>14-18</sup> The potential of MSCs as a delivery platform in tumor-targeted therapy has gradually emerged.

Oncolytic viruses selectively replicate within and lyse tumor cells, inducing a systemic antitumor immune response.<sup>19</sup> By targeting and destroying tumor cells while sparing normal tissues, this approach offers a promising novel strategy for antitumor therapy.<sup>20</sup> Researchers combined MSC with OVs and leveraged MSC's tumor-tropic nature to develop an ideal carrier for OV delivery. One of the key challenges in OV delivery systems is increasing the distribution and penetration of the virus at the tumor site. To address this issue, recent studies have engineered MSCs through gene editing to modify their surface receptors.<sup>21,22</sup> These modifications enhance binding affinity for OVs, enabling them to effectively carry and protect OVs and achieve more effective virus release and activity in the tumor microenvironment (TME). Additionally, by enhancing the stability of the virus via MSC, it can effectively prevent immune clearance *in vivo* and increase the half-life of OVs in the body.<sup>21</sup> Another important advancement is the regulation of the TME by MSCs (e.g., controlling immune cell infiltration and enhancing local immune responses in the tumor),<sup>23,24</sup> thereby enhancing the therapeutic effect of OVs. Currently, the spectrum of OVs used with MSCs is expanding from early candidates such as herpes simplex virus,<sup>21</sup> measles virus,<sup>18</sup> and adenovirus<sup>25</sup> to the recent adeno-associated virus,<sup>26</sup> which, with the assistance of MSC carriers, has demonstrated varying degrees of tumor-killing effects. Moreover, the combined use of MSCs and viruses, in combination with immune checkpoint inhibitors<sup>27</sup> and chemotherapy drugs,<sup>28</sup> has significantly improved the clinical efficacy of OV therapy. These studies demonstrate

that MSC, as an OV delivery system, can not only improve the targeting and persistence of the virus but also enhance therapeutic efficacy, offering new ideas for advancing clinical OV therapy.

However, although the application of MSCs in OV delivery shows great potential, this field still faces several challenges. First, limited homing efficiency and poor tumor penetration remain critical barriers restricting the clinical application of MSCs. Second, MSCs exhibit significant heterogeneity depending on their tissue source and preparation protocols. The MSC–OV combination strategy still faces many controversies, including host immune remodeling, tumor-promoting/inhibiting effects, long-term safety, and regulatory issues for large-scale production. The relevant evidence remains mostly fragmented across *in vitro* and low-sample animal experiments. To date, there is a lack of comprehensive reviews that synthesize this information into a cohesive knowledge framework.

Bibliometrics (the study of citation data) uses tools such as CiteSpace,<sup>29</sup> VOSviewer,<sup>30</sup> and the R language<sup>31</sup> to comprehensively analyze indicators such as publication volume, citation frequency, national/institutional author collaboration networks, journal distribution, co-citation, and keyword co-occurrence clustering. Although there have been several bibliometric studies that have separately summarized the research landscape and development trends of OV therapy<sup>32</sup> and MSC-related therapies<sup>33</sup> as a whole, there is currently a lack of systematic bibliometric analysis and knowledge graph construction for the key cross-disciplinary direction of “MSCs as a delivery platform for OVs.” This study aims to use the 100 most-cited relevant papers as a sample set to construct a knowledge graph in the field of MSC–OV delivery. While the temporal evolution trajectory and geographical distribution describe macro-level research, the meso-level analysis focuses on identifying the dominant virus platform, primary MSC sources, and main technical strategies. The micro-level research aims to explore the theoretical basis, core bottlenecks, and frontier hotspots reflected by the highly cited papers, thereby providing quantitative evidence and strategic perspectives for optimizing the basic research layout and clinical trial design of MSCs as an OV delivery system, and providing a structured evidence basis for revealing the research progress, challenges, and future directions in this field.

## 2. Methodology

### 2.1. Data source and retrieval strategy

The literature data were retrieved from the Web of Science Core Collection (WoSCC), which was selected for its

standardized citation metrics and compatibility with bibliometric analysis tools. A topic search was conducted using a systematic search formula combining mesenchymal stem/stromal cells and OV-related terms: (“mesenchymal stem cell\*” OR “mesenchymal stromal cell\*” OR “MSC\*”) AND (“oncolytic virus\*” OR “oncolytic virotherapy” OR “oncolytic adenovirus” OR “oncolytic therapy” OR “oncolytic adenovirotherapy” OR “oncolytic reovirus”).

The search was limited to articles and reviews published in English between January 1, 2000, and October 31, 2025. All retrieved records were screened for relevance, yielding 173 eligible articles for the initial literature pool. Highly cited articles were further manually reviewed to confirm relevance to major OV platforms.

## 2.2. Literature screening process

### 2.2.1. Full-text assessment

The full texts of the literature that passed the initial screening were downloaded and reviewed. Two researchers independently assessed whether the content aligned with the scope of the study, focusing on the mechanisms of MSCs as delivery vectors, in vitro and in vivo experiments, efficacy evaluation, safety analysis, and technical improvements. The following exclusion criteria were strictly applied: (i) those involving only MSCs or OVs in a single direction, without clearly studying the combination of both as a delivery system; (ii) those mainly focusing on other applications of MSCs (such as immunomodulation and tissue repair) or other delivery methods of OVs (such as direct injection and liposome encapsulation); (iii) conference abstracts, editorials, letters, patents, and non-research literature; and (iv) literature with incomplete data or duplicate publications. After applying the inclusion and exclusion criteria, a total of 135 eligible articles focusing on MSC-based delivery of OVs were identified.

### 2.2.2. Final determination

In the cases of disagreement between reviewers, a third senior researcher arbitrated until a consensus was reached. To ensure analytical depth and comparability with previous bibliometric studies, the top 100 articles with the highest citation count and relevance to the research topic were defined as the core analysis dataset (i.e., the “Top 100” literature set).

### 2.2.3. Data export and cleaning

Complete records for the final 100 included articles were exported from the WoSCC database, including title, author, institution, country/region, journal, publication year, abstract, keywords, references, and citation frequency. The data were cleaned, the names of institutions and countries/

regions were standardized, and synonymous keywords (such as “mesenchymal stem cells” and “MSCs”) were merged to prepare for subsequent analysis.

## 2.3. Bibliometric analysis methods

### 2.3.1. Basic statistical analysis

We analyzed annual publication output to characterize stages of field development (emergence, development, and maturity). We also calculated the total citations (TCs) and the average citations per item to assess the overall influence of the literature.

### 2.3.2. Country/region and institution analysis

We counted the number of publications, TCs, and average citations per item from different countries/regions and research institutions, and identified the core research countries and leading institutions in the field. We constructed a network map of country/region cooperation and an institution cooperation network map to analyze the intensity and mode of international and institutional cooperation.

### 2.3.3. Author analysis

We identified high-productivity authors and their publication volumes and citation status, calculated the degree of collaboration (the average number of authors per paper), and built an author collaboration network map to identify core and collaborative author groups.

### 2.3.4. Journal analysis

We analyzed the distribution of source journals in the literature to identify the core journals that publish high-impact works on this topic.

### 2.3.5. Keyword analysis

We analyzed keywords to reveal research hotspots and frontiers. For keyword frequency analysis, we counted the frequency of author keywords and WoSCC supplementary keywords and identified high-frequency keywords to reflect research hotspots. For keyword co-occurrence analysis, we analyzed the frequency of keyword co-occurrence within the same paper and constructed a keyword co-occurrence network. We used cluster analysis (such as based on modular algorithms) to cluster the co-occurrence network and identify different research topics (such as “tumor homing mechanism of MSCs,” “engineering modification of OV,” “preclinical animal model research,” “targeted delivery efficiency and safety assessment,” and “combined treatment strategies”). For the keyword time evolution analysis, the emergence and fluctuations of keywords were analyzed across different time intervals to reveal dynamic

trends in research hotspots. A timeline view was employed to visually map the lifespan and developmental trajectory of each research topic.

### 2.3.6. Burst detection

We identified keywords that were suddenly and frequently used within a specific period (burst words). They often indicate emerging research frontiers or technologies that have suddenly gained attention (such as a specific type of OV, a new modification method for MSCs, or a certain combined therapy).

### 2.3.7. Reference literature analysis

We analyzed the cited references in the included literature to identify key foundational literature in the field. We also conducted a document co-citation analysis to reveal the correlation between the knowledge foundation literature and the academic schools that publish it. Additionally, we performed an author co-citation analysis to identify the group of scholars with significant influence in the field.

## 2.4. Visualization and statistical tools

To present the analysis results intuitively, this study employed multiple professional software programs for data visualization and statistical analysis.

### 2.4.1. CiteSpace (version 6.4.R1)

CiteSpace was primarily used for drawing keyword co-occurrence network diagrams, clustering views (including clustering identifiers), timelines, emergent word detection diagrams, and literature/author co-citation network diagrams. It is adept at revealing the dynamic evolution of research frontiers and potential changes in the knowledge structure. However, parameter settings, such as time slicing, and selection criteria, such as the g-index, must be clearly described.

### 2.4.2. VOSviewer (version 1.6.20)

VOSviewer was primarily used for drawing country/region cooperation network diagrams, institution cooperation network diagrams, author cooperation network diagrams, and keyword co-occurrence network density or overlay network diagrams. It is highly effective in presenting the overall structure, clustering, and density of cooperation networks and keyword networks. However, the calculation methods for correlation strength and clustering resolution parameters must be explained.

### 2.4.3. Bibliometrix (R package, version 4.5.1)/Biblioshiny (web interface)

Bibliometrix and Biblioshiny were used for a comprehensive bibliometric analysis, including basic statistics (publication

and citation volumes), three-field analysis (countries, institutions, and journals), partial visualization (such as thematic strategy diagrams), and data preprocessing and export. Its thematic map (Thematic Map) helped to divide research topics into four quadrants: core (motor themes), emerging/receding (emerging or declining themes), basic (basic themes), and marginal (niche themes).

### 2.4.4. Microsoft Excel

Excel was used for basic data organization, cleaning, and drawing simple trend diagrams, such as annual publication volume line graphs.

### 2.4.5. GraphPad Prism (version 10.0)/R (version 4.5.1)

GraphPad Prism/R were used for necessary statistical tests (such as correlation analysis and trend tests), but bibliometric analysis was mainly descriptive statistics and network analysis.

## 2.5. Research ethics

All data for this study were sourced from public academic databases (WoSCC), and the analysis process strictly adhered to academic standards. All analysis results were based on objective bibliometric data and did not involve any human intervention or fabricated data. The viewpoints and conclusions cited in the research were all derived directly from the sources.

## 3. Results

### 3.1. Literature screening and data analysis process

As of October 2025, a total of 189 relevant articles on “mesenchymal stem cells” and “oncolytic viruses” were retrieved. Firstly, non-academic articles and commentaries were excluded, leaving 174 articles that met the academic standards. Next, the types of articles were further screened to ensure that only “articles” and “review articles” were included, ultimately selecting 173 articles closely related to the research topic. In the language screening stage, only English articles were retained, resulting in a final number of 173 documents. To ensure the relevance and academic value of the literature, an independent review process was conducted. Records were manually screened according to the following criteria:

- (i) Inclusion criteria: The included literature should focus on cell transformation therapy research using MSCs and OVs, with particular emphasis on the direction where MSCs are used as the delivery vector for OVs, specifically prioritizing studies investigating MSCs. The content includes, but is not limited to, achieving targeted delivery of the virus using cell carriers, exploring the therapeutic mechanism, validating

efficacy in preclinical models, and engineering strategies for the cell and virus vectors.

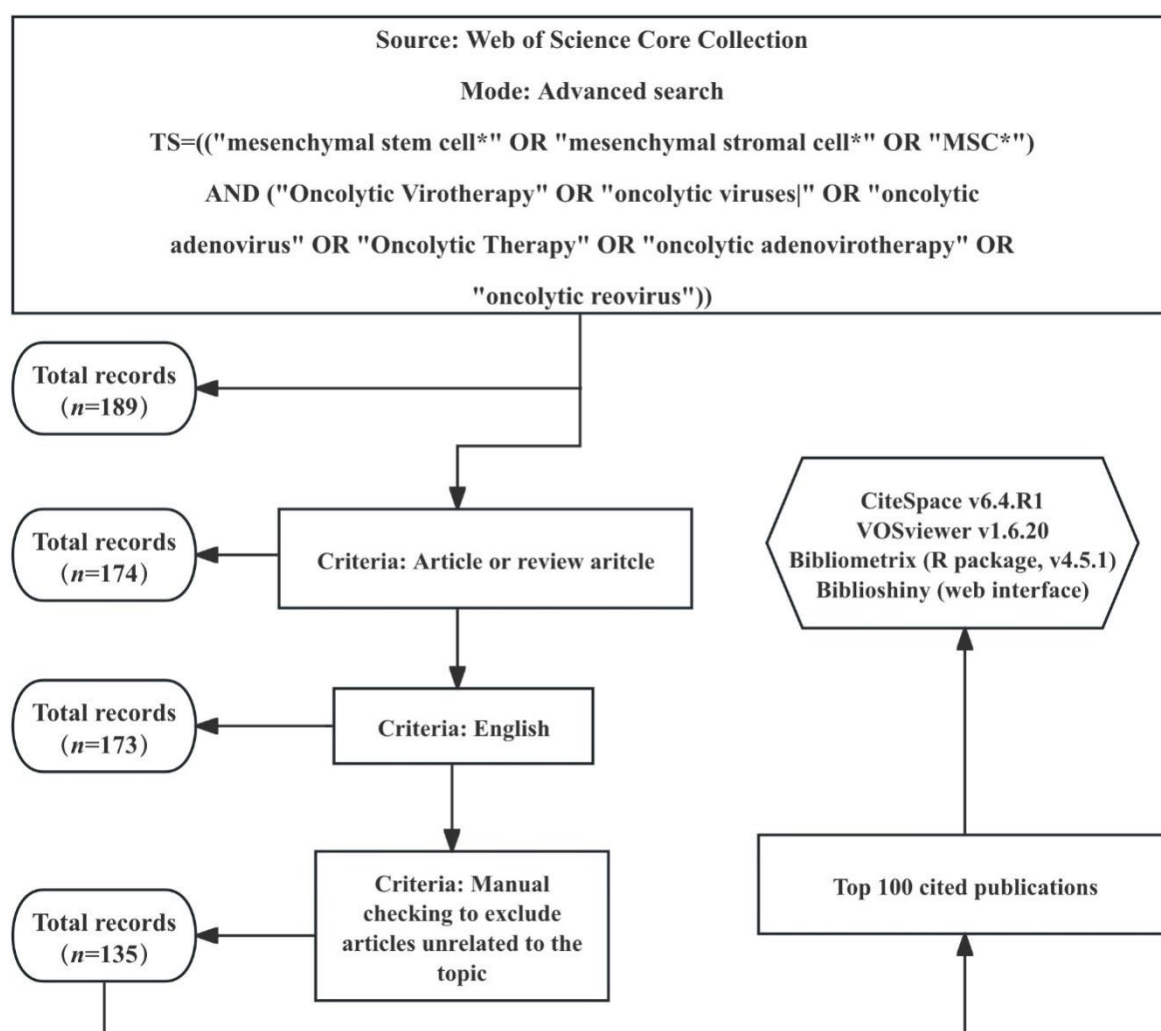
- (ii) Quality standards: The included literature must follow a complete academic paper structure, including an abstract, author information, keywords, and references, among other necessary components. Additionally, the manuscript length should not be less than two pages.

Manuscripts that did not meet the above format and length requirements would not be considered. Ultimately, 135 of the most representative and high-quality

publications were selected to form the final set of highly cited articles for this study. Figure 1 illustrates the specific process involved.

### 3.2. Publication year and citation count analysis

The top 100 papers related to “mesenchymal stem cells” and “oncolytic viruses” were published between 2007 and 2025 (Supplementary File). The annual publication output showed a gradual increase over time, with the highest number of publications recorded in 2021 (22 papers), followed by 2020 (19 papers).



**Figure 1.** Flow chart of the literature screening and selection. A total of 135 eligible articles were identified after quality screening, from which the top 100 most-cited articles were selected for bibliometric analysis.

Abbreviation: TS: Topic search.

The TC counts of the included papers ranged from 10 to 1,344, with an average of 61.74 citations per paper. Local citation counts ranged from 12 to 373, averaging 95.45 citations per paper. The year 2012 exhibited the highest average citation count (Figure 2). The most frequently cited paper, with 1,344 citations, was authored by Russell *et al.*,<sup>34</sup> followed by papers authored by Sonabend *et al.*<sup>35</sup> (431 citations) and Yong *et al.*<sup>36</sup> (235 citations).

Collectively, the top 100 papers garnered 1,811 citations, accounting for 29.3% of the TCs in the eligible literature dataset. A notable increase in publication output was observed in recent years, particularly in 2020, 2021, and 2024, with 19, 22, and 11 papers published, respectively. These figures account for approximately one quarter of the total publications during the study period.

### 3.3. Country-level contributions

Figure 3A shows that a total of 24 countries participated in the publication of the top 100 most-cited papers. Table 1 reveals that the country with the highest TCs and the largest number of published papers is the United States of America (USA), which received 2,667 citations and published 32 papers. The ratio of multi-country collaborative publications (22.2%) was significantly lower than that of Iran (63.6%) and Germany (53.8%). South

Korea published a total of 6 articles, but its average citations per article was second only to the USA (40 vs. 83). China's inaugural publication in this field appeared in 2013, three years after the first USA article was published in 2010. Since then, China's research output has grown rapidly, following a trajectory similar to that of the USA. By 2022, China surpassed Spain in total publication volume, ranking second globally (Figure 3B). Over the past decade, Chinese research has primarily focused on antitumor applications and cancer therapies, reflecting the rising prominence of this field (Figure 3C).

### 3.4. Author distribution and influence analysis

All the papers had at least two authors. Among the top 100 most-cited papers, there were a total of 594 authors. Approximately 80% of the papers had 10 or fewer authors. Figure 4A shows the top 10 most-active authors in this field in terms of publication volume. From the perspective of academic output and influence, the two most active authors were from Spain: García-Castro J. (10 papers) and Alemany R. (9 papers) (Table 2). Their h-index, g-index, and m-index were among the highest in the dataset, demonstrating their outstanding ability to continuously produce high-quality research and maintain a stable influence in this field. The third place was held by Lesniak M.S. from the USA, who has published eight

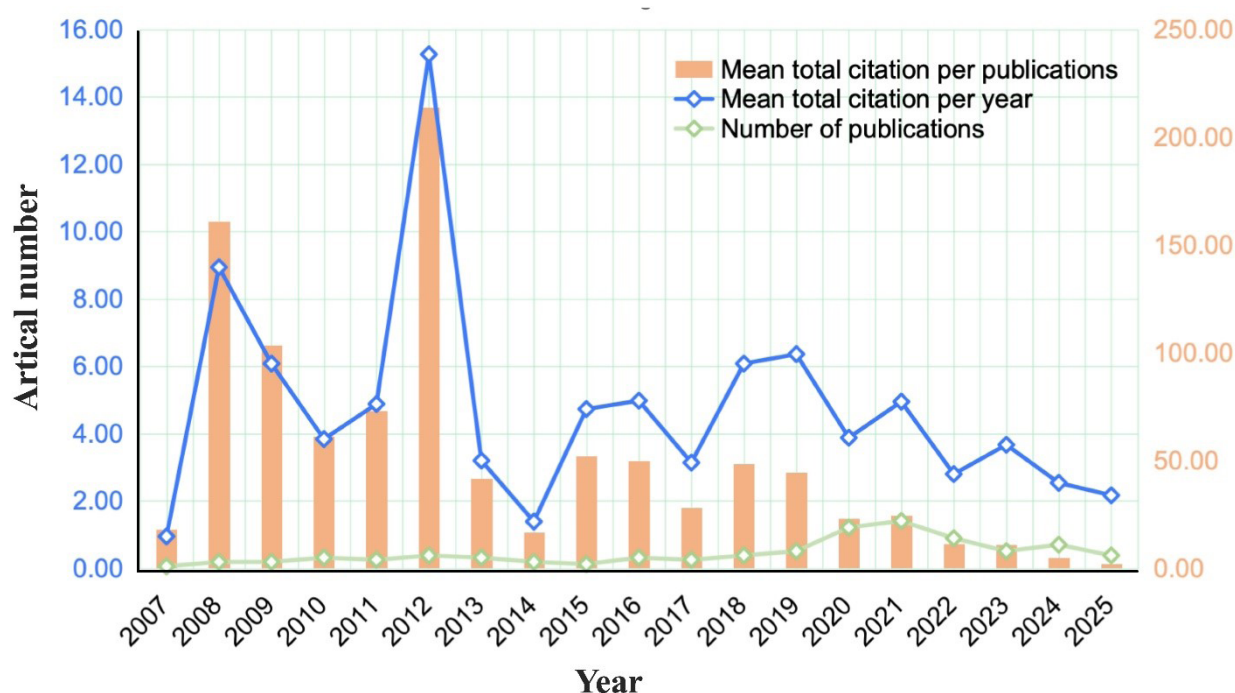
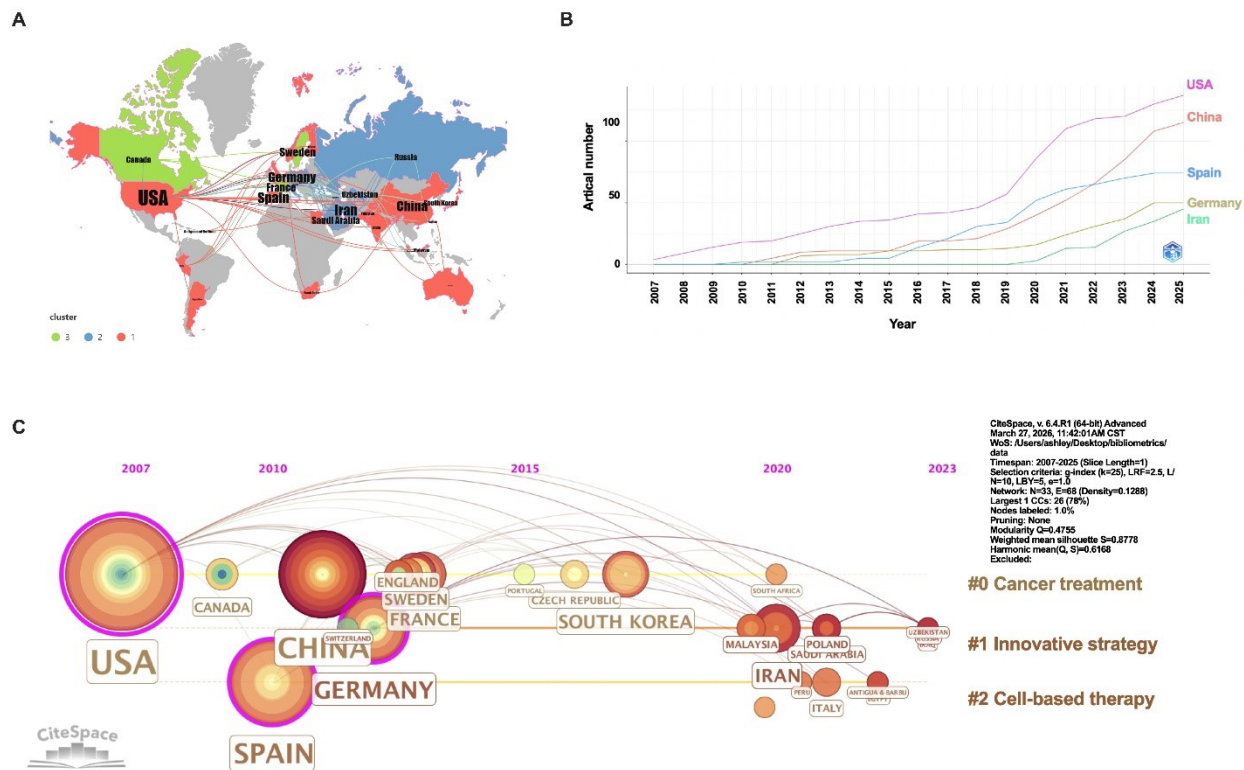


Figure 2. Research output and impact of MSC-based oncolytic virotherapy: Annual publications and citation metrics





**Figure 3.** Global distribution and temporal trends of the 100 most-cited articles (2000–2025) on “mesenchymal stem cells (MSCs)” and “oncolytic viruses.” (A) The world map depicts the geographic distribution of countries/regions contributing to the 100 most-cited publications in this field. Lines connecting nodes indicate the strength of collaborative activity between countries/regions, and the color of each node corresponds to the cluster classification shown in the legend. (B) Illustration of the annual contribution of the top five countries to the publication output over time. (C) The timeline visualization of country-level co-authorship from 2000 to 2025 shows the evolution of research on MSCs as delivery vehicles for oncolytic viruses; clusters are labeled from #0 to #2, with cluster size decreasing from #0 to #2, and arranged from left to right to represent the time span from 2000 to 2025.

**Table 1. The top 10 countries with the most publications (in descending order)**

Country	Articles	Articles (%)	SCP	MCP	MCP (%)	Total citation	Average citations per article
USA	32	23.7	24	8	25.0	2,667	83
China	27	20.0	21	6	22.2	514	19
Spain	20	14.8	17	3	15.0	661	33
Germany	13	9.6	6	7	53.8	224	17
Iran	11	8.1	4	7	63.6	139	13
South Korea	6	4.4	4	2	33.3	239	40
France	4	3.0	2	2	50.0	285	71
Japan	3	2.2	2	1	33.3	5	2
Poland	3	2.2	0	3	100.0	48	16
Italy	2	1.5	1	1	50.0	16	8

Abbreviations: MCP: Multiple-country publications; SCP: Single-country publications (all authors are from only one country); USA: United States of America.

papers. Additionally, these three authors showed the highest local citation counts within the analyzed dataset, further indicating that their research not only has a strong influence globally but also generates significant academic impact within their respective countries or regions. The author with the most citations was Lesniak M.S., whose TCs (TC = 582) ranked at the top of the dataset. The average citation per paper was 72.75, and there were 32 link strengths. This further confirms that their research results have been widely recognized and adopted by the scientific community. Lesniak M.S. has published in this field since at least 2008. Moreover, from Table 3, the other author from the USA, Russell S.J., reported the lowest local citation/global citation ratio = (1.33%) and the highest normalized global citations (normalized global citations = 5.3). In 2012, he published a review summarizing the status and core challenges of OV therapy. Figure 4B highlights the collaboration network relationships among authors from different institutions within this field. For instance, there was close collaboration between Sonabend A.M. and Yong R.L., and other authors, such as Rincón E. and Mader E.K., had academic partnerships within their research groups.

### 3.5. Journal analysis

As shown in Table 4, the top 10 journals published a total of 36 papers. These core journals were: (i) 5 papers: *Cancers*;

(ii) 4 papers: *Cancer Letters*, *Cancer Research*, *Molecular Therapy-Oncolytics*, and *Cancer Gene Therapy*; and (iii) 3 papers: *Cells*, *Journal of Translational Medicine*, *Molecular Pharmaceutics*, *Molecular Therapy*, and *Neuro-Oncology*. *Cancers* published the most papers but had the lowest citation rate. *Cancer Letters* ranked second with 4 papers and 233 citations, while *Cancer Research* ranked third with 4 papers and 408 citations; it had the highest number of citations.

### 3.6. Institution analysis

This study systematically analyzed the contributions and collaborations of various institutions. Regarding corresponding-author affiliations, the University of Barcelona in Spain showed the strongest citation burst, with the highest burst strength (1.11) during 2016–2017, followed by Assistance Publique Hopitaux Paris (APHP) and Sorbonne Université from France, both with an intensity of 0.89 and a burst period from 2016 to 2018. In terms of co-authorship, the Instituto de Salud Carlos III and the Hosp. Univ. Niño Jesús in Spain stood out, contributing significantly to the construction of the collaboration network. Table 5 lists the information of the top 10 institutions ranked by citation peak, with most of them located in Spain and China. In terms of the total number of published papers, UT MD Anderson Cancer

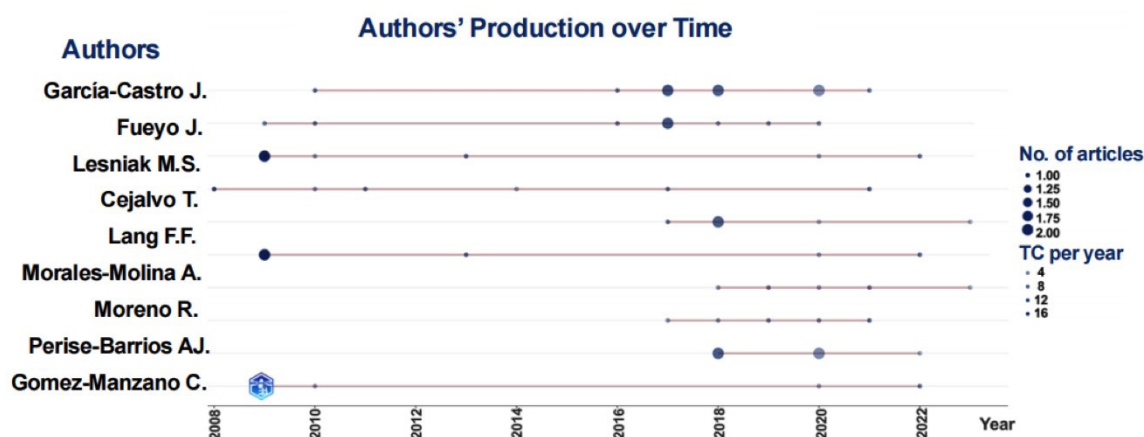
**Table 2. Top 10 authors with the highest academic productivity with global and local impact**

Author	Country	NP	h_index	g_index	m_index	TC	PY_start	Local citations
García-Castro J.	Spain	10	9	10	0.563	457	2010	90
Aleman R.	Spain	9	9	9	0.529	532	2009	92
Lesniak M.S.	USA	8	8	8	0.444	582	2008	92
Fueyo J.	USA	6	6	6	0.353	450	2009	43
Lang F.F.	USA	6	6	6	0.353	422	2009	38
Moreno R.	Spain	5	5	5	0.556	150	2017	56
Cejalvo T.	Spain	4	4	4	0.444	127	2017	24
Gomez-Manzano C.	USA	4	4	4	0.235	165	2009	12
Gumin J.	USA	4	4	4	0.235	324	2009	34
Han Y.	Spain	4	4	4	0.250	265	2010	53

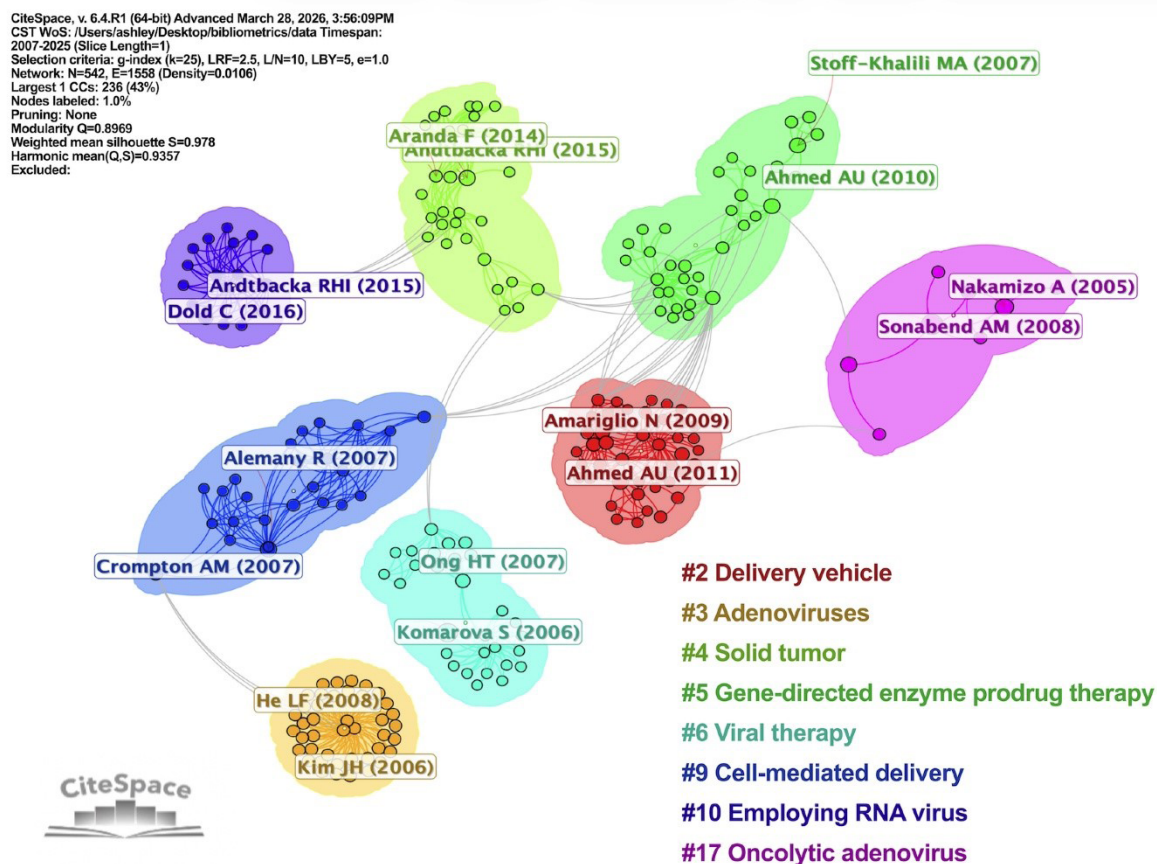
Abbreviations: g\_index: Gumbert index; h\_index: Hirsch index; m\_index: M-quotient; NP: Number of publications; PY: Publication year; TC: Total citations; USA: United States of America.



A



B



**Figure 4.** Trend chart of academic output and influence evolution. (A) The top 10 most-active authors during the years 2007–2025. (B) A collaboration network of authors in the fields of mesenchymal stem cells and oncolytic viruses. Different colors represent different research groups or author clusters, and each node represents an author.

**Table 3. Top 10 authors with the greatest global and local influence and their citation information**

Author	Author country	Year	Journal	PMID	LCs	GCs	LC/GC ratio (%)	Normalized LCs	Normalized GCs
Russell S.J.	USA	2012	<i>Nat Biotechnol</i>	22781695	15	1,132	1.33	3.33	5.30
Yong R.L.	USA	2009	<i>Cancer Res</i>	19920199	35	198	17.68	2.76	1.92
Ahmed A.U.	USA	2011	<i>Mol Pharmaceut</i>	21718006	21	111	18.92	2.47	1.52
Sonabend A.M.	USA	2008	<i>Stem Cells</i>	18192232	42	212	19.81	2.86	1.32
Yoon A.R.	South Korea	2019	<i>Cancer Res</i>	31289131	22	85	25.88	2.29	1.91
Ruano D.	Spain	2020	<i>Mol Ther</i>	32053771	23	85	27.06	5.68	3.65
García-Castro J.	Spain	2010	<i>Cancer Gene Ther</i>	20168350	33	113	29.20	2.58	1.84
Ahmed A.U.	USA	2010	<i>Mol Ther</i>	20588259	21	57	36.84	1.64	0.93
Rincón E.	Spain	2017	<i>Oncotarget</i>	28525366	24	59	40.68	2.67	2.09
Melen G.J.	Spain	2016	<i>Cancer Lett</i>	26655276	27	65	41.54	3.38	1.31

Notes: Global citations (GCs) indicate citations received in the broader database. Local citations (LCs) indicate citations within the local dataset (i.e., the top-100 collection used for analysis). The LC/GC ratio reflects the extent to which citations originate from within the analyzed collection.

Abbreviation: USA: United States of America.

**Table 4. Top 10 journals by publication count and impact metrics**

Journal	h_index	g_index	m_index	TC	NP	PY_start
<i>Cancers</i>	5	5	0.833	60	5	2020
<i>Cancer Letters</i>	4	4	0.222	233	4	2008
<i>Cancer Research</i>	4	4	0.235	408	4	2009
<i>Molecular Therapy-Oncolytics</i>	4	4	0.571	88	4	2019
<i>Cancer Gene Therapy</i>	3	4	0.188	190	4	2010
<i>Cells</i>	3	3	0.500	130	3	2020
<i>Journal of Translational Medicine</i>	3	3	0.214	81	3	2012
<i>Molecular Pharmaceutics</i>	3	3	0.200	244	3	2011
<i>Molecular Therapy</i>	3	3	0.188	193	3	2010
<i>Neuro-Oncology</i>	3	3	0.214	101	3	2012

Abbreviations: g\_index: Gumbert index; h\_index: Hirsch index; m\_index: M-quotient; NP: Number of publications; PY: Publication year; TC: Total citation.

Center in the USA published the most papers (29), followed by Instituto de Salud Carlos III and Guizhou Medical University in China (11) (Table 6). The association strength of Instituto de Salud Carlos III reached 91, ranking first. Other institutions, such as the Chinese Academy of Medical Sciences-Peking Union Medical College, Hanyang University, and Guizhou Medical University, published fewer papers but showed a relatively strong collaboration intensity, with association strengths ranging from 37 to 39.

### 3.7. Citation analysis

The top 10 high-impact publications with the strongest citation bursts in this research field are shown in Table 7. These papers collectively reflect the core research directions and key advancements in this field. The review “Oncolytic virotherapy” published by Russell *et al.*<sup>34</sup> in *Nature Biotechnology* in 2012 was the most cited document in this field, with a TC of 1,132, an average annual citation of 80.86, and a standardized citation of 5.3, followed by the studies by Sonabend *et al.*<sup>35</sup> (2008, *Stem Cells*) and Yong *et al.*<sup>36</sup> (2009, *Cancer Research*) on the delivery of oncolytic adenovirus to glioma using MSCs, which were cited 212

times and 198 times, respectively. Further analysis showed that several important papers focus on the efficacy and mechanism exploration of different stem cell carriers (such as bone marrow-derived MSCs and neural stem cells) in delivering OV (such as adenovirus delta24-RGD) for the treatment of glioma and neuroblastoma, including those by García-Castro *et al.*<sup>37</sup> and Ahmed *et al.*<sup>38</sup> These studies collectively form the core body of evidence of the “cell carrier–oncolytic virus” combined strategy. It is notable that in recent years, this field has begun to expand toward nanotechnology and precise delivery. For example, the review by Briolay *et al.*<sup>39</sup> (2021, *Molecular Cancer*) on synthetic and biomimetic nanocarriers for cancer therapy delivery reported 94 citations and exhibited the highest annual citation rate (18.80). Shinojima *et al.*<sup>40</sup> reported on the role of transforming growth factor-beta (TGF- $\beta$ ) signaling in MSC homing to glioma stem cells.

### 3.8. Research areas and hotspots

The keyword cloud analysis (Figure 5A) revealed that research in this field was predominantly concentrated on two major directions: cell carrier therapy and

**Table 5. Top 10 institutions with the strongest citation bursts**

Institutions	Year	Strength	Begin	End	2007–2025
University of Barcelona	2016	1.11	2016	2017	
Assistance Publique Hopitaux Paris	2016	0.89	2016	2018	
Sorbonne Université	2016	0.89	2016	2018	
Karolinska University Hospital	2016	0.89	2016	2018	
Institut Catala d'Oncologia	2016	1.57	2017	2020	
Institut d'Investigació Biomedica de Bellvitge	2016	1.57	2017	2020	
Instituto de Salud Carlos III	2016	0.91	2017	2018	
Hanyang University	2019	1.44	2019	2020	
Beckman Research Institute of City of Hope	2019	0.95	2019	2020	
Hangzhou Medical College	2019	0.95	2019	2020	

Table 6. Top 10 institutions with the strongest total link strength

Affiliation	Articles	Citations	Total link strength	Country
Instituto de Salud Carlos III	11	282	91	Spain
Hosp Univ Niño Jesús	2	306	57	Spain
University Of Chicago	8	484	54	USA
Chinese Academy Of Medical Sciences-Peking Union Medical College	8	57	39	China
Hanyang University	4	183	38	South Korea
Guizhou Medical University	11	27	37	China
Zunyi Medical University	5	27	37	China
Institut D'investigacio Biomedica De Bellvitge	10	90	36	Spain
Isfahan University Of Medical Sciences	4	57	33	Iran
UT MD Anderson Cancer Center	29	479	12	USA

Abbreviations: USA: United States of America; UT: University of Texas.

Table 7. Top 10 publications with the strongest citation bursts and their information

PMID	First author	Year	Journal	TC	TC per year	Normalized TC
22781695	Russell S.J.	2012	<i>Nat Biotechnol</i>	1,132	80.86	5.30
18192232	Sonabend A.M.	2008	<i>Stem Cells</i>	212	11.78	1.32
19920199	Yong R.L.	2009	<i>Cancer Res</i>	198	11.65	1.92
18328829	Guo Z.S.	2008	<i>Bba-Rev Cancer</i>	159	8.83	0.99
20168350	García-Castro J.	2010	<i>Cancer Gene Ther</i>	113	7.06	1.84
18502571	Altaner C.	2008	<i>Cancer Lett</i>	112	6.22	0.70
21718006	Ahmed A.U.	2011	<i>Mol Pharmaceut</i>	111	7.40	1.52
21126047	Pesonen S.	2011	<i>Mol Pharmaceut</i>	102	6.80	1.39
33761944	Briolay T.	2021	<i>Mol Cancer</i>	94	18.80	3.80
23365134	Shinojima N.	2013	<i>Cancer Res</i>	87	6.69	2.09

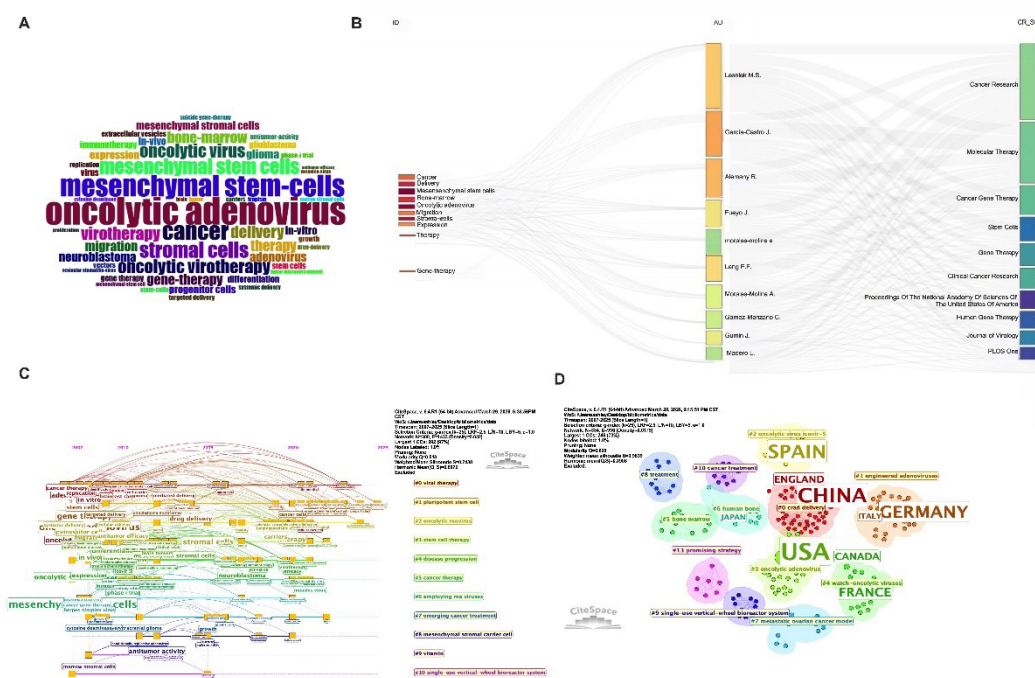
OV treatment. The top-ranked frequent keywords included “mesenchymal stromal cells,” “oncolytic virus,” “extracellular vesicles,” “immunotherapy,” and “gene therapy.” The results of the Sankey diagram analysis (Figure 5B) further confirm these trends and illustrate key authors, such as Lesniak M.S. and Alemany R., along with their representative research achievements and citation networks, across high-level academic platforms (e.g., *Cancer Research*, *Molecular Therapy*, and *Clinical Cancer Research*). This network shows the key researchers and their collaborations. Figure 5C reveals a clear temporal evolution of research hotspots, shifting from an early emphasis on viral vectors and gene therapy to a more diversified landscape that integrates cell-based carriers, immunotherapy, and advanced drug delivery strategies. Over time, the scope gradually expanded to include mesenchymal stem cells, the tumor microenvironment, and combined treatment strategies. In Figure 5D, the first group was marked in red, including China, the USA, Japan, and Sweden. International cooperation among

these countries played a core role in human MSCs research and cancer treatment. The second group was marked in green, including South Korea, England, Italy, and Spain. They focused on anti-cancer therapeutic efficacy. The third group, the “cancer treatment” cluster, was marked in purple. Countries like Germany, Iran, and Poland have made significant contributions to this cluster.

## 4. Discussion

### 4.1. Evolution of research themes and knowledge structure in mesenchymal stem cell-based oncolytic virotherapy

In this review, we systematically analyzed the application of MSCs in OV delivery systems for the first time using bibliometric methods. Additionally, we explored the top 100 most-cited articles over the past 25 years to identify the key research focuses and developmental trajectories of MSCs–OVs, providing a comprehensive framework that elucidates the evolutionary trends in this field.



**Figure 5.** Research trends, key authors, and thematic focus in cancer therapy from 2000 to 2025. (A) Keyword word cloud analysis. (B) Network map illustrating the associations among keywords, authors, and journals in cancer research. (C) Emerging innovative strategies and technological frontiers in cancer treatment. (D) The global research clusters and cooperation patterns, with node sizes corresponding to publication influence and links representing the intensity of international cooperation among countries.

Abbreviations: AU: Author; CR\_SO: Cited Reference Source (Source Journal).

Our analysis indicates that the use of MSCs as a delivery system in OV immunotherapy for cancer is predominantly led by a few countries with strong scientific research capabilities, notably the USA, which holds a clear advantage in publication volume and TC frequency. This leadership is attributable to the complex nature of stem cell therapy and MSC preparation, which involves multiple interconnected steps, lengthy development cycles, and significant technical challenges. Consequently, substantial funding and advanced infrastructure are required.<sup>41–43</sup> Previous studies have highlighted that cell therapy manufacturing is significantly more expensive than traditional drug production, with considerable variability in batch costs depending on the product and facility conditions. Furthermore, clinical-grade MSC production must comply with current Good Manufacturing Practice (GMP) standards and faces challenges related to large-scale manufacturing and regulatory approval.<sup>44</sup> Similarly, advancing OVs to clinical application demands an ample supply of high-quality, GMP-compliant viral products and robust supporting process systems. These high costs and technical barriers likely confer a sustained investment advantage to high-income countries, enabling them to better manage the financial and accessibility challenges associated with the substantial upfront costs during treatment implementation.

Despite the USA leading in overall research output, its proportion of multi-country collaborative publications remains relatively low. In contrast, emerging research powerhouses may rely more heavily on international cooperation to enhance research visibility. Although China's research in this domain began relatively late—approximately three years after the USA—its output exhibited a robust upward trajectory, ranking second globally by 2022. This growth aligns with rising national investments in life sciences. Chinese scholars have primarily contributed to basic and applied research areas, such as the isolation and cultivation of MSCs, genetic engineering, and the development of tissue-engineering scaffolds.<sup>45</sup> Nevertheless, compared to the USA, gaps remain in leading clinical translational research, and a truly transnational, deeply integrated cooperation network at the intercontinental level has yet to be established.

From a temporal perspective, the bibliometric landscape identifies 2012 as a critical inflection point (Figure 2 and Figure 4), marked by the highest average citation count among the top 100 most-cited publications. This peak corresponds to the maturation of the field from foundational theoretical discussions to early-stage translational modeling. The most-cited article—the 2012 review by Russell *et al.*<sup>34</sup>—served as a conceptual anchor by

systematically articulating translational bottlenecks such as premature viral clearance and host humoral neutralization. Data extracted from the citation network revealed that this work identified MSCs as viable cellular delivery vehicles capable of circumventing humoral immune barriers while maintaining viral infectivity. This pivotal reference point correlated with a measurable shift in research focus from direct viral administration to bioengineered cellular delivery platforms, supported by early translational milestones, such as those reported by Sonabend *et al.*<sup>35</sup> and Yong *et al.*,<sup>36</sup> which demonstrated feasibility in glioma models and highlighted the impact of MSC biological heterogeneity on therapeutic efficacy.

As the field has evolved, the “cell carrier–oncolytic virus” strategy has transitioned toward greater technological precision and mechanistic depth. As summarized in Table 7, the distribution of high-impact publications indicates a trajectory moving from OV-centric biological validation to the integration of nanotechnology and TME dissection. Notably, the review by Briolay *et al.*<sup>39</sup> on synthetic and biomimetic nanocarriers achieved the highest average annual citation rate in the dataset, suggesting that nanocarrier-enabled delivery is becoming a rapidly expanding axis of the broader MSC–OV landscape. Concurrently, studies such as that by Shinojima *et al.*<sup>40</sup> have deepened our understanding of TME interactions, providing evidence that pathways like TGF- $\beta$  signaling are critical for mediating MSC homing. Collectively, these citation indicators suggest that the future of the field lies in the convergence of precision-delivery technologies and the mechanistic modulation of niche interactions within the TME.

#### 4.2. Key challenges in clinical translation

While the application of MSCs in OV delivery shows great promise, its clinical translation faces several challenges. One major issue is the limited homing efficiency and poor tumor penetration of MSCs.<sup>46</sup> Although MSCs naturally migrate to tumors, their ability to penetrate deeply into tumor tissue remains a critical barrier to their effectiveness as delivery vehicles. Recent studies have employed gene-editing techniques to enhance the homing capabilities of MSCs, including modifying their surface receptors to increase binding affinity for OVs or tumor ligands.<sup>47</sup> These genetic modifications are crucial for improving the distribution and penetration of OVs at the tumor site, thereby increasing the therapeutic effectiveness of OV therapy.

Furthermore, MSCs exhibit significant heterogeneity depending on their tissue origin and preparation methods.<sup>48</sup> This variability can affect the consistency and predictability



of their behavior, which poses challenges for their clinical application. For instance, different MSC sources, such as bone marrow-derived MSCs or adipose-derived MSCs, may vary in their ability to deliver OV<sub>s</sub> effectively, which requires standardization of MSC preparation protocols.<sup>49</sup>

Further analysis of the thematic evolution revealed that influential research and reviews in the early stages primarily established the theoretical and mechanistic foundations of OV therapy. Over the past decade, as the field has matured, the research focus has gradually shifted from proof-of-concept to targeted tumor treatment, with an increasing incorporation of immunotherapy and gene therapy models. This includes comparisons of different stem cell sources, viral platforms, and interactions with the TME, collectively forming a robust evidence base for the cell–virus combination strategy. This transformation indicates that the combined treatment of MSCs and OV<sub>s</sub> is progressively advancing from the proof-of-concept phase toward the development stage of translational medicine and clinical application, aligning closely with the global trajectory of tumor biological therapy research. The dynamics of time-related keywords suggest that recent trends have shifted toward optimizing systemic administration, enhancing tumor targeting<sup>50</sup> and validating antitumor efficacy, reflecting a continuous progression toward translational research.<sup>21,51,52</sup>

### 4.3 Limitations

This study has several limitations that should be acknowledged. First, the bibliometric analysis relied on a single database, potentially resulting in incomplete coverage of all relevant publications. Nevertheless, WoSCC is widely recognized for its high-quality citation indexing and is frequently used in bibliometric analyses in oncology and stem cell research.<sup>53</sup>

Second, while virus-specific terms were not exhaustively listed in the initial search strategy, the use of the broader term “oncolytic virus” allowed the inclusion of studies across multiple virus platforms. Manual verification of highly cited records confirmed the presence of key virus systems, including adenovirus, herpes simplex virus, measles virus, and vaccinia virus. Importantly, the main bibliometric patterns and thematic structures identified in this study were stable and consistent,<sup>32</sup> suggesting that the overall conclusions are robust despite these methodological constraints.

## 5. Conclusion

Although MSCs used as delivery vectors for OV<sub>s</sub> have demonstrated significant potential in tumor treatment, their clinical translation faces several critical challenges.

These include the heterogeneity of stem cell sources and functions, limitations in in vivo targeting and tissue penetration, uncertainties regarding long-term safety and immunological risks, and complex requirements for large-scale production and regulatory compliance. These issues represent core controversies in the field and, to some extent, hinder the translation of research findings into clinical application. Future research should focus on more precise cell and virus engineering strategies, conduct in-depth analyses of delivery and therapeutic mechanisms, establish standardized and reproducible production processes, and systematically overcome these bottlenecks through rigorously designed translational studies and clinical trials. Ultimately, the safe, effective, and sustainable application of the combined MSC–OV strategy in cancer treatment will depend heavily on interdisciplinary collaboration and coordinated advancement alongside regulatory frameworks.

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The authors declare they have no competing interests.

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## Ethics approval and consent to participate

Not applicable.

## Consent for publication

Not applicable.

## Availability of data

The raw bibliographic data were retrieved from the Web of Science Core Collection database, accessible through institutional subscription. The complete search strategy—including database selection, search terms, time range, document types, and inclusion/exclusion criteria—is provided in the Methods section to ensure reproducibility.

In compliance with Clarivate Analytics' data usage policies, the original downloaded datasets cannot be publicly shared. However, the processed and cleaned dataset, along with analysis parameter files for CiteSpace, Bibliometrix, and VOSviewer, are available from the corresponding author upon reasonable request.

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