

# Stem Cell Therapy for Neuropathic Pain: A Bibliometric and Visual Analysis

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**Purpose:** Neuropathic pain is intractable and current treatment modalities are ineffective to cure this intractable pain, which has become a global problem. In recent years, there have been an increasing number of studies on stem cell therapy for neuropathic pain that have shown enormous potential. Using a visual analysis approach of the existing literature on stem cell therapy for neuropathic pain, we hope to understand the current research status and hot issues in this field and to provide valuable predictions for future research in this field.

**Methods:** We used Citespace software to visually analyze 291 articles and reviews indexed by the Web of Science Core Collection Database exploring stem cell-based treatment of neuropathic pain from 1995 to 2021. The Gunmap online world map evaluated the number of countries and regional articles separately. Microsoft Excel 2016 was used to generate a graph of trends in annual publications.

**Results:** Visualization analysis revealed that the number of publications has increased yearly. The top three countries in terms of number of articles published are United States, China, and Japan. Analysis of highly co-cited articles revealed that the contents of these articles primarily involved the expression of IL-1 $\beta$ , IL-10, NPY, TRPA1, p-p38, p-ERK1/2, TGF- $\beta$ , PKC $\delta$ , CaMKII $\alpha$ , P2X4, P2X7 and TNF- $\alpha$ . Keywords and citation burst analysis demonstrated that activation, regeneration, chemotherapy, and expression are likely the research hotspots and future directions of stem cell research in neuropathic pain.

**Conclusion:** Stem cell therapy may be a potential means of future treatment of neuropathic pain. The study of the mechanisms underlying stem cell therapy for neuropathic pain is still a focus of future research.

**Keywords:** neuropathic pain, stem cell, CiteSpace, Web of Science, bibliometric analysis, visualization analysis

## Introduction

Neuropathic pain (NP) is pain caused by a lesion or disease of the somatosensory nervous system.<sup>1</sup> The International Association for the Study of Pain (IASP) classifies neuropathic pain in detail according to the latest version of the World Health Organization ICD-11 classification of diseases, subdividing the condition into peripheral neuropathic pain and central neuropathic pain.<sup>2</sup> There are multiple mechanisms responsible for the development of neuropathic pain, but it is not clear why nerve injury transforms into a chronic inflammatory and painful state.<sup>3</sup> Current treatments for neuropathic pain include pharmacotherapy, platelet-rich plasma therapy, and neuromodulation therapy.<sup>4-6</sup> Despite numerous treatment options, the current treatment for neuropathic pain is not satisfactory. In recent decades, stem cells have shown remarkable efficacy in handling and repairing neuropathic pain rather than temporary analgesia.<sup>7</sup> Stem cells promise to be effective therapies for neuropathic pain.

Bibliometrics refers to using mathematical and statistical methods to quantitatively analyze published scientific literature to help researchers quantitatively identify detailed research trends and hot spots.<sup>8</sup> CiteSpace is an excellent bibliometric software that visualizes the relationships between the literature as a scientific knowledge

map, helping to unravel past research trajectories and obtain a general idea of future research prospects.<sup>9</sup> Citespace is used to analyze the current state of research and hot spots in a research area and is increasingly valued by researchers.

In this study, we use Citespace software to visualize and analyze research related to the use of stem cells for the treatment of neuropathic pain and anticipate future directions in this field.

## Data and Methods

### Retrieval Strategy

The first author extracted relevant studies addressing stem cell therapy for neuropathic pain published from 1995 to 2021.

### Databases Retrieved

We retrieved the studies from databases from the Web of Science (WOS) Core Collection Database, including the Science Citation Index Expanded (SCIE), the Social Science Citation Index (SSCI), and the Emerging Sources Citation Index (ESCI).

### Search Strategy

This study used stem cell and neuropathic pain for the MeSH keywords (<https://www.ncbi.nlm.nih.gov/mesh>) search. Further description of the specific classification of neuropathic pain was based on the International Classification of Diseases 11th Revision (<https://icd.who.int/en>). We selected articles from 1995 to 2021. The study included original reports and reviews as publication types. The search terms and strategies are given in Table 1.

### Qualification

Full-text retrieval was performed.

### Inclusion Criteria

After reading the title and abstract, all topics related to stem cells and neuropathic pain were listed. The style of the publications was limited to original research articles and reviews, but not letters, editorial materials, perspectives or abstracts from meetings.

### Number of Studies Included

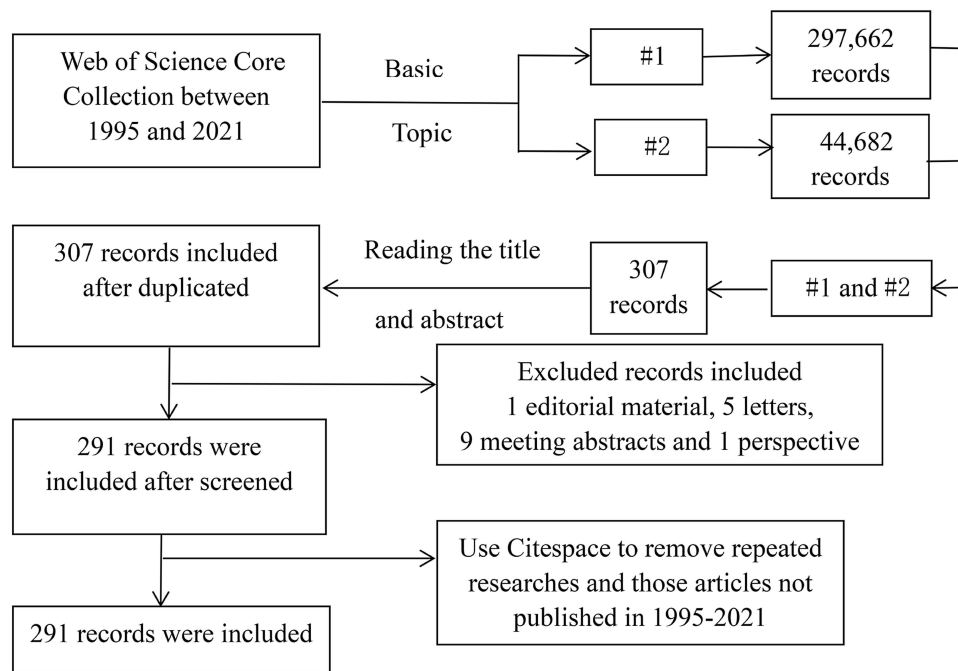
Based on search terms and strategies, a total of 307 records were selected. By reading the abstracts, excluding editorial materials, letters, meeting abstracts and perspectives, a total of 291 records were eventually included (Figure 1).

**Table 1** Search Terms and Strategies

Step	Search Strategy	Result
#1	TS ("Stem Cell") OR TS (Mesenchymal Stem Cells) OR TS ("Mesenchymal Stromal Cell") OR TS (Mesenchymal Progenitor Cell) OR TS ("MSCs")	297,662
#2	TS ("Neuropathic Pain") OR TS ("Trigeminal Neuralgia") OR TS ("Postherpetic Neuralgia") OR TS ("Pain After Peripheral Nerve Injury") OR TS ("Painful Polyneuropathy") OR TS ("Painful Radiculopathy") OR TS ("Painful Diabetic Neuropathy") OR TS ("Diabetic Painful Neuropathy") OR TS ("Chemotherapy Induced Peripheral Neuropathy") OR TS ("Chronic Inflammatory Demyelinating Polyneuropathy") OR TS ("Neuropathic Cancer Pain") OR TS ("Spinal Cord Injury Pain") OR TS ("Central Post-Stroke Pain")	44,682
#3	#1 AND #2	307

**Notes:** Search on 1 February 2022. Retrieval time range: 1 January 1995 to 31 December 2021.

**Abbreviation:** TS, subjects.



**Figure 1** Flowchart of articles inclusion selection.

## Methodology

We analyzed included papers separately for bibliometric and network visualization using Citespace V5.8.R3, 64 bit (<https://citespace.podia.com/>). The Gunmap (<http://lert.co.nz/map/>) online world map evaluated the number of countries and regional articles separately. Microsoft Excel 2016 was utilized to generate a graph of the trends in annual publications.

## Bibliometric and Visual Analysis

All publications elements, including year of publication institutions, countries, co-cited authors, references, and key-words were extracted. Citespace software was used to visualize the relationship between literature with elements such as node circle, link between nodes, centrality, and cluster.

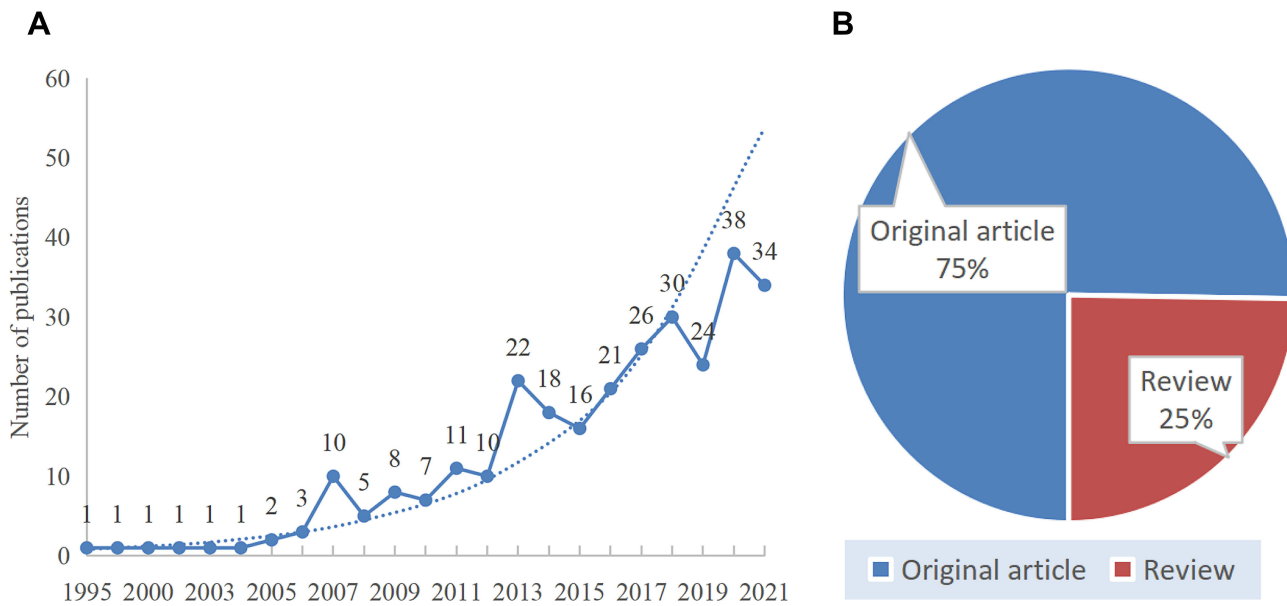
## Results

### Publication Outputs by Year

A total of 291 publications were included in this study. The annual publication rates of articles on stem cell therapy for neuropathic pain tended to increase mainly during 1995–2021 (Figure 2A). The year with the most publications was 2020, with 38, followed by 2021, with 34 publications. A total of 152 articles were published in the last five years alone, accounting for 52% of all publications. Overall, 219 original research articles were published, accounting for 75% of all publications, and 72 review articles, accounting for 25% of all publications (Figure 2B).

### Journals

The top 10 co-citation counts journals are presented in Table 2. The journal *Pain* was cited a total of 146 times and was the highest co-citation journal. Seven of the 10 journals are published in the United States. This indicates that the US has significant influence in this area. The journal *Blood* had the highest intermediary centrality (Centrality = 0.18, Figure 3).



**Figure 2** Bibliometric analysis of publication output. A total of 291 publications were included from 1995 to 2021. **(A)** Number of publications. **(B)** Article type distri.

### Co-Authors’ Country and Institution Analysis

According to the bibliometric analysis via CiteSpace, 291 publications were published by research teams from 40 countries. The most prolific country was the United States (n=109, Centrality = 0.41, Figure 4A and B). The three countries that ranked after the United States were China (n=61, Centrality = 0.00), Japan (n=23, Centrality = 0.01), and Germany (n=19, Centrality = 0.10). The United States was far higher than other countries in citation and centrality.

Bibliometric and visual analysis presented a low-density map (Density = 0.0103), which indicated fewer collaborations between different research institutions. The most prolific institution was Johns Hopkins University (n=13, Centrality = 0.04) and Duke University (n=7, Centrality = 0.10) (Figure 4C).

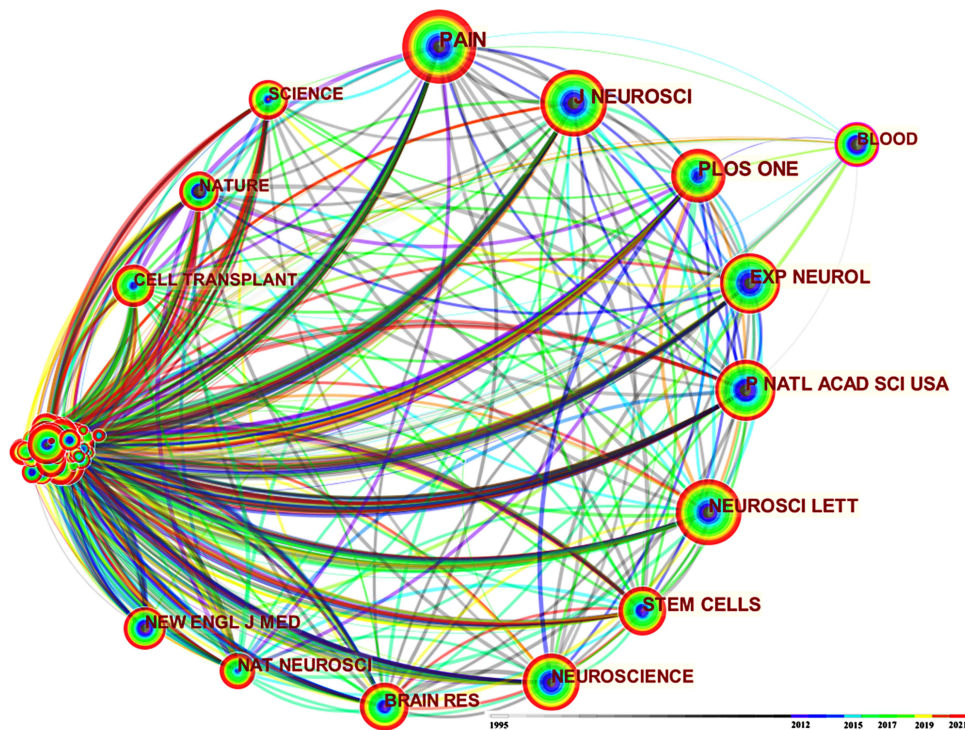
### Co-Citation References Analysis

The top 10 highly cited documents are listed in Table 3.<sup>10-19</sup> The most cited articles were from Siniscalco. Furthermore, this author had the strongest citation bursts (strength=6.19), starting in 2013 and ending in 2018.<sup>10</sup> Top 16 references with the strongest citation bursts were showed in Figure 5.<sup>10,11,13-18,20-27</sup> There were 4 references

**Table 2** The Top 10 Co-Cited Journal Information

Rank	Counts	Centrality	Cited Journal	IF (2020)	Country Affiliation
1	146	0.01	<i>Pain</i>	6.961	United States
2	120	0.06	<i>Journal of Neuroscience</i>	6.167	United States
3	113	0.01	<i>Plos One</i>	3.240	United States
4	103	0.02	<i>Experimental Neurology</i>	5.330	United States
5	102	0.03	<i>Proceedings of the National Academy of Sciences of the United States of America</i>	11.205	United States
6	100	0.03	<i>Neuroscience Letters</i>	3.046	Netherlands
7	96	0.02	<i>Stem Cells</i>	6.277	United States
8	88	0.05	<i>Neuroscience</i>	3.590	England
9	84	0.05	<i>Brain Research</i>	3.252	Netherlands
10	81	0.02	<i>Nature Neuroscience</i>	24.884	United States





**Figure 3** Co-citation analysis of journals. *Pain* was the highest co-cited journal. *Blood* was the journal with the highest central intermediation.

with citation bursts lasting until 2021, which indicated that these four references were still the hotspots of current researches.<sup>11,14,26,27</sup> Co-citation analysis of the top 10 cited documents were showed in Figure 6.<sup>10–19</sup> Chen, Sacerdote, Franchi and Schafer ranked second to fifth highest cited, but these nodes were circled in red, indicating that these citations had been cited recently.<sup>11–14</sup>

Presently, stem cell therapy for neuropathic pain is mainly focused on pre-clinical studies. The number of clinical studies on stem cell therapy for neuropathic pain is relatively limited, focusing mainly on spinal cord injuries. To understand the development of clinical studies, the clinical studies were listed in Table 4.<sup>28–38</sup>

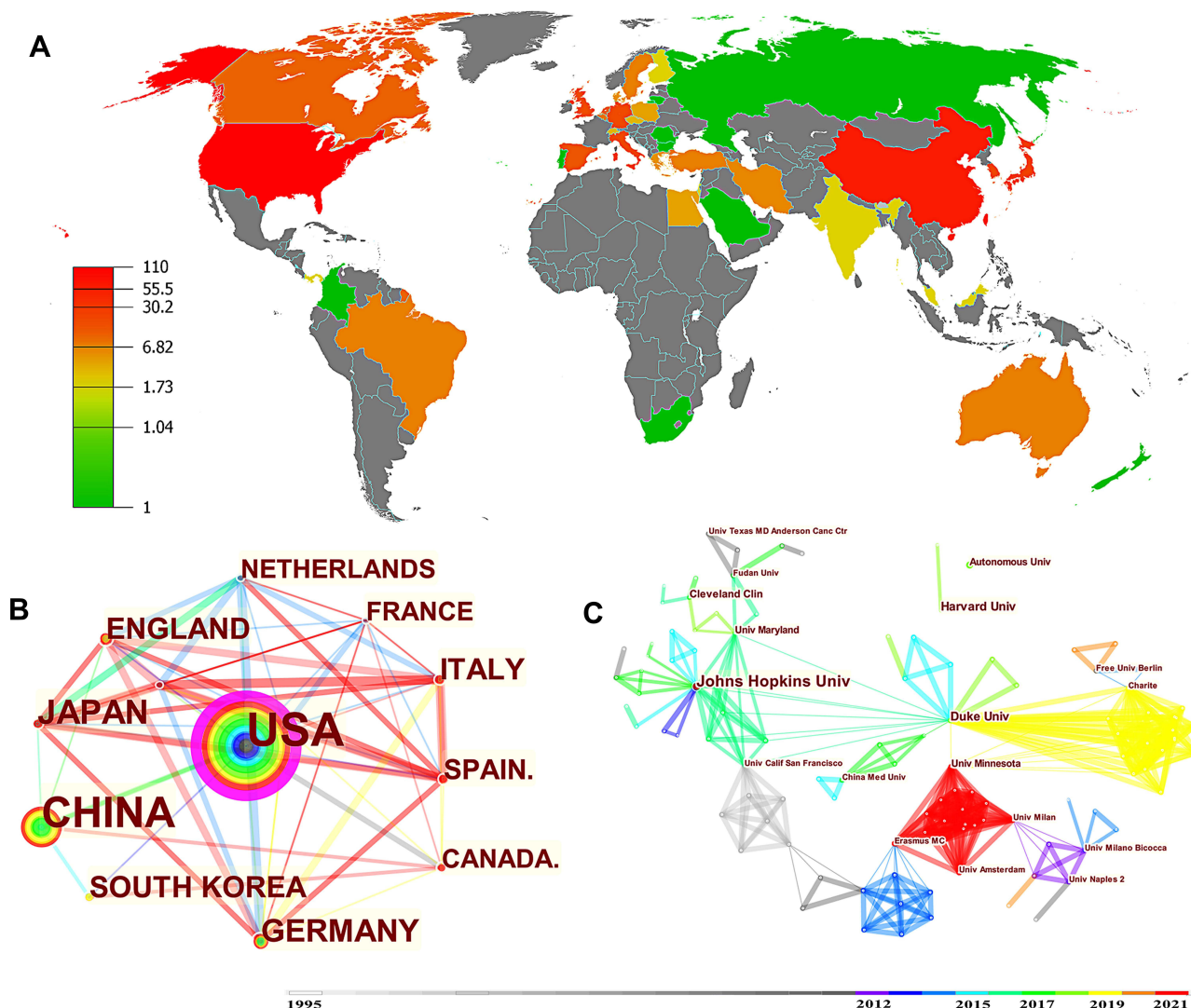
## Keywords

A total of 437 keywords were retrieved from 291 documents. As shown in Figure 7, the high-frequency keywords were neuropathic pain, transplantation, mesenchymal stem cell, and spinal cord injury, demonstrating that these keywords were the research hotspots. Transplantation had the highest centrality in all 437 keywords, which implied that most studies were related to transplantation.

During the past decade, therapy ranked first with the highest burst strength (3.26), followed by bone marrow stromal cells (2.72) and regeneration (2.55). Based on the end time of the bursts, we found that an increasing number of researchers focused their attention on expression, chronic pain, marrow stromal cell, regeneration, and activation in recent years (Figure 8).

To further understand different types of stem cells research trends in the last 10 years, we perform a co-occurrence analysis (Figure 9). Mesenchymal stem cells were the most studied, while neural stem cells and embryonic stem cells were less studied.

Co-occurrence cluster analysis from 1995 to 2021 revealed 437 keywords from stem cell and neuropathic pain publications. The studies clustered keywords according to the degree of connection tightness. A total of 10 cluster labels were obtained and numbered 0 to 9 (Figure 10). The smaller the number, the more keywords are contained in the clusters. Not surprisingly, the most frequent occurrence was the mechanism (cluster 0). Figure 11 showed a timeline view of the keyword clusters to visualize the keyword associations at different



**Figure 4** Co-authors' country and institution analysis. **(A)** World map showing the country analysis of the coauthors according to stem cell therapy for NP research. North America, East Asia, and Western Europe had more publications. **(B)** The network map of the country analysis of the coauthors. The top three countries in terms of size were the *United States*, *China*, and *Japan*. The *United States* has central intermediacy. **(C)** Map of the co-authors' institutions. The two leading institutions were Johns Hopkins University and Duke University.

times. Therefore, the study of stem cells and the mechanisms involved in neuropathic pain are currently the most researched areas.

## Discussion

In this study, a total of 291 articles on stem cells and neuropathic pain from 1995–2021 were visually analyzed using a bibliometric approach, mainly involving articles (75.26%) and reviews (24.74%). Stem cells and studies on neuropathic pain fluctuated in growth between 1995 and 2021 and reached a peak in 2020. This curve indicates that the field of stem cell therapy for neuropathic pain is increasing in intensity. Researchers were increasingly focused on the potential of stem cell therapy for neuropathic pain. In terms of research institutions, journals, and publications, the United States was the leader in the field of stem cell therapy for neuropathic pain. Johns Hopkins University and Duke University, two of the most cited institutions, had made outstanding contributions to the study of stem cells and neuropathic pain.

We analyzed the most highly cited journals and the top 3 journals were *Pain*, *Journal of Neuroscience*, *PLoS One*. The country of publication of these magazines is the United States, indicating that the United States has

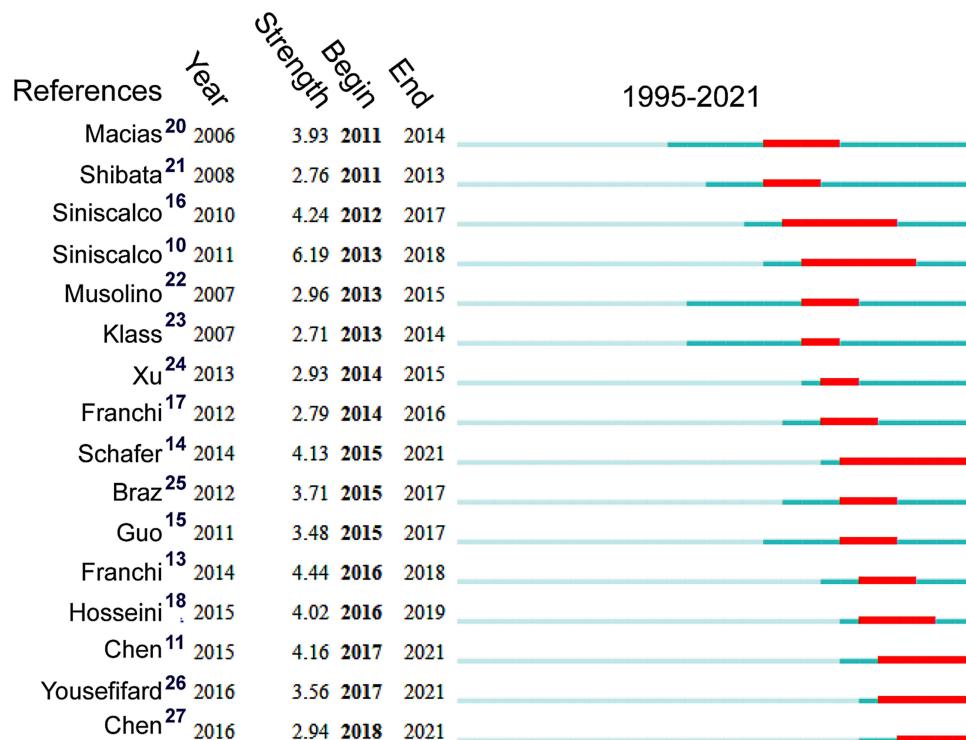
**Table 3** Top 10 Cited Articles in the Field of Stem Cell Therapy for Neuropathic Pain

Rank	Author	Counts	Centrality	Bursts	Design	Cells	NP
1	Siniscalco <sup>10</sup> (2011)	26	0.03	6.1898	Animal study	hMSCs	SNI
2	Chen <sup>11</sup> (2015)	21	0.03	4.1604	Animal study	BMSCs	CCI
3	Sacerdote <sup>12</sup> (2013)	19	0.03	0.05	Animal study	hASCs	CCI
4	Franchi <sup>13</sup> (2014)	18	0.04	4.4351	Review	NSCs, UC-MSC, BMSCs	CCI, DP
5	Schafer <sup>14</sup> (2014)	16	0.02	4.1271	Animal study	MSCs	PSNL
6	Guo <sup>15</sup> (2011)	15	0.06	3.4796	Animal study	BMSCs	CCI
7	Siniscalco <sup>16</sup> (2010)	15	0.01	4.2365	Animal study	hMSCs	SNI
8	Franchi <sup>17</sup> (2012)	14	0.03	2.7854	Animal study	NSCs	CCI
9	Hosseini <sup>18</sup> (2015)	11	0.02	4.0206	Review with meta analysis	BMSCs	CCI, SCI, SNL, SLN
10	Watanabe <sup>19</sup> (2015)	9	0.01	2.3042	Animal study	BMSCs	SCI

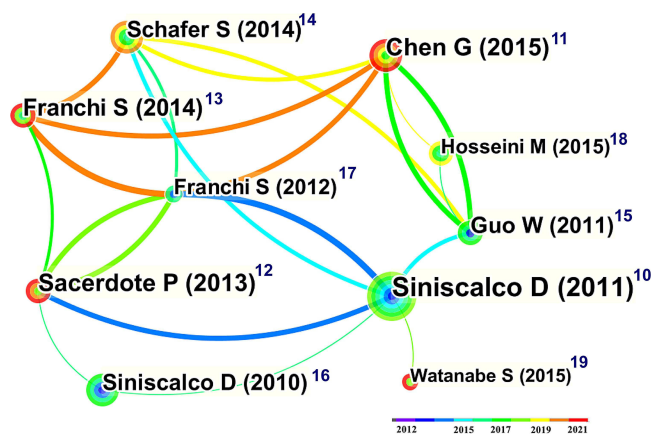
**Abbreviations:** hMSCs, human mesenchymal stem cells; BMSCs, bone marrow stromal cells; hASCs, human adipose tissue derived MSCs; NSCs, neural stem cells; MSC, mesenchymal stem cells; UC-MSC, umbilical cord-derived mesenchymal stem cells; PSNL, partial sciatic nerve ligation; CCI, chronic constriction injury; SCI, spinal cord injury; SLN, single ligature nerve; SNL, spinal nerve ligation; DP, diabetic polyneuropathy.

a leadership position in the field. We analyzed the research areas of these journals and find that most of the leading research areas focus on neuroscience. Therefore, stem cells are being studied more widely in neuroscience.

The 10 most cited publications are listed in Table 3, and 8 of these are research articles. The report published by Siniscalco et al in 2011 had the highest co-citation counts (26 times). This study confirmed that pain-like behaviors, such as mechanical allodynia and thermal hyperalgesia, could be improved by tail vein injection of hMSCs.<sup>10</sup> The effect may be related to the ability of hAMSCs to reduce pro-inflammatory interleukin (IL-1 $\beta$ ) levels and increase anti-inflammatory interleukin (IL-10).<sup>12</sup> Franchi et al concluded that NSCs could decrease c-FOS, IL-1 $\beta$  and IL-6 expression, and increase IL-10, substance P expression.<sup>17</sup> Siniscalco et al found that



**Figure 5** Top 16 references with the strongest citation bursts. The reference Siniscalco et al (2011) had the strongest citation bursts (6.19). Of the 16 references, there were citation bursts for 4 references up to 2021.



**Figure 6** Co-citation analysis of the top 10 cited documents. These nodes and lines indicate the association between references and co-citations included in the study, separately. The higher the number of reference co-citations, the larger the node. The color of the node and line represents the reference time, the warmer the color, the more recent the reference time.

injection of hBMSCs through the lateral ventricle inhibited the over-activation of neural  $\beta$ -galactosidase in the prefrontal cortex and reduced IL-1 $\beta$  mRNA expression.<sup>10,16</sup> Watanabe et al injected BMSCs into the spinal cord to treat spinal cord injury. BMSCs transplantation improved motor function and relieved hypersensitivities to thermal and mechanical stimulation, p-p38 and p-ERK1/2 expression were increased.<sup>19</sup> Chen et al suggested that BMSC inhibition of neuropathic pain was associated with TGF- $\beta$  but not with IL-10.<sup>11</sup> Schafer et al concluded that the intrathecal injection of MSCs had no effect on pain and did not influence IBA-1 expression or the underlying

**Table 4** Clinical Studies in the Field of Stem Cell Therapy for Neuropathic Pain

Author	Year	Journal	Design	Cells	Transplantation	NP	Outcomes
Vermeulen <sup>28</sup>	2007	Journal of Neurology Neurosurgery and Psychiatry	Case Report	CD 34+ stem cells	No description	CIDP	Remission lasted 5 years
Yoon <sup>29</sup>	2007	Stem Cells	Non-RCT, Open-label safety trial	hBMSCs	Intramedullary	SCI	Increased incidence of NP
Kishk <sup>30</sup>	2010	Neurorehabilitation and Neural Repair	Non-RCT	BMSCs	Intramedullary	SCI	Increased incidence of NP
Vickers <sup>31</sup>	2014	Journal of Pain Research	Self control study	ADMSCs	Local injection	Trigeminal pain	Significantly improve
Hua <sup>32</sup>	2016	Pain Physician	Case Report	UCMSCs	Intrathecal	SCI	Significantly improve
Vaquero <sup>33</sup>	2017	Cytotherapy	Self control study	BMSCs	Intrathecal	SCI	2 patients improved significantly; 1 patient improved slightly; 1 patient showed no improvement

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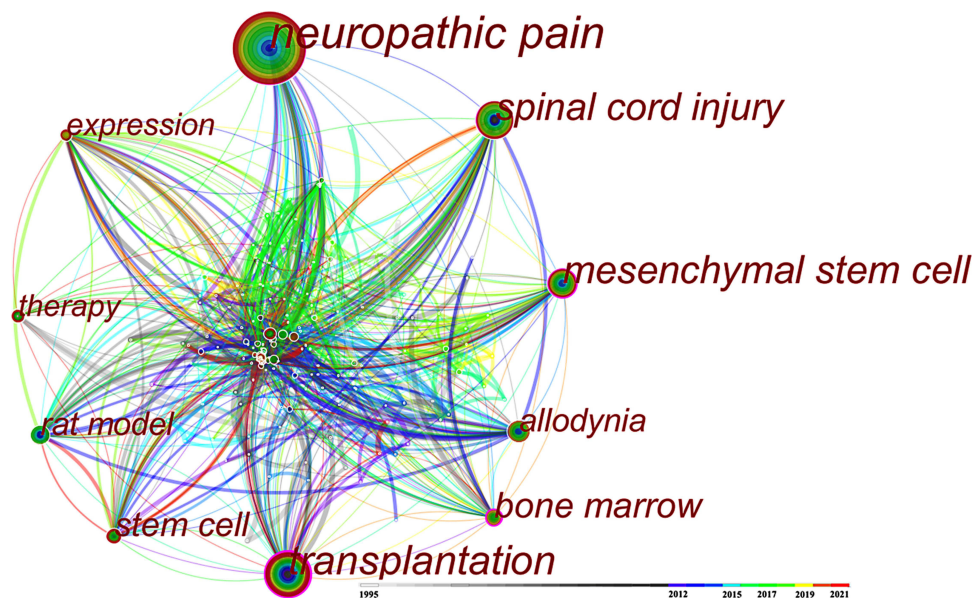
**Table 4** (Continued).

Author	Year	Journal	Design	Cells	Transplantation	NP	Outcomes
Vaquero <sup>34</sup>	2018	Neuroscience Letters	Self control study	BMSCs	Intrathecal	SCI	NP was significantly reduced in every patient except one
Vaquero <sup>35</sup>	2018	Cytotherapy	Self control study	BMSCs	Intrathecal	SCI	NP was significantly reduced
Prat <sup>36</sup>	2018	Journal of Tissue Engineering and Regenerative Medicine	Case Report	BMSCs	Local transplantation of tissue engineering products	Pseudoarthrosis with NP	One case satisfactory, one case uncertainty
Levi <sup>37</sup>	2018	Neurosurgery	Self control study	HuCNS-SCs	Intramedullary	SCI	Without emerging NP
Albu <sup>38</sup>	2021	Cytotherapy	RCT	UCWJ-MSCs	Intrathecal	SCI	Without emerging NP

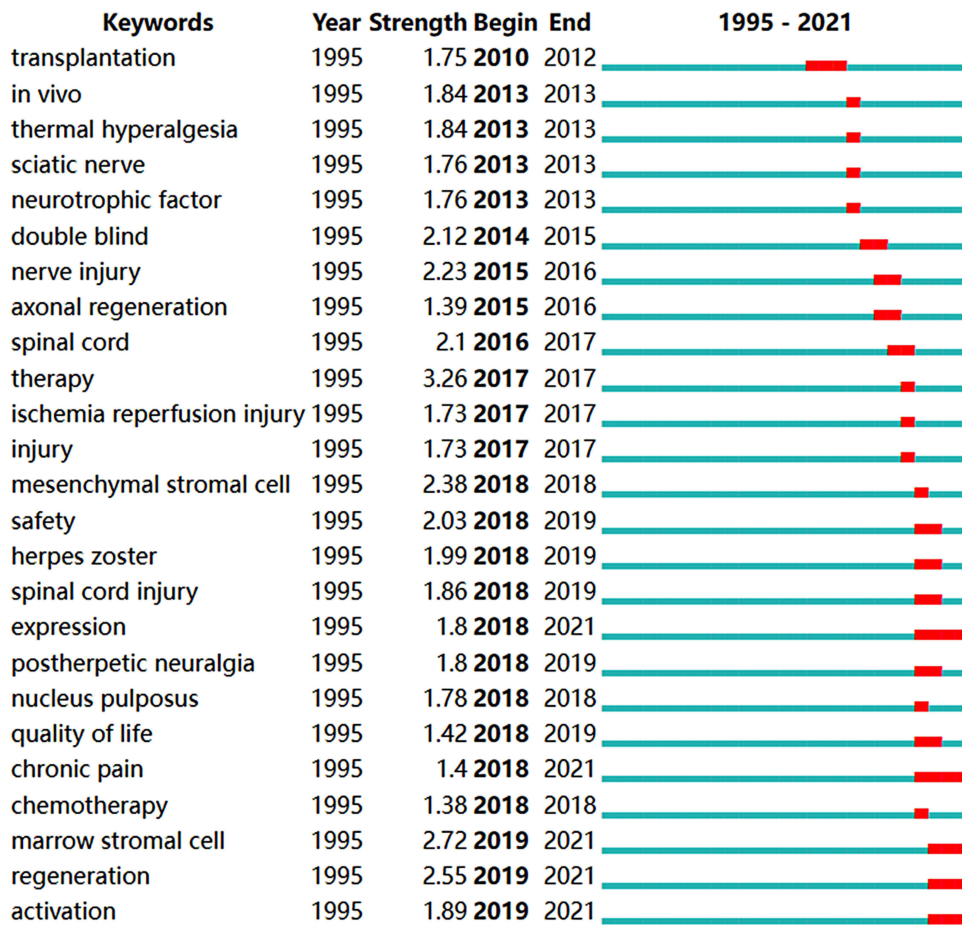
**Abbreviations:** HuCNS-SCs, human central nervous system stem cells; ADMSCs, adipose-derived mesenchymal stem cells; UCMSC, umbilical cord-derived mesenchymal stem cells; UCWJ-MSCs, umbilical cord-derived Wharton jelly mesenchymal stromal cells; CIDP, chronic inflammatory demyelinating polyneuropathy; SCI, spinal cord injury; NP, neuropathic pain; RCT, randomized controlled study.

neuroinflammatory processes in the spinal cord.<sup>14</sup> BMSCs reduced the expression of galanin and NPY in DRG, and reduced the activation of TRPA1, PKC $\delta$ , CaMKII $\alpha$ , P2X4, P2X7, which might be the mechanism of neuropathic pain improvement.<sup>39–41</sup> Therefore, there is still controversy regarding the mechanism of stem cell therapy for neuropathic pain. The main mechanism of stem cell modulation of neuropathic pain is shown in Figure 12.

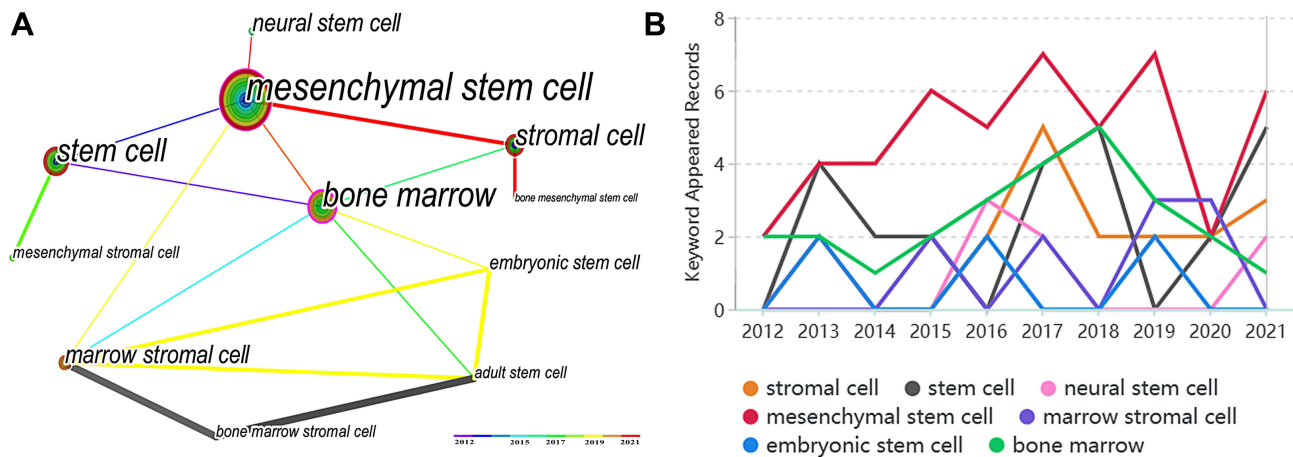
Although there are many pre-clinical studies that demonstrate the promise of stem cell therapy for neuropathic pain, clinical studies are still relatively limited. In clinical studies, stem cell therapy for neuropathic pain were



**Figure 7** Keyword co-occurrence network. The larger the node, the more frequently the keyword appears. Nodes with purple circles at the edges indicate a central intermediary. The line between the nodes represents two keywords co-occurring in the same paper.

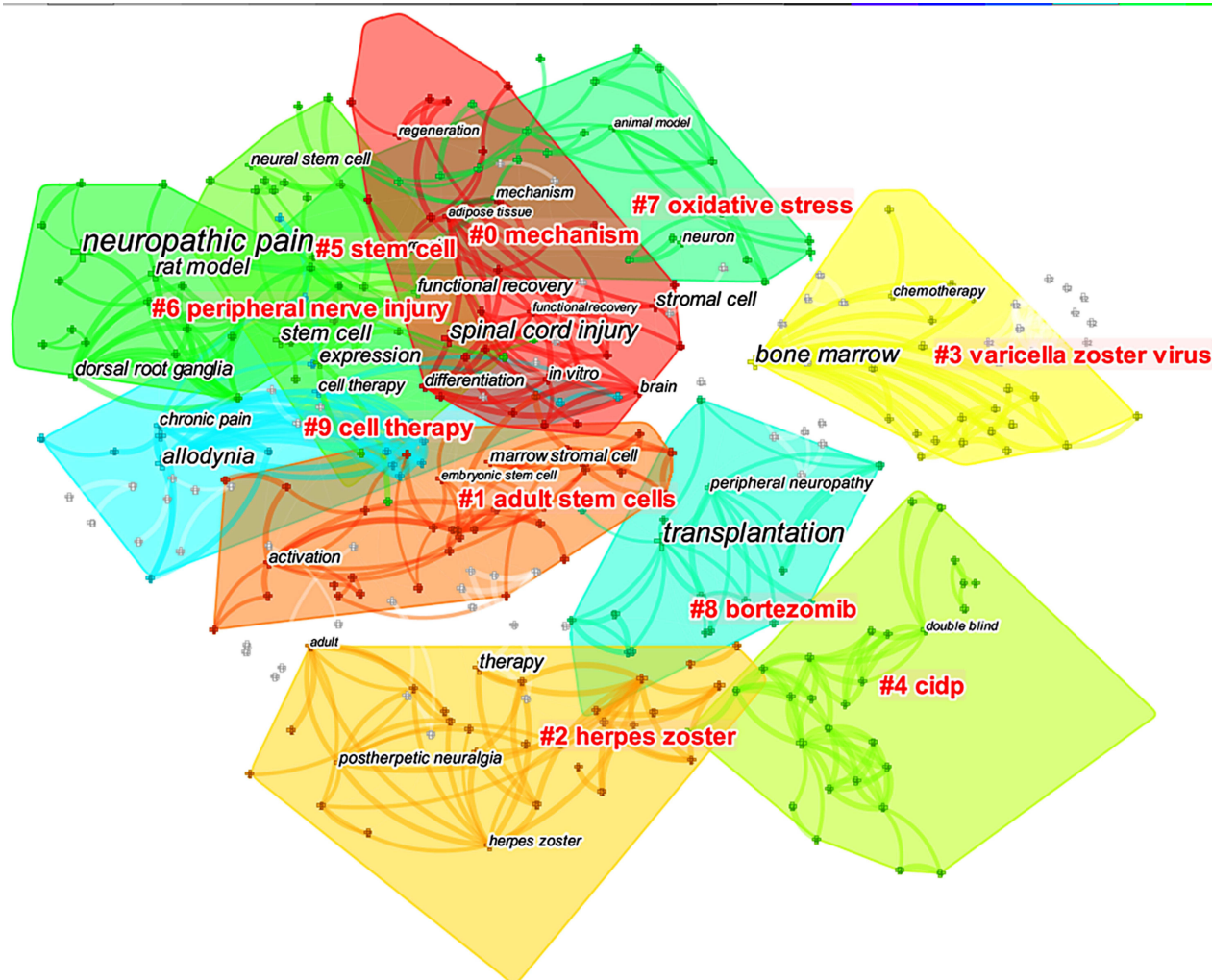


**Figure 8** Top 25 keywords with the strongest citation bursts. The length of the red line represents the strength of the citation burst. The beginning and end of the red line represent the start and end time, respectively.



**Figure 9** Different types of stem cells used for the treatment of neuropathic pain. (A) Co-occurrence analysis of stem cell types. (B) Occurrences of different types of stem cells as keywords in the last 10 years.

mainly in the field of spinal cord injury, but the outcomes appeared to be inconsistently. The different results may be related to the type of stem cells or the route of injection. Clinical efficacy of stem cell therapy for neuropathic pain still need to be further explored in the future. The laws and policies on the use of stem cells in different



**Figure 10** The keywords cluster network. The keywords co-occurrence network clusters into irregular regions, each corresponding to a label. The order is from 0 to 9, the smaller the number, the more keywords are included in the clusters, and each group is composed of multiple closely related keywords.

countries and regions may be one of the factors affecting the application of it. The ethics and safety of stem cell applications also need to be considered seriously.

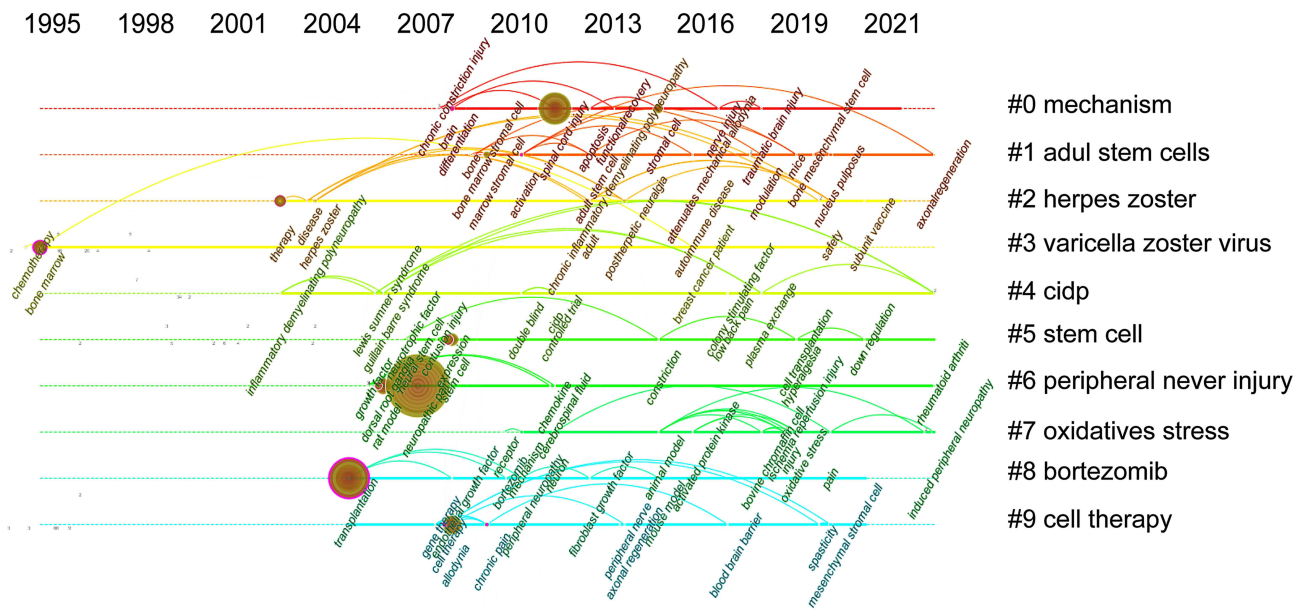
From the keyword analysis, we observe that MSCs transplantation for neuropathic pain is the current research hotspot. Among the different types of stem cells, MSCs are the most prevalent stem cell type studied. MSCs have unique advantages over other stem cells and offer a new approach to treat neuropathic pain in the future. In addition to causing motor dysfunction, spinal cord injuries can cause persistent and severe neuropathic pain.<sup>42</sup> Stem cell transplantation for spinal cord injury has shown great potential to provide a valuable therapeutic tool to address this challenge.<sup>43</sup>

For neuropathic pain research, a keyword co-citation analysis of stem cell therapy produced ten co-citation clusters. Keyword clustering analysis finds that mechanism research is the most researched area. Furthermore, burst detection showed that expression, chronic pain, regeneration, and activation were the new hot spots within the field of stem cell and neuropathic pain. Therefore, the application of stem cells for modulating the mechanisms underlying neuropathic pain remains a hot and critical topic in current and future research.

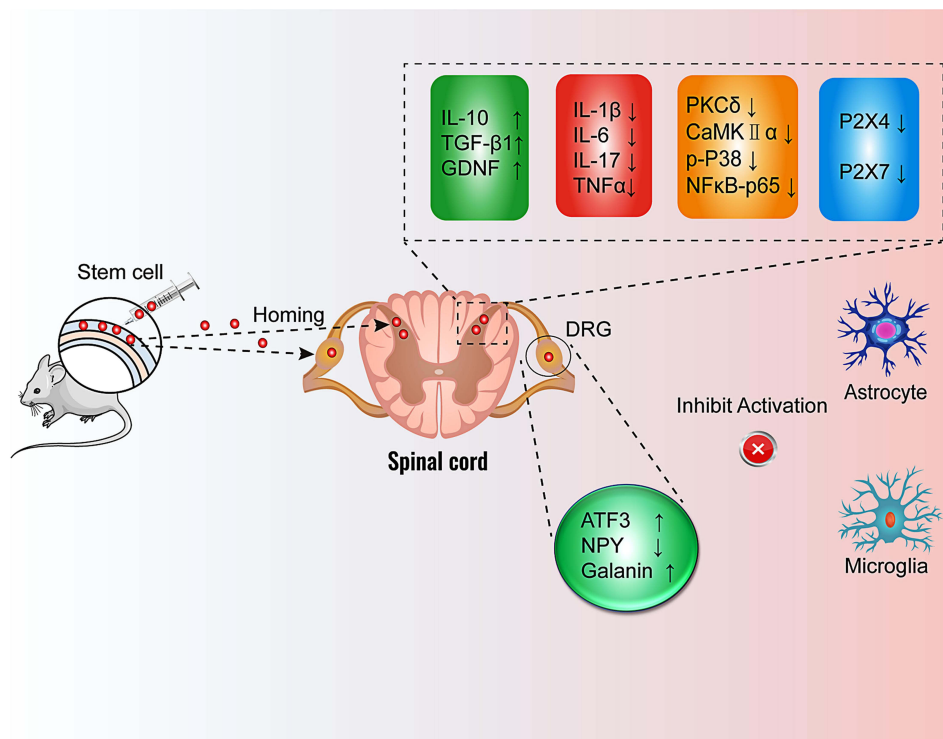
## Limitations

Although this paper systematically analyzed the current status of stem cell therapy for neuropathic pain, there are some limitations to be considered. First, although we included all relevant literature to the greatest extent possible, there are





**Figure 11** The timeline view of keyword clusters. The timeline view shows the keywords included in the clusters on a line from left to right according to the year of the first occurrence. The size of the node represents the number of times the keyword has been cited. The line between nodes represents the co-occurrence of keywords.



**Figure 12** The main mechanism of stem cell modulation of neuropathic pain. Intrathecally injected stem cells can home to the spinal cord and dorsal root ganglia to exert analgesic effect. Inhibition of glial cell activation through upregulation or inhibition of protein molecule expression.

many classifications for neuropathic pain and therefore relevant literature may have been missed and not included in this study. Second, we searched only the WOS core collection, thus, any potentially missed papers were not included in the core collection. Third, stem cells contain multiple types, we only analyzed research trends in different types of stem cells, but did not further analyze their mechanisms. Fourth, the routes of injection (intrathecal, intramedullary, intracranial) also

seemed to influence the therapeutic effect, however, it were not analysed in depth in this paper. Furthermore, we also did not analyze stem cell-derived exosome therapy for neuropathic pain.

## Prospects

Research on the mechanism, the homing effect of different stem cell injection routes, and the efficacy of different types of stem cells are hot directions for future research. Stem cell therapy for neuropathic pain is primarily focused on animal experiments. The mechanisms of stem cell therapy for neuropathic pain are still not well understood and efficacy outcomes are inconsistent, so further research is essential. Clinical studies should be undertaken with caution until more mechanisms are explored, but this will be a promising field.

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## Author Contributions

All authors made a significant contribution to this work in the conception, study design, execution, acquisition of data, analysis and interpretation; took part in composing the article or revising it critically; agreed to submit to this journal; reviewed and agreed on all versions of the article before submission and gave final approval of the version to be published; and agree to take responsibility and be accountable for the contents of the article.

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## Disclosure

The authors declare no potential conflicts of interest in this research.

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