

Bibliometric and Visual Analysis of Trained Immunity from 2005 to 2024

Zhengang Yang^{1,*}, Jingxia Hu^{2,*}, Li Kang², Hao He²

¹Department of Otolaryngology, The Affiliated Taian City Central Hospital of Qingdao University, Taian, Shandong, People's Republic of China;

²Department of Immunology, Shandong First Medical University & Shandong Academy of Medical Sciences, Jinan, Shandong, People's Republic of China

*These authors contributed equally to this work

Correspondence: Hao He; Li Kang, Department of Immunology, Shandong First Medical University & Shandong Academy of Medical Sciences, No. 6699 Qingdao Road, Huaiyin District, Jinan, Shandong, People's Republic of China, Email hehao3000@qq.com; kang0724@163.com

Purpose: Trained immunity refers to the long-term functional adaptation of innate immune responses following an initial stimulus, representing a conceptual expansion of immune memory beyond adaptive immunity. Given the rapid expansion of this field, this study aimed to systematically map the research landscape of trained immunity and to identify major research hotspots and emerging frontiers using bibliometric approaches.

Methods: Publications related to trained immunity published between 2005 and 2024 were retrieved from the Web of Science Core Collection (WoSCC). Bibliometric and visualization analyses were performed using CiteSpace, VOSviewer, and Bibliometrix to evaluate publication trends, collaboration patterns, and thematic evolution.

Results: A total of 1,526 publications were included. Bibliometric indicators demonstrate a marked acceleration in research output following the formal conceptualization of trained immunity. The United States, the Netherlands, and Germany emerged as leading contributors, with Radboud University Nijmegen and the University of Bonn identified as central institutional hubs. Thematic and keyword-based analyses revealed that research hotspots have evolved along three interconnected dimensions: an expansion of cellular targets from classical myeloid cells to hematopoietic stem and progenitor cells and selected non-immune cells; sustained focus on epigenetic and metabolic reprogramming as core mechanistic axes; and a growing body of literature linking trained immunity to infectious diseases, chronic inflammation, and cancer-related applications.

Conclusion: By integrating multiple bibliometric indicators, this study delineates the developmental trajectory and thematic structure of trained immunity research. The findings provide an updated overview of the field and highlight evolving research priorities, offering a reference framework for future investigations into innate immune memory and its translational potential.

Keywords: trained immunity, bibliometric analysis, VOSviewer, citespace

Introduction

Traditionally, immunological memory has been regarded as a defining feature exclusive to the adaptive immune system. However, accumulating evidence over the past two decades has demonstrated that the innate immune system can also acquire a memory-like state through a process termed trained immunity.^{1,2} Although nonspecific immune enhancement had been observed earlier—most notably in studies of *Bacillus Calmette–Guérin* (BCG) vaccination and heterologous protection—the formal conceptualization of trained immunity by Netea et al provided a unifying framework to explain these phenomena within innate immunity.³ Subsequent studies established that trained immunity is mediated by persistent yet reversible epigenetic reprogramming, including histone modifications,^{4–6} together with metabolic remodeling such as enhanced aerobic glycolysis.^{7,8} These molecular adaptations enable innate immune cells and their progenitors to mount amplified responses upon secondary homologous or heterologous challenges, thereby strengthening host defense.^{9,10}

Beyond its mechanistic definition, trained immunity has progressively emerged as a broad biological principle rather than a phenomenon confined to a single cell type or stimulus. From an evolutionary perspective, systemic acquired resistance in

plants represents an early form of innate immune memory, in which transcriptional reprogramming confers enhanced resistance to reinfection.¹¹ In vertebrates, trained immunity was initially described in peripheral monocytes, macrophages and NK cells but has since been extended to encompass hematopoietic stem and progenitor cells (HSPCs), which can be durably reprogrammed in the bone marrow to bias myelopoiesis and confer long-term nonspecific protection—a process often referred to as central trained immunity.¹² In parallel, tissue-resident immune cells such as alveolar macrophages, microglia and innate lymphoid cells, as well as non-immune cells including epithelial and stromal populations, have been shown to exhibit memory-like responses, further expanding the conceptual boundaries of immune memory.^{13,14} Collectively, these findings indicate that trained immunity represents a multi-layered and spatially distributed form of immune adaptation.

As the scope of trained immunity research has broadened, its relevance to human health and disease has become increasingly apparent. On the one hand, vaccines and microbial stimuli capable of inducing trained immunity have been associated with enhanced resistance to unrelated infections and reduced all-cause mortality, underscoring their potential value in public health and vaccine design.¹⁵ On the other hand, sustained or dysregulated trained immune responses have been implicated in the pathogenesis of chronic inflammatory and autoimmune diseases, including atherosclerosis, rheumatoid arthritis, and systemic lupus erythematosus.^{16–18} More recently, growing interest has focused on the potential role of trained immunity in cancer, particularly in the context of antitumor immune surveillance and immunotherapy.¹⁹ Rather than representing isolated observations, these diverse disease associations reflect a gradual shift in research attention toward understanding both the beneficial and pathological consequences of innate immune memory.²⁰

Concomitant with these conceptual advances, the volume of trained immunity-related publications has increased sharply, particularly in recent years, indicating rapid expansion and diversification of the field. This accelerating growth highlights the need for systematic and quantitative approaches to map the intellectual structure, developmental trajectory, and emerging research directions of trained immunity research. Bibliometric analysis, which integrates mathematical and statistical methods to analyze publication metadata, has been widely applied to characterize research landscapes, identify influential contributors, and detect evolving thematic trends across scientific disciplines.^{21–23} Despite inherent limitations such as dependence on database coverage and analytical algorithms,²⁴ bibliometric approaches are particularly well suited to capturing shifts in research focus and interdisciplinary convergence that may not be readily apparent from narrative reviews alone.²⁵

A previous bibliometric study provided an initial overview of trained immunity research.²⁶ However, the present study substantially extends this work by analyzing literature published up to the end of 2024, a period marked by exponential growth and rapid diversification of the field. In addition, we applied a more integrative bibliometric framework by combining multiple complementary approaches, enabling cross-validation of findings across different analytical dimensions. This expanded analysis identified a greater number of research hotspots and knowledge clusters, which are systematically visualized and directly presented in the Results section rather than being summarized retrospectively. Together, these advances provide a more comprehensive and up-to-date depiction of the evolving research landscape and emerging frontiers of trained immunity.

In this study, we employed a comprehensive bibliometric and visual analysis of trained immunity research using data from the Web of Science Core Collection (WoSCC), covering publications from 2005 to 2024. By integrating CiteSpace, VOSviewer, and Bibliometrix, we systematically examined publication outputs, collaborative networks, co-citation patterns, keyword dynamics, and thematic evolution. Rather than providing a narrative synthesis of biological mechanisms, our analysis focuses on identifying research hotspots, tracing the migration of scientific attention, and highlighting emerging frontiers within the trained immunity field. This updated and integrative overview aims to support researchers—particularly those entering or crossing into this rapidly evolving area—by offering a structured map of its research landscape and future directions.

Materials and Methods

Data Collection

The bibliometric data utilized in this study were retrieved from the WoSCC, a well-established and extensively used academic database that indexes peer-reviewed and citation-validated journals across diverse scientific disciplines, thereby minimizing the inclusion of predatory or non-academic publications.²⁷ In WoSCC, “TS” denotes “Topic,” referring to

keywords searched in the title, abstract, author keywords, and keywords plus. The applied search strategy was as follows: TS = (“trained immunit” OR “trained NEAR/0 innate immunit” OR “innate immune memor*” OR “innate memor*”) NOT DT = Retracted Publication NOT DT = Retraction Notice. The retrieval was confined to records published between January 1, 2005, and December 31, 2024. To ensure relevance and quality, only documents categorized as “Article” or “Review” and published in English were selected, yielding a total of 1526 records (Figure 1). The search results were exported as plain text files in txt or CSV formats for subsequent analysis. Data acquisition was finalized on June 1, 2025, to avoid potential biases caused by ongoing database updates. No additional Impact Factor threshold was applied, as the goal was to capture a comprehensive overview of the trained immunity research landscape.

Data Analysis

To perform a comprehensive bibliometric analysis of trained immunity research, three specialized tools were utilized: CiteSpace, VOSviewer, and Bibliometrix. CiteSpace (version 6.1.R3) focuses on detecting emerging trends and hotspots in scientific literature by constructing co-citation networks, identifying citation bursts, and drawing knowledge maps over time.²⁸ VOSviewer (version 1.6.18) specializes in constructing and visualizing bibliometric networks based on co-authorship, co-citation, and keyword co-occurrence, offering intuitive cluster visualization and density maps.²⁹ Bibliometrix (R package) enabled quantitative analyses such as publication trends, author productivity, and thematic mapping,³⁰ and was also used to identify keywords with high popularity. In addition, the R package ggplot2 was used to generate high-quality visualizations of selected bibliometric indicators, thereby improving the clarity and interpretability of the results.³¹

To characterize the temporal growth pattern of publications and citations in the trained immunity field, curve-fitting approaches were applied to annual publication output and cumulative citation counts. Logistic and second-degree linear models were used as descriptive tools to compare different growth trajectories, focusing on overall fitting performance rather than statistical inference or causal interpretation.

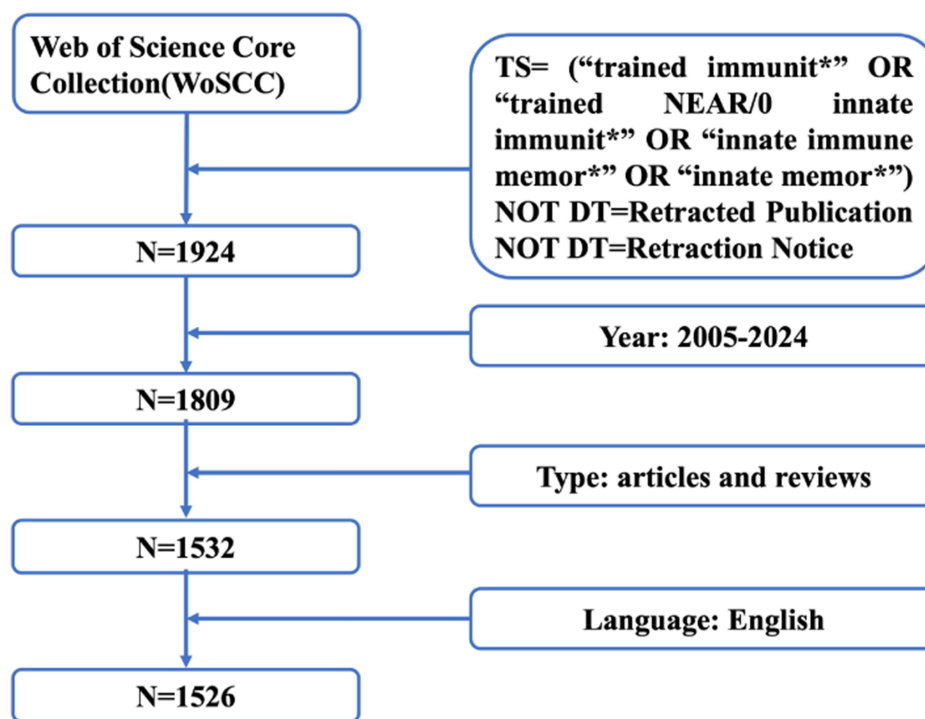


Figure 1 Flow chart of data collection.

Results

Trends in Publications and Citations

Research on trained immunity exhibits significant interdisciplinary characteristics, with current efforts primarily concentrated in immunology, biochemistry, molecular biology, cell biology, microbiology, biotechnology, pharmacology, and pharmacy (Figure 2A). We conducted a bibliometric analysis of publication output and citation dynamics in this field from 2005 to 2024. Overall, the number of publications has shown a steady increase over time, accompanied by a continuous rise in cumulative citation count (Figure 2B). Specifically, annual publication output remained relatively low before 2014, followed by a marked growth between 2014 and 2019, and a sharp increase since 2020. Notably, several early publications (eg, 2010, 2011, 2012, and 2014) demonstrated high annual average citation count, indicating substantial academic influence (Figure 2C). To further characterize the growth trajectory of trained immunity research, curve-fitting analyses were applied to annual publication output and cumulative citation counts using logistic and second-degree linear models.³² Both models demonstrated high goodness-of-fit, with R^2 values of 0.984 (logistic) and 0.947 (linear) for annual publication output (Figure 2D), and 0.993 (logistic) and 0.966 (linear) for cumulative citation count (Figure 2E). These results indicate a rapidly accelerating growth pattern, consistent with an exponential expansion phase of the field. The fitted curves provide a descriptive overview of publication dynamics rather than precise predictions.

Analysis of Countries/Regions

A total of 95 countries/regions contributed to trained immunity research. As shown in Figure 3A, the top 10 contributors by publication output were led by the USA (473 publications), the Netherlands (311 publications), and Germany (296 publications). When ranked by citation counts, the Netherlands, USA, and Germany each exceeded 20,000 citations (Figure 3B). In the international collaboration network, node size represents the number of publications, while purple outer ring indicates higher betweenness centrality (≥ 0.1). The USA, the Netherlands, Germany, Australia, the United Kingdom, and Sweden exhibited higher betweenness centrality, suggesting their central roles in global collaboration networks (Figure 3C). Notably, strong collaborations were observed between the Netherlands and Germany, the Netherlands and Romania, Germany and the USA, and the Netherlands and the USA (Figure 3D).

Analysis of Institutions

A total of 371 institutions contributed to trained immunity research. As shown in Figure 4A, the top 10 institutions by publication output featured Radboud University Nijmegen (Netherlands; 226 publications) and University of Bonn (Germany; 173 publications) as leading contributors. When ranked by citation count, these two institutions maintained their leading positions with 27,611 and 16,730 citations, respectively (Figure 4B). It should be noted that these rankings and influence assessments are based solely on data retrieved from the WoSCC, and may vary when analyzed using other databases. Institutional collaboration network analysis revealed that the University of Melbourne, the French National Centre for Scientific Research (CNRS), the French National Institute of Health and Medical Research (INSERM), the Helmholtz Association, and Harvard University exhibited high betweenness centrality (Figure 4C), indicating their pivotal roles as global collaborative hubs. Further cluster analysis identified three major collaborative modules (Figure 4D), with Radboud University Nijmegen/University of Bonn, Harvard Medical School/Technische Universität Dresden, and Consiglio Nazionale delle Ricerche/Chinese Academy of Sciences exhibiting both high productivity and extensive collaborations within their respective modules.

Analysis of Journals

A total of 442 journals have published articles related to trained immunity. Among the top 10 journals by publication output, half are ranked in JCR Q1, with *Frontiers in Immunology* (215 publications) far exceeding other journals (Figure 5A). In terms of citation counts, all top 10 journals belong to JCR Q1, with leading positions held by *Frontiers in Immunology* (6,671 citations, IF = 5.7), *Science* (5,095 citations, IF = 44.7), *Cell* (4,873 citations, IF = 45.5), and *Cell Host & Microbe* (3,681 citations, IF = 20.6) (Figure 5B). Multidimensional comparison of the top three journals ranked by publications and citations revealed that *Cell* and *Science* stood out in terms of impact factor and citations, particularly

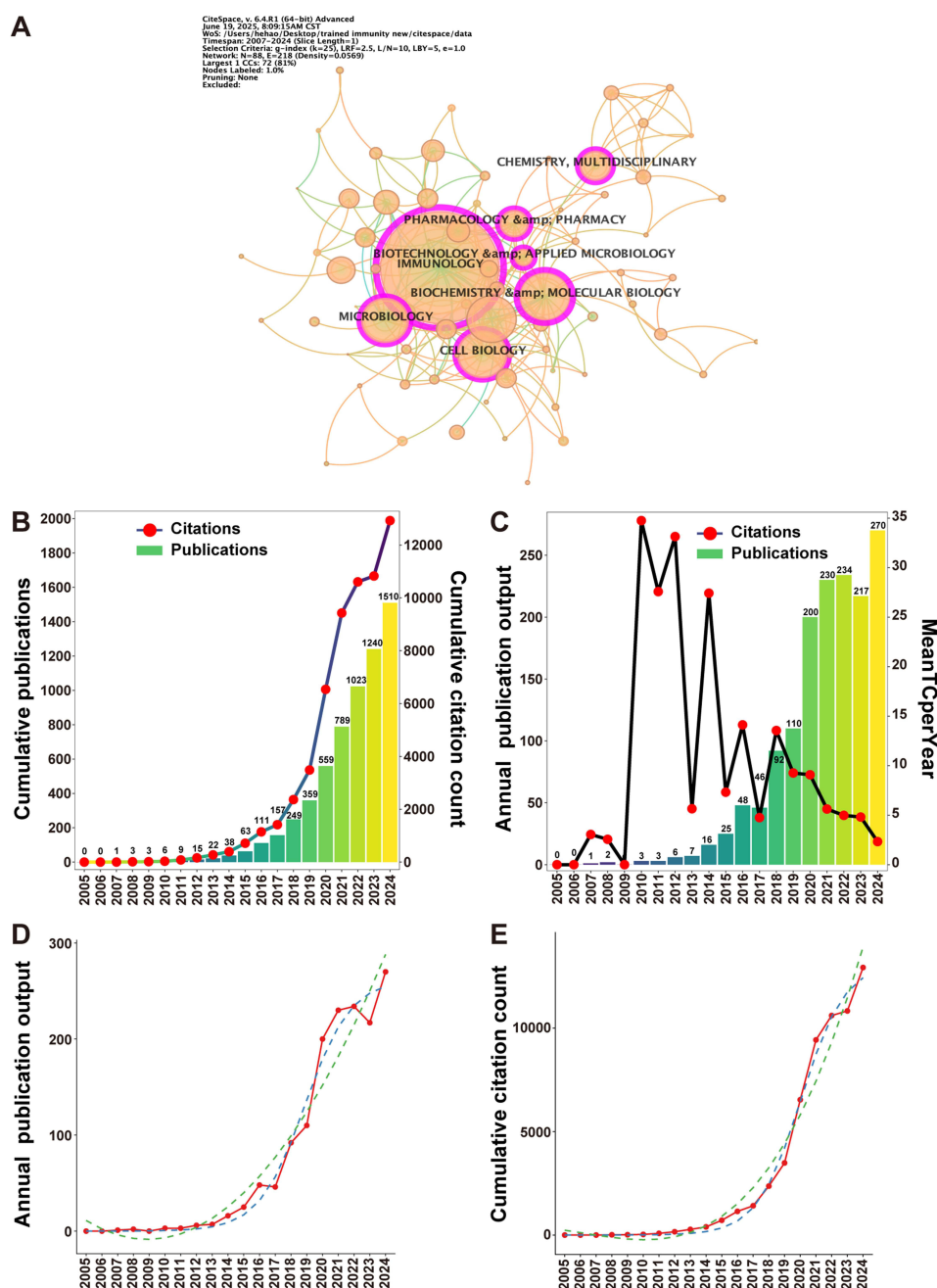


Figure 2 Publication and citation trends in the field of trained immunity. **(A)** Analysis of research fields using CiteSpace. **(B)** Cumulative publication output and cumulative citation counts over time. **(C)** Annual publication output and mean total citations per year (MeanTCperYear). **(D)** Curve-fitting of annual publication output using logistic and second-degree linear models to characterize growth patterns. **(E)** Curve-fitting of cumulative citation counts using logistic and second-degree linear models to illustrate overall citation dynamics.

excelling in impact factor. Meanwhile, *Frontiers in Immunology* performed well across multiple metrics including publication output, citation count, h-index, m-index, and g-index (Figure 5C). Furthermore, a journal dual-map overlay analysis was conducted to examine subject distribution and citation pathways. The results showed that journals in the fields of molecular biology, immunology, medicine, and clinical research frequently cited publications from journals in the areas of molecular biology and genetics (Figure 5D).

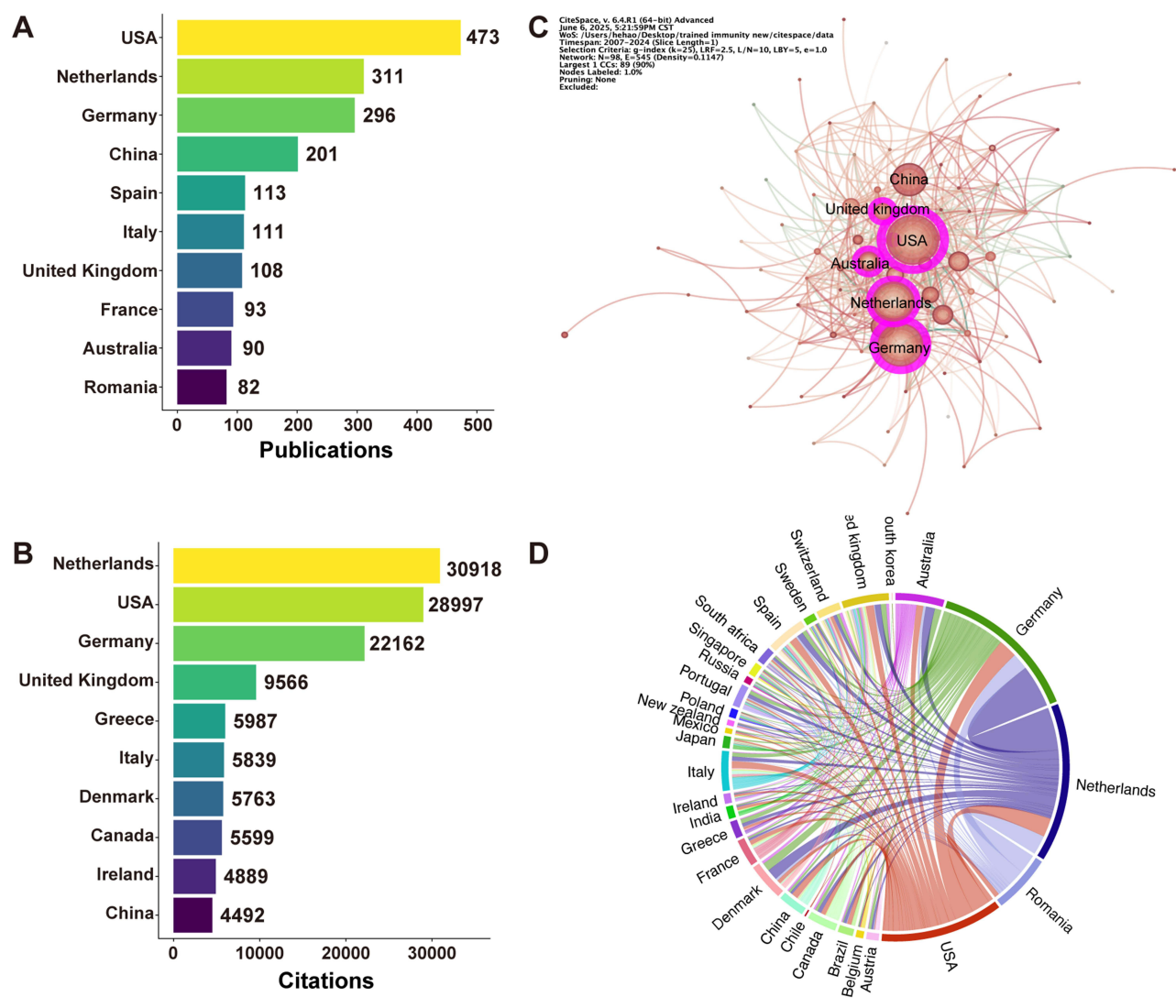


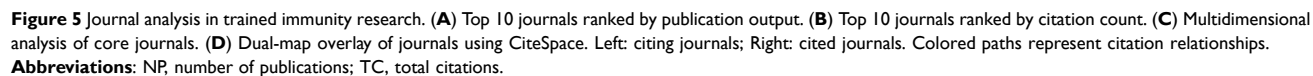
Figure 3 Country/region analysis in trained immunity research. **(A)** Top 10 countries/regions ranked by publication output. **(B)** Top 10 countries/regions ranked by citation count. **(C)** Country/region co-occurrence network constructed with CiteSpace. Node size represents the number of publications, and purple outer rings indicate high betweenness centrality (≥ 0.1). **(D)** Collaboration network among major countries/regions.

Analysis of Authors

A total of 7691 authors contributed to research on trained immunity. **Figure 6A** presents the top 10 authors in terms of publication output, while **Figure 6B** lists the 10 most frequently cited authors. Among them, Mihai G. Netea and Leo A.B. Joosten stand out, with 204 and 118 publications, and a total of 21,820 and 15,717 citations, respectively. They consistently rank first and second in both metrics, indicating their leading roles in this field. Author collaboration network analysis revealed several tightly connected clusters (**Figure 6C**). Notably, Mihai G. Netea and Leo A. B. Joosten formed the core of the largest collaborative network, while several smaller, relatively independent research groups also exist. In contrast, the author co-citation network, which reflects similarity in academic perspectives or research content, identified five major clusters representing distinct themes (**Figure 6D**). In summary, the systematic analysis of authors not only highlights the core contributors in the field but also provides valuable insights for potential future collaborations.

Analysis of References

To elucidate the knowledge structure and developmental trajectory of trained immunity research, a co-citation analysis was conducted, identifying 14 major clusters with their interrelationships (**Figure 7A**) and temporal evolution



8 <https://doi.org/10.2147/JIR.S561807> Journal of Inflammation Research 2026:19

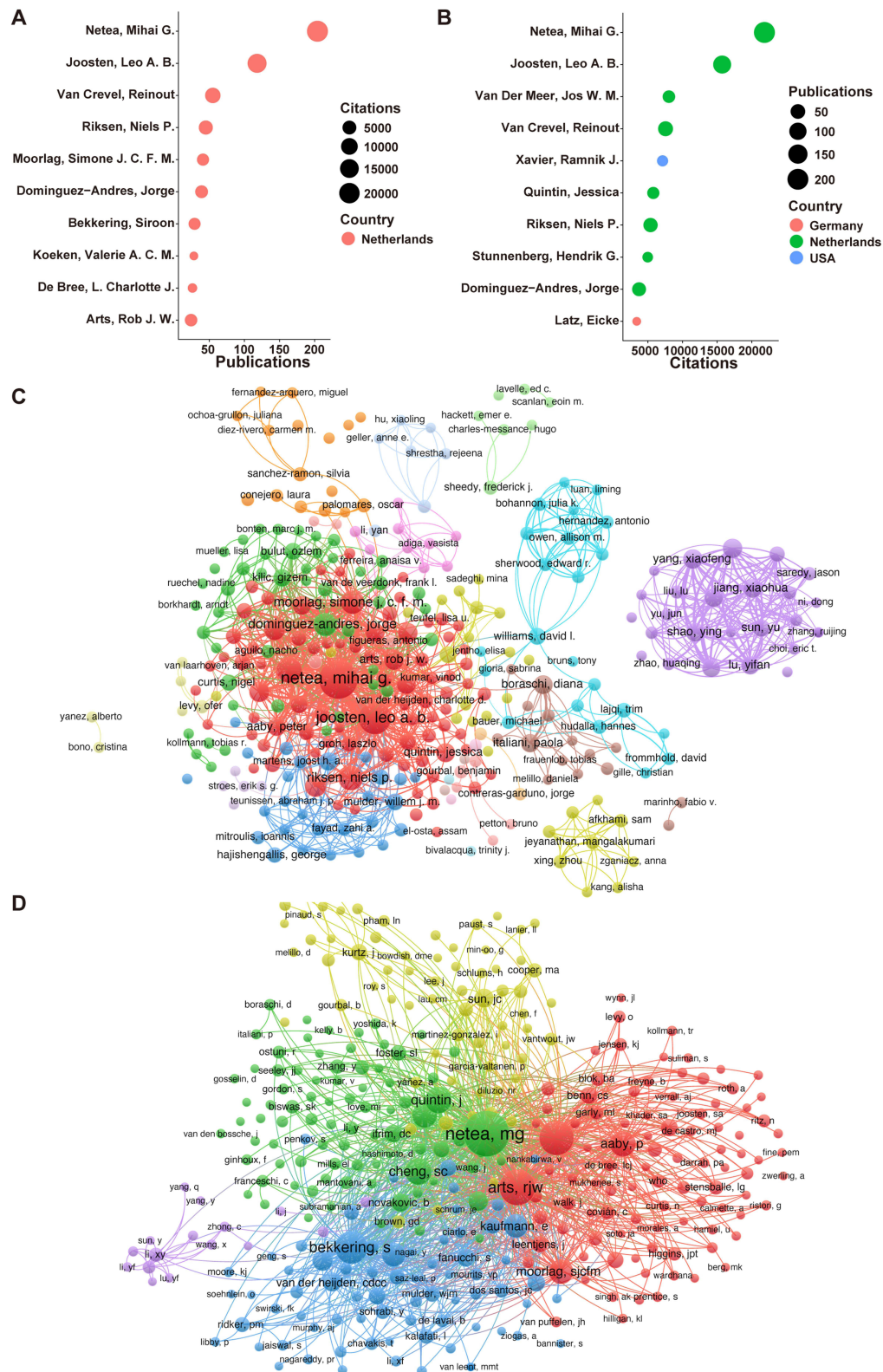




Figure 7 Co-citation analysis of references by CiteSpace. **(A)** Cluster analysis of co-citation network. Colors represent distinct clusters, with arrows indicating dependency relationships. **(B)** Temporal evolution of co-cited publications (Timeline viewer). Node position represents initial citation year, with size denoting betweenness centrality.

largest cluster, dominating current infection-focused research. Cluster #14 “Trained immunity in atherosclerosis” integrates findings across multiple areas, introducing trained immunity into cardiovascular research. Clusters #12 “BCG-driven nonspecific immunity and autophagy” and #9 “Training vs tolerance in innate immunity” were once research hotspots and provided foundational knowledge for Cluster #1 “Trained immunity in chronic inflammatory disorders”, which emphasizes the adverse effect of trained immunity on the body.

To identify the core knowledge in the field, we identified top 10 highly cited references ranked by citation count (Table 1), with 7 exceeding 1,000 citations. The earliest landmark paper was published in *Nature Reviews Neurology* in

Table 1 The Top 10 Highly Cited References Concerning Trained Immunity

Rank	Representative Author	Title	Year	Citation Count	Journal	Type of Research
1	Mihai G. Netea ¹	Trained immunity: A program of innate immune memory in health and disease	2016	1800	Science	Review
2	Mihai G. Netea ⁶	mTOR- and HIF-1 α -mediated aerobic glycolysis as metabolic basis for trained immunity	2014	1569	Science	Article
3	Eicke Latz ¹⁰	Defining trained immunity and its role in health and disease	2020	1535	Nat Rev Immunol	Review
4	V.Hugh Perry ³³	Microglia in neurodegenerative disease	2010	1295	Nat Rev Neurol	Review
5	Mihai G. Netea ³⁴	Bacille Calmette-Guerin induces NOD2-dependent nonspecific protection from reinfection via epigenetic reprogramming of monocytes	2012	1249	Proc Natl Acad Sci USA	Article
6	Hendrik G. Stunnenberg ⁴	Epigenetic programming of monocyte-to-macrophage differentiation and trained innate immunity	2014	1210	Science	Article
7	Mihai G. Netea ³	Trained Immunity: A Memory for innate host defense	2011	1123	Cell Host Microbe	Article
8	Mihai G. Netea ³⁵	Candida albicans infection affords protection against reinfection via functional reprogramming of monocytes	2012	910	Cell Host Microbe	Article
9	Mihai G. Netea ⁹	BCG vaccination protects against experimental viral infection in humans through the induction of cytokines associated with trained immunity	2018	836	Cell Host Microbe	Article
10	Marziah Divangahi ¹²	BCG educates hematopoietic stem cells to generate protective innate immunity against tuberculosis	2018	804	Cell	Article

Notes: The representative author refers to the corresponding author of each publication. Six of the ten most-cited studies were conducted by the same core research group led by Mihai G. Netea.

2010, discussing immune memory of microglia in neurodegenerative diseases (1,295 citations). A 2011 article in *Cell Host & Microbe* first introduced the concept of trained immunity (1,123 citations). A 2014 study published in *Science* identified mTOR/HIF-1 α -mediated aerobic glycolytic reprogramming as a key mechanism underlying trained immunity (1,569 citations). The most-cited reference is a 2016 review in *Science*, summarizing major advances in the field (1,800 citations). The most recent highly cited publication is a 2020 review in *Nature Reviews Immunology*, which provided an updated summary of progress in trained immunity research (1,535 citations). Other highly cited references covered topics such as nonspecific protective effects of vaccine, pro-inflammatory epigenetic reprogramming in monocytes, and phenotypic reprogramming of HSPCs. Notably, the representative author listed in [Table 1](#) refers to the corresponding author of each publication, reflecting the principal investigator responsible for the study. Among the top 10 highly cited papers, five independent research groups were identified. Six of these publications originated from the same core team led by Mihai G. Netea, underscoring this group's pioneering role in shaping the concept of trained immunity and highlighting the current concentration of foundational work within the field.

To explore research hotspots and emerging frontiers, we performed citation burst analysis to detect publications exhibiting a sharp surge in citations during specific periods. Historical bursts reflect past research hotspots, while recent or ongoing bursts may indicate current frontiers. [Figure 8A](#) displays the top 25 references ranked by burst strength. The earliest burst was triggered by an article published in 2011, which first proposed the concept of trained immunity. The strongest burst strength corresponds to

A

Top 25 references with the strongest citation bursts

References	Year	Strength	Begin	End	2007 - 2024
Netea MG, 2011, CELL HOST MICROBE, V9, P355, DOI 10.1016/j.chom.2011.04.006, DOI	2011	39	2012	2016	
Aaby P, 2011, J INFECT DIS, V204, P245, DOI 10.1093/infdis/jir240, DOI	2011	14.41	2012	2016	
Quintin J, 2012, CELL HOST MICROBE, V12, P223, DOI 10.1016/j.chom.2012.06.006, DOI	2012	40.97	2013	2017	
Kleinnijenhuis J, 2012, P NATL ACAD SCI USA, V109, P17537, DOI 10.1073/pnas.1202870109, DOI	2012	38.51	2013	2017	
Kleinnijenhuis J, 2014, J INNATE IMMUN, V6, P152, DOI 10.1159/000355628, DOI	2014	26.79	2014	2019	
Ifrim DC, 2014, CLIN VACCINE IMMUNOL, V21, P534, DOI 10.1128/CVI.00688-13, DOI	2014	21.02	2014	2019	
Benn CS, 2013, TRENDS IMMUNOL, V34, P431, DOI 10.1016/j.it.2013.04.004, DOI	2013	18.76	2014	2018	
Ostuni R, 2013, CELL, V152, P157, DOI 10.1016/j.cell.2012.12.018, DOI	2013	18.2	2014	2018	
Saeed S, 2014, SCIENCE, V345, P1578, DOI 10.1126/science.1251086, DOI	2014	67.02	2015	2019	
Cheng SC, 2014, SCIENCE, V345, P1579, DOI 10.1126/science.1250684, DOI	2014	65.52	2015	2019	
Kleinnijenhuis J, 2014, CLIN IMMUNOL, V155, P213, DOI 10.1016/j.clim.2014.10.005, DOI	2014	28.86	2015	2019	
Bekkering S, 2014, ARTERIOSCL THROM VAS, V34, P1731, DOI 10.1161/ATVBAHA.114.303887, DOI	2014	21.98	2015	2019	
Buffen K, 2014, PLOS PATHOG, V10, P0, DOI 10.1371/journal.ppat.1004485, DOI	2014	13.17	2015	2019	
Blok BA, 2015, J LEUKOCYTE BIOL, V98, P347, DOI 10.1189/jlb.5RI0315-096R, DOI	2015	14.2	2016	2020	
Leentjens J, 2015, J INFECT DIS, V212, P1930, DOI 10.1093/infdis/jiv332, DOI	2015	11.58	2016	2020	
Netea MG, 2016, SCIENCE, V352, P0, DOI 10.1126/science.aaf1098, DOI	2016	70.02	2017	2021	
Arts RJW, 2016, CELL METAB, V24, P807, DOI 10.1016/j.cmet.2016.10.008, DOI	2016	36.13	2017	2021	
van der Meer JWM, 2015, MOL IMMUNOL, V68, P40, DOI 10.1016/j.molimm.2015.06.019, DOI	2015	12.29	2017	2020	
Arts RJW, 2016, SEMIN IMMUNOL, V28, P425, DOI 10.1016/j.smim.2016.09.002, DOI	2016	11.77	2017	2021	
Arts RJW, 2016, CELL REP, V17, P2562, DOI 10.1016/j.celrep.2016.11.011, DOI	2016	36.36	2018	2021	
Novakovic B, 2016, CELL, V167, P1354, DOI 10.1016/j.cell.2016.09.034, DOI	2016	26.73	2018	2021	
Bekkering S, 2016, CLIN VACCINE IMMUNOL, V23, P926, DOI 10.1128/CVI.00349-16, DOI	2016	22.31	2018	2021	
Divangahi M, 2021, NAT IMMUNOL, V22, P2, DOI 10.1038/s41590-020-00845-6, DOI	2021	20.25	2022	2024	
Kalafati L, 2020, CELL, V183, P771, DOI 10.1016/j.cell.2020.09.058, DOI	2020	13.14	2022	2024	
Moorlag SJCFM, 2020, CELL REP, V33, P0, DOI 10.1016/j.celrep.2020.108387, DOI	2020	11.93	2022	2024	

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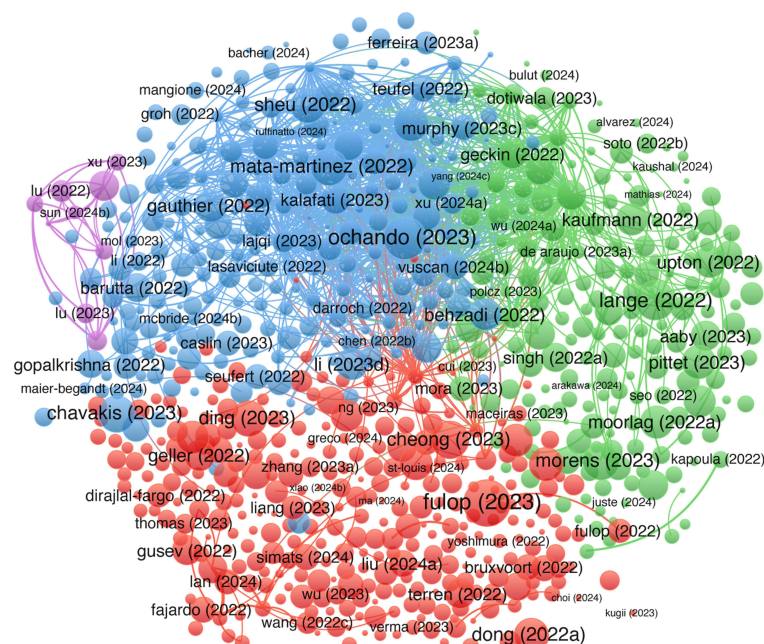


Figure 8 Citation burst analysis and bibliographic coupling analysis. **(A)** Citation burst analysis of references using CiteSpace, highlighting the top 25 references with the strongest burst strengths. **(B)** Bibliographic coupling analysis of 721 articles from 2022 to 2024 by VOSviewer.

a review in *Science* in 2016, which has since become a foundational work in the field. Three publications are still in the burst phase, focusing on the standardization of experimental protocols, trained immunity in tumor treatment, and neutrophil-mediated trained immunity. These indicate emerging research frontiers. Other bursts cover a range of research hotspots, including effector cells involved in trained immunity (eg, monocytes, macrophages, NK cells), core mechanisms (eg, metabolic and epigenetic

reprogramming), nonspecific effects (eg, vaccine-induced broad-spectrum protection), and potential risks (eg, exacerbation of atherosclerosis and other chronic inflammatory conditions).

In addition, a bibliographic coupling analysis of 721 publications from 2022 to 2024 was conducted to identify current research hotspots. The results revealed four major clusters (Figure 8B): Cluster #1: Multifaceted mechanisms and applications of trained immunity; Cluster #2: Trained immunity in chronic inflammatory diseases; Cluster #3: Trained immunity in vaccinology and cross-protection; and Cluster #4: Metabolic drivers of trained immunity in cardiovascular disease. While Cluster #1 has a broad thematic scope, the other clusters have well-defined research focuses, suggesting that the field is currently characterized by the coexistence of multiple active hotspots.

Analysis of Keywords

At the thematic and content level, keyword co-occurrence analysis provides a rapid insight into research hotspots and developmental trends. Using timeline viewer analysis, we clustered the keyword co-occurrence network and visualized the dynamic evolution of each cluster. As shown in Figure 9A, eleven clusters were identified, most of which have sustained persistent attention, reflecting the coexistence of multiple long-active research hotspots in this field. Specifically, the phenomenon of trained immunity has been observed in various pathological conditions including infections, tumors, cardiovascular diseases, autoimmune disorders, neurodegenerative diseases, and aging. The underlying mechanisms primarily involve epigenetic and metabolic reprogramming, which not only regulates the function of mature myeloid cells but also affects hematopoiesis. Moreover, the nonspecific protective effects induced by trained immunity offer potential for developing broad-spectrum vaccines.

Keyword burst analysis provides an alternative approach to identifying research hotspots and emerging trends. A sharp increase in the frequency of specific keywords within a given period typically reflects heightened research interests in the field. As shown in Figure 9B, among the top 25 keywords ranked by burst strength, *heterologous immunity* emerged earliest and exhibited the strongest burst intensity (strength = 3.37). *Immunological memory* had the longest burst duration, lasting for seven years. In contrast, *systemic inflammation*, *histone modifications*, and *atherosclerotic cardiovascular disease* appeared most recently and remained in their burst phase since 2022, indicating current and ongoing research frontiers.

To comprehensively identify research priorities in the field of trained immunity, we analyzed the top 100 keywords by annual popularity from 2011 to 2024. As illustrated in Figure 10A, keywords including *BCG*, *inflammation*, *innate immunity*, *epigenetics*, *metabolism*, *macrophage*, *monocyte*, and *cytokine* maintained high popularity over the years, indicating sustained research interest. In 2024, keywords such as *vaccine*, *nonspecific effects*, *heterologous effects*, *heterologous immunity*, and *atherosclerosis* gained prominence, reflecting their emergence as new research focus.

Furthermore, we categorized these high-frequency keywords into 15 research hotspots encompassing cell types, mechanistic studies, clinical diseases, and vaccine applications (Figure 10B). Subsequent temporal visualization of keyword occurrence frequencies revealed distinct evolutionary trajectories among these hotspots: early-emerging topics (eg, trained immunity in vaccination), recently-developed foci (eg, regulation of HSPCs, allergic and neurodegenerative diseases), rapidly-growing fields (eg, metabolic reprogramming mechanisms), linearly progressing themes (eg, innate immune cells, epigenetic reprogramming, and Infection-protective effects), and fluctuating themes (eg, impacts on cytokine, autoimmunity, mucosal immunity, cancer, and metabolic/cardiovascular diseases). Collectively, these research hotspots have continued to attract attention.

Discussion

General Information

Immunological memory has long been considered an exclusive feature of the adaptive immune system. The recognition that innate immune cells can also develop functional memory, a phenomenon termed trained immunity, has fundamentally reshaped this view. Based on publications indexed in the WoSCC, this bibliometric study provides a descriptive and exploratory overview of the evolution of trained immunity research from 2005 to 2024. By analyzing 1,526 publications authored by 7,631 researchers from 371 institutions across 95 countries/regions and published in 442 journals, we sought to characterize research output, collaboration patterns, and thematic development, rather than to infer biological mechanisms or causal relationships.

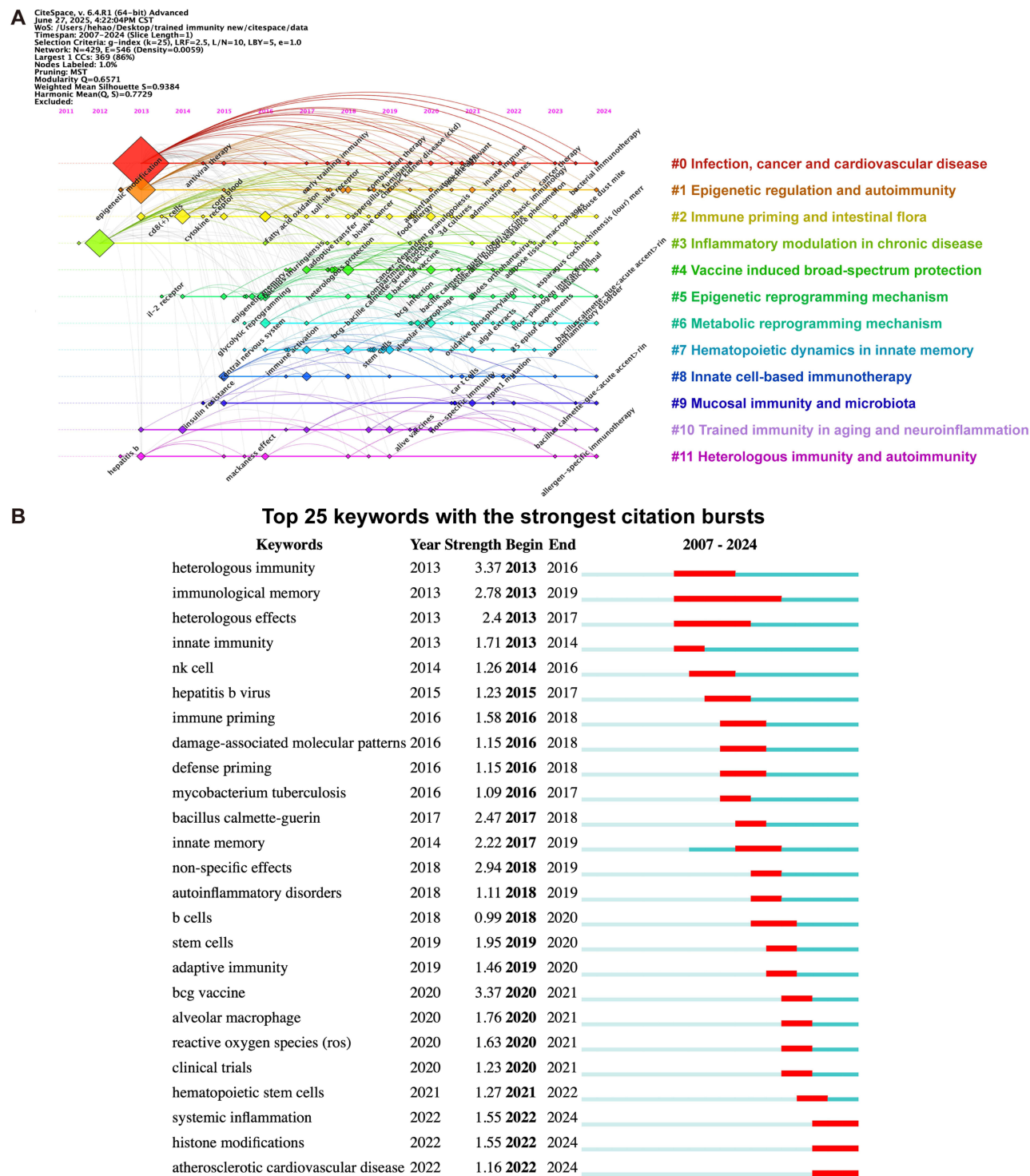
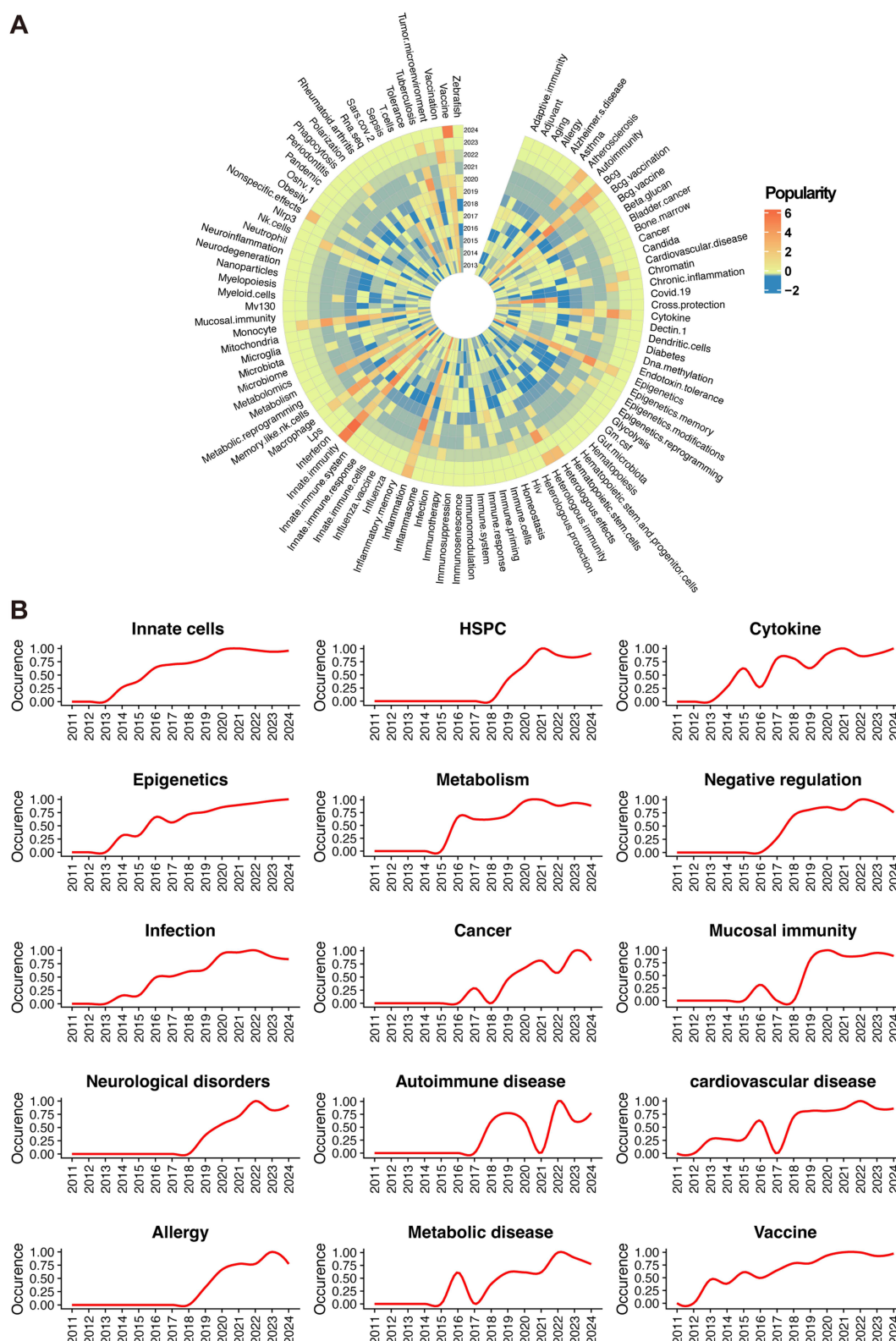


Figure 9 Keyword co-occurrence and burst analysis by CiteSpace. **(A)** Timeline viewer analysis of keyword co-occurrence. Node position indicates the time of first appearance, and node size reflects betweenness centrality. **(B)** Keyword burst analysis, listing the top 25 keywords with the highest burst strengths.

Since the formal introduction of the concept of trained immunity in 2011,³ research activity in this field has increased markedly, with publication output in 2024 reaching approximately sixteen times that of a decade earlier. The United States, the Netherlands, and Germany emerged as the most productive contributors. Radboud University Nijmegen and the University of Bonn were identified as highly influential institutions, while broader international collaboration



networks were observed around institutions such as the University of Melbourne, CNRS, INSERM, the Helmholtz Association, and Harvard University. Journal analysis indicated that *Frontiers in Immunology* published the largest number of articles, whereas journals such as *Science* and *Cell*, despite fewer publications, exerted substantial influence through high citation impact. From an authorship perspective, Mihai G. Netea and Leo A.B. Joosten were central figures, reflecting the foundational role of their work in shaping the field.

Hotspots and Frontiers

Analysis of journal distribution, subject categories, and thematic clustering indicates that trained immunity research spans multiple disciplines and exhibits marked thematic heterogeneity. To identify research hotspots and emerging frontiers, this study integrated co-citation analysis, citation burst detection, bibliographic coupling, keyword timeline visualization, keyword burst analysis, and keyword popularity mapping. Although each method emphasizes different aspects of the literature, their convergence enables a robust identification of dominant research themes and evolving directions. Overall, the hotspots and frontiers of trained immunity research can be summarized from three interconnected dimensions: cellular targets, molecular mechanisms, and disease relevance with translational applications. Importantly, these observations reflect patterns of scholarly attention rather than definitive biological hierarchies.

Cells: From Mature Myeloid Cells to HSPCs and Tissue-Resident Populations

Keyword popularity and co-occurrence analyses consistently indicate that cellular heterogeneity constitutes a central and evolving research hotspot in trained immunity studies. Early high-frequency keywords and citation bursts were predominantly centered on monocytes, macrophages and NK cells, reflecting the foundational experimental models used to establish the concept of trained immunity.^{3,32,36–41} Highly cited references consistently highlight that β -glucan or BCG exposure induces long-lasting functional reprogramming in these cells, characterized by enhanced cytokine production upon secondary stimulation, underscoring their central role in shaping the initial framework of innate immune memory.^{4,34,35}

Subsequent shifts in keyword prominence reveal a progressive expansion of research attention toward additional immune cell lineages. Dendritic cells and neutrophils emerged as notable cellular targets, as reflected by increasing keyword frequency or citation burst, suggesting growing recognition of trained immunity beyond classical mononuclear phagocytes.^{42–45} These bibliometric trends correspond to accumulating evidence of memory-like functional adaptations across diverse innate immune populations, highlighting a broadening conceptual landscape rather than reliance on a single dominant cellular model.²⁰

More recently, multiple bibliometric indicators identified HSPCs as a prominent emerging hotspot. This reflects increasing attention to the concept of “central trained immunity,” whereby primary stimuli reprogram HSPCs and transmit trained phenotypes to peripheral myeloid progeny.^{12,46} Highly cited studies involving β -glucan, BCG, and endotoxin-driven remodeling of HSPC transcriptional and epigenetic landscapes consistently anchor this cluster, marking a conceptual shift from short-lived peripheral training toward durable, stem cell–based immune memory.^{47–51}

In parallel, tissue-resident immune cells—including alveolar macrophages, microglia, and innate lymphoid cell subsets^{52–57}—as well as non-immune cell populations such as epithelial and stromal cells,^{58–61} have formed the basis of several recent clusters identified by keyword popularity and timeline analyses. This pattern reflects growing interest in “peripheral trained immunity” or “inflammatory memory” within specific tissue niches.¹³ Collectively, these studies suggest that local microenvironmental cues contribute to long-term functional adaptation of resident cells, further extending the trained immunity framework beyond circulating immune compartments.

Taken together, these bibliometric patterns indicate that current research frontiers are shifting from single-cell-type models toward integrated, multi-lineage frameworks encompassing central, peripheral, and tissue-specific dimensions of trained immunity.

Mechanisms: From Epigenetic and Metabolic Reprogramming to Regulatory Constraints

Mechanistic themes represent one of the most cohesive and stable clusters identified in the bibliometric landscape of trained immunity research. Co-citation, citation burst, and keyword clustering analyses consistently highlight epigenetic

and metabolic reprogramming as dominant mechanistic axes, reflecting sustained scholarly attention to the molecular foundations of innate immune memory.

Highly cited mechanistic studies consistently report that initial immune activation leaves durable epigenetic marks at promoters and enhancers of inflammatory genes, with particular emphasis on histone modifications as key molecular substrates of trained immunity.^{4,35,62,63} Keywords such as “H3K4me1,” “H3K27Ac,” “H3K4me3,” and “chromatin accessibility” exhibit long-term citation strength and frequent co-occurrence, indicating their central role in shaping the mechanistic discourse of the field.^{64,65}

Metabolic reprogramming constitutes a second major mechanistic axis,⁶⁶ as evidenced by the frequent co-occurrence of keywords including “glycolysis,” “mTOR,” “HIF-1 α ,” “mitochondria” and “metabolism.” Citation bursts associated with these terms correspond to seminal studies demonstrating that shifts toward aerobic glycolysis and altered tricarboxylic acid cycle intermediates provide the metabolic foundation for epigenetic remodeling.^{6,7,67–70} The tight coupling between metabolic and epigenetic keywords across bibliometric analyses underscores their integrated role in sustaining trained immune phenotypes.^{66,71}

In contrast to the early emphasis on activation mechanisms, more recent bibliometric signals point to increasing attention to regulatory and inhibitory pathways.^{72–74} Emerging keywords such as “tolerance” and “immunosuppression” reflect growing recognition of the need to balance trained immunity to prevent pathological inflammation. Studies highlighting IL-37–mediated suppression of metabolic and epigenetic training pathways appear within newer citation clusters,^{75,76} indicating a maturation of the field toward understanding both amplification and restraint of innate immune memory.

Overall, bibliometric patterns suggest a transition from identifying core epigenetic and metabolic mechanisms toward exploring multilayered regulatory networks—including non-coding RNAs, chromatin architecture, and immune-inhibitory circuits—which are likely to define future mechanistic frontiers.

Diseases and Applications: From Heterologous Protection to Chronic Inflammation and Cancer

Thematic mapping of keywords and citation clusters reveals a gradual yet consistent expansion of trained immunity research toward disease relevance and translational applications.⁷⁷ Early disease-oriented clusters were closely associated with vaccines and infectious diseases, reflecting initial interest in heterologous protection and nonspecific immune enhancement.²⁰ Highly cited epidemiological and clinical studies linking BCG and other vaccines to reduced all-cause mortality or enhanced resistance to unrelated infections form a central pillar of this translational theme.^{9,15,78–80}

Subsequent bibliometric analyses reveal a growing body of literature associating trained immunity with chronic inflammatory and autoimmune diseases.^{19,81,82} Citation clusters involving atherosclerosis, systemic lupus erythematosus, rheumatoid arthritis, gout, allergy, and neuroinflammation indicate increasing attention to the potential maladaptive consequences of sustained immune training.^{16,18,33,83–91} These trends suggest that persistent metabolic and epigenetic reprogramming of HSPCs or circulating myeloid cells may contribute to long-term inflammatory pathology,^{92–95} marking a conceptual shift from protective to pathogenic roles of trained immunity.

More recently, cancer-related keywords have emerged as a distinct and expanding frontier. Popular keywords including “cancer,” “tumor microenvironment,” and “immunotherapy” coincide with preclinical and clinical studies reporting trained immunity–mediated antitumor effects.^{19,96,97} Highly cited publications on BCG therapy in bladder cancer, β -glucan–induced myeloid training, and infection-driven enhancement of tumor surveillance reflect growing interest in integrating trained immunity concepts into cancer immunotherapy strategies.^{45,98–101}

Importantly, these disease- and application-oriented trends should be interpreted as indicators of evolving research focus rather than direct evidence of clinical efficacy. From a bibliometric perspective, the observed expansion into translational domains highlights shifting scientific attention and interdisciplinary convergence, pointing to future research opportunities at the interface of innate immune memory, disease pathogenesis, and therapeutic innovation.

Limitation

This study has several limitations inherent to bibliometric analyses. First, data were retrieved exclusively from the WoSCC, which, despite its broad coverage and standardized citation data, may underrepresent publications indexed in other databases such as Scopus or PubMed. Second, restriction to English-language literature introduces potential

linguistic bias. Third, citation-based indicators are subject to cumulative advantage effects, including the Matthew effect, whereby well-established authors, institutions, or journals may receive disproportionate citation attention. In addition, bibliometric outcomes may be influenced by author name ambiguity, variations in citation practices across disciplines, and software-dependent analytical algorithms. These factors should be considered when interpreting the results, which primarily reflect research attention and knowledge structure rather than scientific quality or causal relationships.

Conclusion

Trained immunity has rapidly emerged as a dynamic and influential research domain within immunology. Bibliometric evidence indicates that the United States, the Netherlands, and Germany constitute the core contributors to this field, with institutions such as Radboud University Nijmegen and the University of Bonn serving as central nodes in the global research network. The seminal contributions of Mihai G. Netea and collaborators have played a pivotal role in shaping both the conceptual framework and mechanistic foundations of trained immunity.

From a thematic perspective, the research landscape has progressively shifted from an initial focus on classical myeloid cells toward a broader, multi-lineage framework encompassing hematopoietic stem and progenitor cells, tissue-resident immune populations, and selected non-immune cells. This evolution is accompanied by sustained attention to epigenetic and metabolic reprogramming as the core mechanisms underpinning innate immune memory. At the application level, bibliometric trends reveal an expanding research focus from heterologous protection against infections to the dual roles of trained immunity in chronic inflammatory diseases and cancer.

By systematically mapping publication patterns, collaboration networks, and thematic evolution, this bibliometric analysis delineates the developmental trajectory and emerging research hotspots of trained immunity. The findings provide an updated, integrative overview of the field and highlight directions for future investigation at the interface of innate immune memory, disease pathogenesis, and translational innovation.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Author Contributions

Conceptualization, H.H. and L.K.; Methodology, H.H. and L.K.; Investigation: Z.Y. and J.H.; Data curation, Z.Y.; Formal analysis, Z.Y.; Visualization, J.H.; Validation, J.H.; Supervision, H.H.; Project administration, L.K.; Funding acquisition, H.H.; Writing—original draft preparation, L.K.; Writing—review and editing, H.H., Z.Y. and J.H. All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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