Research Article

The Future of Mesenchymal Stromal Cells in Cancer: A Bibliometric Analysis

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ABSTRACT

Background: Mesenchymal stromal/stem cells have garnered much interest in the field of cancer biology. Bibliometric analysis of a scientific field has the potential to reveal insights pertaining to the maturity of the field, the hotspot sources of publication and temporal shifts in research subcategories within the field. Despite the benefits of such an analysis, one has not been conducted to date.

Methods: The Web of Science™ database and VOS viewer software were used to analyse publication and citation data for all publications relating to Mesenchymal Stromal/Stem Cells in oncology. Contributions to the literature were also identified by country, journal and cancer type. Keyword analysis identified trends in developing research categories.

Results: 9927 published articles were analysed. The current publication rate fits an exponential trend (e=0.97). The U.S. and the People's Republic of China have the highest overall publications but when corrected for population and citations per article, the most successful countries are Singapore, Luxembourg and Switzerland. In the past 15 years 74% of articles have been in cancer specific journals. Breast cancer publications account for 42% of common cancer articles. Most articles were published in journals that had a basic science focus (44%). Keyword analysis resulted in 3 distinct clusters aligned with 1. Characterisation and nomenclature, 2. Clinical and 3. Molecular function. The most recent publications favour topics on Molecular function.

Conclusions: Research on Mesenchymal Stromal/Stem Cells in oncology is experiencing exponential growth. There is widespread acceptance of basic science research on Mesenchymal Stem Cell (MSC) in cancer specific journals and a niche for more translational and clinically focused studies.

Keywords: Mesenchymal stromal cell; Bibliometric analysis; Translational research; Mesenchymal stem cell; Cancer; Neoplasia

Abbreviations: MSC: Mesenchymal Stromal Cell; ISCT: International Society for Cell therapy; TME: Tumour Microenvironment; EMT: Epithelial to Mesenchymal transition; WoS: Web of Science

INTRODUCTION

In the 1980's Friedenstein and Owen described a fibroblastic cell that was isolated from the bone marrow of rodents and formed colonies when cultured *in vitro*. The described population were a heterogeneous collection of cells whose differentiation could be manipulated *in vitro* and were labelled "bone marrow osteogenic stem cells" [1,2]. In 1991 the term "Mesenchymal Stem Cell' was coined to describe these multipotent progenitors, a term which has persisted [3]. Subsequently the International Society for Cellular Therapy (ISCT) recommended an amendment to the nomenclature. In a 2006 position paper the term 'Mesenchymal Stromal Cell' (MSC) was recommended for the description of these cells. The ISCT paper was in response to inter-investigator variability in cell isolation, expansion and characterisation and aimed to standardise scientific reporting and acknowledge the variability in cells determined by their tissue of origin [4].

Aside from their multipotent differentiation, other functions of MSCs have been uncovered that demonstrate potential for translational application particularly in tissue healing and autoimmune conditions [5-7]. MSCs have also garnered

much interest in the field of cancer research. Authors have demonstrated that MSCs home to the site of tumours and can have a pro-tumorigenic influence [8]. MSCs native to the cancer's tissue of origin have also been implicated [9,10].

Within the Tumour Microenvironment (TME) the pro-tumourogenic influences of MSCs include induction of angiogenesis promotion of cancer cell migration and Epithelial to Mesenchymal Transition (EMT) the latter of which constitutes enhanced resistance to chemotherapies [10-13]. More recently, the immunosuppressive abilities of MSCs have been particularly interesting as they allow for the cancer to evade the immune response of the host [14,15].

Prior to the digital age any given field of study would command a small number of print publications from which new findings could be accessed. The coming of the digital age has provided researchers with access to a quantity of data that was heretofore unimaginable. There is now a growing expanse of print and electronic sources. The freedom and speed with which knowledge is disseminated confers an obvious benefit but also presents a challenge. Experimentation is based on a hypothesis, which in turn is generated from robust knowledge of the prior research. In an era of monumental research output, incomplete knowledge of prior research can lead to error in study design [16].

Bibliometric analysis, conceived by Paul Otlet in 1934, provides a solution for a robust understanding of the ocean of print and digital data. Bibliometrics focuses on the data related to the reading and writing of books and documents rather than the content which would be the focus of a traditional literature review [17]. By utilising the advancements in bibliometric and indexing software, one can access large volumes of publication metadata and draw conclusions about the trends of a particular field of study, the untapped niches and the maturity of that scientific field. Employing bibliometrics, researchers have been able to analyse whole research fields to provide insights in HIV, cancer and microRNAs among others [18-20].

Despite the benefits of bibliometric analyses and the growth of the field of MSCs in oncology, analysis of the topic has not been conducted to date. To conduct such an analysis would highlight areas of the globe producing high quality research, sites of highest productivity, evidence of trends and topics requiring further exploration.

MATERIALS AND METHODS

Bibliometric data and search strategy

The Web of Science TM (WoS) database, produced by Clarivate Analytics was accessed. The WoS core collection comprising of the following was interrogated; Science Citation Index Expanded (SCI-Expanded), Social Sciences Citation Index (SSCI), Arts and Humanities Citation Index (A and HCI), Emerging Sources Citation Index (ESCI), Conference Proceedings Citation Index Science (CPCIS), Conference Proceedings Citation Index-Social Sciences and Humanities (CPCI-SSH), Book Citation Index–Science (BKCIS), Book Citation Index–Social Sciences and Humanities (BKCI-SSH), Current Chemical Reactions (CCR-Expanded) and Index Chemicus (IC) [21].

The search terms used were "Mesenchymal Stromal Cells" and

"Mesenchymal Stem Cells" with the Boolean operator "OR". Initial results were further refined using the WoS category "Oncology". Duplicates were identified and removed. All languages and years of publication were included, as were all publication types. Data extracted included; Title, Author names, abstract, place of publication, language, year of publication, publishing journal, type of publication, WoS Category, number of citations and H-Index.

All data were extracted on a single day in April 2019 as WoS is an open database which is regularly updated with new publications. The use of a single source bibliometric database was conducted due to its comprehensive indexing of journals, suitability and extensive use for similar analyses in the literature [20,22-24].

The description of publishing journals, on their journal website was accessed. The focus of journals as either cancer specific or general scientific was determined. Journals were deemed to have a cancer specific focus if their description included any of the following terms; cancer, tumour, tumor, malignancy, oncology, neoplasia, carcinoma or carcinogenesis and generalised science if they had none of the above terms in their description. Journals were also categorised based on their focus on either basic, translational or clinical research by the same process. Descriptors indicating a basic science focus included the following; basic science, basic biology, bench research, preclinical, laboratory, cell biology or molecular. Descriptors of a translational focus; translation, bench-to-bedside, translational and a clinical focus if; clinical, surgical, clinical trial or clinic were included. Journals that had more than one research focus were recorded in each of the relevant categories. The top 6 most common cancers and top 5 most common causes of cancer death as per the World Health Organisation were recorded among search results [25].

Data analysis and visualisation

All data were input into Microsoft Excel 2010$^{\copyright}$ for the generation of graphical data. WoS data tools were used for the generation of several elements of data analysis eg. Generating citation reports, H-Indices and WoS categorisation.

The Java program VOS viewer (version 1.6.11) was used to provide a keyword cluster analysis [26]. To perform this a network visualisation was conducted using search result titles', authors, institutions and abstracts input in .txt format. Co-occurrence of key words was performed for all key words that appear in the search results a minimum of 10 times.

RESULTS

In total, our search strategy yielded 9,927 publications across the field of Mesenchymal Stem/Stromal Cells in cancer research, spanning a period of 32 years. From the first publication in 1986 there was a gradual increase in the number of publications. From the year 2000 onwards, the field gained significant momentum and grew annually to a maximum of 1410 publications in 2017. The growth rate of publications fits an exponential trend with an R_2 value of 0.97 (Figure 1A). There were 341,359 citations of papers published in this field during this period and an average number of citations of 34.39 per publication (Figure 1B). The average citations per article peaked in 1998 and trended downwards thereafter (Figure 1C). The H-Index for the field was

223. The H-Index is used as a measure of the success of a field, in this instance 223 of the publications achieved 223 citations or more [27]. The H-index and total number of citations peaked circa 2006-2008, plateaued and dropped as the number of total publications spiked a decade later (Figure 1D). The spike in both H-index and average number of citations per article (Figure 1C) precede the significant exponential growth from the year 2000 onwards (Figure 1A). The trend of total publications and those relating to citations have a somewhat inverse relationship to one another. This relationship is intuitive when considered; in the beginning there were only a small number of publications from which future authors could cite, as the number of publications increased so did the citations of those fewer, older papers. After a point however there was a significant repository of papers, each of which received less citations and prominence.

Publications by country

90 countries in total contributed to the field of MSCs and oncology during this time. The top 25 countries are illustrated in (Figure 2A). Of the 90 countries publishing on this topic, 59.5% of the publications come from the United States and the Peoples' Republic of China. To further outline the contribution of each country, the citation data from each country was analysed as were their number of publications in respect of population size. Among the top 25 countries by average citation, the contribution has a more balanced distribution (Figure 2B), and is led by Singapore 61, Luxembourg 60 and Switzerland 55. These same 3 countries publish the most per 100,000 of the population as per the United Nations Population Division as illustrated in Figure 2C [28]. When corrected for population size several countries move up the ranks e.g. Finland, Ireland and Denmark while others no longer appear in the top 25 e.g. Japan, the Peoples' Republic of China or Spain (Figures 2A and 2C).

Research focus

Figure 3A shows the top 15 journals in this field during this period. The top publishing journal in this field was Stem Cells (1156) followed by Oncotarget (837) and Cancer Research (571). Focusing exclusively on the past 15 years the publishing journals were explored in more detail. In 2004, 38% of the papers investigating MSCs in oncology were published in journals with a cancer specific focus. From 2004 to 2018 there was a steady increase in publications in cancer specific journals which was highest in 2018 at 84% of all publications. In total over the 15-year period 74% of all publications occurred in these cancer specific journals (Figure 3B). This demonstrates that there is good acceptance of papers on MSCs in oncology among the mainstream cancer research community and that its growth has been considerable between 2004-2018.

To further consider the nature of studies conducted in this area of research, publications were classified as basic, translational or clinical research based on the journal they were published in. Figure 3C demonstrates quite clearly that basic science publications are the most prevalent followed by clinical and translational. This trend was consistent over the 15 years represented in the graph. In 2004 basic science accounted for 39% of publications and experienced a marginal gain to 46% in 2018. The publication of clinical science papers remained relatively steady accounting for 33% in 2004 and again in 2018. While basic science had a marginal gain over the 15 years, there was a consequent loss in the prevalence of translational research publications which went from 27% in 2004 to 21% 15 years later.

To provide insight into the most commonly researched malignancies in the field, the 9927 publications were filtered for specific cancers. This process was limited to the most common cancers (Figure 4A) and the most common causes of cancer mortality (Figure 4B), according to the World Health Organisation publications [25]. The most common cancer to be published on in this field was breast cancer (42% of publications), followed by lung (17%) and colorectal (14%) (Figure 4C). Of these most common cancers, breast accounts for 22% of cases worldwide, lung 22% and colorectal 19% (Figure 4A). The distribution of mortality is lung 37%, colorectal 18% and breast 13% (Figure 4B). These results demonstrate that breast cancer is disproportionately represented in the published literature, in respect of its prevalence worldwide and contribution to cancer related mortality.

Keyword analysis

Title, authors, abstracts and keywords were extracted for all of the 9927 publications as detailed above and a specific focus on keyword occurrence was undertaken.

The relevant output is provided by VOS viewer in the form of a bubble plot. Each keyword that achieved the threshold for occurrences can be identified as a single bubble. The frequency with which any particular keyword appears corresponds to the size of the respective bubble. Proximity between bubbles is inversely related to the frequency with which they co-occur in the published literature. In line with this, VOS viewer grouped keywords into 3 separate general clusters relating to; characterisation and nomenclature (Figure 5A), clinical focus (Figure 5A) and molecular function in cancer biology (Figure 5A). The most prevalent keywords were "Mesenchymal Stem Cell", "Metastasis", "emt" (Epithelial to Mesenchymal Transition) and "Bone Marrow".

The VOS viewer output for keyword analysis was also stratified according to the temporal frequency of keywords within the literature. In Figure 5B older terms are coloured blue and the most recent terms are coloured yellow. In considering this particular figure there is a temporal shift from keywords relating to isolation and characterisation of MSCs eg. "donor", "mesenchymal stem cell", "bone marrow", to their involvement in TME eg. "e-cadherin", "emt", "microRNA" (Figure 5B). This finding is consistent with the original efforts by researchers to isolate, identify and culture these cells *in vitro* until a standardisation of this process was established. After such a point that there was general consensus about the nomenclature and characterisation of these cells, new avenues pertaining to their function within the context of cancer biology was possible. It is worth noting that the cluster pertaining to clinical focus (Figure 5A), has the fewest keywords and some of the least frequently identified in the literature. This finding provides an insight into the current state of MSCs in clinical cancer research. The 3 most prominent keywords within the clinical focus cluster are "review", "case" and "concept", leading us to believe that clinical research in this field is currently in its infancy with much of the published literature being of a theoretical nature, rather than applied clinical research.
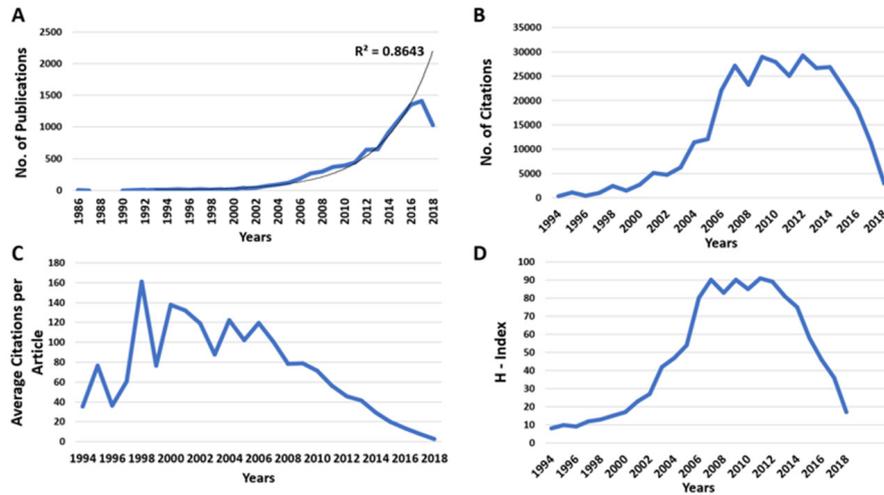
Figure 1: Overall Publications and Citations. (A) Total number of publications by year and exponential line of best fit (B) Total number of citations by year (C) Citations per article by year and (D) H–index for the entire field by year.
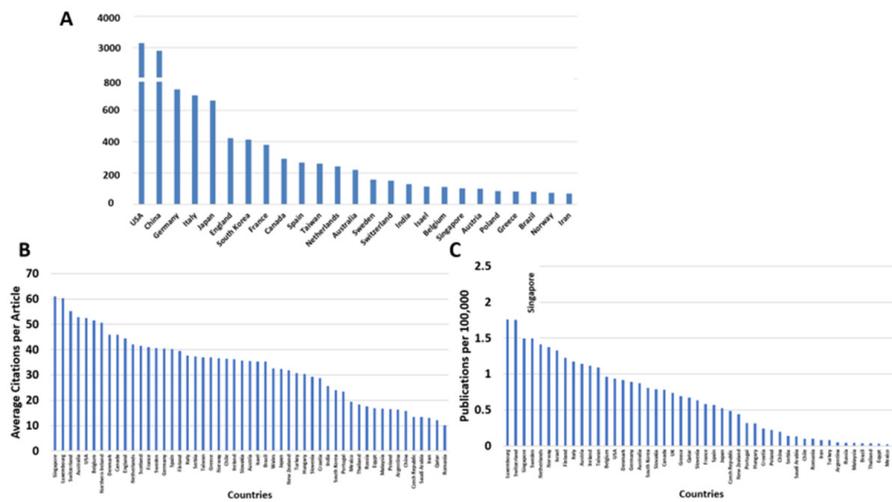
Figure 2: Global variations in publication and citation. (A) Top 25 countries according to overall publication volume (B) Top 25 countries according to the average number of citations per article (C) Top 25 countries according to the volume of publications per 100,000 of population.
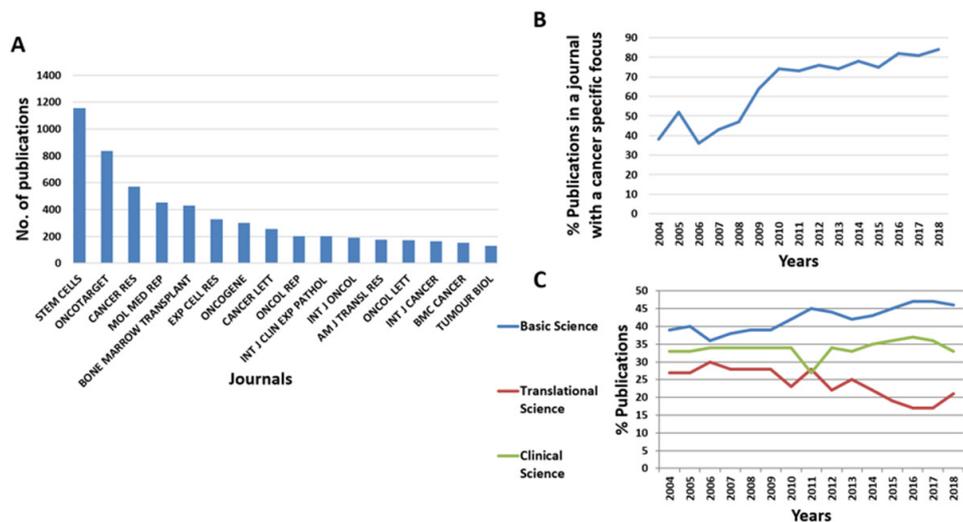
Figure 3: Publishing Journals. (A) Most prolific journals publishing in this field (B) Articles published in a journal with a cancer specific focus over the past 15 years (C). **Note:** (—) Articles published in journals with a basic science, (—) Translational Science, (—) Clinical Science.
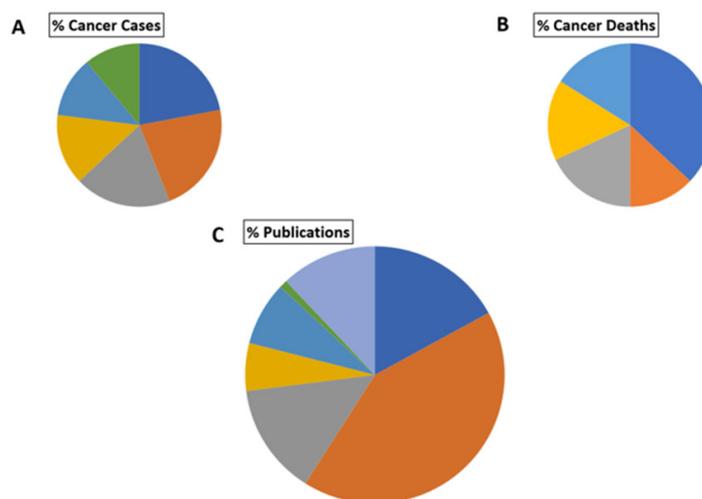
Figure 4: Cancers of Interest. (A) 6 most common cancers worldwide according to the WHO (29) (B) 5 most common causes of cancer death worldwide (29) (C) The proportional representation of the above cancers in the literature. **Note:** A: (▪) Lungs 17%, (▪) Breast 42%, (▪) Colorectal 19%, (▪) Prostate 14% , (▪) Skin cancer (Non melanoma) 12%, (▪) Stomach 11% ; B: (▪) Lungs 37%,(▪) Breast 13%, (▪) Colorectal 18%, (▪) Liver 16%, (▪) Stomach 16%; C: (▪) Lungs 17%, (▪) Breast 42%, (▪) Colorectal 14%, (▪) Liver 6% , (▪) Stomach 8%, (▪) Skin 1%, (▪) Prostate 12%).
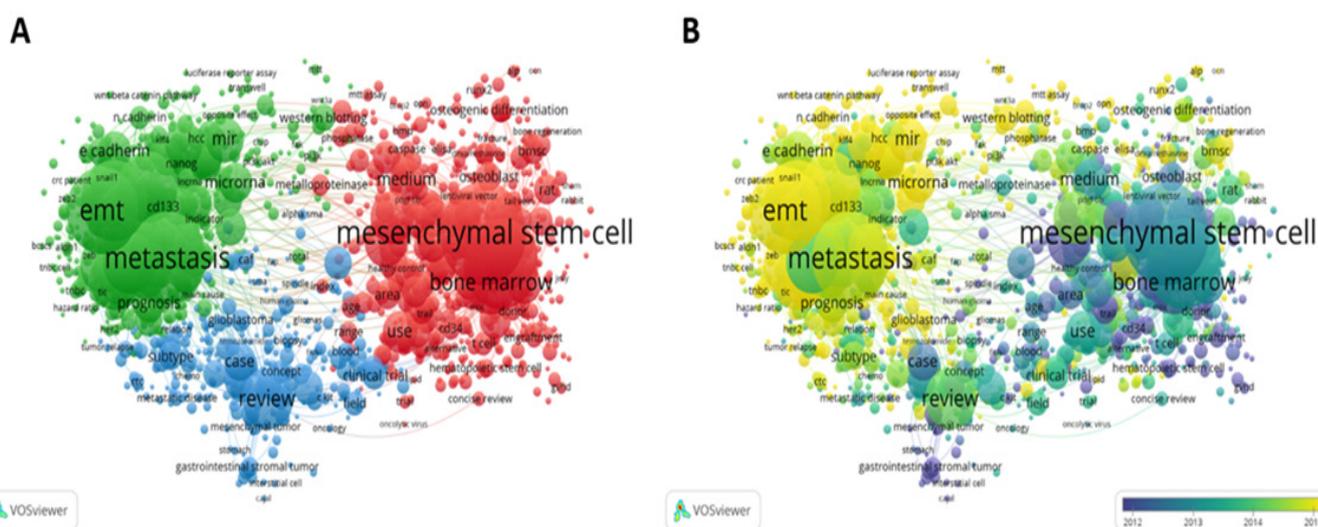
Figure 5: Keyword Analysis. (A) Bubble plot of keywords organized in 3 distinct clusters; (B) Bubble plot of keywords colored according to their appearance in the literature, as indicated by the inset legend, keywords at the blue end of the spectrum were the oldest and those on the yellow end are more recent. **Note:** (●) Characterization and nomenclature, (●) Clinical focus and (●) Molecular function; (▬) oldest; (▬) more recent.

DISCUSSION

By utilising the techniques of bibliometric analysis, it is possible to access a large repository of publications and make certain judgements regarding the field of interest based on bibliometric parameters. The unique strength of bibliometric analysis over a traditional literature review is that the analysis facilitates the input of a far greater number of articles, which in turn constitutes more meaningful recommendations to researchers. From the outset of this paper, the aim of the authors was to make a commentary on the current state of the field of MSCs in cancer research and provide insights into which research streams are worthy of attention in the future.

Our analysis has included almost 10,000 publications from which the field of MSCs in oncology has been assessed and the

publication data shows considerable growth within the field over the past 20 years, peaking in 2017. Less publications in 2018 however, does not preclude the possibility that the field is still undergoing continued growth. It has been noted previously that delayed indexing of published articles on the WoS platform can result in an underrepresentation of the publication statistics for more recent years [20]. Another reason for the drop in 2018 can be attributed to the natural progression of the field commonly seen in bibliometric analyses. As research fields become more mature and publications of a rudimentary nature saturate the field, research naturally shifts towards more novel niches of investigation. Turning points such as this have been documented in numerous fields of study previously [29,30]. When considering the publications from 2018, one must also make a note of nomenclature. Mesenchymal Stromal Cells are closely related to the alternatively named Cancer Associated Fibroblasts

(CAFs), both of which are fibroblastic cells that support cancer proliferation, survival, chemoresistance and immune-evasion in the TME [31]. An increase in the use of the "CAF" terminology may also have contributed to the number of MSC publications in 2018.

Development of research fields is said to follow four stages; initially only a small number of contributors publish on a topic until the field receives wider acceptance and enjoys exponential growth. Upon saturation of the field, publications plateau at maturity until an ultimate decline in publications [32,33]. Based on the data we have presented and the strong R_2 value of 0.97, the field of MSCs in cancer research are currently undergoing the exponential phase of growth similar to that seen in other fields of study [33]. This identified trend in the field of MSCs in cancer research is encouraging news for prospective cell biologists and cancer researchers with an interest in the TME, as it indicates a continued appetite for this type of research among the scientific community.

The citation data also aligns itself with the aforementioned 4 phases of research field maturity. In the early phases, the small number of publications were highly cited as interest in the field grew, resulting in more publications. The consequence of this high output however corresponded with an exponential decrease in the number of citations per item, the inverse of publication volume. While this citation bias is understandable as the field matures, researchers need to have an awareness of such phenomena when considering the merit of prior research and should also seek out the high citation articles that provided the foundation for the field's subsequent exponential growth.

Geographically, this field receives contribution from many jurisdictions, with over 90 countries contributing. The United States and the Peoples' Republic of China account for a significant volume. Both of these countries have been identified previously as power houses for publishing research in the field of cancer and others [34-38]. Despite their high overall output, correction for population has highlighted research hotspots such as Luxembourg, Switzerland and Singapore who lead the world in publications per capita but also have the highest average citations among all countries. In considering collaborative working, these findings can inform researchers within this field of study. Particularly, when collaborations are sought within Europe, the impressive performances of Luxembourg and Switzerland make institutions from those countries worthy of research partnerships.

In relation to the journals that publish most prolifically, there is a mix of dedicated cell biology journals such as "Stem Cells" but also those with a broader cancer research focus such as "Oncotarget". Over time, publications on MSCs in oncology were increasingly seen in journals with a deliberate cancer focus (Figure 3B), this suggests that while publications were originally in journals dedicated to studying cells eg. "Stem Cells", future research will be most appropriately published in cancer journals. This finding is a positive development as it demonstrates a wider acceptance of MSC research in the cancer community rather than exclusively the interest of cell biologists.

As a field matures, it is expected that publications will shift from preclinical to translational and ultimately clinical. This process has been studied in detail by Weber, et al. who describe the challenge of accurately determining what stage a field is at by bibliometric analysis [39]. In our attempt to make this determination about MSCs in cancer research we have taken a similar approach to Narin, et al, whereby publishing journals were designated as either basic, translational or clinical and their publication data was subsequently analysed over time (Figure 3C) [40]. Our findings demonstrate strong predominance of basic science/preclinical research which increased over a 15 year period. One may expect that basic science research would decrease overtime while translational and clinical publications increased. At this point that is not the case and there seems to be a continued appetite for bench research on MSCs in cancer. In the interest of developing future projects this indicates that while, basic science studies are still in demand, the aspiring cancer researcher who incorporates translational or clinical components will fill a relatively unmet need within the literature.

Of the cancers analysed, studies on breast cancer were most frequently published. The proportion of publications relating to breast cancer exceeded both its incidence and rate of mortality relative to the other cancers examined. This finding is not particularly novel as other bibliometric analyses indicate that breast cancer predominates various cancer research fields and also enjoys considerable funding [41-43]. For those embarking on research involving MSCs in oncology, the implications of this finding are twofold. Firstly, institutions publishing on breast cancer have an established process and a strong track record of published outputs, making them promising collaborators. Secondly, given the near saturation of publications relating to breast cancer, the lesser studied cancers may contain novel findings that remain uncovered.

The keyword analysis (Figures 5A and 5B) provides an insight into the content of published articles relating to MSCs in cancer research. There are a number of familiar keywords among the more prevalent in the literature, for example "Mesenchymal Stem Cell" and "emt". Epithelial to Mesenchymal Transition (emt) has long been identified as a mechanism by which MSCs support tumour progression and cancer cell survival within the TME [44]. Furthermore, EMT has previously been identified as a research hotspot in cancer research, by bibliometric analysis [45]. While its frequency within the literature supports its importance in MSC research and the expertise that exists within the scientific community, the search for novelty is likely to be found elsewhere within the cluster analysis. The cluster relating to clinical research (Figure 5A), is noticeably underdeveloped compared to the other two. Prominent keywords such as "case", "concept" and "review" suggest that original, applied MSC research in this area is underrepresented. Consistent with the underdevelopment of translational research, this cluster demonstrates a need for future research on MSCs in oncology that has a translational or clinical component. The cluster analysis also demonstrates the change in keyword prevalence over time within the literature (Figure 5B). The older terms along this spectrum include "Mesenchymal Stem Cell", "Media", "Osteoblast" and "Bone Marrow" and are almost exclusively situated within the cluster relating to the identification and characterisation of these cells. This is not peculiar as earlier research will be expected to focus on identification of MSCs in tumours and determining their characteristics. Conversely, the more current keywords include the aforementioned "emt" along with "microRNA", "Metastasis" and "e cadherin" all of which reside within the cluster pertaining to molecular function (Figure 5A). The temporal shift towards MSC function in the TME alongside our other data certainly suggest that future directions in the field will be on the functional elements of MSCs and how these can be manipulated to clinical and therapeutic advantage.

CONCLUSION

Bibliometric analysis has allowed for the assessment of over 9000 publications relating to the field of MSCs in cancer research. It has demonstrated exponential growth in the outputs of the field over the past 2 decades that persists. Analysis of research focuses and publishing countries have highlighted global hotspots of activity but also research quality. The acceptance of this field of study in mainstream cancer research and lag in clinical based publications can aid investigators in this field in hypothesis generation for future studies. Heeding the temporal shift of important keywords in the published literature will enable researchers to design new studies of enhanced scientific merit that harness essential bench research and transition it into the clinical setting.

DISCLOSURES

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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