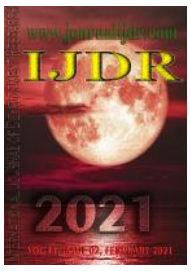
ISSN: 2230-9926

Available online at http://www.journalijdr.com

IJDR

International Journal of Development Research
Vol. 11, Issue, 02, pp.44442-44448, February, 2021
https://doi.org/10.37118/ijdr.21052.02.2021



RESEARCH ARTICLE OPEN ACCESS

SCIENCE IN INTERNATIONAL COLLABORATION: BRAZILIAN PUBLICATIONS ON REGENERATIVE MEDICINE

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ARTICLE INFO

Article History:

Received 10th December, 2020
Received in revised form
15th December, 2020
Accepted 22nd January, 2021
Published online 24th February, 2021

Key Words:

Scientific publications; Regenerative medicine; International collaboration; Emerging Countries Capabilities; Health Cooperation; Global scientific Asymmetries; Scientific Advances; Stem cell Research; Cellular Therapy; Coauthorship.

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ABSTRACT

International scientific cooperation has become a key factor in opening new doors to research, publication, and funding for emerging countries. However, it involves asymmetries where emerging countries' contributions are not valued as highly within the international division of labour in science. This article explored the expansion of regenerative medicine in Brazil by surveying studies by Brazilian researchers alone and those by Brazilians with foreign coauthors during the last two decades. Designed as a qualitative and quantitative study, it analysed local scientific capabilities by drawing upon secondary information and in-depth interviews of the Brazilian and United Kingdom leadership as well as substantial analysis of data on the Web of Science platform. It concluded that in the last decade Brazilian authors have seen a significant increase in their scientific publications with foreign researchers, most especially those in advanced countries, but also those of other emerging economies within and beyond Latin America. Local researchers have also published their own articles that have had global impact. However, these scientific exchanges have not always been fair for Brazilian contributors, which can partly be attributed to ambiguous local regulation on international collaboration and asymmetries in the global structure of scientific activities.

Citation: Liliana Acero and Helena Espellet Klein, 2021. "Science in international collaboration: Brazilian publications on regenerative medicine", *International Journal of Development Research*, 11, (02), 44442-44448

INTRODUCTION

Regenerative medicine (RM), a subfield of stem cell research (SCR) (which also encompasses applications like immunotherapy), has changed conventional medical practices (Webster *et al*., 2011). It focuses on the repair and regeneration of cells and tissues using different kinds of stem cells harvested from human bodies and usually reproduced in vitro (EuroStemcell, 2011). This line of research has been accompanied by narratives of hope for new cures through the invention of cellular-based therapies (CT) to treat incurable fatal diseases, though not without key concerns (Morrison, 2012). At present, the sector is at the stage of developing and implementing CT, i.e., the translation of laboratory research into clinical practice. Unresolved scientific and regulatory uncertainties in this emergent field demand new forms of innovative governance, especially with regard to transnational collaboration in research and publications, the organization of multicentric clinical trials, and the commercialization of cellular therapies (CT). Though the sector's dynamic is increasingly global, local territories are still a privileged locus of institutional responses to some of the new challenges (Jasanoff, 2006).

As such, in Brazil national scientific policies, institutional arrangements, and regulation play a central role in the defining of the parameters for production in RM. International scientific and technical cooperation has become a key factor for emerging countries to open new doors for local actors in terms of research advancement, publication, and funding, as attested within innovation and development studies (e.g., Velho, 2011; Lema *et al*., 2015). In Brazilian RM, this cooperation can be broadly characterized as based upon a "resource dependent model" (Hallonsten, 2014, p. 6), i.e., one mainly associated with coauthorship with foreign partners, international cofunding of clinical trials and imports of material inputs such as reagents for cell culture and advanced laboratory equipment (INCT-Regenera, 2020). International cooperation has substantially influenced the design and implementation of science policy and social practices in Latin America (Palma, 2015; Kreimer, Vessuri, 2018). Although collaboration is acknowledged within Brazilian public policy as an opportunity for bettering the country's position on RM from the standpoint of global competition (xxx, 2011), power asymmetries between local and international actors prevail as is apparent from the lack of international recognition of differences and hybrid forms of local knowledge production and/or adaptation. Collaboration entails a fundamental ethos of reciprocity. But it does

not imply the absence of competition and has intrinsic risks. The types of risk usually depend on the style of collaboration adopted as well as on rule -setting and governance (Morandi, 2013; Ankrah, Al-Tabbaa, 2015). The possibilities of unequal reciprocity and of malicious behavior exist. In science, these include being scooped for ideas, data, authorship and intellectual property rights, concerns documented in other RM contexts (e.g., Grubb, Easterbrook, 2011; Zhao, Strotmann, 2011). Nevertheless, collaboration in RM publications and multicenter CT trials is growing worldwide (Li *et al.*, 2014). Policy mechanisms for addressing this issue in RM need to be improved globally (Kaye *et al*., 2018; Kim et al., 2017). The present article explores the evolution of the scientific capacities of Brazilian groups engaged in research in RM, the role played by internal and external scientific collaboration, and the coauthorship and impact of Brazilian publications as measured by number of citations. It addresses three interrelated questions:

- What is the recent trend in knowledge production in RM in Brazil?
- Who are the main actors responsible for Brazilian RM publications?
- What are the global impacts of their publications?

METHODOLOGY

The present study is designed following a qualitative and quantitative approach. It explores local scientific capability in RM by drawing upon secondary information gathered on the sector, interviews of 15 leaders in Brazilian RM conducted intermittently between 2012 and 2019 and of 10 United Kingdom leaders, as well as substantial analysis of data found on the Web of Science (WOS) publication platform. The secondary sources utilized were publicly available official reports of various key governmental agencies in Brazil, relevant institutional archives/press releases and scientific community websites for the period 2009–2020. In addition, approximately half of the local leading stakeholders - knowledgeable agents in the field of Brazilian and UK RM - participated in face-to-face semi-structured in-depth interviews. A search of the WOS platform of Thomson Reuters that targeted publications in the sector was conducted. This platform has more than 55 million records of global peer-reviewed journals and conference proceedings on science (Web of Science, 2017) and is linked to the Scielo database (Scientific Electronic Library Online) (Scielo Citation Index, 2017), a Brazilian database of Latin American, Spanish, Portuguese, Caribbean, and South African open access journals. Beyond the Science Citation Index Expanded (SCI-EXPANDED), the index most frequently used for similar studies, other indexes were reviewed (from 2015 forward): the Social Sciences Citation Index (SSCI), the Arts & Humanities Citation Index (A&HCI), the Conference Proceedings Citation Index - Science (CPCI-S) and the Conference Proceedings Citation Index - Social Science & Humanities (CPCI-SSH), and the Emerging Sources Citation Index (ESCI), in order to standardize information from different data basis. Another source of data was the Brazilian platform of the National Research Council (CNPq), which tracks scientific publications across all disciplines, such as the social sciences for example. Lastly, the tools that WOS provides were used: the citations index, the rank of countries in a field, the science-field classification, the collaboration among countries in a specific field, and the document type classification (Thomson Routers, 2013). Articles, abstracts, meeting abstracts, and review articles were included, the last because WOS at times misclassifies original research articles as review articles.

On the Web of Science platform, the following search parameters were used to identify publications: (1) the words “stem cell”; “stem cells”; “cell therapy”; “cell therapies” and “regenerative medicine” in the “topic” (title, abstract, and keywords) for the period 2000–20/11/2020; and (2) Brazil was mentioned in the address of one or more of the authors. The tools for the analysis of these results were used to create rankings of Brazilian institutions, i.e., Brazilian authors with the highest number of publications, and of the countries of origin of foreign researchers coauthoring publications with Brazilians. The main research themes of each relevant author were also analyzed through a search in the Lattes Platform of CNPq, which stores university-level curriculum vitae.

RESULTS AND DISCUSSION

Collaboration on RM in Brazil: Brazilian governments implemented a range of policies on international scientific collaboration during the period of 2000–20/11/2020. In the first half of the period, the country tried to generate its own science and technology development in strategic sectors, such as biotechnology (MCT, 2007) and RM, with policies and laws that prioritized domestic over international research collaboration (Rezaie *et al*., 2008). Legislative obstacles and periods of government instability disrupted funding continuity. In the early 2000s, domestic university-industry collaboration was promoted, notably in public health initiatives (Cassiolatto, Soares, 2015). For example, the 2004 Innovation Law N 10,973 (Brasil, 2004) encouraged the establishment of technology incubators interacting with research institutes and the patenting of local innovations and their dissemination through technology transfer. After 2010, Brazil changed its strategy, turning to international scientific collaboration to support economic development. For example, the government of Brazil (as have those of Latin American countries generally) has encouraged collaboration with US and European Union researchers; in recent years Brazilian papers on RM have tended to have international coauthors. Stem cell research in Brazil started around 1999, using adult stem cells (ASC) (Acero, 2011) and public financing, with funding provided mainly by the Department of Science and Technology (Decit) of the Ministry of Health (MS), supplemented by the sectorial funds of the Ministry of Science and Technology (MCT); research project scholarships, fellowships, and grants of the National Research Council (CNPq); and more recently support from the National Bank for Economic Development (BNDES) (MS, 2010; MCT, 2007; Acero, 2011). Research has been expanding consistently and has resulted in some pioneering discoveries by Brazilian researchers.

A general public funding policy - instead of a selective one - and government support of a wide spectrum of scientific capabilities facilitated the initial development of the sector. Other incentives focused on building networks for the diffusion of knowledge at the national level and on the increase in the rate of scientific publication, as shall be seen later. Various public policy initiatives have substantively contributed to Brazil’s positioning in RM clinical research: (1) the foundation in 2008 of the National Network of Cellular Therapy (RNCT), for academic exchanges between members of 52 research groups geographically well distributed; (2) the establishment of 8 public Centers of Cellular Therapy (CTC), in 2008, for the expansion in culture of different types of human stem cells for clinical research; (3) the creation of the National Laboratory of Embryonic Stem Cells (LaNCE) in Rio de Janeiro and São Paulo in 2009, for the generation and distribution to research teams of embryonic stem cells lines and somatically induced pluripotent cell lines (iPS); (4) guidelines issued in 2018 and 2019 by the National Sanitary Vigilance Agency (ANVISA, 2018a, 2018b, 2019) to tackle safety concerns, efficacy in clinical trials, best manufacturing practices, and systems of approval of new CT. According to interviewees, these rules have accelerated the pace of RM innovation; and finally, (5) the approval in October 2020 of the first genetic therapy in Brazil, Luxturna, produced by the American firm Spark Therapeutics and used for children 12 months old and older and adults in the treatment of hereditary retina dystrophy (ANVISA, 2020). The ClinicalTrials.gov database of the US National Institutes of Health (NIH) lists 24 clinical studies on RM registered through June 24, 2010, involving 2,253 subjects. Only 4 of those trials were multicentric and sponsored by the transnational pharmaceutical industry (Acero, 2011). The most important Brazilian trial of ASC began in 2004, a publicly financed randomized multicentric study of CT in cardiopathies (EMRTCC), carried out with 1200 patients in 40 institutions located in different states.

It produced promising results, most especially in relation to Chagas disease-induced heart deficiencies (Mendez-Otero, Carvalho, 2012). At the time the study was initiated, international collaboration in clinical trials in Brazil was only just beginning. A more recent search conducted of clinical trials registered on the NIH platform using the keywords "stem cells" and/or "cell therapy" for the period 01/01/2010 through 15/11/2020 found 65 new studies. These represent only 1.62% of those registered globally. The largest number (almost one-third of the total) of the Brazilian trials deal with cancer (29 cases, 44.62%) with trials involving blood diseases being the second largest (9 cases, 13.85%). Trials related to other health conditions, especially musculoskeletal and eye diseases (5 and 4 trials, respectively) are also included. A considerable number of trials (41.5%) were completed at the time of the search, but as of today more than half are still active or at the recruitment stage. These clinical RM trials are evenly distributed between those sponsored by a foreign institution, and local trials involving one or more institutions in the same state in Brazil. In spite of the existence of significant local research capabilities, Brazilian RM publications tend to receive limited recognition in the global scientific community and the sector faces some obstacles in the development of international partnerships. For example, the leaders of the British Research Councils, interviewed in 2012, stated that collaboration with foreign partners had been established as a priority in the UK new government strategy for RM (MRC, 2012). But they added that Brazil had been assigned only an intermediate priority in these exchanges, in contrast to advanced countries and those in the emerging Asian region. These leaders also mentioned that the main obstacles in cooperating with Brazil on RM were the scarcity of articles published in English, insufficient institutional agreements, and the lack of locally produced stem cell lines deposited in international banks (e.g., the United Kingdom Stem Cell Bank and the American NIH National Bank of Stem Cells). An important scientific and technological research collaboration agreement was signed in 2011 between the São Paulo State Foundation for Research Support (FAPESP) and the British Research Councils. It has lately had a very positive impact in Brazilian RM, in terms of financial support, publication, and the definition of research topics for transnational projects.

The Brazilian scientists interviewed argue that the rules governing transnational collaboration and its management are not well defined in Brazil. They also contend that the local scientific community and sectors dealing with public policy are inexperienced in international negotiations and that public legal advice on Brazilian participation in international partnerships is not available, as the following two narratives detail:

> We follow the ISSRC recommendations translated into Portuguese and published in our RNTC website. They are very complete**.** But in Brazil the regulation is unspecific and that makes things difficult. Also, because projects have a double route of approval and get held up between ANVISA and the institutional research committees on ethics. It takes a lot of time, more than two years**.** England has centralized everything into only one set of rules. Much better! (Male young adult scientist)

> We are not good at negotiating. Our place is in the lab. We are expected to carry out tasks for which we have no adequate skills or training. This is just a way to increase conflicts with our international partners. We do not have adequate coaching. So, we face obstacles and cannot advance properly and thus we are hindered in our profession. (Female young adult scientist)

Symmetrical exchanges and the equitable distribution of benefits in partnerships are not easily achieved by local scientists. A prominent Brazilian scientist reports that:

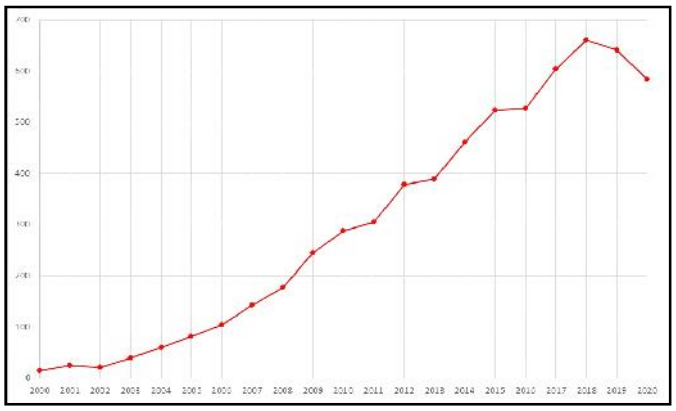
> In general, I think these exchanges are advantageous provided the rules of collaboration are very clearly set from the very beginning, before exchanges begin. . . I had a problem. We made an animal model for a genetic disease and, at the moment of publishing the article, the order of authors was altered without our permission; but also, I had not put my foot down enough. (Male adult scientist)

Visible inequities exist in foreign proposals of cooperation in multicentric clinical trials, according to local interviewees. These often reflect prejudice or a lack of confidence in the capacities of scientists in emerging countries, and sometimes take the form of disrespect and exploitation of indigenous knowledge and experience, as illustrated by the following quotation:

> Foreign researchers think that here everything will happen very easily and to their liking. Some of them come to Brazil with unseemly proposals. Industry does that a lot. One frequently encounters someone who says something like this: "I have a Phase 2 study of that drug in the USA and I will give you ten treatments for patients here". It is not like that; it is not simply a case of arriving here and profiting or making extensive use of our resources. (Male adult policy-maker)

Local researchers have developed various forms of collaboration internal to their institutions and nationally with public support, especially in basic and clinical research. International collaboration has gradually been expanding, but local scientists still feel somewhat unprepared for some of the specific tasks involved. The following sections analyze how this situation is reflected in the evolution of academic publications.

RM publications by authors based in Brazilian institutions over the last two decades: During the period 2000–20/11/2020, there was a high rate of growth in the number of RM publications with authors linked to Brazilian institutions, with the total number of indexed publications being 6,270 (Figure 1).



*Source***:** Own research based on data from the WOS.

Figure 1. Number of publications with Brazilian authors (2000-20/11/2020)

There were 684 new publications in 2019 and 584 new articles in 2020, and it should be noted that this research was carried out before 2020 had concluded. The year 2018 saw the highest number of publications, 660 articles, probably because of the expansion in public funding of RM research in previous years and the regulation of clinical practice by ANVISA, which made scientists optimistic concerning returns on their endeavors. Publication numbers present steady yearly growth, with the exception of the years 2002, 2019, and 2020. The decline over the last two years was probably due to the new government's funding cuts for scientific activities. The increase in the rate of growth beginning in 2003 can be associated with an expansion of funding for this type of research in Brazil (xxx, 2011; 2013). Since 2009, the local scientific and medical community has been gaining experience in the field, with specific discoveries at the national level having had some global impact (McMahon, 2010). Public universities are important institutional supporters of Brazilian authors of publications on RM, a finding that has been reported for other local research sectors (Israel Leon *et al*., 2018; Sidone *et al*., 2017; Hoppen, Souza Vanz, 2016).

The role of universities in Brazil is mainly defined as that of knowledge production, a model also often used in other Latin American countries (Gibbons *et al*., 2010). Among the top 10 local institutions in terms of number of publications by associated authors in the period under study, the University of São Paulo (USP) was first with 2,094 articles and the Federal University of São Paulo (UNIFESP) was second with 697 articles (Table 1). The top 8 institutions in this ranking are all public universities, with the last two being the Oswaldo Cruz Foundation, a public research center, and a training and research institute linked to the private Israelite Hospital Albert Einstein, which is directed by a charity. Most of these RM research centers are concentrated in the Southeast Region (8) and the South Region (2) of Brazil; among them, five are located in the State of São Paulo and two of them in the State of Rio de Janeiro, regions and states that have concentrated research centers in RM. There is low participation in publishing on the topic of RM by the clinical and hospital sector as well as by local firms, start-ups and spin-offs, which are responsible for a very low proportion of research endeavors in the country (Acero, 2020; Zorzanelli *et al.*, 2017).

Table1. Top 10 Brazilian institutions in terms of numbers of publications in RM (2000-20/11/2020)

Rank	Institutions	Publications*
1	Sao paulo university (usp)	2084
2	Federal university of são paulo (unifesp)	697
3	Federal university of rio de janeiro (ufrj)	696
4	State university of campinas (unicamp)	515
5	Federal university of rio grande do sul (ufrgs)	441
6	Federal university of minas gerais (ufmg)	416
7	State university of são paulo (unesp)	405
8	Federal university of parana (ufpa)	277
9	Oswaldo cruz foundation (fiocruz)	265
10	Israelite hospital albert einstein	240

Note: *It includes publications with at least one author linked to any of these institutions. Each institution is counted once per publication. *Source***:** Own research based on data from the WOS.

The publications of Prof. Hamerschlak predominate during the period under study. According to his curriculum vitae and work profile, this author is affiliated with two private institutions: the Postgraduate Program of the Israelite Institute of Training and Research, where he is a professor of molecular medicine, and the Israelite Hospital Albert Einstein, where he is dedicated to clinical research and treatment in hematology and hemotherapy. The second-highest number of publications is by Dr. Dimas Covas, at present technical director of the public São Paulo Butantan Institute and also working mainly on blood-related transplants and diseases, e.g., sickle cell anemia.

Publications coauthored by Brazilian researchers' foreign counterparts: Publications by authors affiliated with Brazilian institutions, mainly universities, are substantially higher during the period of study than those coauthored with foreign researchers, with the exception of 2020, which saw international collaboration in publications (n=296) slightly exceed the production of solely local authors (n=288). Brazilian researchers publishing on their own during the period under study, account for almost 61% of all publications, i.e., a total of 3,870 publications. Following the general trend of the increase of publications, 2018 saw the highest number of coauthored articles (n=381), again reflecting the higher research funding in previous years (Table 2).

Table 2. Top 10 countries of residence of scientists coauthoring publications with Brazilians (2000–20/11/2020)

Rank	Country*	Publications	(%)**
1	USA	1354	21,60
2	England	344	5,49
3	Germany	320	5,10
4	Italy	304	4,85
5	France	301	4,80
6	Canada	229	3,65
7	Spain	193	3,08
8	Netherland	166	2,65
9	Japan	140	2,23
10	Australia	139	2,22

Notes: *As listed in the address of an author of a publication. Each country is counted only once per publication. **Percentages are of the total number of publications (6.270) reviewed. *Source*: Own research based on data from the WOS.

Throughout most of these years, the fraction of publications coauthored by Brazilian scientists with foreign counterparts varies between one-quarter and one-third. From 2015 on, however, international collaborations increased significantly and permanently, amounting in 2020 to somewhat more than half the total of articles published (n=296, 50.68%). In recent years, as mentioned before, government policy was inclined to promote greater cooperation of Brazilian scientists with their foreign counterparts. Authors from a hundred different countries have collaborated on publications with Brazilian authors, representing a ranking with 49 positions of collaboration – in which countries with the same number of joint publications are considered within the same position (Acero,Klein, 2013). The United States of America (USA) is the country with the largest number of collaborators. In the period under study, almost 21% (n=1,354) of the publications were coauthored by Brazilians and at least one US resident. Brazilian institutions have established a number of training and scientific research exchange agreements with American universities, research centers, and the National Science Foundation, such as the California Institute of Regenerative Medicine, Harvard Stem Cell Institute (HSCI), Center for Regenerative Medicine, and the Mayo Clinic (e.g., FAPESP/ CIRM, 2010). The USA has always been a major partner in Brazilian general scientific collaboration (Leta, Chiamovic, 2002). Among the remaining leading countries of residence of collaborators, those that are global leaders in RM, like the UK, Germany, Italy, and France predominate, with the number of coauthored articles ranging between 300 and 350. In the UK, a leader with a long tradition in the area, interview data shows that the institution with which the largest number of coauthors (n=12) is Kings College London, a pioneer in the development of embryonic stem cell lines that has research teams on multiple topics associated with RM. Canada's policy of international expansion in the area over recent decades accounts for its interest in promoting collaboration between Canadian and Brazilian researchers (e.g., McMahon, 2010). In the case of Germany, its pioneering role in the study of cardiopathies (Wilson-Kovacs *et al*., 2010), which aligns with Brazilian research priorities, may explain the substantial participation of that country's scientists in joint publication with Brazilian counterparts.

The participation of authors from the US and Europe tends to favor their hegemony within the collaboration network (González-Alcaide *et al*., 2017; Satin *et al*., 2015). Their dominant position is also a result of the interconnections between the US and European countries as well as among the latter group, there being geographical proximity and high resource mobility within the European Union. In particular, European hegemony is a product of the European Commission initiatives in its Framework Programs that fund collaborative research networks (World Bank Group, 2016). Scientists in these countries have the capacity and resources to access, contact, adopt and/or make use of authors from the South (Israel Leon *et al*., 2018). Collaboration in papers coauthored by Brazilian scientists and those based in the other BRICS countries[2] – that include Brazil, Russia, India, China, and South Africa - is incipient and responsible for a much smaller number of publications (n=202) than collaboration with researchers from advanced countries. China predominates as the country of origin of coauthors, while India and Russia are in second place, though with half the publications of China. Researchers based in South Africa account for less than a quarter of all articles jointly authored with researchers in other BRICS countries. In the rankings discussed above, South Africa occupies the 32nd position with scientists there coauthoring 21 articles with Brazilian scientists, and China an intermediary one, 14th, with scientists in that country having coauthored just 86 articles with Brazilian scientists. This can be traced to the fact that collaboration between Brazilian researchers and those in the other BRICS countries did not begin until 2007.

In the case of China, the Brazilian researchers interviewed expressed certain reservations regarding partnerships with Chinese scientists in RM due to uncertainties in that country's regulatory standards, in the words of one of the scientists interviewed:

> There (meaning in China) they do all sorts of things, they use experimental treatments in CT even with Brazilian patients who travel. And then SUS (the public health system) is obliged to pay for some of those treatments demanded through lawsuits. But there it is allowed. We follow the ISSRC recommendations translated into Portuguese and published in our RNTC website (Male young adult scientist).

Of the other BRICS countries, only India seems to have seen substantive development in the RM field that is relevant to Brazilian goals (Salter, 2008). It might be desirable for Brazilian researchers to cooperate further with those based in South Africa, especially in bone marrow and umbilical cord transplants, areas well established in both countries (Chima, Mamdoo, 2011; Ballo *et al.*, 2013). It seems the BRICS countries need to better articulate efforts to strengthen quality scientific exchanges between emerging countries in RM. Cooperation between BRICS countries has been publicly promoted as a strategic international platform by Brazil in other biomedical areas in past years (Hurrel *et al*., 2009).

Researchers in Brazil collaborated on publications somewhat more often with researchers based in other Latin American countries (n=272) than with researchers based in the BRICS countries (n=202) during the period under study, with a noticeable rise since 2011. Brazilian scientists have coauthored articles with researchers from 23 different countries across Latin America, notably Argentina (n=69, 17$^{th.}$ in the ranking), Chile (44), Mexico (31), Colombia (30), and Uruguay (30). In 2009, the Ministry of Health (MS), through the scientific network RNCT, was able to ratify an agreement between Argentina and Brazil called the Binational Program of Cellular Therapy (PROBIOTEC). Its purpose was to intensify scientific cooperation and support research activities, technological development, and training of qualified personnel in RM for a period of five years; the program could be renewed indefinitely, pending evaluation. The program, which has facilitated the exchange and joint projects of many postgraduate students and researchers on numerous topics on basic and clinical RM, is ongoing. It is interesting to observe that researchers in three very small Caribbean countries - the Bahamas, Aruba, and Saint Kitts and Nevis - are collaborating with Brazilian researchers on publications, the number is small and they are ranked in the last or 49$^{th.}$ position. These collaborations have pursued topics like pediatric cancer, bone marrow transplants, neurological conditions, and research with bovines.

Expansion of this type of South-South RM collaboration seems especially relevant, considering that the biotechnology-related sector and the life sciences in general have been locally defined and promoted as one of Brazil's strategic priorities (Velho, 2011). Such an intensification and diversification of partnerships could help consolidate Brazil's leading role in RM in Latin America. This could also help focus research on diseases of shared interest, given the emerging non-communicable disease burden among Latin American populations, examples of which are obesity, hypertension, diabetes, and breast and cervical cancer, as well as communicable diseases such as HPV and HIV and neglected diseases (Webber *et al*., 2012). The pattern of international collaboration by Brazilian scientists has changed from that reported by Glanzel *et al*. (2006) for the first decade under study. During that period, across scientific activities the level of collaboration between researchers based in Brazil and those based in the USA and in the European Union was roughly comparable to that between Brazilian researchers and those in countries in the Latin American region (Acero, Klein, 2013). However, in the next decade and especially since 2015, Brazilian scientists intensified their international collaboration with the leading research actors in RM and there was comparatively less collaboration with scientists in neighboring countries. Except in the case of Argentina, as already mentioned, this modest engagement can be attributed to the lack of stable, well-resourced programs for scientific cooperation within Latin America as well as the focus on the US that Brazil and Brazilian researchers seek to strengthen.

Publications of Impact: The International Committee of Medical Journal Editors (ICMJE, 2016) sets criteria to establish when a single author or multiple authors should be assigned credit for research papers published in medical journals. Authorship rules in the health sciences consider the main contributors: the first author and corresponding author, and by extension their countries and institutions of affiliation. It is assumed that they have contributed the most to the work, and authors listed subsequently have successively less weight (Avula, Avula, 2015; Gonzalez-Alcaide *et al*., 2017). With papers produced through transnational collaboration, the order of signatures can provide information about leadership and influence in research and potentially reveal asymmetries between North and South authors participating in joint activities (Kim, 2006). In spite of this, the 2019 update of the ICMJE Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals does not clarify how to establish the order of authors (ICMJE, 2019). It thus eliminates previous guidelines that required the corresponding author to explain the order, leaving this task mainly to the editors of the specific journals. This constitutes a potential source of conflict, especially for junior coauthors and those from emerging countries who often have less power within the author network. It can also contribute to the invisibility of authors in emerging country. Moreover, this practice can establish a 'closed up' and 'self-feeding loop' of exclusion, which, it has been argued, is reinforced by the tendency of Brazilian authors to cite prominent international authors more than their fellow local colleagues (Meneghini, 2008), for example. The search of the WOS platform showed that of the 6,270 articles with Brazilian authors for the period studied, the one most cited internationally is a 2006 article, "Mesenchymal stem cells reside in virtual all postnatal organs and tissues", which presents research findings on how to generate these cells. The article's first author and the corresponding author are both affiliated with the Federal University of Rio Grande do Sul (UFRGS). The article was authored by Brazilian researchers exclusively and had been cited 1,350 times. Another article, published in 2016, authored solely by researchers linked to Brazilian institutions was ranked 9th, having been cited 537 times during the period of study. It deals with the Zika virus and presents work by researchers with the private D'Or Institute for Research and Education, located in Rio de Janeiro, who collaborated with academics with the Federal University of Rio de Janeiro (UFRJ) (Table 3).

Table 3. Ten most cited publications with Brazilian coauthors (2000–20/11/2020)*

Rank	Year of Publication	Country of coauthors	Citations
1	2006	-	1.350
2	2003	USA;	936
3	2007	Australia; Austria; Canada; Germany; USA	851
4	2009	USA;	797
5	2015	Austria; Canada; Germany, Japan; Spain; USA	699
6	2008	USA	688
7	2009	Canada; Germany; Norway; USA	627
8	2010	France; Japan, Netherlands; Norway	614
9	2016	-	537
10	2007	USA	504

*Source***:** Own research based on data from the WOS.

Among the rest, five articles had first or corresponding American coauthor(s) and were often prominent, occupying the 2nd (936 citations), 4th, 5th, 7th and 10th positions in the ranking; though two of these publications presented also contributions from other advanced countries authors. Those publications in 2nd, 4th, 6th and 10$^{th.}$ ranking position were coauthored only by American researchers with Brazilians. Only the article in the 8$^{th.}$ position is written just by authors from other advanced countries together with Brazilians. In general, the most cited articles had been available for longer periods of time. However, there are 2 exceptions, a 2015 publication cited 537 times and the 2016 publication, previously commented, cited 699 times. In agreement with wider trends found in publications of

authors from emerging countries, the most cited articles overall were those authored in partnership with colleagues from America, Europe, and other leaders in RM such as Canada and Australia. While there was some variation, either the first or the corresponding author tended to be based in advanced countries. The predominant topics of the articles most often cited were bone marrow blood transplants, different blood-related therapies (both with hematopoietic and mesenchymal cells), and the effects of transplants on patient immunity. Those therapies are the most thoroughly tested and widely implemented globally, figure as central in the international RM literature, and are ones in which Brazilian medicine has a long track record of expertise, going back to the end of the 1970s. The diseases the cited articles describe include cardiopathies, diabetes type 1, eye conditions and different type of carcinomas, in relation to which the Brazilian research community has made significant pioneering developments (Acero, 2011). Between 2018 and 2020, publications began to report topics of a clinical nature, related to trials and therapies.

CONCLUSIONS

This study considered trends in RM publications by Brazilian coauthors just as one of the many indicators of the country's advancement in terms of scientific activities and capacities. Furthermore, the relevance and high productivity of Brazilian research teams in RM are demonstrated by a range of achievements, such as their multiple scientific and therapeutic discoveries, the participation of researchers in national and international research networks, the expansion of local research institutions and scientific cooperation, and the upgrading of regulation of the sector. This article has also reported on some aspects of the unequal reproduction of the global structure of science that influence publication practices and policies. These tend to reduce the visibility of research by authors based in emerging economies and contribute to biases in scientific publication. At the same time, the analysis noted an increase over the second half of the period of study in the quantity of articles with Brazilian authors only and of those coauthored with foreign researchers published in internationally indexed scientific journals of relevance. Moreover, two of the articles with the highest international impact were authored by Brazilian researchers exclusively, one of which was the most cited article over the last two decades. This reveals not only the quality of the work of Brazilian RM researchers, but also the importance of publishing research results on cutting- edge topics.

Another finding of this study is that some of the most often cited publications were the result of transnational partnerships, particularly with researchers in advanced countries, i.e., American and European colleagues, reflecting the importance of Brazilian policies promoting such collaboration. In addition, South/South cooperation on publications, involving researchers based in the BRICS countries, needs to be fostered more; there has been a positive evolution over the second half of the period under study in relation to coauthorship with researchers in other Latin American countries. However, the international visibility and reputation of Brazilian research production in RM is still limited. This is due partly to present asymmetries in collaborative relationships between researchers in advanced and emerging countries and partly to the lack of proper implementation of local incentives for the negotiation of adequate terms in exchanges, even though local norms and regulations have been lately updated to best guide and monitor the sector.

Notes

[1] ASC are mainly found in the bone marrow and the umbilical cord and placenta blood and are capable of differentiating only into the types of cells of the organs in which they originate. ESC are derived from embryo cells until the fifth day of embryo development. iPS are somatic cells transformed into pluripotent cells, capable of differentiating into any kind of tissue.

[2] Defined as emerging countries whose economic and social development mainly relies upon science, technology and innovation and whose growth promotion strategies prioritize a substantial investment in R&D.

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