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MAGNETIC HYPERTHERMIA AS A CANCER TREATMENT IN BRAZIL: TWO DECADES OF SCIENTIFIC ADVANCES

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Abstract: In Brazil, studies in magnetic hyperthermia, i.e. a treatment of cancer based on heating cancer cells, started in the late 90s, mainly centered in the Southeast and Central West of Brazil, where consolidated institutions are found, i.e., institutions that have done research in the field since the 90s and 2000s. However, rising institutions, i.e., institutions that have recently contributed to the field, are found in all Brazil's regions. Usually, consolidated and rising institutions collaborate between them and with international institutions overseas, leading to a significant role of Brazil in the international scenario, mainly in Latin America. Furthermore, researchers in Brazil have contributed with theoretical and experimental studies from which most are interdisciplinary. Finally,

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despite advances in magnetic hyperthermia in Brazil, there is a lack of clinical trials to make this treatment available in clinical practice.

Keywords: Magnetic Hyperthermia, Cancer, History of Science

HIPERTERMIA MAGNÉTICA COMO TRATAMENTO DE CÂNCER NO BRASIL: DUAS DÉCADAS DE AVANÇOS CIENTÍFICOS

Resumo: No Brasil, os estudos em hipertermia magnética, i.e. tratamento de câncer baseado no aquecimento de células tumorais, começaram no final da década de 90, principalmente centrados nas regiões Sudeste e Centro-Oeste, onde encontram-se instituições consolidadas, ou seja, instituições que realizam pesquisas na área desde as décadas de 90 e 2000. No entanto, instituições em ascensão, ou seja, instituições que contribuem recentemente para esta área, estão presentes em todas as regiões do Brasil. Frequentemente, instituições consolidadas e em ascensão colaboram entre si e com instituições no exterior, destacando o Brasil no cenário internacional, principalmente na América Latina. Além disso, pesquisadores no Brasil têm contribuído com estudos teóricos e experimentais, sendo a maioria interdisciplinar. Apesar dos avanços da hipertermia magnética no Brasil, faltam ensaios clínicos para disponibilizar esse tratamento na prática clínica.

Palavras-chave: Hipertermia magnética, Tratamento de Câncer, História da Ciência

HIPERTERMIA MAGNÉTICA COMO TRATAMIENTO DEL CÁNCER EN BRASIL: DOS DÉCADAS DE AVANCES CIENTÍFICOS

Resumen: En Brasil, los estudios en hipertermia magnética comenzaron a fines de la década de 1990, centrados principalmente en el Sudeste y Medio Oeste de Brasil, donde se encuentran instituciones consolidadas, es decir, instituciones que han realizado investigaciones en el campo desde las décadas de 1990 y 2000. Sin embargo, las instituciones emergentes, es decir, las instituciones que han contribuido recientemente al campo, se encuentran en las regiones de Brasil. Habitualmente, instituciones consolidadas y nacientes colaboran entre sí y con instituciones internacionales en el exterior, lo que lleva a un papel significativo de Brasil en el escenario internacional, principalmente en América Latina. Además, los investigadores en Brasil han contribuido con estudios teóricos y experimentales, de los cuales la mayoría son interdisciplinarios. Finalmente, a pesar de los avances en hipertermia magnética en Brasil, faltan ensayos clínicos para que este tratamiento esté disponible en la práctica clínica.

Palabras clave: Hipertermia Magnética, Cáncer, Historia de la Ciencia.

L'HYPERTHERMIE MAGNÉTIQUE COMME TRAITEMENT DU CANCER AU BRÉSIL: DEUX DÉCENNIES D'AVANCÉES SCIENTIFIQUES

Résumé: Au Brésil, les études sur l'hyperthermie magnétique ont commencé à la fin des années 90, principalement centrées dans le sud-est et le moyen-ouest du Brésil, où se trouvent des institutions consolidées, c'est-à-dire des institutions qui ont fait des recherches dans le domaine depuis les années 90 et 2000. Cependant, des institutions montantes, c'est-à-dire des institutions qui ont récemment contribué au domaine, se trouvent dans les régions du Brésil. Habituellement, les institutions consolidées et en croissance collaborent entre elles et avec des institutions internationales à l'étranger, ce qui confère au Brésil un rôle important sur la scène internationale, principalement en Amérique latine. De plus, des chercheurs brésiliens ont contribué à des études théoriques et expérimentales dont la plupart sont interdisciplinaires. Enfin, malgré les progrès de l'hyperthermie magnétique au Brésil, il y a un manque d'essais cliniques pour rendre ce traitement disponible en pratique clinique.

Mots-clés: Hyperthermie Magnétique, Cancer, Histoire des Sciences

INTRODUCTION

In this work, we reviewed the history of magnetic hyperthermia in Brazil, focusing on the main researchers, institutions, and scientific development from 1999 to January 2022. To do so, the authors of this review performed a search on the SCOPUS, PUBMED, and Web of Science databases, using the following combinations of words: (TITLE-ABS-KEY (magnetic AND hyperthermia) OR TITLE-ABS-KEY (hyperthermia) AND TITLE-ABS-KEY (cancer) OR TITLE-ABS-KEY (neoplasia) OR TITLE-ABS-KEY (tumor) AND AFFILCOUNTRY (brazil) OR AFFILCOUNTRY (brasil)). From this search in the three mentioned databases, we chose only those articles that were strictly related to magnetic hyperthermia in Brazil, yielding 305 works published in indexed journals.

Based on these works, we investigated the history of magnetic hyperthermia in Brazil, the main researchers and institutions, how these institutions collaborate between them and with international institutions, and the main advances in the field. By reviewing the history of magnetic hyperthermia in Brazil, we can understand how this therapy has been advancing, and what are the challenges and opportunities to be taken by new researchers in the field.

MAGNETIC HYPERTHERMIA IN BRAZIL

Hyperthermia is a word derived from two Greek words: hyper, which means rise, and therme which means heat. In this sense, hyperthermia is a type of treatment that consists of heating the whole body or a specific organ of a patient to bring a therapeutic effect (WATMOUGH; ROSS, 1986). There are reports of hyperthermia treatment since the Egyptian society (2655-2600 B.C.), but other ancient civilizations also used heat as a treatment, such as the Greeks, Chinese, Indians, and Romans (SEEGENSCHMIEDT; FESSENDEN; VERNON, 1995)

The history of magnetic hyperthermia, i.e., hyperthermia derived from magnetic particles, starts in 1957 in the USA, when Gilchrist et al. published the paper “Selective inductive heating of lymph nodes” (GILGCHRIST et al., 1957). However, the basis for the development of magnetic hyperthermia was found in the 40s, when Gilchrist and David, while studying how cancer cells spread through the lymphatic system, showed that a suspension containing submicron particles of carbon was able to pass through the lymph node (GILCHRIST; DAVID, 1940). They concluded that tumors in the lymph nodes do not block fluid transport until being at advanced stages.

Understanding the reasons why magnetic hyperthermia can cause a controlled rise in the temperature involves understanding the physics behind this treatment. In brief, if ferromagnetic submicron particles are exposed to an external alternating magnetic field, the spins will be continuously changing their direction due to their alignment with the magnetic field. However, due to magnetic domains, magnetic losses happen due to the domain wall effect. These magnetic losses occur through energy dissipation as heat. The magnetic losses are proportional to the hysteresis area of an MxH curve of the magnetic particle. However, if the particle is nanosized, the whole particle behaves like a single magnetic domain, and magnetic losses due to the domain wall effect can be neglected. In this case, magnetic losses happen via Néel or Brownian relaxation. Néel relaxation is related to an energy loss caused by the spin relaxation time, while Brownian relaxation is associated with energy loss caused by the friction between the nanoparticle and the fluid due to the nanoparticle movement during their spin alignment with the magnetic field. In other words, Neel relaxation is a magnetic phenomenon, while Brownian relaxation is mechanical (GAS, 2011). For detailed information about the physics applied in magnetic hyperthermia, we suggest reading the reference (GAS, 2011).

In this sense, if submicron or nanoparticles can convert magnetic energy into heat, they can be used to heat tumors until cancer cells' death, which is the basis of magnetic hyperthermia based on nanoparticles. In 1977, D.W. Dewey et al. performed in vitro studies with mammalian cell culture, exposing healthy and cancer cells to 40 °C for 30 min. They observed a significant cancer cell death while still preserving healthy cells alive. Moreover, if the temperature was higher than 42.5 °C, cancer cell death was even more pronounced (DEWEY et al., 1997). Thereby, this study was the first one to advert the need for precise control of temperature during hyperthermia treatments (GAS, 2011). With the advance in reliable results from hyperthermia treatments, there was the establishment of scientific associations and events for hyperthermia studies. The first conference on hyperthermia studies, the International Symposium on Cancer Treatment by Hyperthermia and Radiation, was held in Washington, D.C., in 1975. A few years later, prominent societies were established, such as the North American Hyperthermia Society, the European Society for Hyperthermic Oncology, and the Japanese Society of Hyperthermia Oncology.

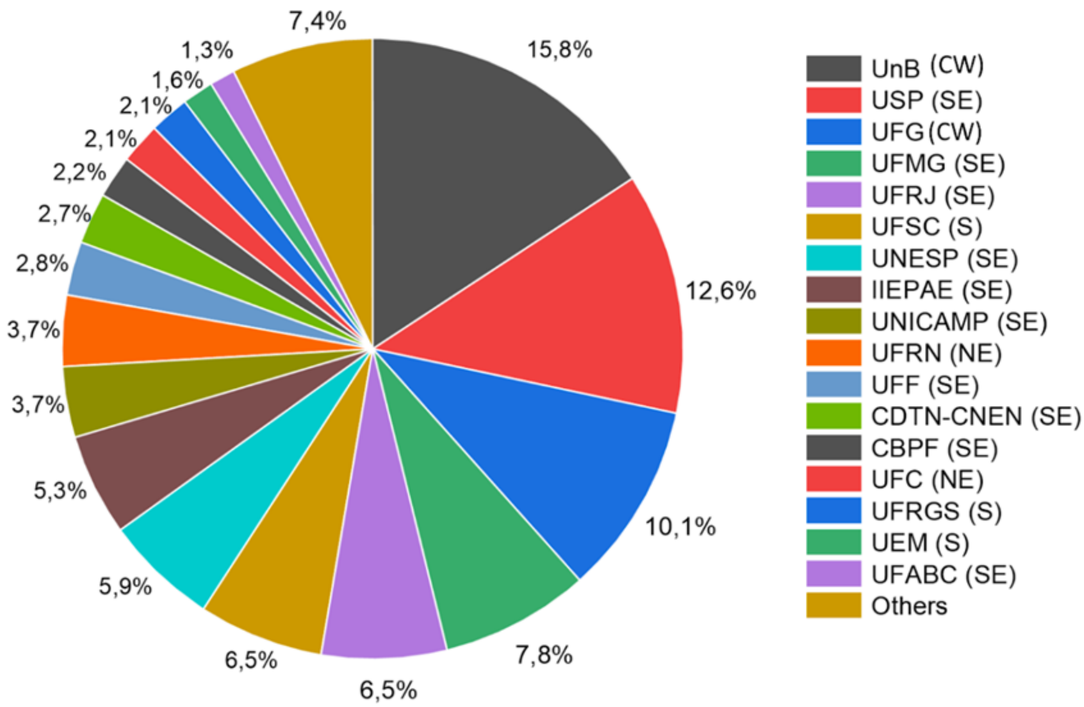
The Brazilian history of hyperthermia as a therapeutic approach had an unusual beginning – note that we are referring to hyperthermia and not to magnetic hyperthermia, specifically. According to our methodology approach, the first article related to hyperthermia in Brazil dates back to 1992, by Dr. Salatiel Menezes dos Santos and Dr. Pedro Celso Nogueira Teixeira (Ph.D. student of Dr. Salatiel at that time), both from the Institute of Biophysics "Carlos Chagas Filho" at the Federal University of Rio de Janeiro. They applied the combination of hyperthermia and photodynamic therapy in in vitro studies using cell culture of E. coli bacteria. Although the authors did not use cancer cells to evaluate the effectiveness of hyperthermia and photodynamic therapy, they established that the synergetic results of both therapies could be similar in cancer cells (MENEZES; TEIXEIRA, 1992).

Five years later, in 1997, Dr. Ruy G. Bevilacqua and Dr. Renato S. Oliveira Filho from the Hospital A.C. Camargo, in collaboration with Dr. Roger Chammas from the Ludwig Cancer Research, performed the first studies of in vitro hyperthermia in cancer cells (B16-F10 murine melanoma cells) (OLIVEIRA-FILHO; BEVILACQUA; CHAMMAS, 1997). Interestingly, none of the aforementioned Brazilian researchers remained in the field of hyperthermia as a cancer treatment for a long period and did not bring further contributions to this area of knowledge. Also, all these studies performed hyperthermia in cells using an incubator and did not perform hyperthermia through electronic devices, such as magnetic or dielectric hyperthermia.

We understand that magnetic hyperthermia has been continuously researched in Brazil since 1999, when a team of researchers from the University of Brasilia (UnB), led by Dr. Zulmira G.M. Lacava and Dr. Paulo Cesar de Morais, began the studies of synthesis and cytotoxicity of magnetic fluid and magnetic nanoparticles (LACAVA et al., 1999a, 1999b). However, the consolidation of magnetic hyperthermia as cancer treatment therapy was only possible when this team developed the first device for magnetic hyperthermia (GUEDES et al., 2004b). After that, researchers from the UnB and the Federal University of Goias (UFG) published several papers on magnetic hyperthermia, some in collaboration with the University of São Paulo (USP), establishing the embryo of a network of magnetic hyperthermia in Brazil (GUEDES et al., 2004b; OLIVEIRA et al., 2005a; MACAROFF et al., 2006a; PRIMO et al., 2007d, 2007a; SIMIONI et al., 2007; PRIMO et al., 2008d; ESTEVANATO et al., 2012a; MIRANDA-VILELA et al., 2013a, 2014a; PINHEIRO et al., 2020). Besides, the biological evaluation of magnetic nanoparticles, also performed by Dr. Lacava and Dr. Morais, is also related to the beginning of nanotoxicology and nanobiotechnology in Brazil.

Table 1 shows the 10 most productive researchers in magnetic hyperthermia according to our methodology. Note that most of them are from pioneer institutions like UFG, UnB, and USP. Besides, all the listed researchers have already collaborated with at least one researcher of the same Table, evidencing the prominence of the Southeast and Central West in studies of magnetic hyperthermia. Indeed, Figure 1 shows the percentage of researchers from different Brazilian institutions of teaching and research. More than 50% of the researchers in the field of magnetic hyperthermia belong to the UnB (15.8%), USP (12.6%), UFG (10.1%), the Federal University of Minas Gerais, (UFMG, 7.8%), and the Federal University of Rio de Janeiro (UFRJ, 6.5 %). These five Universities, together with the Federal University of Santa Catarina (UFSC), the State University of Sao Paulo (UNESP), the Israeli Institute of Teaching and Research “Albert Einstein” (IIPEA), the State University of Campinas (Unicamp) and the Federal University of Rio Grande do Norte (UFRN) were considered as consolidated institutions in research on magnetic hyperthermia due to their significant contributions in the field since the 2000s, productivity, and their role as hubs for national collaboration.

Figure 1 – Percentage of researchers affiliated with Brazilian institutions (abbreviated expressed) with published articles in the field of magnetic hyperthermia. Please consult the text for the full name of the acronyms. The institutions belong to different regions of Brazil: Central West (CW), North (N), Northeast (NE), South (S), and Southeast (SE)



Source: Original results from this research

In contrast, other institutions like the Fluminense Federal University (UFF), the Center of Energy and Nuclear Technology (CDTN/CNEN), the Brazilian Center of Research on Physics (CBPF), the Federal University of Ceará (UFC), the Federal University of Rio Grande do Sul (UFRGS), the State University of Maringá (UEM), the Federal University of ABC (UFABC), among others, are considered as rising institutions. These institutions have recently contributed to this field, gaining significant prominence, but they are not as consolidated as the other institutions that have been contributing to the field since the 2000s.

Although the researchers belong to institutions from different regions of Brazil, Southeastern and Central Western institutions are overrepresented, evidencing a heterogeneous geographical distribution of researchers in the Brazilian territory. According to Table 2, taken together, the Southeast and the Central West regions account for more than 80% of researchers in magnetic hyperthermia. Considering that consolidated institutions are concentrated in these two regions of Brazil, it is reasonable that most of the researchers are from these areas.

Table 1 – The top 10 most productive Brazilian researchers in the field of magnetic hyperthermia applied in cancer treatment. Their respective institution is indicated in brackets.

Brazilian Researchers	*Number of published articles*	*References*
Andris Figueiroa Bakuzis (UFG)	34	(FACHINI; BAKUZIS, 2010; LANDI; BAKUZIS, 2012a; OLIVEIRA et al., 2012; VERDE et al., 2012b, 2012a; BAKUZIS et al., 2013; BRANQUINHO et al., 2013a; RODRIGUES et al., 2013a; CARRIAO; NETO; BAKUZIS, 2014; NUNES et al., 2014; QUINI et al., 2015; CARRIÃO; BAKUZIS, 2016; SALVADOR et al., 2016; CARRIAO et al., 2017; LADINO et al., 2017; LANDI et al., 2017; QUINI et al., 2017; RODRIGUES et al., 2017; SILVA et al., 2017; SOETAERT et al., 2017a; OLIVEIRA et al., 2018; RIBEIRO et al., 2018; AQUINO et al., 2019; NUNES et al., 2019; PRABHAKARAN et al., 2019; AQUINO et al., 2020; BAKUZIS, 2020; CAPISTRANO et al., 2020; RODRIGUES; CAPISTRANO; BAKUZIS, 2020; SOUSA-JUNIOR et al., 2020; THANDAPANI et al., 2020; JIVAGO et al., 2021; NIRAULA et al., 2021b, 2021a; VINÍCIUS-ARAÚJO et al., 2021a)
Paulo Cesar de Morais (UnB / UCB)	31	(GUEDES et al., 2005a; MACAROFF et al., 2005a; OLIVEIRA et al., 2005a; BARBOSA et al., 2006; MACAROFF et al., 2006b; OLIVEIRA et al., 2006a; PRIMO et al., 2007b, 2007d; SIMIONI et al., 2007; PRIMO et al., 2008a; RODRIGUES et al., 2009a; PRIMO et al., 2010a; FALQUEIRO et al., 2011a; SIMIONI et al., 2011; BOLFARINI et al., 2012a; DE PAULA et al., 2012a; ESTEVANATO et al., 2012b; FALQUEIRO et al., 2012; VACCARI et al., 2012; DU et al., 2014; RUIZ et al., 2014; ZHONG et al., 2014b; DE PAULA et al., 2015a; PI et al., 2015; DE PAULA et al., 2017a; SILVA et al., 2017; PELLOSI et al., 2018a; MOSINIEWICZ-SZABLEWSKA et al., 2020; PIAZZA et al., 2020a)
Antonio Claudio Tedesco (USP)	22	(MACAROFF et al., 2005a; OLIVEIRA et al., 2005a; BARBOSA et al., 2006; MACAROFF et al., 2006b; OLIVEIRA et al., 2006a; PRIMO et al., 2007d, 2007b; SIMIONI et al., 2007; PRIMO et al., 2008d, 2008a; RODRIGUES et al., 2009a; PRIMO et al., 2010a; FALQUEIRO et al., 2011a; SIMIONI et al., 2011; DE PAULA et al., 2012a; ESTEVANATO et al., 2012b; FALQUEIRO et al., 2012; VACCARI et al., 2012; DE PAULA et al., 2015a, 2017a; PELLOSI et al., 2018a; MOSINIEWICZ-SZABLEWSKA et al., 2020)
Zulmira Guerrero Marques Lacava (UnB)	16	(GUEDES et al., 2004a, 2005a; MACAROFF et al., 2005a; OLIVEIRA et al., 2005a; BARBOSA et al., 2006; MACAROFF et al., 2006b; OLIVEIRA et al., 2006a; PRIMO et al., 2007b, 2007d; SIMIONI et al., 2007; ESTEVANATO et al., 2012b; CANDIDO et al., 2014a; MIRANDA-VILELA

		et al., 2014a, 2014b; RUIZ et al., 2014; PINHEIRO et al., 2020)
Diego Muraca (UNICAMP / UFABC)	14	(MURACA et al., 2012; DE SOUSA et al., 2013; CORAL et al., 2014; BROLLO et al., 2016; DE SOUSA et al., 2016a; MEIORIN et al., 2016; OROZCO-HENAO et al., 2016; SARVEENA et al., 2016; CORAL et al., 2018a; TANCREDI et al., 2018; MEDINA et al., 2020; OROZCO-HENAO et al., 2020; NIRAULA et al., 2021e, 2021b, 2021a)
Rodolfo César Costa Flesch (UFSC)	14	(TANG; FLESCH; JIN, 2017a, 2017b; TANG; JIN; FLESCH, 2017a; TANG et al., 2018a; TANG; FLESCH; JIN, 2018a; TANG; JIN; FLESCH, 2018a; TANG; FLESCH; JIN, 2018c, 2019a; TANG et al., 2020a; TANG; JIN; FLESCH, 2020a; TANG et al., 2021d, 2021b, 2021a, 2022)
Fernando Lucas Primo (USP / UNESP)	13	(MACAROFF et al., 2006b; PRIMO et al., 2007b, 2007d; SIMIONI et al., 2007; PRIMO et al., 2008d, 2008a, 2010a; FALQUEIRO et al., 2011a; SIMIONI et al., 2011; DE PAULA et al., 2012a; FALQUEIRO et al., 2012; DE PAULA et al., 2015a, 2017a)
Rosana Zacarias Domingues (UFMG / CDTN-CNEN)	13	(FERREIRA et al., 2011, 2016b, 2016c; FERREIRA; FABRIS; DOMINGUES, 2011; ANDRADE et al., 2013, 2015a, 2017, 2020a, 2020b; SILVA et al., 2018; RIBEIRO et al., 2020; FERRAZ et al., 2020; MACHADO et al., 2021)
Jose Domingos Ardisson (CDTN – CNEN)	11	(ANDRADE et al., 2012, 2013; CHAGAS et al., 2013; FERREIRA et al., 2016e; ANDRADE et al., 2017; CAETANO et al., 2018; CABRAL et al., 2019; LEONEL et al., 2019a; OLIVEIRA et al., 2019a; ANDRADE et al., 2020a, 2020b; LEONEL et al., 2021a)
José Domingos Fabris (UFMG / UFVJM /UFU) Clique ou toque aqui para inserir o texto.	11	(FERREIRA; FABRIS; DOMINGUES, 2011; ANDRADE et al., 2012; FERREIRA; FABRIS; DOMINGUES, 2012; CHAGAS et al., 2013; ANDRADE et al., 2015a; FERREIRA et al., 2016a, 2016e; ANDRADE et al., 2017, 2020b, 2020a; MACHADO et al., 2021)

Source: Original result from this research

Table 2 – Percentage of researchers that belongs to the regions of Brazil

Regions of Brazil	***Percentage of researchers that belong to these regions***
Southeast	55%
Central West	25,1%
South	10,9%
Northeast	8,4%
North	0,5%

Source: Original result from this research

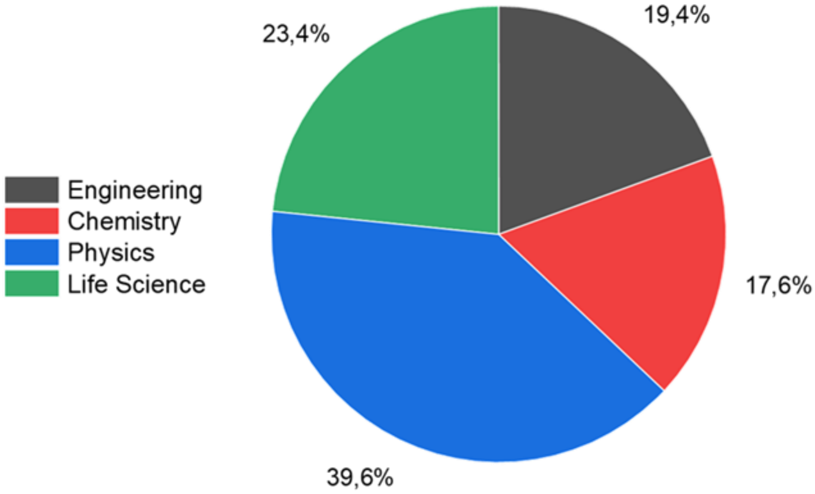
Such heterogeneities may also be related to the investments in science and technology in Brazil, which are mostly founded by public administration through the National Council for Scientific and Technological Development (CNPq), National Found of Scientific and Technological Development (FNDCT), Brazilian Innovation Agency

(FINEP), Brazilian Development Bank (BNDES) and the Research Support Foundations (FAPs). Historically, the Southeast receives the biggest share of investment from the Federal Government, while the State of São Paulo makes massive investments through the São Paulo Research Support Foundation (FAPESP). This scenario favors cutting-edge science and higher productivity in institutions in the State of Sao Paulo (DUDZIAK, 2020).

In addition, the Central West and the South are the other regions of Brazil that receive more investments than the Northeast and the North, increasing the disparities between Northern and Southern Brazil (DUDZIAK, 2020). Redistributing the investment around all the regions in Brazil is essential to guarantee economic subsidies to research groups, including the financing of human resources and support for scientific development. Consequently, these investments could be converted into technological advances in the local community, increasing the autonomy of the regions, making them less dependent on imported technologies, and more able to contribute to the national scientific development (ARRUDA; LIMA; BORIN, 2016).

Magnetic hyperthermia is an interdisciplinary science covering knowledge associated with physics, chemistry, engineering, and life sciences. For disambiguation purposes, we considered health science contemplated within life science, which includes disciplines like biology, biochemistry, medical sciences, and biomedical sciences. Based on the articles and reviews retrieved from our search from databases, we noticed theoretical, simulation, and experimental research from all of the aforementioned fields. Interestingly, there are more researchers associated with departments of physics (39.6%), while life sciences (23.4%), engineering (19.4%), and chemistry (17.6%) have a similar number of researchers (Figure 2). Besides, in many of the analyzed published articles, there were researchers from different departments in the same article, emphasizing the interdisciplinary aspect of this field.

Figure 2 – Percentage of authors belonging to the main four areas of knowledge explored in magnetic hyperthermia in Brazil.



Source: Original results from this research

NATIONAL AND INTERNATIONAL COLLABORATION

The collaboration between researchers from different groups and institutions promotes the sharing of ideas, which is essential for the development of science and technology (LI et al., 2018). Complimentarily, international collaborations intensify the diplomatic relationship between countries, besides also contributing to fastening the conversion of applied sciences into technological development (CHOI; YANG; PARK, 2015). Moreover, in the context of cancer treatment, scientific innovations are required to meet the demand for more efficient treatments (TRIMBLE et al., 2009).

Despite the recent history of magnetic hyperthermia in Brazil, its development was supported by the national collaboration between institutions from the same region (e.g. UnB and UFG, CDTN and UFMG, IIPEA and USP) or from different regions (e.g. UnB and USP, UFG and USP, UNICAMP and UFMA). Table 3 shows the national collaboration between Brazilian institutions that published at least five scientific articles until January 2022. Furthermore, Table 3 shows two interesting trends: i) due to the pioneering of consolidated institutions in the field, they have a strong collaboration between them; ii) consolidated institutions also collaborate with rising institutions, not only contributing to the spreading of magnetic hyperthermia in different institutions of Brazil but also strengthening this field. Notwithstanding, currently magnetic hyperthermia is researched in all regions of Brazil, as previously emphasized.

When the research on magnetic hyperthermia is analyzed in the light of international productivity and collaboration, it becomes evident the importance of Brazil in the international scenario. According to the platform Web of Science, when the topic “magnetic hyperthermia” is searched, a total of 7879 articles are found, and Brazil is ranked in the 11th position in productivity in this field, only behind the USA, China, India, Germany, Spain, Japan, France, Iran, Italy, and South Korea, respectively (CLARIVATE, 2022).

In addition, among the 305 articles published by Brazilian institutions on magnetic hyperthermia, 145 showed international collaboration, corresponding to approximately 47.7 % of total production. Table 4 shows a list of countries that have collaborated with Brazilian researchers until January 2022. It is noticed that Brazil has a strong collaboration with Spain, China, Argentina, and the USA, as all of them have more than 20 articles published in collaboration with a Brazilian institution. Notice that Spain, China, and the USA are among the most productive countries in the field (CLARIVATE, 2022), which shows the efforts of Brazilian researchers in collaborating with institutions with prominent importance in magnetic hyperthermia. When Brazil is analyzed under the context of Latin America, Brazil is the most productive country in the field, besides collaborating with other Latin-American countries like Argentina, Cuba, Peru, Colombia, and Mexico.

Table 3 – Pairs of Brazilian institutions that have published at least five research articles together until January 2022.

Institutions	Number of published articles	References
University of Brasilia (UnB) and University of São Paulo (USP)	25	(OLIVEIRA et al., 2005b, 2006b; MACAROFF et al., 2005b, 2006c; BARBOSA et al., 2006; PRIMO et al., 2007c, 2007e, 2008d, 2008b, 2010b; SIMIONI et al., 2007, 2011; RODRIGUES et al., 2009b; PAVON et al., 2010; FALQUEIRO et al., 2011b, 2012; BOLFARINI et al., 2012c; DE PAULA et al., 2012b; VACCARI et al., 2012; VERDE et al., 2012a, 2012b; DE PAULA et al., 2017b; ESTEVANATO et al., 2012c; PELLOSI et al., 2018b; MOSINIEWICZ-SZABLEWSKA et al., 2020)
University of Brasilia (UnB) and Federal University of Goiás (UFG)	20	(OLIVEIRA et al., 2005b, 2006b; MACAROFF et al., 2005b; BARBOSA et al., 2006; VERDE et al., 2012b, 2012a; BAKUZIS et al., 2013; MIRANDA-VILELA et al., 2014c; BRANQUINHO et al., 2013b; MIRANDA-VILELA et al., 2013b; NUNES et al., 2014; CANDIDO et al., 2014b; CARRIAO; NETO;

		BAKUZIS, 2014; SILVA et al., 2017; CARRIAO et al., 2017; AQUINO et al., 2020; NIRAULA et al., 2021b, 2021a; VINICIUS-ARAUJO et al., 2021; JIVAGO et al., 2021)
Center for the Development of Nuclear Technology (CDTN) and Federal University of Minas Gerais (UFMG)	14	(DE SOUZA; MOHALLEM; DE SOUSA, 2011; ANDRADE et al., 2013; CHAGAS et al., 2013; AZEVEDO et al., 2014; FERREIRA et al., 2016f; ANDRADE et al., 2017; CAETANO et al., 2018; FERREIRA et al., 2018; CABRAL et al., 2019; LEONEL et al., 2019b; OLIVEIRA et al., 2019b; ANDRADE et al., 2020b, 2020a; LEONEL et al., 2021b)
Federal University of Goiás (UFG) and University of São Paulo (USP)	11	(MACAROFF et al., 2005b; OLIVEIRA et al., 2005b, 2006b; BARBOSA et al., 2006; VERDE et al., 2012b; LANDI; BAKUZIS, 2012b; VERDE et al., 2012a; QUINI et al., 2015, 2017; LADINO et al., 2017; LANDI et al., 2017)
Israeli Hospital Albert Einstein (IIPAE) and University of São Paulo (USP)	9	(GAMARRA et al., 2009; PAVON et al., 2010; CARDENAS et al., 2012; REGO et al., 2019, 2020b; VERCOZA et al., 2019; MAMANI et al., 2020, 2021a; LEONEL et al., 2021b)
Federal University of Minas Gerais (UFMG) and Federal University of Vales do Jequitinhonha e Mucuri (UFVJM)	8	(ANDRADE et al., 2013, 2015b, 2017, 2020b, 2020a; CHAGAS et al., 2013; FERREIRA et al., 2016f, 2016d)
Center for the Development of Nuclear Technology (CDTN) and Federal University of Vales do Jequitinhonha and Mucuri (UFVJM)	7	(ANDRADE et al., 2012, 2013, 2017, 2020b, 2020a; CHAGAS et al., 2013; FERREIRA et al., 2016f)
Federal University of Goiás (UFG) and State University of São Paulo (UNESP)	6	(CANDIDO et al., 2014b; QUINI et al., 2015, 2017; NUNES et al., 2019; SOUSA et al., 2020; RODRIGUEZ et al., 2021)
Federal University of Ouro Preto (UFOP) and Federal University of Vales do Jequitinhonha e Mucuri (UFVJM)	6	(ANDRADE et al., 2012, 2013, 2015b, 2017, 2020b, 2020a)
University of Brasília (UnB) and State University of São Paulo (UNESP)	5	(PAVON et al., 2010; CANDIDO et al., 2014b; ORTEGA et al., 2014; DE PAULA et al., 2017b; PIAZZA et al., 2020b)
University of Brasília (UnB) and	5	(ORTEGA et al., 2014; ARAUJO et al., 2015; NETO et al., 2018, 2021b; NASCIMENTO et al., 2020)

Federal University of Rio de Janeiro (UFRJ)		
University of São Paulo (USP) and Federal University of Rio de Janeiro (UFRJ)	5	(FEUSER et al., 2015a, 2015b; SRINIVASAN et al., 2019; VERCOZA et al., 2019; MATERÓN et al., 2021)
State University of Campinas (UNICAMP) and Federal University of Maranhão (UFMA)	5	(OROZCO-HENAO et al., 2016; SARVEENA et al., 2016; NIRAULA et al., 2021e, 2021b, 2021a)
Federal University of ABC (UFABC) and Federal University of Goiás (UFG)	5	(BAKUZIS et al., 2013; BRANQUINHO et al., 2013b; SALVADOR et al., 2016; CARRIAO et al., 2017; LANDI et al., 2017)

Source: Original results from this research

Table 4 – List of countries that most collaborate with Brazilian researchers in the field of magnetic hyperthermia until January 2022

Partner Country	Published articles in collaboration with Brazilian Institutions	References
Spain	27	(SIMIONI et al., 2007; GOYA et al., 2008; SANTOS et al., 2011a; GRAZÚ et al., 2012; LIMA et al., 2013b; PISCIOTTI et al., 2014; RUIZ et al., 2014; SILVA et al., 2014; GUTIERREZ et al., 2015; CORAL et al., 2016; DA SILVA et al., 2017; DE TORO et al., 2017; LANDI et al., 2017; CORAL et al., 2018b; GOMEZ-POLO et al., 2018; JARDIM et al., 2018b; ORTGIES et al., 2018; PILATI et al., 2018; FELIX et al., 2019; SALAKHOVA et al., 2019; BERMEO VARON et al., 2020; FUENTES-GARCIA et al., 2020; THANDAPANI et al., 2020; IGLESIAS et al., 2021; NIRAULA et al., 2021b, 2021e; PILATI et al., 2021)
China	25	(ZHONG et al., 2012, 2014a, 2014b; DU et al., 2014; RUIZ et al., 2014; PI et al., 2015; DE PAULA et al., 2017b; TANG; FLESCH; JIN, 2017c, 2017d, 2018b, 2018d, 2019b; TANG; JIN; FLESCH, 2017b, 2018b, 2020b; SILVA et al., 2017; TANG et al., 2021c, 2021e, 2021a, 2022, 2018b, 2020b, 2020c; NASCIMENTO et al., 2020; DE LIMA et al., 2021)
Argentina	23	(MURACA et al., 2012; LIMA et al., 2013b, 2013a; DE SOUSA et al., 2013, 2016b; CORAL et al., 2014, 2016; PISCIOTTI et al., 2014; CORAL et al., 2018b; LAMIEN et al., 2014, 2017; MEIORIN et al., 2016; OROZCO-HENAO et al., 2016, 2020; SARVEENA et al., 2016; FEUSER et al., 2016a; LAMIEN; ORLANDE; ELICABE, 2017; LAVORATO et al., 2020; RONCO et al., 2018; TANCREDI et al., 2018; LAVORATO et al., 2018; MEDINA et al., 2020; RIVERA-CHAVERRA et al., 2020)

United States of America	21	(REGMI et al., 2009; BRANQUINHO et al., 2013b; OLIVEIRA et al., 2013c, 2013a; ATTALURI et al., 2016; ROMERO et al., 2016; QUINI et al., 2017; RADHAKRISHNAN et al., 2017; SOETAERT et al., 2017b; DE TORO et al., 2017; PACHECO et al., 2018b, 2018a; PIMENTEL et al., 2018; VARGAS et al., 2018; BAFFA et al., 2019; PEREZ et al., 2020; LAVORATO et al., 2020; ABICALIL et al., 2021; SRINIVASAN et al., 2021; DE OLIVEIRA et al., 2021; NAGESETTI et al., 2021)
France	17	(MEDEIROS et al., 2011; VACCARI et al., 2012; LIMA-TENORIO et al., 2015, 2016a, 2016b; CAETANO et al., 2016; COPPOLA et al., 2016; SARVEENA et al., 2016; MARTINS et al., 2017, 2021; DE TORO et al., 2017; PILATI et al., 2018; SALAKHOVA et al., 2019; DE SANTANA et al., 2020, 2021; KHIZAR et al., 2020; LARREUR; LAMIEN; ORLANDE, 2021)
Portugal	11	(SILVA et al., 2009; ANDRADE et al., 2012; GRILLO et al., 2016a; DE ALMEIDA et al., 2017; PIMENTEL et al., 2018; ANDRADE et al., 2020a, 2020b; DE MOURA et al., 2020a; FERREIRA et al., 2021; MACHADO et al., 2021; TEIXEIRA et al., 2021)
India	8	(FERREIRA et al., 2016d; SARVEENA et al., 2016; SRINIVASAN et al., 2019; PEREIRA et al., 2020; NIRAULA et al., 2021e, 2021b, 2021c; SRINIVASAN et al., 2021)
Germany	7	(PRIMO et al., 2007e; SILVA et al., 2014; ATTALURI et al., 2016; TANCREDI et al., 2018; PEREZ et al., 2020; RAMOS-GUIVAR; MORALES; LITTERST, 2020a; RODRIGUEZ et al., 2021)
Cuba	6	(YERO; GONZÁLEZ; RAIZER, 2013; ICART et al., 2016b, 2018; LENART et al., 2018; MORAES et al., 2018a; RODRIGUES et al., 2019)
Italia	6	(FREIRE et al., 2013; RIBEIRO et al., 2013; DE TORO et al., 2017; PIMENTEL et al., 2018; BORGES et al., 2021b; SEDIGHI et al., 2021)
Russia	6	(PAVON et al., 2010; PI et al., 2015; PIMENTEL et al., 2018; SALAKHOVA et al., 2019; GUIMARAES; CUNHA; GONTIJO, 2020; FERREIRA et al., 2021)
Chile	5	(FREIRE et al., 2013; RIBEIRO et al., 2013; PRABHAKARAN et al., 2019; THANDAPANI et al., 2020; NIRAULA et al., 2021e)
Colombia	4	(FERREIRA et al., 2012; PACHECO et al., 2018a; BERMEO VARON et al., 2020; RIVERA-CHAVERRA et al., 2020)
Mexico	4	(CHAVEZ-GUAJARDO et al., 2015; MAZON et al., 2017; JARDIM et al., 2018b; PRABHAKARAN et al., 2019)
Pakistan	4	(LIMA-TENORIO et al., 2015, 2016a; SARVEENA et al., 2016; KHIZAR et al., 2020)
Peru	4	(SANTOS et al., 2011a; FELIX et al., 2020; RAMOS-GUIVAR; MORALES; LITTERST, 2020a; NIRAULA et al., 2021a)
Poland	4	(FALQUEIRO et al., 2011b, 2012; ESTEVANATO et al., 2012c; MOSINIEWICZ-SZABLEWSKA et al., 2020)
Qatar	3	(NIRAULA et al., 2021e, 2021b, 2021a)
United Kingdom	3	(SHARMA et al., 2019; FEUSER et al., 2021; MATERÓN et al., 2021)
Canada	2	(RADHAKRISHNAN et al., 2017; DE LIMA et al., 2021)
Sweden	2	(DE TORO et al., 2017; DE MELO et al., 2018)

Czech Republic	2	(NIRAULA et al., 2021b, 2021a)

Source: Original results from this research

Table 5 – Ranking of the 15 Brazilian institutions that most published research articles in collaboration with international institutions until January 2022

Brazilian Institution	**Published articles under international collaboration**	**References**
University of Brasilia (UnB)	27	(PRIMO et al., 2007e; REGMI et al., 2009; PAVON et al., 2010; FALQUEIRO et al., 2011b; ESTEVANATO et al., 2012c; FALQUEIRO et al., 2012; ZHONG et al., 2012; BRANQUINHO et al., 2013b; DU et al., 2014; RUIZ et al., 2014; ZHONG et al., 2014b, 2014a; ATTALURI et al., 2016; COPPOLA et al., 2016; MARTINS et al., 2017; JARDIM et al., 2018b; PILATI et al., 2018; FELIX et al., 2019, 2020; MOSINIEWICZ-SZABLEWSKA et al., 2020; NASCIMENTO et al., 2020; ABICALIL et al., 2021; MARTINS et al., 2021; NIRAULA et al., 2021b, 2021e, 2021a; PILATI et al., 2021)
Federal University of Santa Catarina (UFSC)	24	(YERO; GONZÁLEZ; RAIZER, 2013; PISCIOTTI et al., 2014; FEUSER et al., 2016a; MAZON et al., 2017; TANG; FLESCH; JIN, 2017d, 2017c; TANG; JIN; FLESCH, 2017b; JARDIM et al., 2018b; TANG et al., 2018b; TANG; FLESCH; JIN, 2018b; TANG; JIN; FLESCH, 2018b; TANG; FLESCH; JIN, 2018d, 2019b; MEDINA et al., 2020; TANG et al., 2020b; TANG; JIN; FLESCH, 2020b; TANG et al., 2020c; FEUSER et al., 2021; IGLESIAS et al., 2021; PILATI et al., 2021; TANG et al., 2021c, 2021e, 2021a, 2022)
University of São Paulo (USP)	21	(PRIMO et al., 2007e; GOYA et al., 2008; PAVON et al., 2010; MEDEIROS et al., 2011; FALQUEIRO et al., 2011b, 2012; ESTEVANATO et al., 2012c; GRAZU et al., 2012; LIMA et al., 2013b; OLIVEIRA et al., 2013c, 2013a; LIMA et al., 2013a; CORAL et al., 2016; QUINI et al., 2017; LANDI et al., 2017; DE MELO et al., 2018; BAFFA et al., 2019; SRINIVASAN et al., 2019, 2021; MOSINIEWICZ-SZABLEWSKA et al., 2020; MATERÓN et al., 2021)
Federal University of Rio de Janeiro (UFRJ)	19	(FERREIRA et al., 2012; LAMIEN et al., 2014, 2017; FEUSER et al., 2016a; ICART et al., 2016b, 2018; LAMIEN; ORLANDE; ELICABE, 2017; LENART et al., 2018; PACHECO et al., 2018b, 2018a; VARGAS et al., 2018; SRINIVASAN et al., 2019; BERMEO VARON et al., 2020; NASCIMENTO et al., 2020; DE LIMA et al., 2021; MACHADO et al., 2021; MATERÓN et al., 2021; NAGESETTI et al., 2021; LARREUR; LAMIEN; ORLANDE, 2021)
State University of Campinas (UNICAMP)	19	(MURACA et al., 2012; DE SOUSA et al., 2013; CORAL et al., 2014; DE SOUSA et al., 2016b; MEIORIN et al., 2016; OROZCO-HENAO et al., 2016; SARVEENA et al., 2016; RADHAKRISHNAN et al., 2017; CORAL et al., 2018b; TANCREDI et al., 2018; PRABHAKARAN et al., 2019;

		OROZCO-HENAO et al., 2020; RIVERA-CHAVERRA et al., 2020; THANDAPANI et al., 2020; FERREIRA et al., 2021; MATERÓN et al., 2021; NIRAULA et al., 2021e, 2021b, 2021a)
Federal University of Goiás (UFG)	11	(BRANQUINHO et al., 2013b; LANDI et al., 2017; QUINI et al., 2017; SOETAERT et al., 2017b; PRABHAKARAN et al., 2019; SHARMA et al., 2019; THANDAPANI et al., 2020; PEREIRA et al., 2020; NIRAULA et al., 2021b, 2021a; RODRIGUEZ et al., 2021)
State University of São Paulo (UNESP)	10	(PAVON et al., 2010; SANTOS et al., 2011a; CAETANO et al., 2016; GRILLO et al., 2016a; QUINI et al., 2017; GOMEZ-POLO et al., 2018; BAFFA et al., 2019; DE SANTANA et al., 2020, 2021; RODRIGUEZ et al., 2021)
Brazilian Center for Research in Physics (CBPF)	9	(FERREIRA et al., 2012; LENART et al., 2018; PIMENTEL et al., 2018; LAVORATO et al., 2020; PEREZ et al., 2020; NIRAULA et al., 2021e, 2021b, 2021a, 2021c)
Fluminense Federal University (UFF)	7	(GUTIERREZ et al., 2015; DA SILVA et al., 2017; PIMENTEL et al., 2018; SALAKHOVA et al., 2019; GUIMARAES; CUNHA; GONTIJO, 2020; LAVORATO et al., 2020; FERREIRA et al., 2021)
State University of Maringá (UEM)	6	(SILVA et al., 2014; LIMA-TENORIO et al., 2015, 2016a, 2016b; LENART et al., 2018; BERMEO VARON et al., 2020)
Federal University of Minas Gerais (UFMG)	6	(RIBEIRO et al., 2013; FERREIRA et al., 2016d; PIMENTEL et al., 2018; ANDRADE et al., 2020a; FEUSER et al., 2021; MACHADO et al., 2021)
Federal University of ABC (UFABC)	5	(BRANQUINHO et al., 2013b; SARVEENA et al., 2016; LANDI et al., 2017; FUENTES-GARCIA et al., 2020; BORGES et al., 2021b)
Federal University of Ceará (UFC)	5	(SILVA et al., 2009; FREIRE et al., 2013; RIBEIRO et al., 2013; DE ALMEIDA et al., 2017; DE MOURA et al., 2020a)
Federal University of Maranhão (UFMA)	5	(OROZCO-HENAO et al., 2016; SARVEENA et al., 2016; NIRAULA et al., 2021e, 2021b, 2021a)
Federal University of Rio Grande do Norte (UFRN)	4	(LAMIEN et al., 2014; RAMOS-GUIVAR; MORALES; LITTERST, 2020a; IGLESIAS et al., 2021; RODRIGUEZ et al., 2021)

Source: Original results from this research

Regarding these mentioned Latin-American countries, more than 39 % of their productivity in the field of magnetic hyperthermia is in collaboration with Brazil

(CLARIVATE, 2022), which evidences the importance of Brazil in strengthening the knowledge in magnetic hyperthermia in Latin America.

The Brazilian institutions that collaborate the most with other countries are listed in Table 5. Either consolidated or rising institutions collaborate with other countries, evidencing that rising institutions are also inserted in the international scenario, despite their recent contributions to magnetic hyperthermia.

THE CONTRIBUTION OF MATERIALS SCIENCE

Magnetic hyperthermia is known by technologies based on iron oxide nanoparticles, such as magnetite, maghemite, and ferrites displaying superparamagnetism or ferromagnetism (SILVA et al., 2011; PÉRIGO et al., 2015). Besides, because magnetite nanoparticles tend to have their surface oxidized, forming a thin layer of maghemite, some researchers call these nanoparticles superparamagnetic iron oxide nanoparticles (SPIONs) (AGIOTIS et al., 2016; FERRAZ et al., 2020; MAMANI et al., 2021b; BORGES et al., 2022). Briefly, iron oxide-based nanoparticles are the most conventional materials in the field, but researchers have been modifying them through doping (MURACA et al., 2012; BROLLO et al., 2016), functionalization/coating (GUEDES et al., 2005b; DE SOUSA et al., 2013; REGO et al., 2019) and core-shell structure (ANDRADE et al., 2015c; LAVORATO et al., 2018; VINÍCIUS-ARAÚJO et al., 2021b) to improve magnetic, biological or colloidal properties. Table 6 shows some examples of magnetite, maghemite, ferrites, and SPIONs doped, functionalized, coated, or in core-shell structures that have been researched by Brazilian institutions.

Doping these iron oxide nanoparticles with elements like Zn, Mn, Co, and Cu is a strategy used to tune the magnetic properties of these nanoparticles (LIMA-TENORIO et al., 2016b; DE MELLO et al., 2019; KHIZAR et al., 2020). However, some elements like Ag are used to add bacterial properties to the nanoparticle (BROLLO et al., 2016). Similarly, by doping the nanoparticles with Gd, they become suitable for magnetic resonance imaging (DEKA et al., 2018). Therefore, doping is an interesting approach to adding functionalities to the nanoparticle.

Similarly, by making core-shell structures, other properties can be achieved on the shell layer. For example, the core-shell structure of CdTe shows luminescent properties, allowing the combination of magnetic hyperthermia with imaging techniques (DE MELO et al., 2018); core-shell structures based on hydroxyapatite improve the biocompatibility and osteointegration of magnetic nanoparticles, making them suitable for bone cancer treatment (FEUSER et al., 2016b); and a shell made of gold allows the combination of magnetic hyperthermia with photothermal therapy (BARROS et al., 2017).

In contrast, functionalization and coating are usually associated with improvements in colloidal properties and biocompatibility. For example, by changing the surface properties of the nanoparticles making them more hydrophobic, and more dispersed in the body fluid environment, it is possible to increase their enhanced permeability and retention (EPR) effect, which means that the nanoparticles can circulate in the human body and invade target tissues more efficiently than uncoated or non-functionalized nanoparticles (RODRIGUES et al., 2009c; MIRANDA-VILELA et al., 2014a; LEONEL et al., 2019c).

Besides the conventional iron oxide nanoparticles, other less conventional materials have also been studied, such as magnetic emulsions (PRIMO et al., 2008c; ICART et al., 2016a; PEÑA ICART et al., 2018), magnetic glass-ceramics (ASPASIO; BORGES; MARCHI, 2016; BORGES et al., 2020, 2022), magnetolipossomes (BARBOSA et al., 2006; BOLFARINI et al., 2012b; FERREIRA et al., 2016c; FEUSER et al., 2016b; SALVADOR et al., 2016), among others. These less conventional materials and their modifications are listed in Table 7. Usually, these less conventional materials and nanostructures are intended to combine magnetic hyperthermia with other therapies, becoming multifunctional materials. For example, magnetic emulsions and magnetolipossomes are good candidates to load drugs, enabling the combination of magnetic hyperthermia with chemotherapy (DOS SANTOS et al., 2020; MANSUR et al., 2020); while magnetic bioactive glass-ceramics or nanocomposites show osteoinduction and biocompatible properties, making them suitable for applications in bone cancer treatment allied with bone regeneration, which is named theraregenerative materials (BORGES et al., 2020, 2022; ZAMBANINI et al., 2021).

Table 6 – Iron oxide-based nanoparticles developed by Brazilian Institutions for use in magnetic hyperthermia

Crystalline structure of the iron oxide	Doping	Functionalization/ Coating	Core-shell structure	References
Magnetite	Ag, Hf, Pt, Zn, Mn	Oleic Acid, Carboxymetyldextran, Citric Acid,	Silica	(GUEDES et al., 2005a; CÓTICA et al., 2010; MURACA et al., 2012;

		Poly(tyofen), Polyetylenomine, Aminosilane, Sodium Oleate, Succinic Acid		DE SOUSA et al., 2013; ARAUJO-NETO et al., 2014; AZEVEDO et al., 2014; CORAL et al., 2014; RODRIGUES et al., 2016; BROLLO et al., 2016; GRILLO et al., 2016b; ANDRADE et al., 2017; MORAES et al., 2018b; RIBEIRO et al., 2018; HADADIAN; RAMOS; PAVAN, 2019; REGO et al., 2019; DE MELLO et al., 2019; FELIX et al., 2020; HADADIAN et al., 2021; SALES et al., 2021)
Maghemite		Albumin, phosphate groups,	Calcium Phosphate, Cadmium Tellurate, Polyphosphate, silica	(MACAROFF et al., 2006b; SIMIONI et al., 2007; CANDIDO et al., 2014a; DE TORO et al., 2017; QUINI et al., 2017; DE MELO et al., 2018; RAMOS-GUIVAR; MORALES; LITTERST, 2020b)
Ferrite	Zn, Mn, Co, Gd, Li, Ni, Al, Mo, Cu	Aminodextran, Citrate, Albumin, Citric Acid		(BARBOSA et al., 2006; VERDE et al., 2012a, 2012b; LIMA-TENORIO et al., 2016b; LAVORATO et al., 2018; NUNES et al., 2019; ERHARDT et al., 2020; KHIZAR et al., 2020; DA SILVA et al., 2021; MARTINS et al., 2021)(PRIMO et al., 2010a; RODRIGUES et al., 2013b, 2017; LIMA et al., 2013a; FONTANIVE et al., 2014; NUNES et al., 2014; QUINI et al., 2015; CARRIAO et al., 2017; MARTINS et al., 2017; PILATI et al., 2018; GOMEZ-POLO et al., 2018; JARDIM et al., 2018a; AQUINO et al., 2019, 2020; PAULA, 2019; PEREIRA et al., 2020; SOUSA-JUNIOR et al., 2020; THANDAPANI et al., 2020; TEIXEIRA et al.,

				2021; JIVAGO et al., 2021)(NOGUEIRA et al., 2015; COPPOLA et al., 2016; HANGAI et al., 2017; VINÍCIUS-ARAÚJO et al., 2021a)
SPIONs		Calcium alginate, Carboxymetylcelulose, Aminosilane, Chitosan, Oleic Acid	Au, Hydroxyapatite, Silica	(DONADEL et al., 2008; FEUSER et al., 2015a; SARVEENA et al., 2016; LEONEL et al., 2019a; REGO et al., 2020c)(FINOTELLI et al., 2008; ANDRADE et al., 2013; NETO et al., 2018)

Source: Original results from this research

Table 7 – Non-conventional materials used in magnetic hyperthermia researched by Brazilian authors

Materials	References
Lipidic nanoparticle	(OLIVEIRA et al., 2018)
$La_{0,75}Sr_{0,25}MnO_3$	(PIMENTEL et al., 2018; SALAKHOVA et al., 2019)
Fe-Cr-Nb-B	(TANG; FLESCH; JIN, 2017b)
$Ni_{1-x}Cu_x$	(ARAUJO-BARBOSA; MORALES, 2019)
$Y_3Fe_{3.35}Al_{1.65}O_{12}$	(BORSARI et al., 2018)
δ-FeOOH	(CHAGAS et al., 2013)
La-Sr Manganites	(FERREIRA et al., 2021)
NdFeB-based alloy	(PÉRIGO et al., 2012)
Magnetolipossomes	(RIBEIRO et al., 2020) (CRUZ DOS SANTOS et al., 2019) (FERREIRA et al., 2011)
Supramolecular magnetonanohybrids	(MANSUR et al., 2020)
Magnetic Hybrid Wax Nanocomposites	(DE MOURA et al., 2020b)
Mesoporous silica-magnetite nanocomposite	(SOUZA; MOHALLEM; SOUSA, 2010)
Nanocomposites based on rare-earth orthoferrites and iron oxides	(OLIVEIRA et al., 2019a)
Ferrite/Graphene Functional Nanocomposites	(PRABHAKARAN et al., 2019)
Magnetic Nanoemulsions	(PRIMO et al., 2008d)
Magnetic Nanoflowers	(NIRAULA et al., 2021d)
Thermosensitive nanosystems	(PEREIRA GOMES et al., 2019)
Nanocomposite based on bioactive glass and SPIONs	(BORGES et al., 2021a)
Magnetic glass-ceramic	(BORGES et al., 2021c) (MARTINELLI et al., 2010)

Source: Original results from this research

THEORETICAL, EXPERIMENTAL AND CLINICAL RESEARCH IN BRAZIL

The development of magnetic hyperthermia in Brazil covers experimental, theoretical, and simulation research. Among the 305 articles retrieved from the databases, 98 (~ 32%) were theoretical or simulation studies, while 207 (~ 68%) were experimental research (including physics, chemistry, engineering, and life science). Usually, the theoretical studies are related to studies of magnetic interaction between nanoparticles, the development of improved hyperthermia devices, and dynamic simulation to study the interaction between magnetic nanoparticles and other molecules.

Regarding the experimental research, besides the development of new materials, biological studies focusing on in vitro and in vivo studies have been carried out, mainly focusing on the use of magnetic hyperthermia in the treatment of bladder (OLIVEIRA et al., 2013b, 2013d; FEUSER et al., 2016b), breast (MIRANDA-VILELA et al., 2014a; MANSUR et al., 2020; RIBEIRO et al., 2020; DOS SANTOS et al., 2021), cervical (MATTOS DOS SANTOS et al., 2018; DOS SANTOS et al., 2020), lung (DE SOUSA et al., 2016c; QUADROS; MOMIN; VERMA, 2021), intestine (PEÑA ICART et al., 2018), liver (MARTINELLI et al., 2010; MIRANDA-VILELA et al., 2014a), skin (BLANCO-ANDUJAR et al., 2016; FEUSER et al., 2016b; CORAL et al., 2018a; NETO et al., 2021a), and bone cancers (VELASCO et al., 2019; BORGES et al., 2020, 2022), besides myeloid leukemia (FEUSER et al., 2016c), adenocarcinoma (DE SOUSA et al., 2016c) and glioblastoma (SILVA et al., 2011; CARVALHO et al., 2019; REGO et al., 2020a; MAMANI et al., 2021c). Other applications of magnetic hyperthermia include their combination with drug delivery (SANTOS et al., 2011b; PEÑA ICART et al., 2018; DE OLIVEIRA GONCALVES et al., 2019; MANSUR et al., 2020; OLIVEIRA et al., 2021), bactericidal properties (DE TOLEDO; ROSSETO; BRUSCHI, 2018; BRUSCHI; DE TOLEDO, 2019), photodynamic therapy (MACAROFF et al., 2005a; PRIMO et al., 2007a; RODRIGUES et al., 2009c; DE PAULA et al., 2015b, 2017c; DE OLIVEIRA GONCALVES et al., 2019; DO NASCIMENTO et al., 2020; QUADROS; MOMIN; VERMA, 2021), and medical imaging (ANDRADE et al., 2015c; TATSUI et al., 2017; MANSUR et al., 2020).

Unfortunately, Brazil still does not have clinical studies in magnetic hyperthermia performed in our territory. We address the lack of a scientific association related to hyperthermia in cancer treatment, such as the North American Hyperthermia Society, the European Society for Hyperthermic Oncology, and the Japanese Society of Hyperthermia Oncology, which might be one strategy of collaborative efforts to capitalize on resources to enable clinical trials. Another issue might be the lack of continuous investments in S&T by the Federal Government, which hinders the development of new technologies (DUDZIAK, 2020). Clinical trials are important not only for technological development but also to train physicians and health workers and to adapt hospital facilities to perform new technologies in clinical practice (ZAGO, 2004). Therefore, only by introducing clinical trials in Brazil, magnetic hyperthermia might become an alternative therapy available either in the private healthcare system or the Brazilian universal healthcare system, the SUS.

Meanwhile, according to a research article recently published by HEALY et al. in collaboration with the Dr. Andris F. Bakuzis (HEALY et al., 2022), one of the main researchers and the most productive author in magnetic hyperthermia in Brazil, magnetic hyperthermia still has some limitations to be overcome: i) limited information on magnetic nanoparticle distribution in tissue; ii) limited spatial control of magnetic hyperthermia; iii) and limited or invasive thermometry to guarantee that the tissue is heated until 43 °C, minimally affecting healthy cells. According to Dr. Bakuzis and colleagues (HEALY et al., 2022), the use of precise thermometry and imaging guarantees spatial resolution and temperature control, thereby a safer hyperthermia procedure. In other words, the future of magnetic hyperthermia might still be limited to the development of multifunctional nanoparticles able to simultaneously perform hyperthermia, thermometry, and imaging.

CONCLUSION

Although magnetic hyperthermia was internationally established as a cancer treatment between the 50 and 60s, it only became popular between the 80 and 90s with the establishment of international societies, such as the European, North America and Japanese. Still, in the 90s, the first studies on magnetic hyperthermia were initially performed in Brazil, evidencing the involvement of Brazil during the popularization of magnetic hyperthermia.

Among the regions that have great eminence in magnetic hyperthermia in Brazil, the Central West and the Southeast are the most productive regions, mainly due to the productivity of institutions like the University of Brasilia, the Federal University of Goiás, the University of São Paulo, Federal University of Rio de Janeiro, and the Federal

University of Minas Gerais. Together, these universities are responsible for more than half of the Brazilian productivity in research articles on magnetic hyperthermia. Therefore, these institutions are recognized as consolidated institutions. Besides, the mentioned institutions collaborate with less consolidated institutions, so-called by us as rising institutions, which evidences the importance of consolidated institutions in establishing a network of researchers in magnetic hyperthermia in the Brazilian territory, also contributing to the spread of magnetic hyperthermia studies in all regions of Brazil (including the South, the Northeast, and the North). However, the network of collaboration in magnetic hyperthermia is not restricted to Brazilian institutions, but also includes international collaboration with countries like Spain, China, Argentina, the United States, and France. In addition, Brazil has been having a fundamental role in consolidating the science of magnetic hyperthermia in Latin America.

Furthermore, Brazil is the 13th most productive country in magnetic hyperthermia in the world and has been contributing to the fields of physics, chemistry, engineering, and life sciences. These contributions are either theoretical, simulation, or experimental (including in vitro and in vivo studies), and are related to the development of devices for magnetic hyperthermia, the interaction between magnetic particles, synthesis, processing, and characterization of magnetic nanoparticles. The applications of magnetic hyperthermia also cover a wide range of cancer, including bladder, cervical, intestine, liver, skin, and bone cancers, besides myeloid leukemia, adenocarcinoma, and glioblastoma.

Finally, magnetic hyperthermia has flourished in Brazil as a potential therapy to be included in clinical practice in the future. However, challenges yet to be overcome, such as its lack of spatial resolution and thermometry, still impede its advance towards clinical practice. At the same time, clinical trials can be an interesting approach to accustom hospital facilities to incorporate magnetic hyperthermia devices, besides training human resources - including surgeons and health workers staff - to perform the therapy in patients. Fortunately, the history of magnetic hyperthermia in Brazil has shown that this country has a well-consolidated network of researchers able to scientifically and technically translate this therapy into a future available therapy in clinical practice.

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