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Structural Trends and State Capacities in Regenerative Medicine in Brazil: Science, Innovation, Regulation, Governance and Social Inclusion

Liliana Acero (Corresponding author)

Postdoctoral Fellow

National Council for Scientific and Technical Development (CNPq)

Research Project Coordinator

National Institute of Science and Technology at the Postgraduate programme on Public Policies, Strategies and Development (INCT/PPED)

Institute of Economics (IE), Federal University of Rio de Janeiro (UFRJ), Brazil

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Abstract

Regenerative medicine has transformed conventional practises in medicine. It focuses on the repair and regeneration of cells, tissue, and genes. Regenerative medicine has led to new forms of regulation of biological inputs and required the upgrading of some state capacities at the public, private, national and supranational levels, as well as the inclusion of new social sectors in the governance of the area. However, there are still many matters of concern on diminishing risks and uncertainties that have not been completely resolved either globally or nationally. The aims of the present study are to analyse the specific manner in which innovation and regulation in regenerative medicine have developed in Brazil; which state capacities are facilitated or hindered and how different social groups participate in the sector. At the methodological level, the research consists of a bibliographical and documentary study that mainly uses secondary data to develop a qualitative analysis of information and a quantitative analysis of statistics. In addition, interviews were conducted with associated social actors, including representatives from patient organisations, on which content analysis of narratives was performed. Public policies present lacunae in the regulation of clinical trials, the inclusion of private capital, and the promotion of local patents, as well as a lack of coordination between public agencies. A set of state dynamic capacities have been developed gradually in Brazil over the last ten years, but mission-oriented public policy has been almost inexistent, state aims are unfocused, and the legitimation of state action is still under

development.

Keywords: regenerative medicine; cellular therapy; genetic therapy; state capacities; mission-oriented policies; publications; clinical trials; patents

1. Introduction

Regenerative medicine (RM) has transformed conventional practises in medicine (Webster et al., 2011). It focuses on the repair and regeneration of cells, tissue, and genes, (Mason & Dunnill, 2008). It frequently includes genetic diagnosis or interventions and raises hopes for new cures (Bubela et al., 2012), most especially to treat fatal or rare diseases or those diseases that lack any other type of treatment. However, risks and uncertainties in the handling of biological materials are still a matter of concern (Martin et al., 2008). RM has led to new forms of regulation of biological inputs and products and required the upgrading of some types of state capacities at the public, private, national and supranational levels (Morrison, 2012; Faulkner, 2016), as well as the inclusion of new social sectors in the governance of the domain of this medical practice. The article aims to describe these tendencies in the sector in Brazil, analysing the following three interconnected questions:

- In which specific manner has innovation and regulation in RM developed in Brazil?
- Which state capacities are facilitated or hindered?
- How do different social groups participate in RM and in particular what role do patient organisations have?

2. Theoretical and Methodological Approach

The coproduction of science, technology, and innovation with society leads to the construction of civic epistemologies or tacit forms of culturally-specific ‘ways of knowing’. Citizens use these in the public sphere to validate knowledge and demand the design and implementation of public policies through the building of identities, institutions, narratives, and representations that contribute to policy proposals (Jasanoff, 2006). The present study analyses how the construction of knowledge and power is validated through the creation of institutions and networks that deal with RM.

Because RM is at the frontier of medical practice public policy design and implementation requires the development of dynamic state capacities that are associated with mission-oriented policies (Kattel & Mazzucatto, 2018). These define concrete problems and the access to new markets through actions based upon specific objectives, especially in the context of the risk, uncertainty and permanent change that are characteristic of RM. The drivers of change are not purely technological, as social well-being is also a factor. Change also requires consensus among bureaucracies to develop arguments in favour of RM. During the rapid changes within RM, dynamic training has to guarantee that institutions encourage the development of a stable capacity for the (re)evaluation, reconfiguration, and redefinition of scientific and regulatory frontiers. Table 1 presents an evaluation of existing state capacities in the case of Brazil, following the conceptual formulation by Kattel and Mazzucatto (2018, p. 10) elaborated for other contexts.

Table 1. Dynamic capacities in mission-oriented policies in RM in Brazil

Levels	Objectives	Characteristics	Factors
State	Lack of focused aims and varying across historical periods.	Gradual legitimisation is underway. Polarised visions are in conflict.	Weak leadership that changes across historical periods. Selective and non-inclusive public engagement.
Public Policies	Partial and informal and/or with ill-defined objectives.	Medium coherence. Ambivalence, lacunae, and little coordination between agencies.	High degree of experimentation, though disorganised, erratic, and lacking a set pattern.
Administrative & Operational	Poor and full of obstacles.	Differs by agency. Little coordination among agencies and with stakeholders.	Initial level that lacks evaluation. Too gradual in light of the speed of change.

Source: Own study.

State capacities depend upon the internal functioning of the state apparatus in its technical and political dimensions and its capability for autonomous decision-making (Perissinotto & Nunez, 2021), as well as on the characteristics of the hegemonic coalition in power. Brazilian RM developed slowly and with lack of oversight over the last two decades until 2016, when the dominant governing coalition established an alliance between the state and domestic groups of middle and popular classes. This process contributed to building new institutions and capacities within the state.

At the methodological level, this research is based on a bibliographical and documentary study that mainly uses secondary data to develop a qualitative analysis of information and a quantitative analysis of statistics. In addition, interviews were carried out in Brazil, 7 with RM key informants, 18 with different social-sector leaders (policy-makers, scientists, and representatives from civil society) and 28 with representatives of patient organisations, and content analysis was applied to the narratives of the interviews.

The recurrent, convergent, and divergent narratives of the representatives of the three social sectors interviewed were identified and analysed, following Mulkay (1976). The main criteria employed were: visions of the beginnings of human life, international scientific collaboration, patenting in the biosciences, and levels of engagement with civil society. The analysis of the interviews on rare diseases with representatives of patient organisations was structured using the following categories: the organisations' main activities in RM, their degree of national and international collaboration with other associations, and their views on existing law and state practices in relation to rare diseases. The main themes in the narratives were coded and checked by a third party.

3. Science and Innovation Capacities

3.1 A Brief Scientific and Institutional History of the Sector

Adult stem cell research in Brazil was initiated in 1999 at the University of São Paulo (USP) and started to expand in a significant way in 2002. It was promoted by policies designed by

the Ministry of Science and Technology (MCT) to address strategic areas for the country's development, one outcome of which was the establishment of the Millennium Institute of Tissue Bioengineering (IMBT) to develop training programmes in RM. These initiatives took place during President Luiz Inácio da Silva's first administration and were largely based upon the work of key leaders in his team who were in favour of RM.

Some of the main events in the history of Brazilian RM are the following: the foundation of the first umbilical cord and placenta bank (BPSCUP) and clinic for bone marrow transplants in 2001, and the creation of the public network, Brasil Cord, for cord blood storage and distribution, in 2004. Between 2003 and 2009, the Ministry of Health (MS) financed 2747 adult stem cell research projects.

In 2004, the MCT and the MS launched a joint programme lasting 6 years for phases 2 and 3 of a clinical trial with heart cell therapy called the Randomized Multicentre Study of Cell Therapy in Cardiopathies (EMRTCC). The trial, in which 66 institutions participated and had funding of more than R$ 13 million, used adult stem cells to treat 1200 patients. The initial reports on the trial results pointed to a certain degree of success in relation to treatment efficacy in the case of heart failures as well as for Chagas disease.

Two years after the approval of the Biosecurity Law of 2005, which will be discussed below in the section on regulation, the scientist and Director of the Molecular Genetic Laboratory of USP Lygia Pereira da Veiga created the first human line of embryonic stem cells, BR-1, using exclusively national inputs. In 2008, Stevens Rehen, adjunct research director of the Biomedical Sciences Institute of the Federal University of Rio de Janeiro (UFRJ), created the first line of induced pluripotent stem cells (IPs) based on the reprogramming of adult cells. Brazil thus became the fifth country in the world where those two types of innovations have been reproduced.

Three new public policy initiatives were decisive in the development of RM: (a) the creation, at the end of 2008, of the National Network of Cellular Therapy (RNCT), to strengthen integration and exchanges between Brazilian scientists; (b) the funding, also in 2008, of 8 Centres of Cellular Therapy (CTC) for the production and expansion in culturing of seven types of human stem cell lines for clinical research; and (c) the construction, in 2010, of two embryonic stem cell banks (CTE), LaNCE at USP and at UFRJ, for the distribution of stem cells to specialised research teams.

In 2010, the National Centre of Bioimage (Cenabio) was launched for the study of the evolution of cancer, heart, and neuromuscular diseases using magnetic nuclear resonance, ultrasound, and bioluminescence, with the aim of supporting preclinical research. In 2011, during the first administration of President Dilma Rousseff, an international agreement for scientific collaboration in RM, Probitec, was signed by Brazil and Argentina (DECIT, 2010).

In 2015, the project 'Human–on-a-chip' at the National Laboratory of Biosciences (LNBio) in Campinas validated the creation and utilisation of micro-physiological models, organoids or 'organs in a chip'. These are composed of tissues cultured in 3-D that enable work with models that replicate the human body and thus facilitate the development of 'personalized

medicine'. Moreover, they also reduce the use of animals in research laboratories (Martin & Pagani, 2018).

The following year in LaNCE at USP a set of iPS stem cells was developed that included the genetic diversity of the Brazilian population. The cells were drawn from 15,105 men and women belonging to the age cohort of between 35 and 74 years old (Toledo, 2018). As of 2019, at USP in collaboration with UFRJ the National Institute of Cancer (INCA) and the State University of Rio de Janeiro (UERJ), had completed the mapping of the genetic profile of the immunity system of 4 million Brazilian citizens in order to feed the National Bank with iPS stem cells.

Key public institutions are involved in research at universities and hospitals, such as INCT-REGENERA at UFRJ, one of the main leaders in RM. At the same time privately funded research has been conducted in some spin-off firms from public universities: e.g. Hygeia and Novageia Biotech (from UFRJ) and *Pluricell Biotech* and Stem Corp (from USP). Diagnostic kits for different diseases were tested in these spin-off firms, based on samples from public university laboratories. The major private firms for the collection and storage of umbilical cord blood in the country such as Cryopraxis stated that in the near future they will focus even more on the development of RM therapies.

Finally, large pharmacological firms have entered the local sector in the last phase (stage 3) of clinical trial development with stem cells. Some examples are the clinical trials of Millennium Pharmaceuticals, Novartis, Janssen Research & Development, and Johnson & Johnson, while international biotechnology firms such as Gamida Cell Ltd, Amgen, Celgene, ReViral, and Genentech, have also conducted clinical trials in Brazil.

Since 2019, under a new ruling coalition, RM research has suffered from broad financial cuts. Some research projects had to be interrupted or scaled down or look for private funding to subsist. However, in November 2020 the MS launched the National Programme of Genomics and Precision Health, Genomas Brasil, to sequence genes carrying rare diseases, heart failure, contagious diseases, and cancer and contribute to their prevention. The project was inspired by the 100000 Genomes programme in the United Kingdom that had begun in 2012 (Vilela, 2020). However, the emergence of the COVID-19 pandemic presented an obstacle to accomplishing the aims of Genomas Brasil in the short term.

3.2 Funding

Funding in the period between 2002 and April of 2021 totalled R$ 467,672,706.08 and involved 1656 projects (Table 2). The National Council of Scientific and Technological Development (CNPq) contributed 38.99% of this amount. Since 2009/2010, there has been substantial incentive for research in this area for its full cycle from basic to clinical research. Funding for start-ups has also increased, though there were only two calls for research projects on genetic therapies.

The MS figures second in the provision of funding (32.24%), which was distributed among 257 projects, half of them financed by the Department of Science and Technology (DECIT) of that ministry and the rest by its partners. The contribution to funding by the Financer of

Studies and Projects (Finep) was 31% and that of the National Bank for Development (BNDES) 16.2%, representing a substantial lower proportion of total funding for RM.

Table 2. Distribution of total funding and number of projects in SC, CT, and RM[1] in Brazil by source, 2002–04/2021

Source	Amount (R$)	%	Number of projects	%
BNDES**	46,135,329.00	9.86	7	0.42
FINEP/MCT***	88,410,031.34	18.90	34	2.05
CNPQ ****	182,354,707.59	38.99	1358	82.00
Total	467,672,706.08	100	1656	100

Source: Own study.

Note. [1] SC= Stem cells, CT= Cellular therapy.

*http://pesquisasaude.saude.gov.br/index.xhtml - only R$ 70,165,733.37 are actually from DECIT.

**https://www.bndes.gov.br/wps/portal/site/home/transparencia/consulta-operacoes-bndes/ (does not show beginning dates; through March 2021).

***http://www.finep.gov.br/transparencia-finep/projetos-contratados-e-valores-liberados—begins in 2002. Five projects appear in duplicate in MS and Finep. If values were counted in duplicate, this would represent an overestimate in the total amount of around R$ 11 million.

**** Information on the number of projects and amounts financed by CNPq was obtained from this institution, but there might be an overlap with some of those reported by MS, in the order of no more than 8 projects maximum and an amount of R$ 385,211.72.

CNPq's project funding was highest in 2009, when the Biosecurity Law was already in effect, and was concentrated afterwards in the period between 2012 and 2016, when RM received better public funding support. For 2020, a higher level of funding is observed (R$ 21,900,217.42 and 37 projects), but it did not reach the 2009 level (Figure 1).

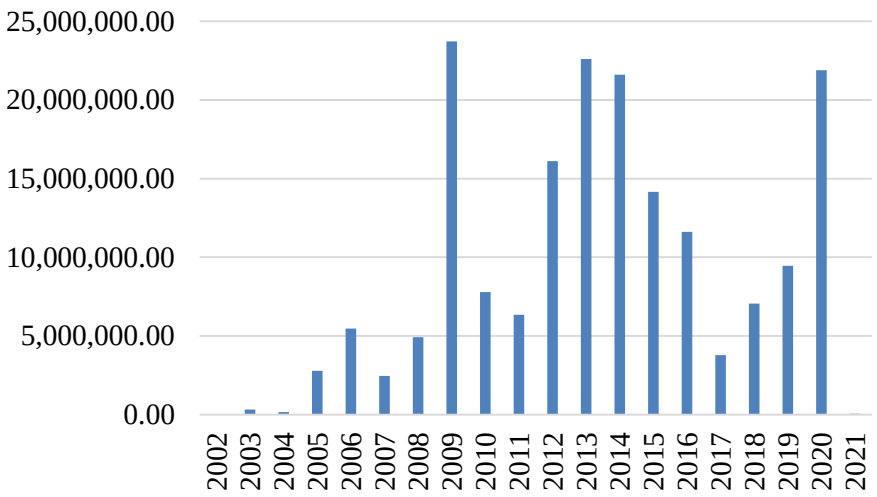

Figure 1. Funding per year by CNPq (2002- 06/2021)

Source: Own study based upon data provided by CNPq.

The number of projects funded by the MS shows a very unequal evolution (Figure 2) and with a greater concentration in 2008. Between 2012 and 2014, there was a certain recovery in the sector, but there was a substantial decline in the number of projects funding beginning in 2015. The sector's expansion diminished in the years when the ruling political coalition in President Dilma Rousseff's government changed to that of President Michel Temer´s government. In 2020, a limited number of projects received funding, the amount of which doubled the support provided in 2014. This was due to the prominence of the Genomas Brasil project as well as an increase in clinical trials in phase 3.

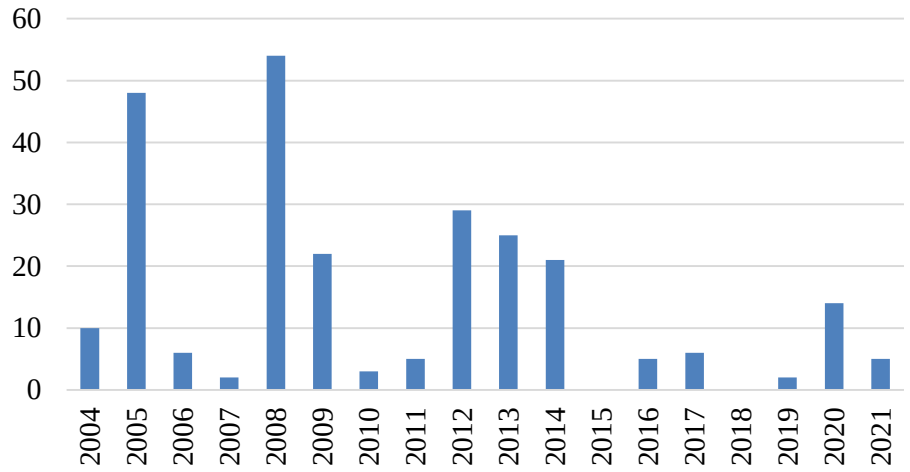

Figure 2. Evolution of the numbers of projects supported by the MS for SC, CT, and RM in Brazil, 2004–04/2021

Source: Own study based upon data provided by the MS.

The inclusion of private capital in the funding of RM research has been incipient till today. Such funding has sometimes even been rejected or questioned by specialised academic teams and the public sector has provided very few incentives for its activities in RM. Some of the leaders interviewed expressed their reservations in relation to 'the potential dominance of the private logic in RM', while others opposed the transfer of scientific knowledge generated in the public domain to the private sector. An interviewee representing a civil society organisation explicitly stated, 'My fear is that this issue of cellular therapy will turn into a situation where the international pharmaceutical industry tries only to obtain more and better patents. And then, the therapies will not be included in the national health system'.

3.3 Research Groups, Themes, Researchers, and Students

The growth in the number of research groups and themes of enquiry in the period under study has been considerable, as has the increase in the number of researchers and students involved in this new type of medicine. In 2021, 148 research groups were listed in the database of CNPq (Table 3).

Table 3. Number and % of research groups in SCR, CT, and RM in Brazil, May 2021

Interest	SRC	CT	RM	TOTAL
n	85	63	30	148*
%	57.43	42.57	20.27	**

Source: Own study based upon the CNPq Platform.

Note. *repetitions excluded; **the total is greater than 100 because one group can belong to more than one category.

These groups are mainly based in the Southeast Region (52.03%) and comprise a total of 1387 researchers who are investigating 236 different research themes.

The majority of researchers in this sector have an academic qualification well above the average for Brazil: 94.23% have postdoctoral studies or doctorate degrees (Sidone et al., 2016). The ratio of researchers to students is also quite atypical by Brazilian standards, as there is one scientist for every two students. A total of 2034 students were involved in the research groups as of May 2021, almost a quarter of whom were concentrated at the levels of master's courses or graduate studies. There is thus good potential for growth in this area in the near future.

3.4 Scientific Publications

Brazil is among a small group of countries (South Korea, China, Singapore, and Mexico are the others) that have seen their scientific production, as represented by publications, increase over the last thirty years at a rate of four times the global average (Almeida & Guimarães, 2013). Between 2001 and 2019, Brazil occupied the 17th position in publications at the international level, while the USA and China were in first and second place, respectively (Machado, 2021).

The total number of Brazilian publications indexed in the area between 2000 and November 2020 was 6270. This represented 1.47% of the publications on RM in the world and a rate of average yearly growth of 33.3%. The upward trend was consistent throughout most of the period, especially between 2004 and 2009, years during which greater funding was available and specifically local discoveries took place (Mendez-Otero & Carvalho, 2012).

Published articles are mainly written by researchers in public universities. Of the ten most-productive institutions, the first place is occupied by USP (*n*=2084), followed by the Federal University of São Paulo (UNIFESP) (*n*=697). The staff of public hospitals and employees of local private firms, which have very limited involvement in research, publish much less, with the exception of a few successful spin-off firms, as well as cord and placenta blood storage firms (Liliana, 2021).

Articles written solely by Brazilian authors (considered as those working at an institution located within Brazil) represent almost 61% of all publications in the period (*n*=3870). From 2015 on, publications by Brazilian authors and foreign collaborators increased significantly, reaching more than half of the total of articles published in 2020 (*n*=296). This fact reflects a change in priorities within national policies: at the beginning of the 2000s domestic

collaborations were prioritised, but since 2015 international collaboration with the main global actors in RM has been emphasised.

Authors from a hundred different countries have collaborated with Brazilian researchers on papers. However, the majority was produced by Brazilians and at least one author linked to an institution in the USA (21%; *n*=1354). Other international collaborators were affiliated with institutions based in other countries that are global leaders in RM, such as England, Germany, Italy, France, and Canada (between 350 and 300 articles per country). In spite of this gradual diversification of partnerships, as well as growing collaboration with Latin American and BRICS authors, Brazil researchers predominantly co-published with USA-based authors (Souza, 2017).

In its role as regional leader in RM, researchers in Brazil have collaborated with researchers in 23 countries in Latin America since 2003. More significantly, only since 2011 have such collaborations been incentivised by the ruling governmental coalition at the time. Collaborations with researchers in Argentina (*n*=69) predominate, as a result of the agreement signed with this country mentioned above (Bortz et al., 2019). Among the ten most-quoted publications in RM, two of them were produced exclusively by authors linked to Brazilian institutions, occupying the 1st (1350 citations) and the 9th positions (537 citations) in the ranking of most quoted articles in the period.

It can thus be concluded that in the last two decades, Brazil significantly increased its scientific co-authorships both domestically as well as internationally and made a global impact. This illustrates the academic quality attained by some sectors of Brazilian RM. Meanwhile, in the last decade the growth in co-authorship mainly involved American and European researchers; authors from other emerging economies were involved to a limited extent.

3.6 Clinical Trials

Unfortunately, data on different sources concerning the clinical trial registries that Brazilian researchers use present contradictions. The international platform of clinical trials of the USA, National Institutes of Health (NIH) (ClinicalTrials.gov) and the Brazilian Registry of Clinical Trials (REBEC)—integrated with the corresponding platform of the World Health Organisation (ICTRP/WHO)—were consulted to make comparisons.

In the database ClinicalTrials.gov, using the keywords ‘stem cells’ or ‘cell therapy’, 65 studies from Brazil were found between 01/01/2010 and 11/15/2020, which represent 62% of the studies registered on that platform. Almost half of them involved cancer (44.62%).

International private capital funded almost two-thirds of these trials, the majority of which are in phase 3. Big Pharma developed 21 trials (32.3% of the total), using resources from donations of specific patients or from local patient organisations as well. The rest of these trials were funded either by public institutions (16 trials, 24.6%) or by private Brazilian organisations (10 trials, 15.38%).

In the REBEC registry, using the same keywords, a total of only 22 trials were located, which

dealt with pathologies that were different from those found on the American platform. It can be observed that more than half of this group of trials fulfil the norm for the registry of clinical trials approved recently by Anvisa. According to our interviewees, this resolution contributed greatly to the expansion of the Brazilian sector towards the translational phase in RM.

Generally speaking, the diversification of registries of clinical trials reflects the specific interests of different members of the local scientific community. Those researchers who have regularised the technical and ethical aspects of their research projects look for official approval of their therapies and hence tend to publish their trials in the mandated registry, i.e. REBEC. Moreover, a substantive number of local clinical trials, especially those in phases 1 and 2, do not appear on any registry platform (e.g. INCT- REGENERA, 2019). In summary, the effort in clinical trials is recent and sparse. There is a considerable delay in local approval of advanced therapies: to date no cellular therapy has been officially approved in Brazil, although four genetic therapies have been.

3.7 Patents

The development of scientific capacities and academic production in the area were analysed to explore whether they are reflected in the deposit of Brazilian and international patents in the country. For this purpose, a search was conducted in the patent deposit of the National Institute of Industrial Property (INPI) for the period 01/01/2007 to 30/04/2021 (there were no data for the period before). The keywords used were ‘stem cell(s)’, ‘progenitor cell(s)’, ‘embryonic cell(s)’, and ‘embryogenic cell(s)’, following the selection of Santos & Guerrante (2007), and adding the words ‘cell therapy (ies)’ and ‘regenerative medicine’.

During the period of study, 470 different requests for patents were presented to INPI, the majority of which (397) were in the area of stem cells. The numbers of requests were larger in 2014 and in 2018, due to the global expansion of the area (Figure 3). The significantly lower number of requests in 2019 can be treated as an outlier, because the publication of a request occurs 18 months after the request is received.

In 2018, there was a larger number of deposits (68), the majority related to stem cells, showing the delayed growth of cellular therapy in comparison to international trends (it is important to note that the use of the concept of RM to define the sector is recent at the global level and particularly in Brazil).

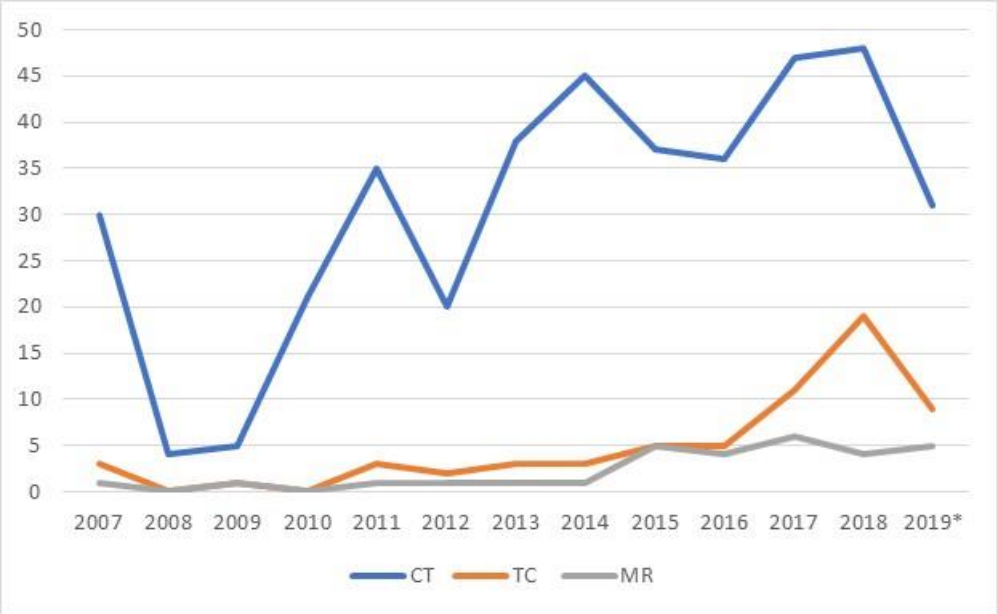

Figure 3. Patent requests per year in SC, CT, and RM in Brazil, 2007–2019

Source: Own study based on data provided by INPI.

Note. *Request publication takes place 18 months after request; art. 30 of Law 9279/96, which is the reason why the year 2019 is not totally covered.

According to the International Patent Classification (IPC) categories found on the website of the World Intellectual Property Organisation (WIPO), among the 28 main IPCs of the 470 patent deposits made, 77% fall into two categories related to associated products, processes, and factors in RM, with therapies not being mentioned. The methods and tools used for purification, conservation, and decontamination of biological materials, crucial in this area, also have greater relevance among requests, as does laboratory equipment.

It is clear that deposits of patents by national institutions are very scarce. There have been only five requests associated with six patent holders. The majority have been presented by public universities and hospitals. In spite of the public policies developed to promote the patenting of national products, such as the economic incentives considered within the Innovation Law (10.973/2004) and the Law of Goods (11.196/2005), the trend in patent deposits in RM is similar to that found in regard to innovation in other Brazilian sectors.

4. Regulation and Governance Capacities

Embryonic stem cell research has flourished in Brazil since 2005. The Biosecurity Law (Law no. 11.105 of 2005) permits adult and embryonic stem cell research, but prohibits human therapeutic and reproductive cloning, as well as genetic engineering of germinal cells. The law was passed with the support of a coalition formed by a large proportion of the specialised scientific community, several patient groups, and the local press. There was however, strong opposition from Catholic and Evangelical practitioners and a claim of unconstitutionality was presented (ADI 3.510) at the Supreme Federal Court (STF), based upon the religious belief

that human life begins at gestation. After a long and active public debate and a number of public hearings, in 2008 the STF decided in favour of this type of research (Liliana, 2010).

The two agencies that regulate the sector are the National Commission of Human Ethics in Research (CONEP) and the National Agency of Vigilance (Anvisa). It has taken quite a long time for the RM regulation process to mature in Brazil, particularly that related to legislation on clinical trials. The new norms integrate clauses similar to those included in regulations of the USA and European countries.

In 2004, Anvisa published a Resolution from the Collegiate Board (RDC 219) to allow the tertiarization of clinical trials by specialised consultancy firms and the presentation of directives on good clinical practice. In 2012, the RDC 3621 simplified the analysis of trials that had already been approved by international regulatory agencies and made obligatory the registration of national clinical trials in advanced therapy with the Brazilian Registry of Clinical Trials (REBEC). The RDC 38 of 2013 regulated advanced medicines within the programme of 'expanded access for patients', 'compassionate use', and 'use after clinical trials'. Based upon the RDC 924 of 2015, the evaluation of clinical trials became centralised, which reduced over five years the average time of evaluation per research project presented.

More recently, Anvisa adopted the definition used by the European Agency of Medicine (EMA), 'medical product of advanced therapy' (PTA), which can either be classified as (a) PTA class I, those processes subjected to minimal manipulation that does not alter significantly their biological characteristics; and (b) PTA class II, therapies that require extensive manipulation. Anvisa also published three other resolutions to regulate PTA: (a) the RDC 214 in February 2018 on good clinical practices in human research with advanced therapy; (b) the RDC 260 in December 2018 on protocols for the development of clinical trials for those therapies; and (c) the RDC 338 in January 2020 on the approval of these products to enter the public health system (SUS) and also be commercialised in Brazil.

The Director of the Department of Blood, Tissue, Cells, and Organs (GSTCO) within Anvisa declared that if the evaluation of a PTA clinical trial by this agency was not completed within 30 days of its presentation, the patient's specialised medical doctor was automatically authorised to apply the treatment (Portal R7, 2020). In this way, the implementation of these therapies by hospitals and within private medical consultations became more flexible, even in cases when the therapies did not form part of a specific clinical trial. This new approach follows new trends in regulation at the global level.

At present, governance in Brazilian RM reveals some contradictions and conflicts of interest that will be difficult to resolve between: (a) the specialised scientific communities and the associated medical sectors, tissue engineers, and Big Data experts; (b) policy-makers and sectors of the academic community who collaborate closely with foreign institutions versus those that are more locally oriented in their practices; (c) specialists, private biotechnology firms, and transnational Big Pharma, and (d) especially between three types of stakeholders: policy-makers, members of the scientific and medical communities, and managers of private firms versus civic organisation representatives and the wider public.

Initially, there was a strong public support in MR for projects by specialised researchers from public institutions, although there was only selective inclusion of medical doctors in research. Serious conflicts between both 'epistemic cultures' (Knorr-Cetina, 2006, p. 28) characterised the sector, with each group following its own cultural and professional norms and values. However, the scientists interviewed for the present study recognised that both types of cultures 'are key to develop[ing] cellular therapies', a viewpoint that is not reflected in their everyday practices. Therefore, in the second stage the RM core group of researchers in Brazil was not able to handle the transition towards clinical research very satisfactorily. There was also significant disinformation among policy-makers dealing with regulation, as is reflected in the late development of adequate regulation on advanced therapies.

In summary, there is a lack of focus in state efforts at the regulatory level. The decentralisation of normative, bioethical, and sanitary competences is one of the causes of reduced state efficacy in the use of its evolving dynamic capacities of leadership and agency coordination. Evaluation of the effects on the sector of the most recent sanitary norms is also lacking. Big challenges for the state are foreseen in terms of governance, partly due to a potential scaling-up of conflicts with groups from organised civil society, as will be discussed next.

5. Social Inclusion State Capacities

Patient organisations have become at the global level a privileged locus for mediating relationships between state and society in reference to health (McGowan et al., 2016). Due to the negative effects of neoliberal policies during the 1990s, vulnerable populations from emerging economies became further unprotected (Souza & Deprá, 2012). The lack of solutions to patients' health problems has contributed to new forms of association between patients and their families. These novel organisations look for their own sources of knowledge, demand redefinition of conventional medical models, and include activists who advocate publicly for changes, based upon their own experiences and knowledge (Rabeharisoa et al., 2014).

European countries designed government strategies to promote citizen dialogue in the biosciences aimed at a 'bottom-up' democratisation of scientific contents (Bussu et al., 2014). By contrast, in Brazil state strategies of public engagement are limited to public consultations by specific agencies on the internet, usually about laws and normative resolutions. These initiatives have little transparency and are mainly directed to selected interest groups. Consultation results are often not systematised or have their access restricted and sometimes results are carelessly reported by the media (Liliana, 2011).

There are two main forms of organisation of Brazilian civil society in relation to RM, beyond the associations of scientists and medical doctors: (a) organisations dealing specifically with RM, as well as those that promote bone marrow donations to public banks and, (b) organisations that include only some aspects of RM within their wider agendas, for example, on ethics and gender, civic and political rights, women's health, and racial discrimination.

The first type of organisation is formed by stakeholders in relation to a specific or chronic

illness, a frequent form of association at the international level. There are 23 associations of this type in Brazil, which are members of the Latin Alliance (a Latin American network), founded in 2006, which comprises more than a hundred patient organisations (https://redalianzalatina.org/pt-br/alianza-latina/membros).

Representatives from five organisations of that type, those connected with RM, were each interviewed for an hour and a half between January and May 2021. The organisations were the Brazilian Association of Amyotrophic Lateral Sclerosis (ABRELA), the Brazilian Association of Lymphoma and Leukaemia (ABRALE), the Brazilian Society of Thalassemia (ABRASTA), and the Brazilian Association of Muscular Dystrophy (ABDIM).

Half of the 23 organisations mentioned above participate in RM research or clinical trials, have a wide range of volunteers, and systematically support their members' health needs. They are mainly financed by individuals' donations, but more than a half of them also receive international funding and one-third funding from private firms in Brazil. But the majority of them only carry out research about their patients' progress in treatment, even though they often participate in study groups run by scientists in RM. Due to limited financial resources, in contrast to the European situation, they do not invest in RM research.

Brazilian rare-disease-patient organisations have been founded more recently than those of chronic disease, are smaller than the latter, and have memberships of at most 7000 families and/or patients. An exception is the Brazilian Federation of Rare Diseases (FEBRARARAS), which groups together 57 rare-disease organisations and has 250,000 members.

The category of 'rare disease' only became relevant in the public domain in Brazil at a congress held in 2009, but took on greater importance after 2014, when the National Policy of Integral Treatment of Patients with Rare Diseases was launched. It was planned as part of this policy to set up seven genetic services at the national level (Nunez Moreira et al., 2018). However, patients in Brazil have no access to global genetic therapies. Out of a total of 400 rare diseases identified in Brazil as of 2018, only 34 have been included at the public health system (SUS) (MS, 2015).

Data from the websites of 40 NGOs in rare disease were also analysed. These organisations were selected from a list of 470 national organisations, according to the criteria of whether they actively supported or otherwise had an interest in research or clinical trials in RM. Two-thirds of them recommended biological medicines and genetic diagnosis to their members and/or participated in RM clinical trials. Twenty-three representatives from these organisations were interviewed individually on line for one hour between January and May 2021.

Frequently, these organisations enter into formal collaboration agreements with universities and hospitals and informal ones with Brazilian specialists. They also actively participate in the recruitment of patients for clinical trials. They follow the progress of the scientific research projects with which they are to some degree involved and invite prominent specialists as speakers to the events they organise. Interviewees commented that partnerships with Big Pharma are very limited. They also explained that the inclusion of patients in clinical trials for

genetic therapies is hindered by the lack of recommendation from local specialists. They consider that the medical doctors' behaviour is based upon social prejudices concerning the efficacy and high costs of RM.

The representatives interviewed also stated that patients usually have access to gene therapies after judicial disputes have been settled. The associations are also involved in political struggles to make genetic medicines and therapies accessible, even in cases when these have already been approved by Anvisa. The low quality of genetic diagnosis, the concentration of those services in the South and Southeast Regions of Brazil, and the under-reporting of the number of registered patients are significant obstacles for the expansion of this type of treatment in the country (Horovitz et al., 2013).

The associations' representatives expressed very different views on the efficacy of the National Policy on Rare Diseases of 2014. Critical appraisals of the policy include 'the law has a flaw when it rules together on very different types of diseases'. The interviewees also emphasised that the law is not correct regarding the amount of rare diseases present in Brazil and the number of patients affected, due to the under-reporting of cases at the national level. Most rare disease patient organisations are also demanding an official registry that groups cases by disease.

These organisations are usually affiliated with key international institutions from which the former receive scientific information, support for participation in international events, and sometimes, medical advice. The Hunter House (Casa Hunter) is the patient organisation most involved in RM research and is a member of the NGO Branch, a Department of the United Nations, that is considered 'very important [for showing] Brazilian demand to the world'.

In summary, though rare disease organisations in Brazil are recent, they have been very active within the local landscape and in building substantive international relationships. They take action to highlight regulatory gaps, influence public policy-making, engage in alternative forms of understanding the rare diseases experienced by their member patients, and offer those members ways of access to genetic diagnosis and treatments.

6. Conclusions

Comparing the initial theoretical perspective presented in the article with the empirical data analysed, it can be concluded that the set of dynamic state capacities in Brazilian RM have been developing gradually, especially during the last ten years. However, mission-oriented public policy is almost inexistent. State aims have also been narrowly focused and the legitimacy of state actions in RM is still publicly considered as weak. State action went from being quite supportive in relation to MR to being characterised lately by very poor policy design since then.

Moreover, RM public policies have had partial reach and are subjected to a high degree of experimentation that is conducted in a disorganised manner. Policies present lacunae in relation to the regulation of clinical trials, the inclusion of private capital, and the promotion of local patenting of products.

There exists a remarkable lack of coordination between the responsible agencies, a fragmentation of the multiple forms of funding, and an innovation pathway that scarcely takes into account social responsibility. In spite of this, in the last decade there has been a certain improvement in the promotion of collaborative scientific networks. Patient organisations' civic epistemologies reveal a permanent need for active verification *in situ* when it comes to the implementation of the public policies' aims.

Beyond this, the lack of a centralised public programme in RM has contributed to an excessive bureaucratisation around project and therapy approval. The recent normative changes made by Anvisa for advanced products may smooth their way to the market and their inclusion at SUS. However, the adjustments by SUS that are necessary to implement these therapies seems the main weak spot in the state system relating to RM.

With RM being a frontier sector, administrative and operational state capacities are not keeping pace with the actual scientific development of the national sector due to a lack of technical capacities among state policy-makers and of training for the promotion of informed public engagement. These deficits also hinder the systematic evaluation of the results of RM public policies for evidence-based planning and the inclusion of civil society. Patient organizations have to put constant pressure on the state to have their rights to advanced therapy acknowledged, even though those rights are supposed to be guaranteed by law.

High-quality scientific and technical development in the production, distribution, and application of advanced therapies may be the next big challenge in the Brazilian context. This will demand the development of partnerships between public and private social actors and the reshaping of institutional networks. It will also require better definitions of (a) technical and ethical norms, (b) the sponsoring of clinical trials by private capital, (c) the specialisation of manufacture, (d) policies for the establishment of affordable therapy prices, and (e) viable systems of cost reimbursement. The gradual preparation of SUS for the wide access of the population to advanced therapies will entail, for example, carrying out specialised training for different categories of health workers and making significant reforms to present infrastructure.

The uncertainties and risks frequently associated with advanced therapy production, the predictable delays between scientific and medical experimentation, and the approval of products and their adoption in the public health system are topics that have been practically absent from public debate and institutional frameworks in Brazil. The state's performance has not kept pace with the national and global scientific and medical evolution in RM.

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