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HEALTH SCIENCES

CRISPR/Cas patents and health-related publications in South America

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Abstract: CRISPR/Cas is being increasingly used for various applications. However, different countries introduce new technologies at different paces and purposes. This study reviews research progress using the CRISPR/Cas system in South America, focusing on health-related applications. The PubMed database was used to identify relevant articles about gene editing with CRISPR/Cas, whereas patents were searched in the Patentscope database. In addition, ClinicalTrials.gov was used to find information on active and recruiting clinical trials. A total of 668 non-duplicated articles (extracted from PubMed) and 225 patents (not all health-related) were found. One hundred ninety-two articles on health-related applications of CRISPR/Cas were analyzed in detail. In 95 out of these, more than 50% of the authors were affiliated with South American institutions. Experimental CRISPR/Cas studies target different diseases, particularly cancer, neurological, and endocrine disorders. Most patents refer to generic applications, but those with clear disease indications are for inborn errors of metabolism, ophthalmological, hematological, and immunological disorders. No clinical trials were found involving Latin American countries. Although research on gene editing in South America is advancing, our data show the low number of national innovations protected by intellectual property in this field.

Key words: gene editing, CRISPR/Cas, CRISPR/Cas9, South America.

INTRODUCTION

The ability to manipulate any genomic sequence by editing genes has created new possibilities for treating genetic diseases, allowing for precise modifications in cell cultures and animal studies (Carvalho et al. 2018). CRISPR/Cas system gene editing is the most promising tool for correcting genetic diseases because of its simplicity and precision, especially compared to other methods, such as TALEN and Zinc Finger (Gonçalves & Paiva 2017, Mills et al. 2020).

As a result of the rapid advance in biotechnology, specifically in gene editing (Ledford 2015, Mills et al. 2020), there is a great promise of applications to develop not only for human health but to improve gene-editing tools for plants, microorganisms, and animals. CRISPR/Cas has been used in human gene editing studies, and it has attracted the attention of scientific and industrial circles. In 2020, Emmanuelle Charpentier and Jennifer Doudna won the Nobel Prize in Chemistry in recognition of their contribution to developing the gene-editing technique using the CRISPR system.

This system consists of a nuclease (Cas9) guided by an RNA (sgRNA, about 20 nucleotides) to the target DNA, resulting in the cleavage of the double strand of DNA at a specific locus (Doudna & Charpentier 2014). This DNA break can be repaired either by non-homologous end-joining (NHEJ) or by homology-directed repair (HDR). The NHEJ occurs predominantly without donor DNA, resulting, in most cases,

in insertions or deletions and the generation of knockout organisms or cells. On the other hand, HDR, predominantly in the presence of donor DNA, generates mainly gene substitutions or additions (Sander & Joung 2014). Thus, the CRISPR/Cas9 technique can remove, replace, or correct non-functional genes (Zhang 2021). This system has continued to evolve in recent years, and many strategies have been developed from basic to applied research, including gene knock-in or knockout (Kherraf et al. 2018), base editing (Gaudelli et al. 2017), and prime editing (Anzalone et al. 2019).

One of the main CRISPR/Cas applications and advantages has been in the generation of disease models and in the development of new treatments for genetic, infectious, and immunological diseases, and cancer, due to its high efficiency and the potential to provide long-term therapy, term after a single treatment (Wu et al. 2020, You et al. 2019, Zhang 2021). In addition, these models can assist in the development of new drug targets. Wu et al. (2020) reviewed the creation of models (cellular and animal) of genetic diseases, preclinical therapies, and clinical trials with the CRISPR/Cas system. In addition, clinical trials involving CRISPR/Cas-based gene editing have been carried out, from applications for correcting disease-causing variants to improving CAR T cell therapy (Li et al. 2020).

Many resources allowed the rapid introduction of the CRISPR system, like specificity, efficiency, precision, and speed. Due to this, the CRISPR/Cas system can be used in less sophisticated laboratories, being considered a low-cost methodology. Since its initial description in late 2012 and early 2013, this technology has gained ground in the scientific scenario. The leading technology researchers found it essential that other laboratories could use this tool, sharing and committing themselves to open science, thus making their original CRISPRs plasmids available. For example, Addgene has distributed over 100,000 CRISPR plasmids to 3,400 laboratories worldwide (LaManna & Barrangou 2018).

In all countries, innovation is essential for economic development and the quality of life for its citizens. Research is fundamental for innovation; therefore, promoting innovation involves encouraging and supporting scientific research. Despite the advantages and facilities of approaches using CRISPR/Cas, when comparing developed and developing countries, there are apparent differences in adopting new technologies, regardless of cost, due to structural deficiencies. South American countries have been trying to increase innovation but still face challenges. Argentina, Brazil, Chile, and Colombia are growing strongly in the number of publications (Olavarrieta & Villena 2014).

In the last twenty years, Brazil has intensified efforts to expand, support, and promote science, technology, and innovation activities (Lima et al. 2019). As a result, in 2014, Brazil dominated the record for publications and was responsible for more than two-thirds of all scientific production in South America and leading publications in Latin America (Olavarrieta & Villena 2014, Van Noorden 2014). In addition, in 2019, the country reached the 23rd position, the first in South America, in the global ranking of scientific quality in the Nature Index (2020).

We have previously shown the progress of gene therapy (Linden & Matte 2014) and of gene and cell therapy (Matte & Peluffo 2020) in South America. Here we present an overview of the progress of gene-editing research in South America. We performed a bibliometric analysis in the PubMed database on research progress using the CRISPR/Cas system in South American countries, focusing on health-related applications. Data on patent filing is

also reported, although not limited to health applications. Finally, the current clinical trials ongoing worldwide are also briefly discussed.

MATERIALS AND METHODS

The PubMed database (https://pubmed.ncbi.nlm.nih.gov) was used to identify relevant articles with the keywords "CRISPR", "CRISPR Cas", "CRISPR/Cas", "CRISPR-Cas", "Gene editing", "Genome editing", AND "Argentina", "Brazil", "Bolivia", "Chile", "Colombia", "Ecuador", "French Guyana", "Guyana", "Paraguay", "Peru", "Suriname", "Uruguay", "Venezuela", published from January 2010 to January 2021. The search was carried out in October 2021. Duplicated publications were removed, and the remaining were pre-evaluated by reading their abstracts. Articles that used other gene-editing techniques were not considered, as well as articles that only mentioned the procedure and articles in any language but English. The remaining articles were classified into four groups according to their topic of study: plants, animals, microorganisms, and health.

The latter group included articles on treating and preventing human disease and were read in full and further characterized. Data on authorship, international collaboration, type of experiment, and disease target were collected. We began by analyzing the distribution of authors in South America. For each article, we counted the authors' countries of affiliation. If more than one author was from the same country, that country was counted only once. Then, articles were classified according to collaboration with international groups. Next, we counted how many authors were affiliated with South American institutions and how many were from foreign institutions for each article. Articles with less than 50% of South American authors were classified as international collaboration. In case of a tie in the number of authors, we considered the first or last author for this classification. Next, the articles were classified according to type: experimental or review. Experimental articles were further divided according to the experiment: *in vitro*, *in vivo*, both (*in vitro* and *in vivo*), and others. In addition, we also verified the target disease of each experimental article.

We also searched for CRISPR/Cas technology patents deposited in South American countries. The research was carried out in the Patentscope database, simple search mode. Data collection was carried out in October 2021. We selected "home page" as the search field, and the terms "CRISPR OR Cas9" were used as keywords for the search. In the "languages" and "offices" fields, we selected "all" and all the South American countries available for consultation (Argentina (AR), Brazil (BR), Chile (CL), Colombia (CO), Ecuador (CE), Peru (PE), Uruguay (UY)). The data collected (request number, publication date, patent title, depositor, and deposit country) were recorded in an Excel spreadsheet to enable analysis and observations of the characteristics of each patent. Patents classified as "world" (WO) were excluded. In further analysis, patents with the same abstract and depositor in different South American countries, or even in the same country, were counted as one.

Clinical trials were reviewed on the website ClinicalTrials.gov, a repository of privately and publicly funded clinical studies conducted worldwide and maintained by the United States National Library of Medicine. Search terms were "CRISPR", "CRISPR/Cas", and "CRISPR/Cas9". The collected data (first posted, official title, phase, estimated enrollment, study type, intervention/treatment, status, condition or disease, sponsors and collaborators) were recorded in an Excel. Studies classified as interventional-diagnostic, observational and not using the CRISPR/Cas system were excluded.

RESULTS

The general steps used in this work are shown in Figure 1. They include: (i) data recovery in publications (extracted from PubMed) and patents (extracted from Patentscope) on gene editing using the CRISPR/Cas technique; (ii) excluding all duplicated items; (iii) reading all abstracts of the remaining articles and exclude articles that do not use or only mention CRISPR/Cas and articles not in English; (iv) exclude patents that do not use the CRISPR/Cas gene-editing technique; (v) classify articles and patents in the subject group. Finally, the remaining articles and patents were analyzed in detail.

Articles

A total of 668 relevant and not duplicated articles were obtained from PubMed. Of these, 435 articles were selected after excluding articles that only mentioned the technique, used techniques other than CRISPR/Cas, or were not in English. These 435 articles were divided into four groups according to the subject: Plants (n=52), Animals (n=37), Microorganisms (n=154), and Health (n=192), as seen in Figure 2.

We focused on exploring in detail the 192 articles classified as health-related. First, the articles were classified according to collaboration with international groups. For 97 out of 192 articles, less than 50% of the authors were affiliated with South American institutions, and the article was classified as international collaboration. The country with the highest number of papers in collaboration was the United States, followed by the United Kingdom, Germany, China, The Netherlands, and Spain. To understand how widespread the studies with CRISPR/Cas from South American countries are, we analyzed the distribution of authors. For each paper, we counted the author's countries of affiliation. Figure 3 shows the countries present in the 192 articles. Brazil

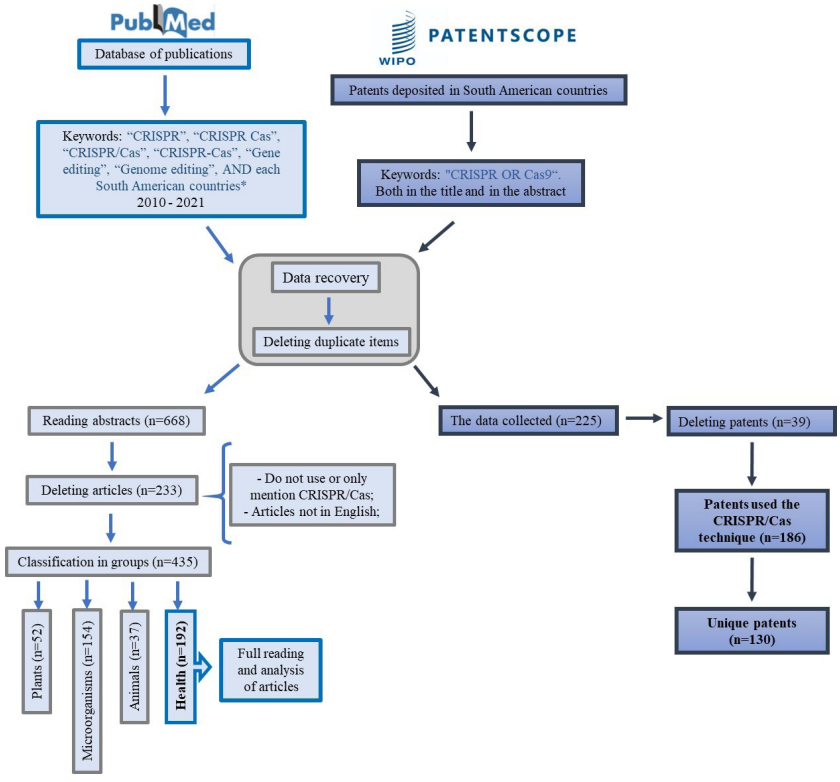

Figure 1. Steps of analysis used in this study. *Argentina, Brazil, Bolivia, Chile, Colombia, Ecuador, French Guyana, Guyana, Paraguay, Peru, Suriname, Uruguay, Venezuela.

was the country with the most publications (n=112), followed by the United States (n= 76), Chile (n=29), Argentina (n=28), and the United Kingdom (n=28). Colombia, with 17 publications, occupied seventh place. Uruguay, Peru, Ecuador, and Paraguay had 8, 5, 2, and 1 publications, respectively. It is important to emphasize that the other countries, "Bolivia," "French Guyana", "Guyana", "Suriname", and "Venezuela", did not return any articles using the CRISPR technique in our search.

All 192 articles were also classified according to the type of article as experimental (n=140) or review (n=52). Figure 4 shows the classification of experimental articles (n=140) regarding the health-related application or topic. In the "others" group, we included articles that did not fit into the other categories, such as ciliopathies, inflammatory bowel disease, cell organization, gene regulation, and Marfan syndrome. Experimental articles (n=140) were further divided according to the type of study into *in vivo* (32), *in vitro* (93), or both (13). Finally, two articles were classified in the "other" category. One article is about opinion polls on CRISPR/Cas9 technology and its application in the future. The other article is about an automated system for predicting large proteins.

Patents

Patent analysis was not restricted to health-related applications. The search for patents deposited in Argentina, Brazil, Chile, Colombia, Ecuador, Peru, and Uruguay at Patentscope returned 225 patents filed until November 2021. All had their summaries read, if available. Patents that did not mention the CRISPR system in their title or abstract were excluded from our analysis (n = 39). The remaining 186 were classified into four groups, according to subject: Plants (n=28), Animals (n=5), Microorganisms (n=11), Disease (n=64) and Generic (n=78) (Figure 5). This last case corresponds to applications to different subjects, such as plants and/or health and/or microorganisms. Brazil was the South American country with the most patents filed (n=128), followed by Argentina (n=23), Colombia (n=14), Chile (n=9), Peru (n=6), Ecuador (n=3), and Uruguay (n=3). After reading patent abstracts,

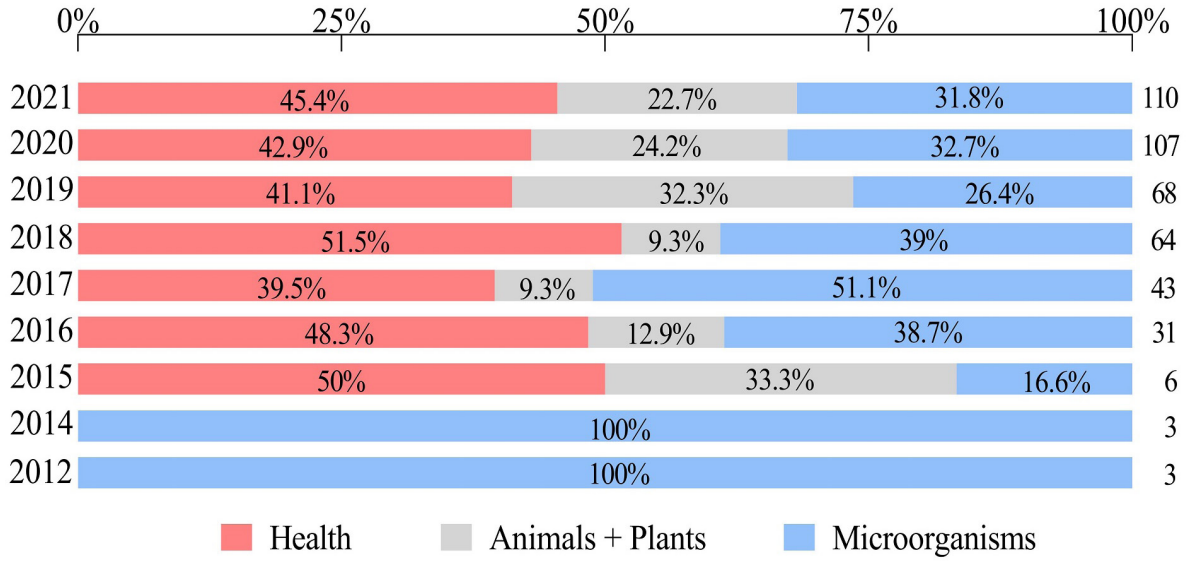

Figure 2. The number of articles per year. Number and type of articles by year of publishing (n=435). Numbers on the right side of the bar correspond to the total number in that year.

duplicated patents filed in different countries were excluded.

The remaining 130 patents were filed by 82 patent depositors, but only two were from Brazilian owners, the only country in South America to own patents. The top 5 patent depositors are the Massachusetts Institute of Technology (MIT) and The Broad Institute, with 15 patents each, followed by the President and Fellows of Harvard College with 14 patents. Pioneer Hi-Bred International comes next with 11 patents, followed by The Institute of Genetics and Developmental Biology and the Chinese Academy of Sciences with six patents (note that some patents are shared among more than one institution).

Disease-related patents (n=40) were also classified according to the target disease (Figure 6). Cancer is the leading topic of experimental research on gene editing conducted in South America, but not in patents. Generic patents correspond to 17.

Clinical trials

Currently, 43 clinical trials with the keyword "CRISPR/Cas9" are registered in the ClinicalTrials.

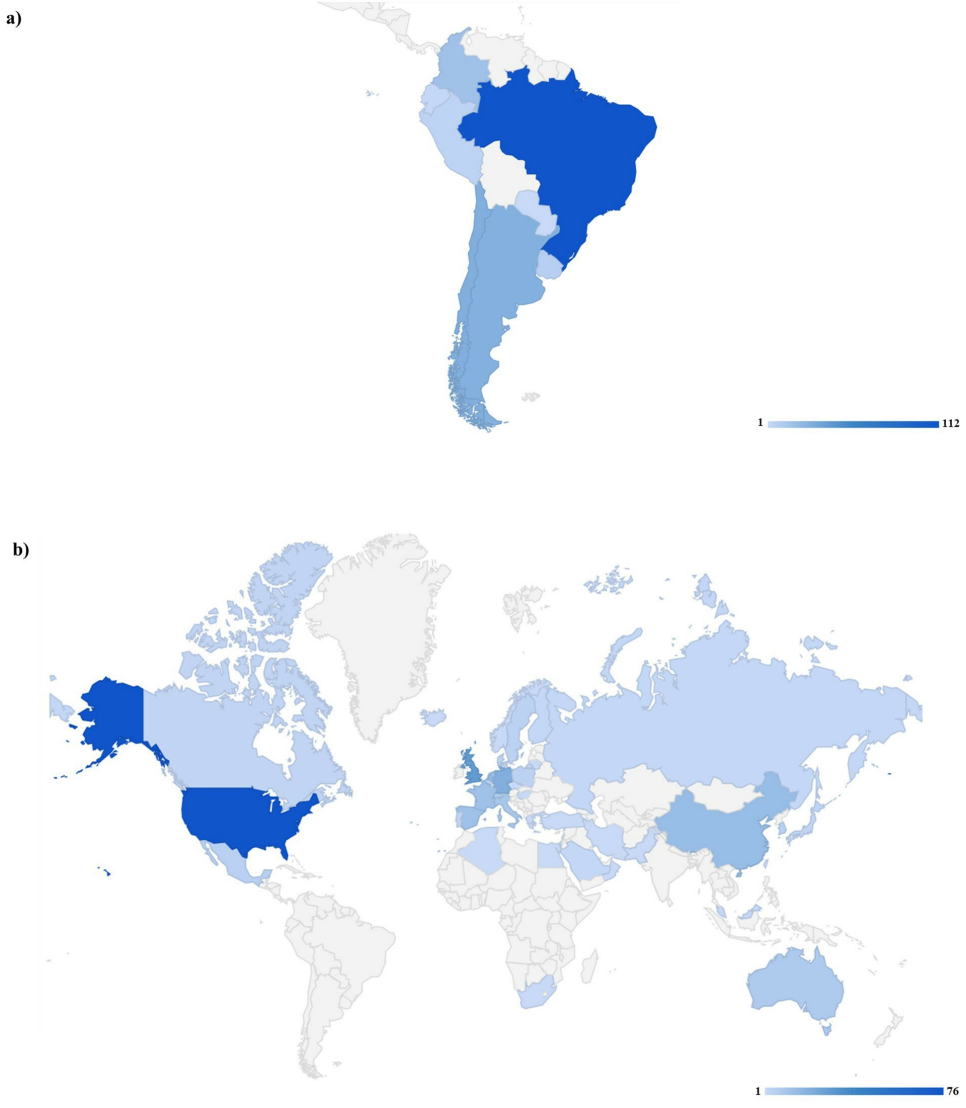

Figure 3. The countries present in articles from the "Health-related" category (n=192). a) South American countries. b) International collaboration. Color intensity shows the number of articles.

Figure 4. Classification of articles and patents by health-related topic. Topics of experimental articles (n=140).

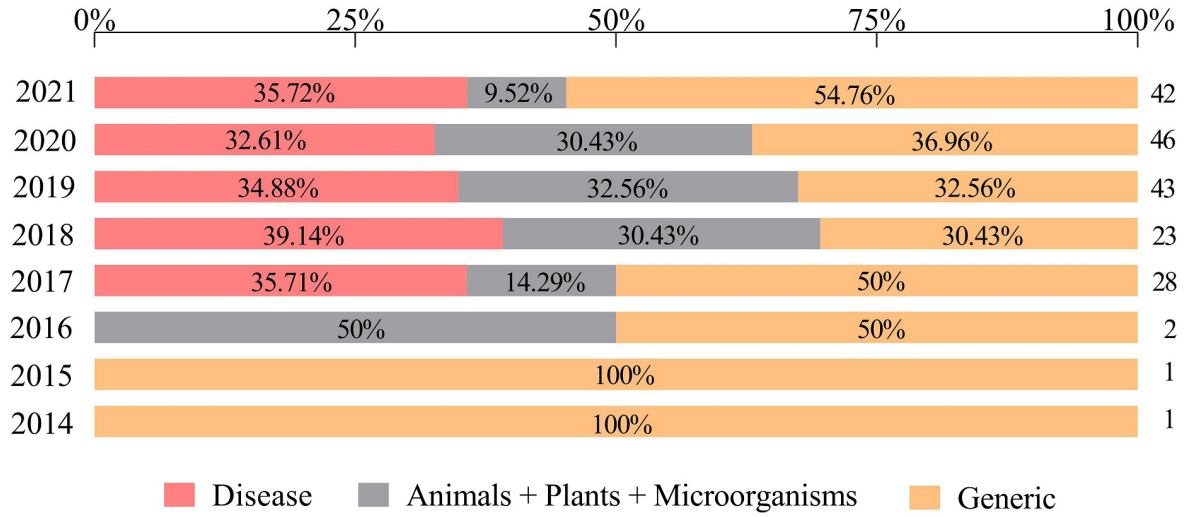

Figure 5. The number of patents per year. Number and type of patents by year of deposit (n=186). Generic = corresponds to applications applied to different subjects, such as plants and/or health and/or microorganisms. Numbers on the right side of the bar correspond to the total number in that year. The same patent will be counted more than once if deposited in two or more countries.

gov clinical database (Supplementary Material - Table SI). There is no clinical trial with the participation of South American countries. China and the United States are the predominant countries conducting clinical trials, with 18 and 19 trials performed with their financial support. Out of the 43 clinical trials, two were suspended due to lack of funding, nine had unknown status, and three were completed. Regarding classification, most clinical trials are on cancer, hematologic, and infectious diseases. Currently, 27 clinical cancer treatment trials with the CRISPR/Cas9 tool are being researched. They target several types of cancer, including skin, gastrointestinal tumors, hematological neoplasms, neurological, gynecological, urological, and lung. Approximately two-thirds of clinical trials performed to date are either phase I or I/II, representing 15,48% of all CRISPR therapy trials. Phase II represents 0,43% of the total, and phases II/III and III represent only 1,72% of all trials.

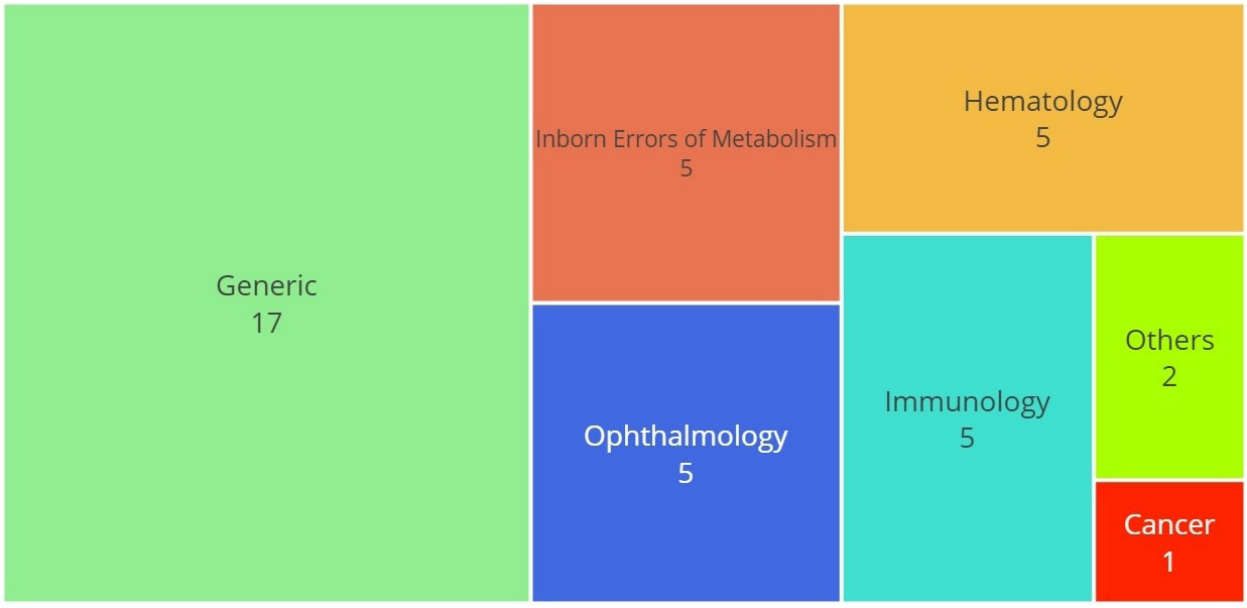

Figure 6. Classification of patents by health-related topic. Topics of the patents in the disease group (n=40). Generic = do not specifically mention which disease.

The first clinical trial, using the CRISPR/Cas9 system, was performed in 2016 to treat lung cancer (NCT02793856). This clinical trial involved editing T-cells to knock out the *PD1* gene in patients with advanced non-small-cell lung cancer. Cells were edited *ex-vivo* and re-infused into the patients, where they were detected in peripheral blood after reinfusion (Lu et al. 2020). Other clinical trials include, for example, lung cancer (NCT02793856), esophageal cancer (NCT03081715), bladder cancer (NCT02863913), and kidney cancer (NCT02867332), and to investigate the safety and efficiency of CAR-T cell therapy mediated by the CRISPR/Cas9 system.

There are also clinical studies related to other diseases, especially hematological diseases such as β-thalassemia and Sickle cell disease (SCD). As inherited blood disorders caused by mutations in the *β*-globin gene (*HBB*), they are considered suitable targets for *ex vivo* therapy in hematopoietic stem cells (HSCs). In 2018, CRISPR Therapeutics and Vertex Pharmaceuticals, in partnership, started a phase 1/2/3 study to evaluate CTX 001 therapy in subjects older than 12 years with β-thalassemia (NCT03655678) and SCD (NCT03745287). The treatment consists of withdrawing and editing patients' CD34+ cells in the *BCL11A* gene before reinjecting the cells in the patients. The modification in the *BCL11A* gene introduces the mutation leading to the persistence of fetal hemoglobin (HbF). Preliminary results in two patients revealed an increase in fetal hemoglobin levels maintained in the bone marrow and peripheral blood cells for more than one year after therapy (Frangoul et al. 2021, Modarai et al. 2021). Vertex Pharmaceuticals has just begun a phase 3 study evaluating CTX 001 in pediatric patients, 2 to 11 years, with both conditions.

Another two clinical trials with satisfactory results were for treating lymphoblastic leukemia (NCT03164135l) and amyloidosis (NCT04601051). For the first, the therapy consisted of the CRISPR/Cas9-mediated disruption of the *CCR5* gene. The results were successful transplant, long-term engraftment, and efficiency of 5,20 to 8,28% in a patient with HIV-1 infection. Lymphoblastic leukemia remission was observed 19 months

after transplant when cells with the modified *CCR5* gene persisted (Xu et al. 2019). For amyloidosis, the *in vivo* therapy consisted of reducing serum TTR concentration. The clinical trial revealed a persistent knockout of *TTR* after a single dose. However, the effects were dose-dependent. For patients who received 0.1 mg/kg, the mean reduction in TTR protein was 52%. While for the group receiving 0.3 mg/kg, the decline was 87% (Gillmore et al. 2021).

There are two clinical studies available for the treatment of ophthalmological diseases: the treatment of Leber Congenital Amaurosis (NCT03872479) and Refractory Viral Keratitis (NCT04560790). In the clinical trial for Leber congenital amaurosis (LCA), a rare genetic eye disorder, is the first retinal gene therapy clinical that consists of EDIT-101 administered via subretinal injection to eliminate the mutation on the CEP290 gene.

DISCUSSION

Among CRISPR/Cas9 applications, one of the most promising is its use for gene therapy. This system presents additional advantages over conventional gene therapy. First, correcting point mutations within the endogenous gene allows for better regulation of gene expression. Second, when gene adding is preferred, CRISPR/Cas9 can target the exogenous gene to genomic safe harbors, regions in which the transgene is not expected to disrupt the function of cellular genes. Finally, it can also be used for knocking out overexpressed genes, as in tumor-related oncogenes (Kelly et al. 2021, Uddin et al. 2020, Zhang et al. 2021). Gene editing has been a great tool in cancer research, with very promising advances (Chen et al. 2018) from the insertion of tumor suppressor genes to immunotherapy. One of its applications has been in screening cancer targets due to its efficiency when compared with the screening approach via blocking gene expression by RNAi (Guo et al. 2022). Another application is to increase the efficiency and safety of CAR-T cell therapy (Eyquem et al. 2017).

As the results of clinical trials show, this strategy is moving towards clinical application, as seen with other types of gene therapy (Ginn et al. 2018). In this scenario, it is strikingly that no clinical trial is associated with a South American country, either in developing or recruiting patients. However, this situation is not specific to gene editing. Most clinical trials for pharmaceutical products in South America are coordinated and sponsored by international companies (da Silva et al. 2018).

In Brazil, as in other countries, a large part of technological innovation comes from universities (De Sandes-Guimaraes et al. 2020). However, in developing countries, there is still a lack of the ability to transform the innovation generated in the university into a final product that can reach the consumer market (Lima et al. 2019). This technological gap is due to factors such as the low number of innovative companies (Melo et al. 2017) and bureaucratic barriers to industry-university partnerships (Turchi & Morais 2017). This can be seen in the low number of gene editing patents registered by South American companies in the Patentscope database.

On the other hand, the scientific contribution of South American countries to the research on CRISPR/Cas9 seems promising. Most publications with or without international collaboration are from Brazil, and the most significant number of patent filings. Most Brazilian papers belong to groups from São Paulo, Rio de Janeiro, and Rio Grande do Sul (data not shown). The regional concentration of resources, financing, and human capital is a characteristic of large developing countries. In Brazil, the most striking example is São Paulo, whose infrastructure and

financing capacity are far superior to the rest of the country (Pereira & Plonski 2010). These three states also host the most significant number of biotechnology companies with applications in human health in the country (Alves et al. 2017). However, the participation in the scientific production of Argentina, Chile, and Colombia is also fundamental since, together with Brazil, they contribute more than 90% of the total production of South America (Carvajal-Tapia & Carvajal-Rodríguez 2018).

According to Picanço-Castro et al. (2020), the low number of patents compared to articles may result from the negative perspective of biotechnology and pharmaceutical companies due to the results of the first gene therapy treatments. They showed that in the early 2000s, the rate of patents was higher than that of publications, with a decline in subsequent years. However, despite the adverse events, several advances have been made in gene therapy, and a return to increasing patenting can be observed. Regarding the worldwide patent landscape related to the CRISPR/Cas9 technology, according to Egelie et al. (2016), there were 93 patent grants and 1363 published patents, ranging from CRISPR/Cas9 components to delivery systems and applications. Therefore, this patent landscape is constantly changing.

Patent filings with the CRISPR technique have increased worldwide; it can be said due to the broad applicability of this technique in several areas: health, plants, biotechnology, and industry. The United States, China, and Europe are the countries that have the most patents and collaborations on articles using this technology (Grobler et al. 2021, Nxumalo et al. 2021). These observations corroborate our data showing the United States, followed by the United Kingdom, Germany, and China, with the highest number of contributions in articles from South American countries.

There are many applications to explore the possibility of patenting with CRISPR technology. Advances in diagnosing pathogens, for example, can be beneficial, especially for developing countries. Mainly due to the scenario we still face with the COVID-19 pandemic, some groups have developed diagnostic methods for SARS-CoV-2 using different Cas (Grobler et al. 2021). In our search, out of 7 publications aiming at pathogen detection, four were focused on SARS-CoV-2. It is also essential that universities and companies foster patent filing to benefit from their applications on an industrial scale.

Cancer is the type of disease most studied for gene editing (Nxumalo et al. 2021) and neurological disorders are second. These observations corroborate the data obtained by Picanço-Castro et al. (2020), which shows cancer as the most studied type of disease worldwide, followed by neurological disorders. Yet, surprisingly, the number of patents for CRISPR cancer-related applications is comparatively lower. Maybe this is due to the advances in non-gene editing cancer therapeutics and the more tailored use of CRISPR/Cas for inherited diseases, even though clinical trials for cancer surpass those for monogenic disease, both by gene editing and gene therapy in general (Ginn et al. 2018).

Analysis of scientific publication and patent filing data, albeit limited, provides essential information and insights for understanding scientific and technological advances. However, it has its limitations. It is important to note that the articles returned in our study do not represent the whole research field in South America, only articles published in journals indexed in PubMed, since this study focused on publications with health-related applications. The search retrieved 435 articles and almost half of them (243) were on microorganisms, animals, or plants. It is worth noticing that these

areas are probably underrepresented as the database used is focused on medical sciences. Even so, the number of publications on plants and animals only confirms South America's strength in agricultural research. The search was not performed in other databases, such as Lilacs, which may result in some bias towards PubMed-indexed publications. Also, non-English journals are underrepresented. Information on ongoing clinical trials was retrieved only from ClinicalTrials.gov, which may not contain all trials performed in South America. According to Silva et al. (2018), in South America, there are only two national registries: The Brazilian Clinical Trials Registry (ReBec) and The Peruvian Clinical Trials Registry (REPEC). However, the search for trials on CRISPR in these databases returned no results.

Our results show that, despite being a relatively easy and low-cost technology for genetic manipulation, CRISPR/Cas is not widely adopted in South America. Even though there are experimental publications, especially in Brazil, most production is performed with international cooperation (and often overseas). More importantly, when considering the intellectual property related to this technology, South American countries are completely surpassed by US and Chinese companies. As a result, the application of this technology in terms of clinical trials is absent in these countries. This reflects the importance of investing in science and fostering partnerships between academic researchers and private companies.

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SUPPLEMENTARY MATERIAL

Table SI.

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LF and MVF conceived the study, analyzed the data, and prepared figures, LF, MVF and UM wrote the manuscript, and UM revised the final version of this paper; all authors read and approved the final version.