WORLD PANORAMA OF SPOROTRICHOSIS PATENT DEPOSIT AND USE OF PATENT INFORMATION FOR PROBLEM SOLVING IN UNDERDEVELOPED COUNTRIES SCENARIO

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To analyze the main patents related to diagnosis of sporotrichosis on Espacenet, a patent base with more than 120 million documents, seeking to select free documents for exploitation, with low cost of reproduction, and that can be used to at least minimize problems related to sporotrichosis. Patent2net, an open-source patent collector, was used to search in Espacenet, a database with more than 120 million of patents, documents that will be freely applied in Brazil. In this experiment, the concept of search of "sporotrichosis" in the Espacenet database used the sequence of descriptors as follows: "(ta=dimorph* AND ta=fung*) OR (ta=sporotr*) OR (ta=subcut* and ta=fung* AND ta=infect*)". We identify a Taiwanese patent related to a kit for rapid detection of Sporothrix infection, that can be freely manufactured Brazil and other underdeveloped countries. The technometric analysis performed with P2N can be replicated by any interested in search of technological solutions for numerous problems. The technometric analysis performed with P2N can be replicated by any interested in the search of technological solutions for numerous problems. Despite the findings of recent species related to Brazil and the growing epidemic in the city of Rio de Janeiro – RJ, Brazil, there are no studies regarding the evolution of patents related to the diagnosis or treatment of sporotrichosis.

Keywords: Sporothricosis, Sporothrix schenckii, Patents, Data-mining, Patent2net



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Abstract

Sporotrichosis is a neglected disease occurring worldwide, described as an occupational risk disease, affecting farmers, gardeners, and agricultural workers. Patents have territorial restrictions, being valid only in countries that have granted a patent license, which allows their free reproduction in countries where protection has not been extended. The use of tools that extract, organize, analyze and allow the targeted selection of interest documents can contribute to solution of problems in technologically less developed countries. This study aims to analyze the main patents related to diagnosis of sporotrichosis on Espacenet, a patent base with more than 120 million documents, seeking to select free documents for exploitation, with low cost of reproduction, and that can be used to at least minimize problems related to sporotrichosis. Patent2net, an open-source patent collector, was used to search in Espacenet, a database with more than 120 million of patents, documents that will be freely applied in Brazil. We identify a Taiwanese patent related to a kit for rapid detection of *Sporothrix* infection, that can be freely manufactured Brazil and other underdeveloped countries. The technometric analysis performed with P2N can be replicated by any interested in search of technological solutions for numerous problems, especially in poor countries.

Keywords: Sporothricosis; Sporothrix schenckii; Patents; Data-mining; Patent2net.

1. Introduction

Neglected diseases represents the most common pathologies among low-income individuals living in Latin America and the Caribbean (Hotez et al., 2008), and have afflicted human societies throughout history (Sands et al., 2016). Sporotrichosis is a neglected disease of humans and animals, occurring worldwide and since it was first noted in the United States in 1898, this mycosis has been described as a disease of occupational risk, affecting farmers, gardeners, and agricultural workers. Recent epidemics have demonstrated the potential for zoonotic transmission of the disease (Queiroz-Telles et al., 2017), and have nearly always involved cats as the main source of infection (Dias et al., 2011; Rodrigues, De Hoog, et al., 2013).

Most of the 51 species embedded in the genus *Sporothrix* are nonpathogenic environmental fungi that are closely related to decaying wood, plants, and soil. However, members of the *Sporothrix schenckii* complex are highly successful mammal pathogens (Gremião et al., 2017; Rodrigues, de Melo Teixeira, et al., 2013) that cause a mycotic infectious disease that is generally acquired by traumatic inoculation of contaminated materials especially from plant debris or through bites and scratches from diseased animals, such as domestic cats (Montenegro et al., 2014).

These species embedded in the *Sporothrix schenckii* complex are frequently agents of human and animal sporotrichosis, that is a subcutaneous mycosis and some of these are responsible for large sapronoses and zoonoses around the warmer temperate regions of the world (Rodrigues et al., 2016), with a worldwide distribution that is currently notable for areas

of especially high endemicity in Latin America (de Lima Barros et al., 2011; Queiroz-Telles et al., 2011).

According to Marimon et al. (2007), the phenotypic and genotypic analyses have led to the identification of four new species in the *Sporothrix* complex: *S. globosa*, a globally distributed fungus (R. Cruz et al., 2012; H. Madrid et al., 2009; Oliveira et al., 2011); *S. brasiliensis*, the species related to the zoonotic epidemic of sporotrichosis in Rio de Janeiro, Brazil (Oliveira et al., 2011); *S. mexicana*, initially limited to Mexico (Marimon et al., 2007) and *S. luriei*, formerly *S. schenckii* var. *luriei* (Marimon et al., 2008).

In Brazil *Sporothrix brasiliensis* is the most prevalent etiological agent, although *S. schenckii* is also found. By means of nail or scratch, the infected cats transmit the fungus to other felines, dogs and also their owners and it affects the skin, lymphatic system, and other organs in the warm-blooded host (Montenegro et al., 2014; Moon, 2017). Sporotrichosis was classified as an implantation mycosis, because this infection may also involves other sites beyond the skin and the subcutaneous tissues, such as lymphatic vessels, muscles, fascia, cartilage, and bones (Queiroz-Telles et al., 2011).

The human sporotrichosis, in Brazilian territory, is not a compulsorily notifiable disease and is concentrated in animals from the periphery and poor communities, which makes treatment difficult due mainly to cost and, therefore, its exact prevalence is unknown (Moon, 2017). According to Almeida-Paes (2014), more than 4,100 human cases in Rio de Janeiro have been diagnosed in only one health institution since 1998. Most patients are children or housewives with frequent contact with domestic and/or stray cats. They need to have cats in their houses as a control against invasion by rodents, because they usually live under poverty conditions in suburban regions of the metropolitan area with poor access to health care and unsanitary living conditions.

However, since 2013, due to the hyperendemic status of sporotrichosis in Rio de Janeiro, the disease has become mandatory reporting in the state. Only Fiocruz Institute, a reference unit in Rio de Janeiro, more than 5,000 human cases and 4,703 feline cases were diagnosed by the year 2015. According to data from the Sanitary Surveillance of Rio de Janeiro city, there were 3,253 cases reported in felines with an increase of 400% in the number of animals diagnosed in 2016. In the same year, the Municipal Health Department of Rio de Janeiro registered the number of 580 cases in human. These statistics refer only to reported cases, but Brazilian researchers point out that the level of underreporting should be large (Moon, 2017).

It is known that patents have territorial restrictions, that is, they are valid only in countries that have granted a patent license, which allows their free reproduction in countries where protection has not been extended (França, 1997). Unfortunately, many challenges still remain regarding the use of no academic information such as patents (Ozcan & Islam, 2017). Thus, the use of computational tools that extract, organize, analyze and allow the targeted selection of interest documents can contribute to the solution of problems in technologically less developed countries (Ozcan & Islam, 2017; You et al., 2017; Ferraz et al., 2016; Caputo, 2006).

Respecting the international legislation related to intellectual property, as well as the logic of R & D investments, belonging to patent depositors, the use of patent information by countries, that not yet reached the status of developed, could contribute to the improvement of

health indicators, such as neglected diseases, especially sporotrichosis, since patents have a lot of information related to innovation (Quoniam et al., 2014).

The exploitation of patents as a source of technological information has not yet been perceived as fundamental in Brazil. Patents are competitive instruments and source of technological information to be used in knowledge management. However, the lack of culture in this regard inhibits the use of patented technology, fundamental for problem solving (Ferreira et al., 2009). Main holders of Brazilian priority patent applications were related to one deposit, as demonstrated in Table 1.

Table 1. Brazilian patent deposited in 2008 related to sporotrichosis.

Number of order	Date of deposit	Title	Holder (s)
PI0802672-6	25-august- 2008	Monoclonal Antibody, Pharmaceutical Composition, Process For Preparing Monoclonal Antibody, Hibridoma, Sporotricose Diagnostic Kit, Sporotrichosis Diagnostic Method And Sporotrichosis Treatment Method	*

Source: http://bv.fapesp.br/pt/papi-nuplitec/948/anticorpo-monoclonal-composicao-farmaceutica-processo-de-preparacao-de-anticorpo-monoclonal-hibri

Despite the findings of recent species related to Brazil and the growing epidemic in the city of Rio de Janeiro – RJ, Brazil, there are no studies regarding the evolution of patents related to the diagnosis or treatment of sporotrichosis. In this sense, the objective of present study is to analyze the main patents related to the diagnosis and treatment of sporotrichosis on Espacenet, a worldwide patent base with more than 120 million documents, seeking to select free documents for exploitation in Brazil, with a low cost of reproduction, and that can be used to at least minimize the problems related to this disease in the Brazilian scenario.

2. Methods

Espacenet is a free patent research service offered by the European Patent Office (EPO) and this service allows searching for full texts of documents from several countries. Patent2net (P2N) is a public domain software used to extract patent documents as a free-use tool that can be used for data mining at Espacenet database (Ferraz et al., 2016; Reymond & Quoniam, 2016). The decision to use Espacenet as the search database rather than, for example, Patentscope, was due to the Application Programming Interface (API) that Espacenet offers (Ferraz et al., 2016).

In this experiment, the concept of search of "sporotrichosis" in the Espacenet database used the sequence of descriptors as follows: "(ta=dimorph* AND ta=fung*) OR (ta=sporotr*) OR (ta=subcut* and ta=fung* AND ta=infect*)". The term "ta" determines that any keyword present should be searched both in the "title" and in the "abstract" of all the patents present in

Espacenet, that are immediately extracted and become part of new database, which will be used for analysis by the tool itself.

The advantage of this data mining software allows Espacenet to only search for patents in .pdf format, not allowing, for example, selecting free documents for reproduction, or even those that have low production costs. In general, P2N executes in sequence many computational modules, since the creation of an account in Espacenet database to authorize the patent collector. The search in Espacenet obtained information about patents classification, depositor company, inventor, country of deposit and other relevant information extracted by P2N related to patents of "sporotrichosis". The program performs the data mining process, extracting bibliographic data and full text of patents corresponding to the search criteria, and presents the results in a format to facilitate analysis.

In this sense, the technological and statistical analysis allows the prior selection of documents of interest, facilitating the selective reading of a reduced number of patents, since the average time to read a patent is approximately 30 minutes. The information obtained from the extractions and analyzes were presented in the form of graphs and reports generated by P2N, allowing qualitative and quantitative evaluation of Science and Technology indicators related to patents. It was possible to make comparisons and to relate information that made possible to evaluate and to know researches and innovations related to the subject in several countries.

The results of this work allow evaluating the geolocation map of deposit patents countries, besides the interface for identification of number of patents deposited, with basis in several epidemiological determinants. The data allow crosses between a series of indicators, and permit to select specific patents based, for example, on a certain free technology in a particular country. Other indicators relating to selected patents can also be observed, such as patent title, inventor name, company and depositor country, international patent classification, date of filing, its legal status, among others.

Analyzing the generated maps, it was possible to identify the major countries that invest in patenting sporotrichosis, as well as where these deposits occur. Through networks it is possible to know the main relationships between countries, inventors and technologies. In order to perform the data information analysis was applied the Content Analysis (CA), considering the rigor of objectivity and the fecundity of subjectivity. This type of analysis leads the researcher to the profound conclusions, since it results in qualitative and / or quantitative indicators (Cappelle et al., 2011). Detailed information about the mechanism of Patent2net operation, especially those of a computational nature, can be found in documentation available on the website (https://github.com/Patent2net/Patent2NET), and in seminal manuscript by Reymond and Quoniam (2016).

3. Results and Discussion

The P2N patent analysis found 94 patents in relation to the search strategy described previously. The titles of each document were previously read to identify possible patents that were not related to *Sporothrix* fungus or sporotrichosis disease. In this prior analysis, none of the patents was discarded (Figure 1).



Figure 1: Data related patent search regarding sporothricosis in Espacenet by P2N. Source: Authors data using P2N.

The countries with the largest number of inventors who patented innovations on sporotrichosis are the United States (49), followed by South Korea (19). Other countries such as Germany (8), China (6), France (4), Canada (4), Japan (2), Portugal (2), Russia (1) and Italy (1) are also among the countries of origin of inventors (Figure 2). Except for Venezuela (8), there are no inventors in other Latin American countries recently registered in Patent2net. Interestingly, although isolated cases of feline sporotrichosis have been documented in Australia, Spain, Japan, and Germany, but there are no reports of zoonotic transmission from these regions (Mackay et al., 1986; Scheufen et al., 2015).

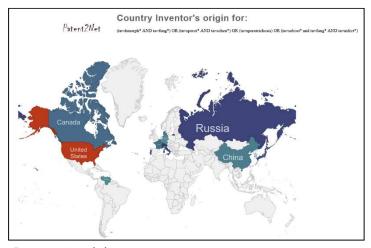


Figure 2: Country Inventor's origin. Source: Authors data using P2N.

The United States (22) and South Korea (7) are the predominant about origin of the new patens requesting. France (4), Germany (3), China (3), Denmark (3), Venezuela (2), Canada

(1), Japan (1), Portugal (1), Russia (1) and Italy (1) are the countries that applied patens about sporotrichosis as demonstrated in Figure 3.

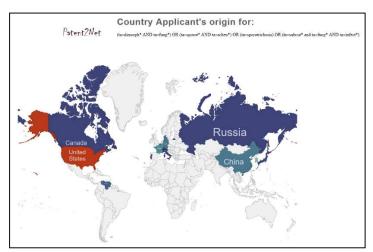


Figure 3: Country Applicant's origin.

Source: Authors data using P2N.

The United States (27), China (11), the United Kingdom (8), Japan (8), France (6) and Canada (6) are the countries where the largest number of patents had requested protection, followed by Germany (3), New Zealand (2), Australia (1), Portugal (1), Russia (1), Switzerland (1), Mexico (1) and South Africa (1) as shown in Figure 4. Brazil is not among the countries that have protected technologies on sporotrichosis.

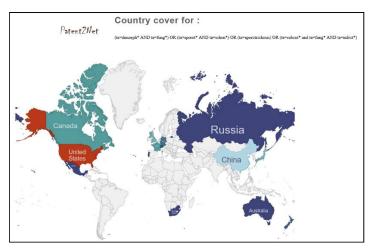


Figure 4: Countries of patent deposit.

Source: Authors data using P2N.

Cat-transmitted sporotrichosis has been documented in isolated cases or in small outbreaks in the American and Asian continents. In Mexico only one case of zoonotic sporotrichosis was described related to a scratch of an infected cat in 2008 (Bove-Sevilla et al., 2008). The results on time evolution by Patent2net showed the highest number of deposited

patents in the year 1981 and two peaks in 1998 and 2003, as shown in the Figure 5. This phenomenon can be explained because the period up to the 1980s, the feline sporotrichosis was rare and its transmission to humans was described in isolated cases or in small outbreaks among veterinarians, technicians, caregivers and owners of cats with the disease (Dunstan et al., 1986; C. Kauffman, 1999; Schubach et al., 2004).

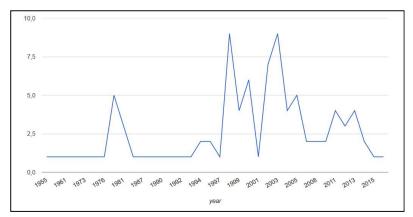


Figure 5: Temporal evolution of deposits.

Source: Authors data using P2N.

In the late twentieth century, some authors claimed that there were few epidemiological studies on the investigation of sporotrichosis, reporting only localized outbreaks like what happened to miners in South Africa (Silva et al., 2012). Isolated cases or small outbreaks were reported in United States from 1952 to 2011, and *S. schenckii* was the etiologic agent (Reed et al., 1993; Rees & Swartzberg, 2011; Singer et al., 1952). In Malaysia, 12 cases of zoonotic transmission related to cats were reported between 1990 and 2010, and five of them were from a small outbreak. In India, one case of zoonotic transmission was reported in 2009 (Tang et al., 2012; Yegneswaran et al., 2009; Zamri-Saad et al., 1990).

It is possible to observe in the Figure 5 that the sporotrichosis patents had an increase with two peaks in the years of 1998 and 2004. This fact can be explained since in this period the cases of sporotrichosis increased in the world, mainly in tropical countries, especially in Brazil. From 1997 to 2011, 4,188 human cases were recorded at Oswaldo Cruz Foundation (Fiocruz), Rio de Janeiro – RJ, Brazil, the main referral center for the treatment of this mycosis in Brazil (Silva et al., 2012). Due to the high incidence of feline sporotrichosis, Rio de Janeiro is presently considered hyperendemic for cat-associated sporotrichosis (Rodrigues et al., 2016).

Cases of feline sporotrichosis and zoonotic transmission have been reported in other Brazilian states (Fleury et al., 2001; I. M. Madrid et al., 2010; Montenegro et al., 2014). Even though the causative species has not yet been reported, the proximity to the Southern region of Brazil and the type of transmission suggests that *S. brasiliensis* may be the species involved in these cases of Argentina (Gremião et al., 2017).

Treatment of sporotrichosis is a challenge because it varies with the type of disease (C. A. Kauffman, 1995). Since most manifestations are subacute to chronic and localized, oral antifungal agents are usually preferred. The choice of antifungal agent in patients with

sporotrichosis is limited. In vitro susceptibility studies and clinical experience support itraconazole as the treatment of choice for patients with most forms of localized sporotrichosis, and amphotericin B as the preferred treatment for patients who are severely ill (Alvarado-Ramírez & Torres-Rodríguez, 2007; C. A. Kauffman et al., 2007), but fluconazole and ketoconazole are poor second-line choices (Horsburgh Jr et al., 1983; C. A. Kauffman et al., 1996). Because of limitations in disease therapy, this explains the protection of treatment patents in technologies network, such as that of A61P31, related to oleyl-phosphocholine, a drug that has been patented in the treatment of canine leishmaniasis (Figure 6).

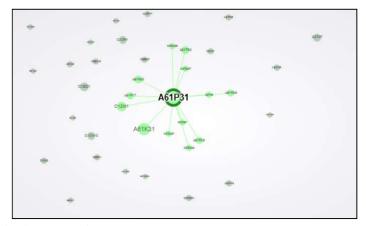


Figure 6: Technologies network. Source: Authors data using P2N.

Results presented in Figure 7 shows patent distribution according kind codes, that represent the legal status of patents, such as granted, denied, evaluated, expired, among others, besides informing, for example, if the patent is a utility model, that mostly have low cost of reproduction, being more inclusive than the other. Unfortunately, in the case of sporotrichosis, there is still no patent classified with the U-code. A complete list with meaning of each kind code can be found on Espacenet website (https://worldwide.espacenet.com/help?locale=en_EP&method=handleHelpTopic&topic=kin dcodes)

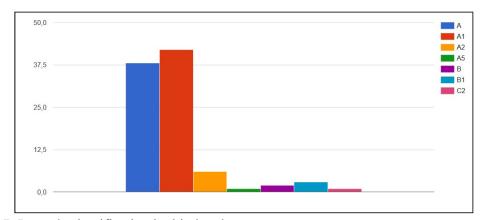


Figure 7: Patent's classification by kind code.

Source: Authors data using P2N.

Although Brazil is a country where sporotrichosis is an endemic disease, there are no inventors, companies or patents specifically protected in Brazil (Figure 8), allowing that the technologies described in the patents, found in this search, to be easily replicable in the country, except the 12 patents with worldwide protection.



Figure 8: There are no patents with participation of Brazilian inventors, applicants or country protection.

Source: Authors data using P2N.

The traditional diagnosis sporotrichosis is time-consuming and difficult to differentiate from that of a clinical sporotrichoid lesion caused by various pathogens. According to Almeida-Paes et al. (2007), the skin material collected is applied as a biopsy confirmed by culture or histochemical staining, but in some patients with clinical sporotrichosis showed absence of histochemical and culture-positive evidence. The Enzyme-Linked Immunosorbent Assay (ELISA) is a test that appears to be especially useful for cutaneous forms of disease, since these are not promptly diagnosed with available immunoprecipitation or agglutination techniques and it is a very sensitive diagnostic tool for the serodiagnosis of sporotrichosis. It was developed for specific antibody detection in serum specimens of patients with sporotrichosis with a sensitivity of 97% and a specificity of 89%, but to ELISA test is necessary the mycelial-phase *S. schenckii* exoantigens, besides, this technique is used in conjunction with conventional methods of diagnosis (making it more expensive), particularly in cases where cross-reactions or false-positive results are experienced with the serodiagnosis (Almeida-Paes et al., 2007).

At present in Brazil, it is challenging to rapidly discover and identify *S. schenckii* and *Sporothrix brasiliensis* in biopsy tissues and to explore new methods for rapid diagnosis of

sporotrichosis from the lesions of clinically suspected, to control the epidemic situation in Rio de Janeiro – RJ, Brazil. The Polymerase Chain Reaction (PCR) is a technique that uses specific primers, that is a short nucleic acid sequence that provides a starting point for DNA synthesis and can rapidly diagnose sporotrichosis with tissues obtained from clinical biopsies. The PCR assay is the high sensitivity and specificity test and can provide rapid diagnosis with sufficient accuracy to be clinically useful for patients with sporotrichosis (Hu et al., 2003; Liu et al., 2013).

The Figure 9 drawn from the P2N demonstrates the patent US20050260584 is related to methods of detecting dimorphic fungus, including differentiating a dimorphic fungus from other fungi are disclosed. This patent was encountered when the word "kit" was wrote in the window named "search", indicated in the Figure 9.

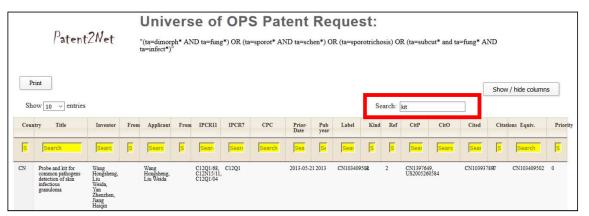


Figure 9: Patent of probe and diagnosis kit for skin granuloma related to *Sporothrix schenkii* infection.

Source: file:///F:/P2N-V2X64/DONNEES/sporotrichosis/sporotrichosis.html

Kits and arrays for carrying out these methods also are disclosed in this patent that was registered to applied in samples suspected of containing a fungus nucleic acid, such as an internal transcribed spacer-2 (ITS2) nucleic acid sequence of a dimorphic fungal rDNA, that is screened for the presence or absence of that nucleic acid. The presence of the nucleic acid indicates the sample was contacted by the fungus. Determining whether the nucleic acid sequence is present in the sample can be accomplished by detecting hybridization between a dimorphic probe, species-specific probe, and/or microbe-specific probe and a nucleic acid sequence corresponding to the ITS2 region of fungal rDNA (Figure 10).

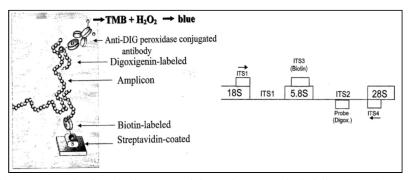


Figure 10: The PCR method and diagram of fungal rDNA, hybridization sites of primers and probes.

Souce:

https://worldwide.espacenet.com/publicationDetails/originalDocument?CC=US&NR=200526 0584A1&KC=A1&FT=D&ND=3&date=20051124&DB=&locale=en EP

The patent method described is capable of differentiating a dimorphic fungus from a non-dimorphic fungus, such as Cryptococcus neoformans, Candida species, Pneumocystis carinii. Penicillium marneffei from Penicillium camembertii, Penicillium caseicolum, Penicillium chrysogenum, Penicillium glabrum, Penicillium griseofulvum, Penicillium italicum, Penicillium janthinellum, Penicillium purpurescens, Penicillium citrinum, Penicillium purpurogenum, Penicillium roquefortii, Penicillium rubefaciens, Penicillium spinulosum, Aspergillus species, a Fusarium species, a Mucor species or Rhizopus species.

According to Cruz (2013), during the last decade there has been a significant increase in clinical cases of sporotrichosis in Brazil, particularly in the State of Rio de Janeiro where an epidemic has manifested itself in humans, which correlates with transmission by cats. Currently this mycosis should be considered an important zoonosis, especially in areas where it is endemic. Important changes have been observed in all the aspects related to ecoepidemiology of this disease, especially in their dissemination and transmission in Rio de Janeiro. With the increasing number of pathogenic species, routine diagnostic procedures of sporotrichosis have changed, with the inclusion of new aspects of morphology, physiology and nutrition. Through sequencing of genes, one has been demonstrated that the species S. schenckii is a complex that consists of the following species: Sporothrix albicans, Sporothrix cryptic brasiliensis, Sporothrix globosa, Sporothrix luriei, Sporothrix mexicana and S. schenckii. In particular embodiments, the importance of this patent method is that it is also capable of differentiating Sporothrix schenckii from a second dimorphic fungus as S. brasiliensis. Besides, this patent can meet the large and rapid demand for the diagnosis and control of the epidemic in Brazil.

4. Conclusion

Sporotrichosis patents analysis conducted by P2N has shown that neither inventors nor Brazilian companies invest in the development of technologies to combat this important neglected disease. However, the results allowed to find a patent related to a kit for rapid detection of *Sporothrix* infection. The patent, protected only in Taiwan, can be freely

reproduced in Brazil or in any other country around the world, with the exception of Taiwan itself, and its exploitation would allow the early start disease treatment, since the current methods of diagnosis are quite inconclusive and time-consuming. The technometric analysis performed with P2N can be replicated by any interested in the search of technological solutions for numerous problems. The next step of this work will be to evaluate the manufacturing cost of selected diagnostic kit and implement its use as soon as possible, in order to perform a more quickly diagnosis of this important underdeveloped countries neglected disease.

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