

Mapping Scientific and Technological Production Related to the MYC Gene

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Abstract

In appropriate activation of c-MYC proto-oncogene contributes to the development of human cancers. Searches for therapies that target genes and proteins related to neoplastic phenotypes have become frequent. Therefore, inhibiting c-MYC expression has been the target for developing and testing multiple drugs and strategies for the treatment of various human cancers. This study aimed to map scientific and technological productions on the MYC gene at the Scielo, PubMed and Orbit Intelligence platforms between 2000 and 2019. The scientific prospecting revealed 1,259 articles. The most detected categories were: molecular biology, MYC mutations and those addressing the MYC as a drug target or therapeutic strategies. A progressive increase in the number of articles in this last category was found. Technological mapping detected 10,059 patent documents, with 20.2% granted. China and the USA were the largest filers, accounting for more than 40%. Biotechnology was the field with the highest number of patents. Biotechnology and the pharmaceutical sector predominated in the second half of the period investigated, both in scientific and technological prospecting. Our study points to a scientific and technological effort in the development of therapeutic strategies against cancer, in which MYC is among the main targets.

Key-words: Scientific Prospecting, Technological Prospecting, MYC Gene, Cancer, Therapeutic Target.

1. Introduction

It has become known over the years that cancer is not a single disease, but a whole set of disorders that constitute at least 300 different histological types: carcinomas are all neoplasms of epithelial origin; sarcomas are derived from connective tissue (mesodermal); leukemias are cancers of blood-forming cells; melanomas are derived from pigment-producing cells (melanocytes); teratomas arise from germ cells or gonadal tissue (Ramalakshmi & Muthuchelian, 2011). Many epithelia also have specialized cells that secrete substances into the ducts or cavities they line. This class of epithelial cells originates the so-called adenocarcinomas (Weinberg, 2008).

Cancer genesis and progression are multi-causal processes in which normal control of cell proliferation and cell-cell interaction are lost. Aberrant activation of proto-oncogenes and unregulated inhibition of tumor suppressor genes and the DNA repair genes represent the foundations of these processes. Hundreds of genes have already been identified as belonging to these categories in human cancers, and certainly many are yet to be identified (Ward, 2002).

Proto-oncogenes are normal cellular genes involved in the regulation of proliferation and differentiation. However, if mutated, proto-oncogenes have the potential to induce neoplastic transformation. The conversion of a proto-oncogene into an oncogene is called activation and can occur through a variety of genetic mechanisms, including transduction, insertional mutagenesis, amplification, punctual mutations and chromosomal translocations (Torry & Cooper, 1991). Among the best documented proto-oncogenes in the human genome, *BCL2*, *CCND*, *MYC*, *RAS* and *SRC* stand out (Weinberg, 2008).

In humans, the *c-MYC* gene is located on chromosome 8 (region 8q24.1), comprising three exons. It encodes the MYC protein, a nuclear phosphoprotein that acts as a transcription factor. In fact, there are three isoforms of the protein, called MYC-1 (67 kDa), MYC-2 (64 kDa) and MYC-3, also called MYC-S (short), the smallest of the three isoforms, with 45 kDa (SPOTTIS et al., 1997). *c-MYC*, which plays a key role in the carcinogenesis process in several human cancers, has strong homology with cellular oncogenes (*c-Myc*) from several vertebrates and also with the avian myelocytomatosis virus *v-Myc* gene (Rocha & Rocha, 2011).

Inappropriate activation of *c-MYC*, which contributes to the development of human tumors, can occur through different mechanisms: chromosomal translocation, as found in Burkitt's lymphoma; gene amplification, increasing the number of copies of *c-MYC*, as frequently occurs in carcinomas of the stomach and colon, among others (Ryan & Birnie, 1996).

As cancers are essentially genetic diseases, the search for adjuvant therapies whose main target is genes and proteins related to neoplastic phenotypes, such as those involved in the dysregulation of cell proliferation, has been very frequent. In this context, inhibition of *c-MYC* gene expression has been the target for developing and testing multiple drugs and strategies for the treatment of various types of human cancers (Chen et al., 2014), mainly because about 20% human cancers have already been related to overexpression of this gene (Dang, 2012). Considering the importance of the *c-MYC* gene and the potential use of this gene as a target in anticancer therapies, the aim of this study was to carry out a scientific and technological prospecting on the *MYC* gene.

2. Methodology

This study was carried out from May to June 2020. As key words, the terms “MYC gene” and “gene MYC” were used both for the survey of scientific articles and to search for patent documents.

For scientific prospecting, the following filters were used: only articles published between 2000 and 2019 and only those containing the terms in the abstract and/or title. The databases used for search were Scielo and PubMed. The articles found were analyzed one by one and categorized to quantify what types of scientific research was being carried out on this gene. Among the categories, articles that related the *MYC* gene with prognosis, diagnosis, anticancer activities and therapeutic potential, review articles, case studies, clinical studies, etc. stand out. Data were analyzed and graphs were constructed in Microsoft Excel® 2017 program.

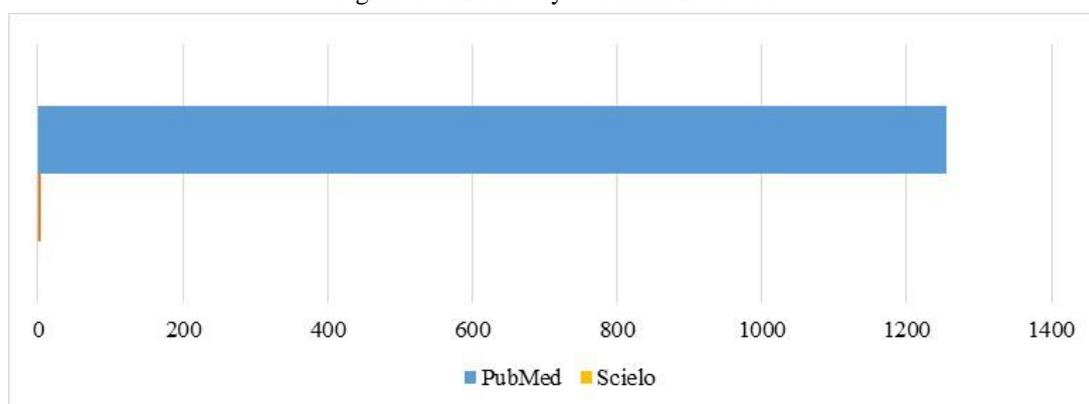
For technological prospecting, the same period (2000 to 2019) was considered and the survey was carried out at the Orbit Intelligence platform, a search and analysis system developed by the Questel Academy, with patent information from more than 90 countries. The software was used to reproduce the searches carried out and to generate specific figures and graphs based on the results obtained.

3. Results and Discussion

Scientific prospecting revealed a very large difference in the number of scientific articles published in the searched databases. While 1,255 indexed scientific articles were found in PubMed, from Scielo, only 4 were retrieved, with the same search parameters (Figure 1). This difference in results between the databases has already been verified. Puccini et al. (2015), for example, in a survey on the topic of medical education, also found that Scielo returned a much lower number of scientific

articles, just one against 10 from PubMed and 434 from Google Scholar. Such results can be explained by the fact that Scielo only compiles periodicals from Latin America and the Caribbean. PubMed, on the other hand, does not have this limitation and can still retrieve scientific articles from Scielo.

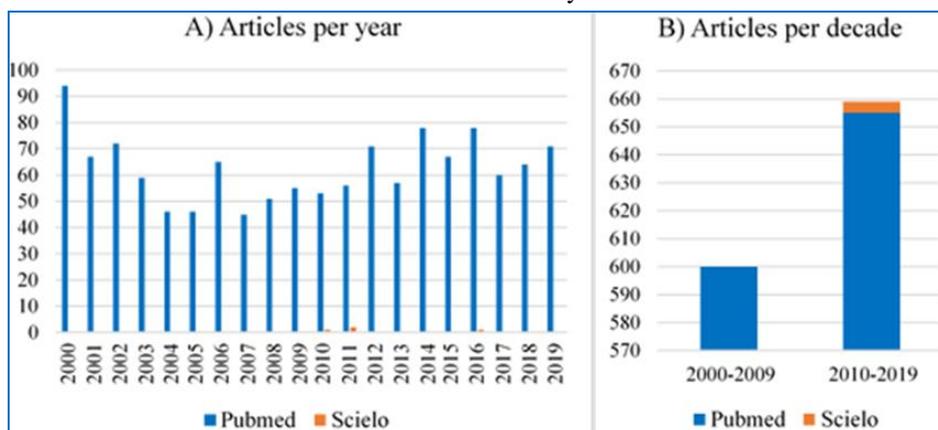
Figure 1 - Articles by Scientific Database



Source: Prepared by the authors (2020)

Regarding the number of articles published per year in the investigated time interval (Figure 2-A), although not statistically significant, according to the chi-square statistics ($p = 0.1021$), there was an increase very close to 10 % in the production of new articles related to the MYC gene in the last decade (Figure 2-B), going from a cumulative 600 articles published between 2000 and 2009 to 659 articles in the following 10 years, between 2010 and 2019. In Scielo, scientific articles were not even found in the first decade mentioned, according to the search parameters; all were published from 2010 onwards.

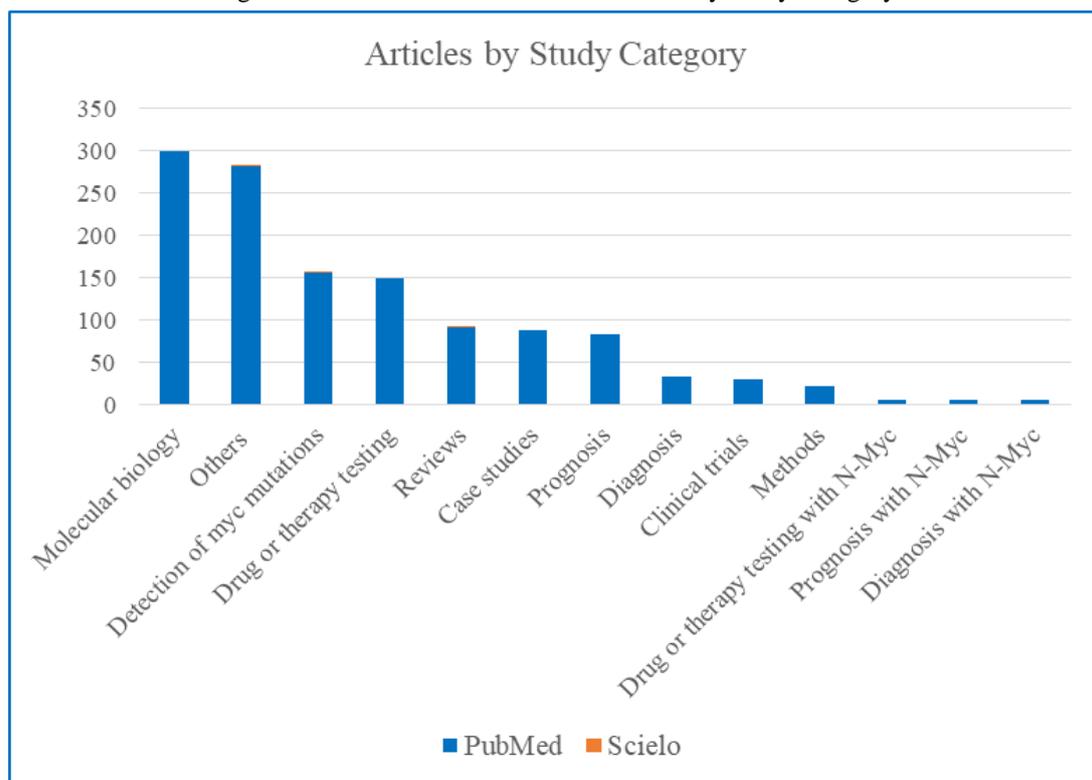
Figure 2 - Annual Evolution of Publication of Articles by Database and for a Period of 10 Years



Source: Prepared by the authors (2020)

After categorizing the articles, it was possible to observe a wide variety of scientific research involving the *MYC* gene, as illustrated in Figure 3. Most studies were related to the understanding of the functioning and structure of the *MYC* gene or its protein, as well as the relationships that the gene or protein molecularly establish with other genes and other proteins – a total of 299 articles. Among the most relevant categories, studies on the detection of mutations in the *MYC* gene (158 articles) and those addressing the *MYC* gene as a target of drugs or new and/or potential therapeutic strategies (150 articles) can be mentioned.

Figure 3 - Distribution of Retrieved Articles by Study Category



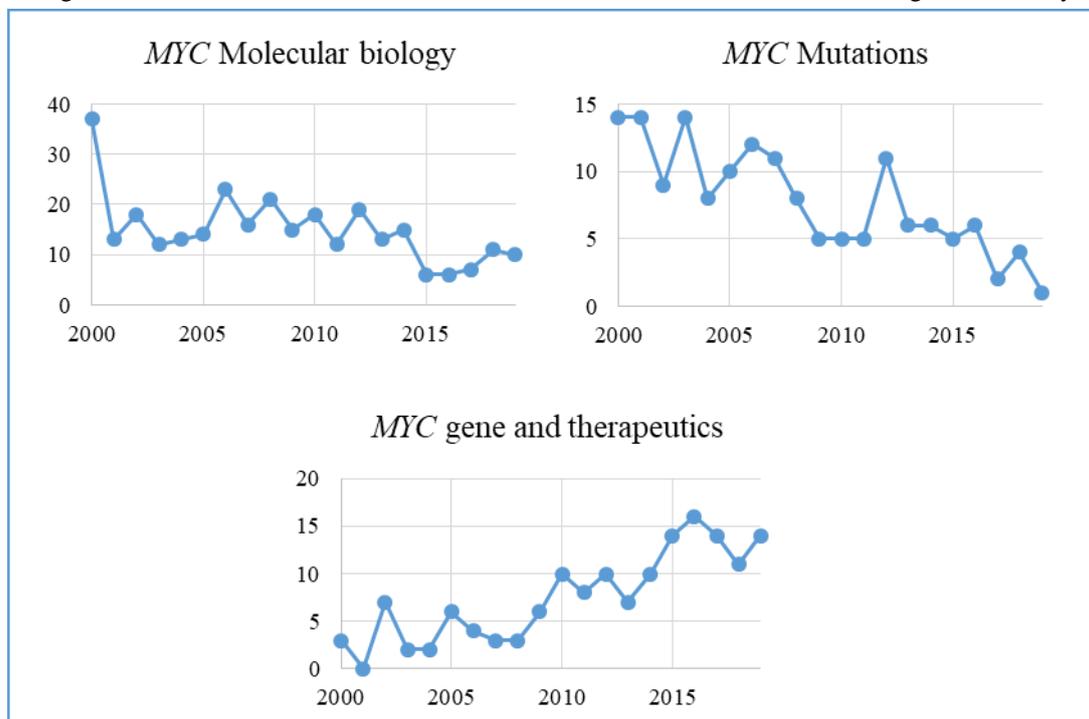
Source: Prepared by the authors (2020)

The *c-MYC* (or simply *MYC*) gene is the first and best-known member of the *MYC* gene family. *n-MYC* also belongs to the family and corresponds to a powerful oncogene, which functions as a transcription factor, although less is known about its transcriptional regulatory circuit (RAHL & YOUNG, 2014). Amplification of *n-MYC* is found in about 25% neuroblastoma cases (the most common extracranial solid tumor in childhood) and is correlated with high-risk disease and poor prognosis. Currently, *n-MYC* amplification remains the best characterized risk genetic marker in

neuroblastoma (HUANG & WEISS, 2013). In this perspective, the n-*MYC* gene is addressed in more than 20 articles retrieved from PubMed.

An interesting aspect of the result can be observed with the most relevant categories over the analyzed period (Figure 4). While publications on molecular biology and *MYC* mutations declined, the number of articles linking the *MYC* gene to drug or therapy testing showed a relative increase.

Figure 4 - Annual Evolution of Publication of Articles on the most Relevant Categories of Study



Source: Prepared by the authors (2020)

Studies of molecular biology and mutations of the *MYC* gene allowed a good understanding of its normal functioning and also of alterations that contribute to the genesis of different types of cancer. As this basic knowledge was consolidated, its application in the search for treatment options became possible and is now increasing. In a very recent publication, Wang et al. (2020) faithfully summarize the current idea: the overexpression of the *MYC* oncogene is a molecular hallmark of both cancer initiation and progression. Thus, targeting *MYC* is a logical and effective cancer therapeutic strategy.

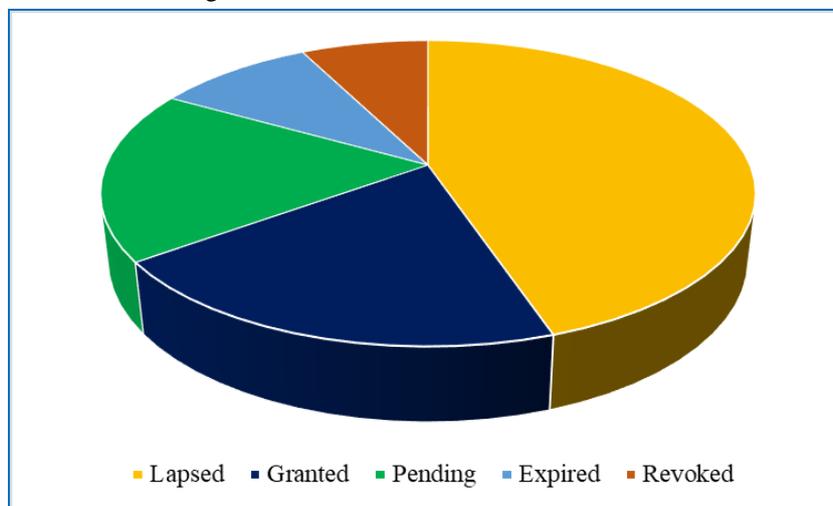
Brazilian research is also represented in this scientific production. For example, in vitro tests of substances against cancer cells, such as kaurenoic acid, tested against gastric cancer strains (Cardoso et al., 2017) and cervical cancer (Rocha et al., 2019) have been published. In both cases, the

treatment significantly reduced the transcription of the *BCL2* and *MYC* oncogenes, in addition to increasing the transcription of the *ATM*, *CHK* and *TP53* genes.

Although it is not in the period considered for this prospecting, the study by Bona et al. (2020) with menadione (a synthetic vitamin K) stands out, which had already been tested in cell lines and has now been used in vivo against gastric cancer induced in a non-human primate (*Sapajus apella*), proving to be an effective antitumor agent via decreased expression of the *CDC25B* gene, which is induced by the *MYC* gene. In this case, the drug did not prevent the increased expression of *MYC*, but acted to block their effects on *CDC25B* in primate stomach tissue. The authors suggest that menadione may be an important ally of chemotherapeutics in the treatment of gastric cancer.

Considering technological prospecting, after searching the Orbit Intelligence tool, 10,059 documents were identified. According to Figure 5, in which the status of patents can be observed, the highest percentage (44.8%) is represented by lapsed patents. On the other hand, the granted patent status includes 20.2% retrieved documents, corresponding to 2,032 filings.

Figure 5 - Status of Patents on the *MYC* Gene



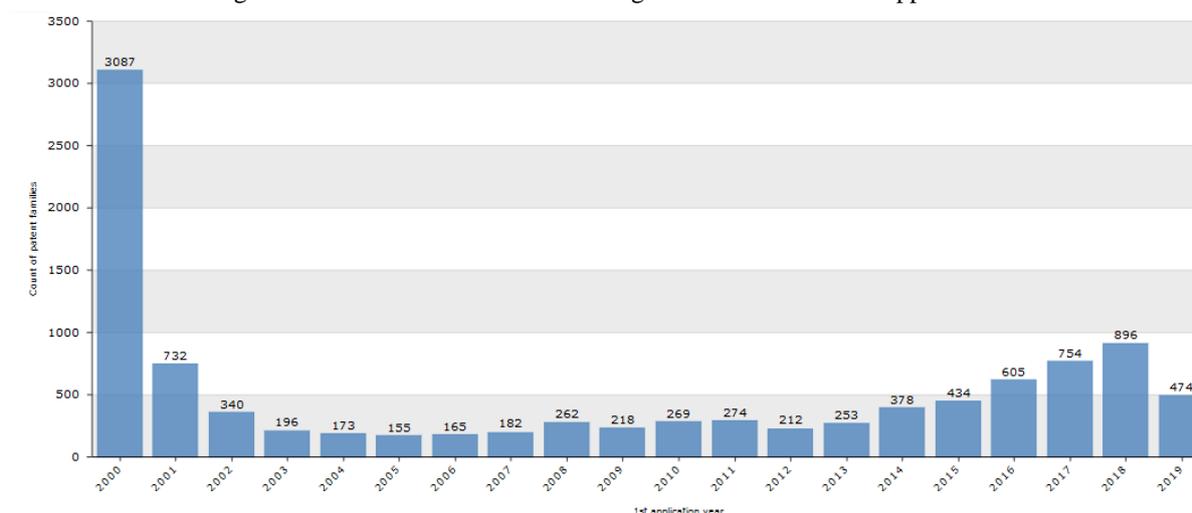
Source: Prepared by the authors from the analysis of the tool of Orbit Intelligence (2020).

Forfeiture is the form of extinction of patent rights as a result of non-compliance with the burden of exploring the invention (Carvalho, 1996). Once the patent has lapsed, the object of the patent falls into the public domain, and any interested party may explore it without payment of any fee or even freely import the product. Maravilhas & Duarte (2014) present an interesting example related to generic drugs. These are no more than the active substance of a drug whose patent has lapsed or expired, thus becoming in the public domain, capable of being manufactured and marketed

by any other company, provided that it does not use the registered trademark, if still in force, by the owner of the expired patent.

In the period analyzed, the largest number of patents (3,087) was filed in 2000 (Figure 6). Then, successive drops in the annual number of patents were observed, reaching the lowest value (155) in 2005. Between 2006 and 2012, there were small fluctuations. From 2012 to 2013, there was an increase of about 20% and the increases continued until 2018, with 896 patents. From the year 2019, 474 patent applications were retrieved, but this number is not yet definitive due to the confidentiality period of up to 18 months of a patent.

Figure 6 - Number of Patents According to the Initial Year of Application



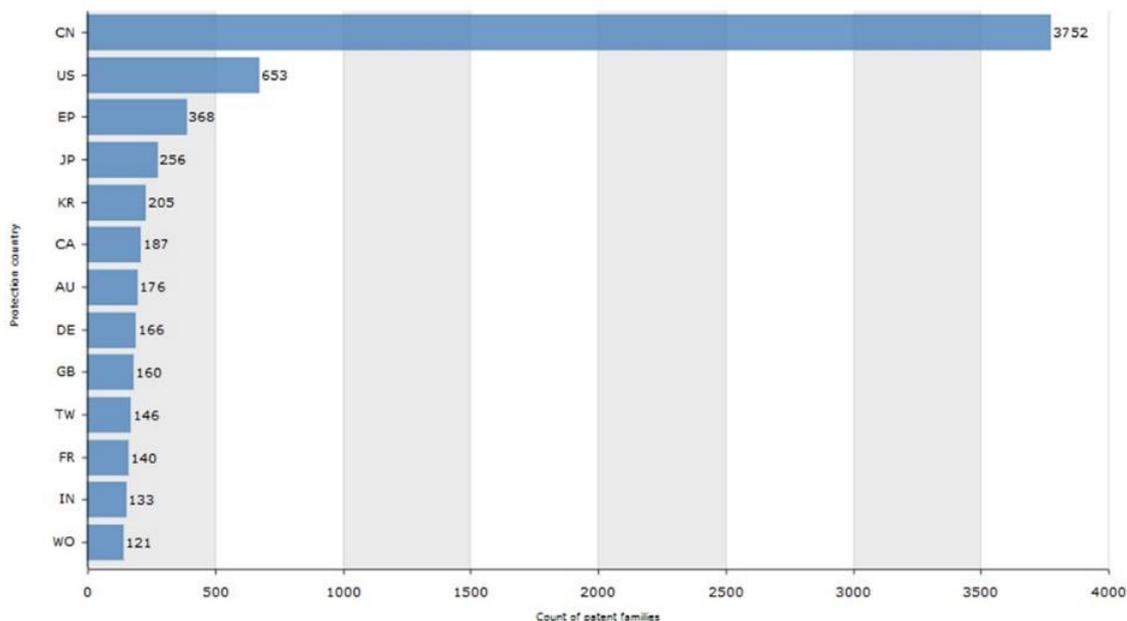
Source: Adapted from Orbit Intelligence (2020)

A large part of the patent documents from the year 2000 are related to the area of molecular biology, such as the use of reporter genes, the immortalization of genetically modified cells and the delay in cell aging. In recent years, patents related to biotechnology and the pharmaceutical sector predominate, such as the document “*c-MYC* Gene Expression Inhibitor and Application Thereof”, which has the order number CN109820866A and was published on May 30, 2019. The invention relates to an inhibitor of *c-MYC* gene expression and its application for the preparation of antitumor drugs. The inhibitor of *c-MYC* expression is a small pyrrole-imidazole polyamide molecule. This small molecule is targeted to a promoter sequence of the *c-MYC* gene through a recognition and pairing mode, and *c-MYC* expression is silenced.

In this prospecting, the main patent applicant by jurisdiction worldwide, in relation to the *MYC* gene, is China (code “CN”), with 3,752 filings. The United States of America (code “US”), with

653 filings, is in second place. It is noticed that the first two already represent more than 40% patent applicants related to the subject (Figure 7). The “EP” code, which appears in the third position (368 filings), corresponds to the European Patent Organization (EPO), an international organization headquartered in Munich, which brings together several countries and has more than 20 member states.

Figure 7 - Results for the Search Regarding the Countries where Patent Applications are Filed

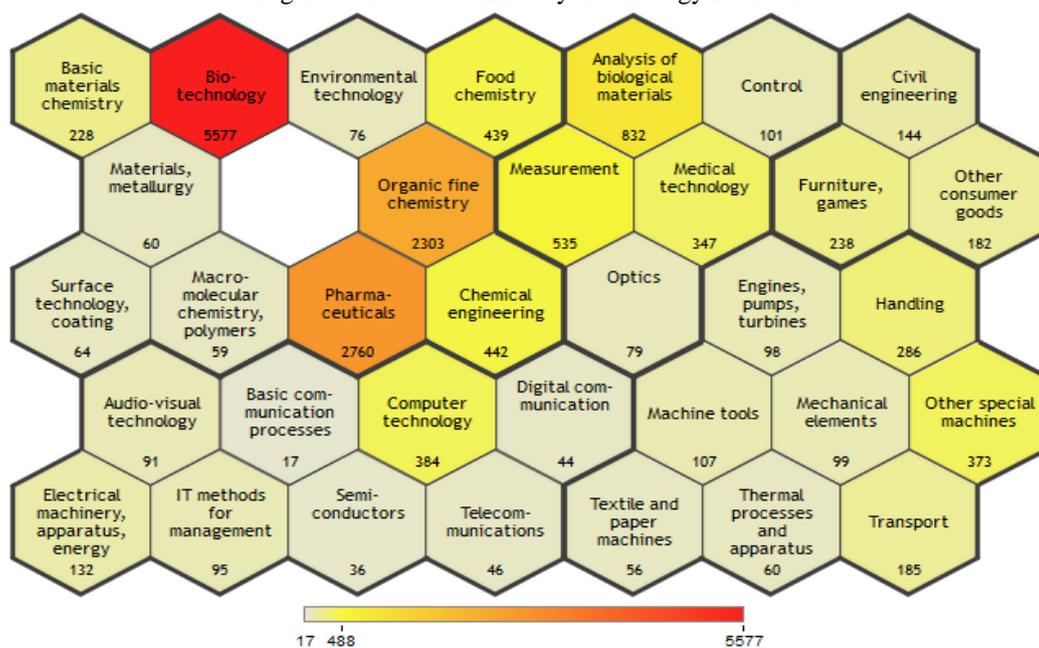


Source: Orbit Intelligence (2020)

Although it no longer appears in the list of largest investors since 2004, the applicant with the highest number of patents related to *MYC* in the period 2000-2019 is the company Shanghai Biowindow Gene Development Co., Ltd., with 3,218 filings, of which less than 5% currently correspond to active patents. In the last five years of the survey (2015-2019), two other Chinese companies stand out, relatively new in this area: Tianjin Hubin Pangu Gene Science Development Co., Ltd. (192 filings) and Guangzhou Kangxinrui Gene Health Technology Co., Ltd. (120 filings).

Figure 8 presents an overview of technology based on International Patent Classification (IPC) codes, grouped into 35 technology fields. As the categorizations by technology domain are based on groupings of IPC codes, the same patent can appear in different categories. In the figure, the darker the technology area, the greater the number of patent registrations. Thus, biotechnology has the largest number of records, followed by the pharmaceutical and fine organic chemistry sector.

Figure 8 - Patent Families by Technology Domain



Source: Orbit Intelligence (2020)

In addition to interesting natural products and chemotherapeutic agents, biotechnology also focuses on small natural and artificial RNAs, which constitute a promising route of therapy with nucleic acid for cancer. Chin et al. (2016) reported that microRNA miRNA159 targets TCF7 (a transcription factor of the Wnt signaling pathway) and can inhibit it, resulting in reduced level of MYC protein.

4. Final Considerations

In this study, bibliometric and patentometric analyses of the production of scientific articles and patent documents related to the *MYC* gene in the period 2000 to 2019 were carried out. The number of retrieved articles (1,259) was much lower than that of patent documents (10,059). Both productions (scientific and technological) had higher numbers at the beginning of the millennium and were mainly related to molecular biology; after successive drops in these numbers, they rose again in the second half of the analyzed period and now predominantly focused on biotechnology and the pharmaceutical sector.

The establishment of the *MYC* gene as a key element in the genesis of several neoplastic processes in humans has guided research in which *MYC* is the main target for the development of therapeutic strategies against cancer. Some well-established drugs and several promising drug

candidates share the property of reducing or silencing MYC by decreasing its expression or blocking the effect of their product. Among the most relevant results supporting the interest in future advances are: the evidence that kaurenoic acid can serve as a raw material for the development of therapeutic agents against cervical cancer with the presence of HPV and that menadione can help in gastric cancer chemotherapy.

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