



Global Patent Landscape in Breast Cancer Metastasis

Gerardo Landeta¹, Maricruz Anaya-Ruiz², Gabriela Sanchez-Esgua¹, Luis Villafaña-Díaz¹ and Martin Perez-Santos^{1*}¹Centro Universitario de Vinculación y Transferencia de Tecnología, Benemérita Universidad Autónoma de Puebla, México²Laboratorio de Biología Celular, Centro de Investigación Biomédica de Oriente, Instituto Mexicano del Seguro Social, México***Corresponding Author:** Martin Perez-Santos, Centro Universitario de Vinculación y Transferencia de Tecnología, Benemérita Universidad Autónoma de Puebla, México.**Received:** May 07, 2018; **Published:** May 25, 2018**Abstract****Objective:** Analyze the patent documents of the five main patent offices in the world to design an overview on the development of alternatives for the treatment of breast cancer metastasis.**Materials and Methods:** Patent documents were obtained from the patent bases of the five main patent offices in the world and patentometric methodologies are used to investigate their contents and relationships. Results: 6574 patents from 1998 to 2017 including "breast cancer metastasis" were retrieved. The US was the leader in patent claims, followed by Australia, China, Germany and South Korea. Conclusions: the results show that the patent activity related to breast cancer metastasis is increasing and the leading countries are the US, Canada, China, Japan, South Korea, Germany, England, France, and Australia. In addition, the data obtained will allow addressing key evaluation questions to define new areas of research.**Keywords:** Breast; Cancer; Metastasis; Patentometric; Landscape**Introduction**

Breast cancer is the most commonly diagnosed cancer in women, with 1.7 million new cases annually and 520,000 deaths globally [1], and metastasis to distant organs is responsible for ~90% of this death. Metastasis is the process by which breast cancer cells spread from the primary tumor to establish colonization at distant organs, such as the bone, lung, liver, and brain. It has been estimated that 85% of patients develop metastasis of bone [2], while 60 - 70%, 50% and 15 - 35% develop metastasis to lung [3], liver [4] and brain [5] respectively.

Despite an increasing trend in breast cancer research, metastasis remains the problem to overcome. Given this situation, it is necessary to evaluate scientific research to establish research policies adjusted to efficiency and effectiveness, and subsequently recommend adjustments to them. Recently, publications trend on breast cancer-originated metastasis was determined; it is notable that the publications trend concerning bone metastasis was above the trend of lung metastasis, whereas the trends of liver and brain metastasis were very similar [6]. It is also important to emphasize that in the last years the production of research publications tries to fulfill the magnitude of the problem.

On the other hand, the patent system allows carrying out various studies where the tendency of patent applications in a certain area of interest is analyzed. This analysis allows knowing the status of a certain scientific-technology area, including who are the leading countries, companies and inventors in a certain field. With this, duplication of efforts in scientific research is avoided. However, trends regarding patents on metastasis in breast cancer have not been addressed. Therefore, the objective of this study is to identify recent patents on breast cancer metastasis with the purpose that, based on the analysis, institutions, companies and scientists promote research policies that do not lead to duplication of efforts by continuing to investigate something that has already been addressed. In addition, a list of the most cited patents in this area is provided.

Materials and Methods

We obtained the patent documents in the databases of patent offices in the US (www.uspto.gov/patents-application-process/search-patents), Europe (worldwide.espacenet.com/advancedSearch?locale=en_EP), China (211.157.104.77:8080/sipo_EN/search/tabSearch.do?method=init), Japan (www4.j-platpat.inpit.go.jp/eng/tokujitsu/tjkt_en/TJKT_EN_GM201_Top.action) and Korea (engpat.kipris.or.kr/engpat/searchLogina.do?next=MainSearch) by using the keywords approach related to breast cancer metastasis. To do this, we executed the search strategy in the title/claims/summary sections by using the following terms: (metast*) and [(breast invasive ductal carcinoma) OR (infiltrating duct carcinoma \$) OR (mammary ductal carcinoma \$) OR (breast cancer) OR (breast neoplasm \$) OR (breast tumor \$ r \$) OR (human mammary neoplasm \$) OR (human mammary carcinoma \$)]; where \$ = any character, * = two or more character. Additionally, the data were recorded to obtain: a) patent trend distribution, b) top applicants, c) top countries, d) main international patent classification codes and e) patents with highest number of citations.

Results and Discussion

A total of 6574 patents (patent families) were obtained for the period 1998 - 2007, observing an increasing trend (Figure 1). The top ten countries in the patent claim are shown in table 1, where the US (2597) was the leader followed by Australia (1031), China (196), Germany (111) and South Korea (91). Additionally, figure 2 shows the top ten of patent applicants. With the exception of Nerviano Medical Sciences (Italy) and Novartis (Switzerland), all the assignees are from the United States. Four are universities (University of Texas, University of California, University Johns Hopkins and Dana Farber Cancer Institute) and one is a government entity (US Health). Likewise, top ten inventors are shown in figure 3; with the exception of Sui Yi Kwok and Bing Lou Wong (both from Taiwan) all the inventors are from the United States.

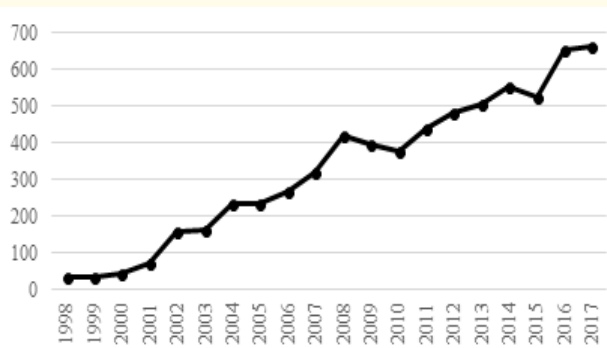


Figure 1: Patent trend distribution analysis based in breast cancer metastasis, 1998-2017. $p > 0.001$.

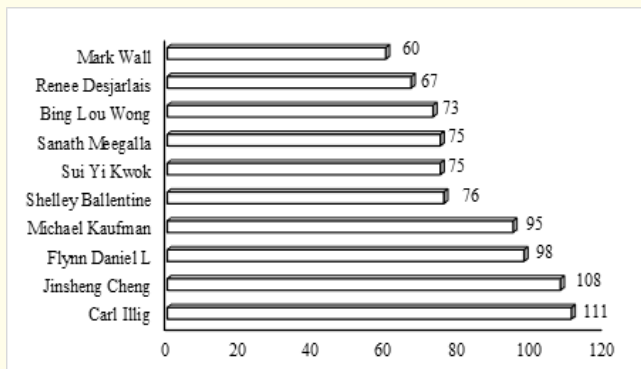


Figure 3: Top ten of inventors with patents on breast cancer metastasis, 1998-2017.

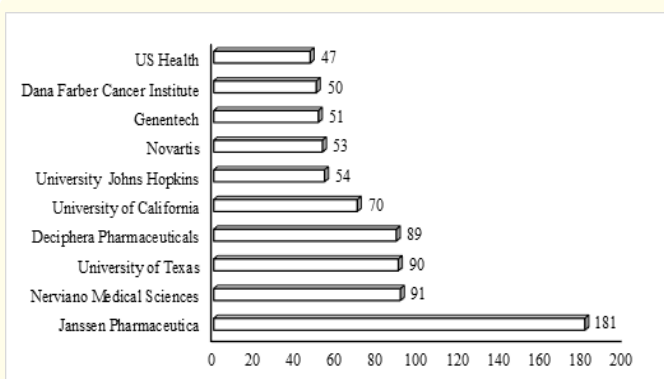


Figure 2: Top ten of applicants with patents on breast cancer metastasis, 1998-2017.

| Country | 1998-2002 | 2003-2007 | 2008-2012 | 2013-2017 | Total |
|-------------|-----------|-----------|-----------|-----------|-------|
| USA | 101 | 482 | 821 | 1193 | 2597 |
| Australia | 93 | 206 | 301 | 431 | 1031 |
| China | 0 | 8 | 69 | 119 | 196 |
| Germany | 1 | 11 | 51 | 48 | 111 |
| South Korea | 2 | 14 | 23 | 52 | 91 |
| England | 7 | 14 | 22 | 45 | 88 |
| Canada | 7 | 14 | 27 | 24 | 72 |
| Japan | 4 | 9 | 13 | 33 | 59 |
| France | 2 | 9 | 15 | 32 | 58 |
| Switzerland | 4 | 9 | 14 | 16 | 43 |

Table 1: Top ten countries with patents on breast cancer metastasis, 1998-2017.

On the other hand, main International Patent Classification codes on breast cancer metastasis are shown in table 2. Two IPC codes (A61P35/00 and A61P35/04) were relevant for drugs based

on chemical compounds; one IPC code (A61K39/395) was relevant for oncology immunotherapy; and one IPC code (C12Q1/68) was relevant for testing processes involving nucleic acids.

| IPC | Definition | 1998-2002 | 2003-2007 | 2008-2012 | 2013-2017 | Total |
|------------|------------------------------------------------------------------------------------------------------------|-----------|-----------|-----------|-----------|-------|
| A61P35/00 | Specific therapeutic activity of chemical compounds or medicinal preparations; antineoplastic agents | 170 | 343 | 926 | 721 | 2150 |
| C12Q1/68 | Measuring or testing processes involving enzymes, nucleic acids or microorganisms; involving nucleic acids | 91 | 238 | 378 | 382 | 1089 |
| A61K39/395 | Medicinal preparations containing antibodies | 47 | 165 | 392 | 357 | 961 |
| G01N33/574 | Investigating or analysing materials by specific methods for cancer | 85 | 200 | 234 | 334 | 853 |
| A61P35/04 | Specific therapeutic activity of chemical compounds or medicinal preparations; specific for metastasis | 74 | 151 | 279 | 174 | 678 |

Table 2: Main International Patent Classification codes on breast cancer metastasis, 1998-2017.

Table 3 shows the twenty leading patents with the highest number of citations about breast cancer metastasis. Interestingly, of the twenty most cited patents twelve are chemical compounds, two of micro-RNA therapy (miR-145, miR-21, miR-155, miR-10b), and one of immunotherapy (macrophages and/or other antigen presenting cells sensitized with heat shock proteins non-covalently bound to peptide complexes and/or antigenic components). It also highlights that eight patents present protein kinases as targets for drugs (Aurora-2, GSK-3, ROCK, JAK, Cdc7, AKT, PAK4, PLK, CK2, KDR, MK2, JNK1, pim 1 and nek 2).

The evaluation of the activity in patents, in comparison with the analysis of scientific publications, will allow to determine which have been the areas already studied, and consequently to determine the research gaps that need to be addressed. This study analyzed the patents related to breast cancer metastasis obtaining some important points about the trend in this area, e.g. leading countries and institutions/enterprises, and main technical fields addressed (through the patent classification system).

| Patent | Title | Applicant | Inventors | Cites |
|--------------------|------------------------------------------------------------------------------------------------------------------------------------|------------------------------|------------------------------------|-------|
| US6057105 [7] | Detection of melanoma or breast metastasis with a multiple marker assay | NGI Cancer Tech | Hoon., <i>et al.</i> | 184 |
| US20030198970 [8] | Genostics | Genostic Pharma | Roberts., <i>et al.</i> | 176 |
| US5985270 [9] | Adoptive immunotherapy using macrophages sensitized with heat shock protein-epitope complexes | University of Fordham | Srivastava., <i>et al.</i> | 142 |
| US6653301 [10] | Pyrazole compounds useful as protein kinase inhibitors | Vertex Pharma | Bebbigton., <i>et al.</i> | 136 |
| US20040077601 [11] | Methods and compositions relating to isoleucine boroproline compounds | Point Therapeutics | Adams., <i>et al.</i> | 122 |
| WO2010129053 [12] | EGFR inhibitors and methods of treating disorders | Dana Farber Cancer Institute | Gray., <i>et al.</i> | 119 |
| US20090203690 [13] | 5-substituted indazoles as kinase inhibitors | Abbott Lab | Akritopoulou-Zanze., <i>et al.</i> | 110 |
| US6037129 [14] | Multi-marker RT-PCR panel for detecting metastatic breast cancer | University of Soutj Carolina | Cole., <i>et al.</i> | 108 |
| US20100029610 [15] | Heteroaryl compounds and uses thereof | Avila Therapeutics | Singh., <i>et al.</i> | 106 |
| US6291504 [16] | Acylsemicarbazides and their uses | Du Pont Pharmaceutical | Nugiel., <i>et al.</i> | 98 |
| US6100248 [17] | Method of inhibiting cancer growth | Golub., <i>et al.</i> | Golub., <i>et al.</i> | 94 |
| US20050148603 [18] | Compositions useful as inhibitors of protein kinases | Jimenez., <i>et al.</i> | Jimenez., <i>et al.</i> | 89 |
| WO2007016548 [19] | Micro-RNA-based methods and compositions for the diagnosis, prognosis and treatment of breast cancer | University of Ohio | Croce and Calin | 86 |
| WO2004016597 [20] | Protein kinase inhibitors and uses thereof | Vertex Pharma | Cochran., <i>et al.</i> | 85 |
| US20080076674 [21] | Novel oligonucleotide compositions and probe sequences useful for detection and analysis of non-coding RNAs associated with cancer | Litman., <i>et al.</i> | Litman., <i>et al.</i> | 81 |
| WO2009140128 [22] | Compounds and compositions as kinase inhibitors | IRM | Albaugh., <i>et al.</i> | 77 |
| US20050137201 [23] | Compositions useful as inhibitors of protein kinases | Aronov., <i>et al.</i> | Aronov., <i>et al.</i> | 75 |
| US20050112630 [24] | Diagnosis, prognosis and identification of potential therapeutic targets of multiple myeloma based on gene expression profiling | Shaughnessy., <i>et al.</i> | Shaughnessy., <i>et al.</i> | 75 |
| US20100215743 [25] | Composition and drug delivery of bisphosphonates | Leonard TW | Leonard TW | 72 |
| US20100249092 [26] | Heteroaryl compounds and uses thereof | Avila Therapeutics | Singh., <i>et al.</i> | 64 |

Table 3: Twenty leading patents with the highest number of citations about breast cancer metastasis, 1998-2017.

Due to the lack of trend studies on patents and breast cancer, it is difficult to make a comparative analysis between countries and companies. However, since patents are generally linked to scientific publications, it could be established that the trends of countries between patents and publications are very similar. In this sense, three studies related to diet [27], reconstructive surgery [28] and imaging [29] in breast cancer established that the leading countries in scientific publications are those included in this study, including the USA. The only study, to the knowledge of the author, that involves the behavior of different countries in terms of patents and breast cancer is that described by Anaya-Ruiz and Perez-Santos, which shows the behavior in patents about gene therapy in breast cancer [30]. This work represents the first patentometric assessment of breast cancer metastasis. Based on the analysis of the results of

this study, the policy makers of research could make new designs of research priorities in terms of breast cancer metastasis, and as a consequence, new policies for patent protection [31].

Conclusion

There is an increasing interest in the development and protection through patents in the area of breast cancer metastasis. USA, Australia, China, Germany and South Korea were the jurisdictions of most important countries in the subject. Likewise, their inventors and US companies were the most relevant.

Conflict of Interest

The author declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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