

NEW TYROSINE KINASE INHIBITORS FOR ONCOLOGICAL AND IMMUNOLOGICAL USE FROM A MEDICINAL CHEMISTRY PERSPECTIVE

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Abstract

A documentary review was carried out on the production and publication of research papers related to the study of the variable Tyrosine Kinase and Oncology. The purpose of the bibliometric analysis proposed in this document is to know the main characteristics of the volume of publications registered in Scopus database during the period between 2016 and 2021, achieving the identification of 739 publications. The information provided by said platform was organized by means of tables and figures categorizing the information by Year of Publication, Country of Origin, Area of Knowledge and Type of Publication. Once these characteristics were described, the position of different authors regarding the proposed topic was referenced by means of a qualitative analysis. Among the main findings of this research, it is found that Brazil, with 368 publications, was the country with the highest production in the Latin American community. The Area of Knowledge that made the greatest contribution to the construction of bibliographic material referring to the study of the new Tyrosine Kinase Inhibitors and their use in Oncological treatments was the area of Medicine with 495 published documents, and the Type of Publication that was most used during the period indicated above was the Journal Article, which represents 75% of the total scientific production.

Keywords: Tyrosine Kinase Inhibitors, Oncology, Medicinal Chemistry.

1. Introduction

Tyrosine kinases are enzymes that catalyze the transfer of phosphates from adenosine triphosphate to certain proteins and play a central role in the modulation of cell growth

signals by intervening in various normal regulatory processes (Calles et al., 2019). Tyrosine kinase inhibitors show positive results compared to chemotherapies in the treatment of cancer patients, such as the evaluated cases of

patients with advanced thyroid cancer who have developed resistance to radioactive iodine treatment (Schneider et al., 2012).

The use of Tyrosine Kinase Inhibitors in oncology patients is carried out with the purpose of achieving the greatest possible effectiveness with the minimum percentage of iatrogenic toxicity in the treatment of cancer (Dominguez, 2019). In addition, their effects on the organism have been the subject of study by health professionals, who have analyzed the main effects they produce. It has even been ruled out that it causes pathologies associated with malnutrition, by means of studies which determine that 21% of the patients to whom this drug is administered present moderate malnutrition and 74.2% weight loss after six months of treatment, but in none of the cases did the patients present BMI < 18.5 kg/m² (Higuera-Pulgar et al., 2019). Therefore, it is of great importance to know the current state of scientific production regarding the topic proposed in this article, in order to describe the main characteristics of the volume of publications carried out in high impact journals indexed in Scopus and thus constitute important material in the generation of new knowledge recognizing the importance of finding new and better alternatives in the treatment of diseases such as cancer. For this reason, the present document review has been proposed with the purpose of answering the question: How has been the

production and publication of research papers related to the study of the variable New Tyrosine Kinase Inhibitors in the treatment of cancer during the period 2016-2021?

2. General Objective

To analyze from a bibliometric and bibliographic perspective, the production of high impact research papers on the variable Tyrosine Kinase Inhibitors and Oncology during the period from 2016 to 2021.

3. Methodology

Quantitative analysis of the information provided by Scopus is performed under a bibliometric approach on the scientific production related to the study of the New Tyrosine Kinase Inhibitors and their application in the area of Oncology. Likewise, it is analyzed from a qualitative perspective, examples of some research works published in the area of study mentioned above, from a bibliographic approach to describe the position of different authors on the proposed topic.

The search is performed through the tool provided by Scopus and the parameters referenced in Table 1 are established.

Table 1. Methodological design.

	PHASE	DESCRIPTION	CLASSIFICATION
PHASE 1	DATA COLLECTION	Data was collected using the Scopus web page search tool, through which a total of 48 publications were identified.	Published documents whose study variables are related to the study of the importance of Financial Education in Basic Education. Research papers published during the 2016-2021 period. Limited to Latin American countries. Without distinction of area of knowledge. Without distinction of type of publication.

PHASE 2	CONSTRUCTION OF ANALYSIS MATERIAL	The information identified in the previous phase is organized. The classification will be made by means of graphs, figures and tables based on data provided by Scopus.	Word Co-occurrence. Year of publication Country of origin of the publication. Area of knowledge. Type of publication
PHASE 3	DRAFTING OF CONCLUSIONS AND FINAL DOCUMENT	After the analysis carried out in the previous phase, the study proceeds to the drafting of the conclusions and the preparation of the final document.	

Source: Own elaboration (2022)

4. Results

The results of the proposed bibliometric analysis are presented below, as well as the development of the bibliographic review of some examples to

determine the position of different authors on the subject referenced in this article.

4.1 Co-occurrence of words

Figure 1 shows the use and frequency of keywords in the research identified in Phase 1 of the methodological design.

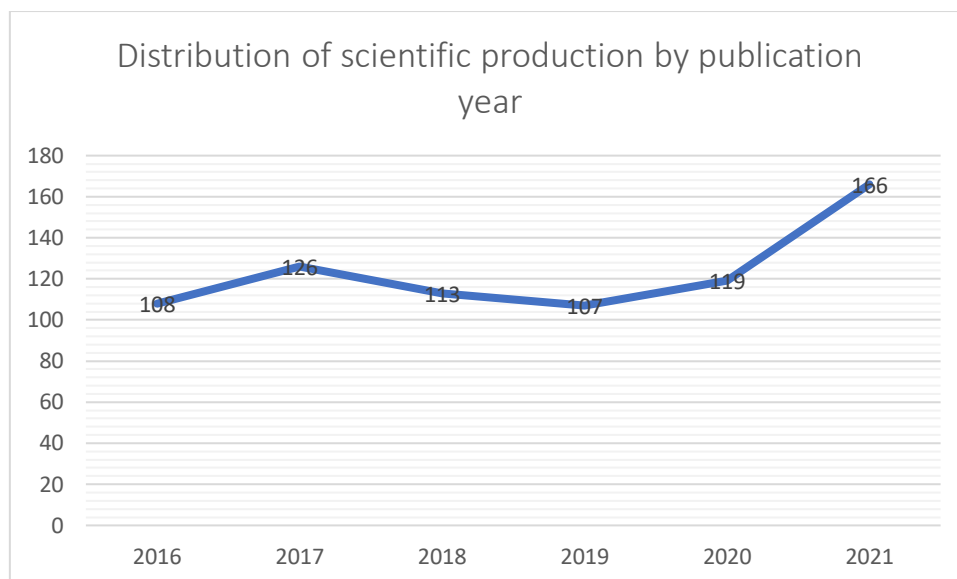


Figure 2. Distribution of scientific production by year of publication.

Source: Own elaboration (2022); based on data provided by Scopus.

The volume of publications has been relatively uniform during the years related in Figure 1, however, in 2021 the largest number of research papers published in high impact journals was registered in Scopus, a total of 166 scientific papers reported by Latin American institutions in that platform. Among these, the article entitled “*Efficacy of treatment of high-grade multiple cutaneous mastocytoma with tyrosine kinase inhibitor and vinblastine: a case report*” was found (Mujica et al., 2021), whose purpose was to document the case of a canine patient who presented erythematous masses on the medial aspect of the right hind limb, and who was started on treatment with omeprazole and a chemotherapy protocol based on a combination of vinblastine, prednisone and tyrosine kinase

inhibitor, which proved to be effective after analyzing the patient's monthly controls, registering partial remission of the masses. After seven months of treatment, the application of vinblastine was suspended without allowing the appearance of new masses; however, it did cause the appearance of new erythematous and ulcerated neoplasms in another region of the affected hind limb. The analysis of the case shown in the referenced article demonstrates that the genetic nature of neoplasms of the same type, in the same patient, could be different and, therefore, condition the response to treatment and the prognosis.

4.3 Distribution of scientific production by country of origin.

Figure 3 shows how scientific production is distributed according to the country of origin of the institutions with which the authors are affiliated.

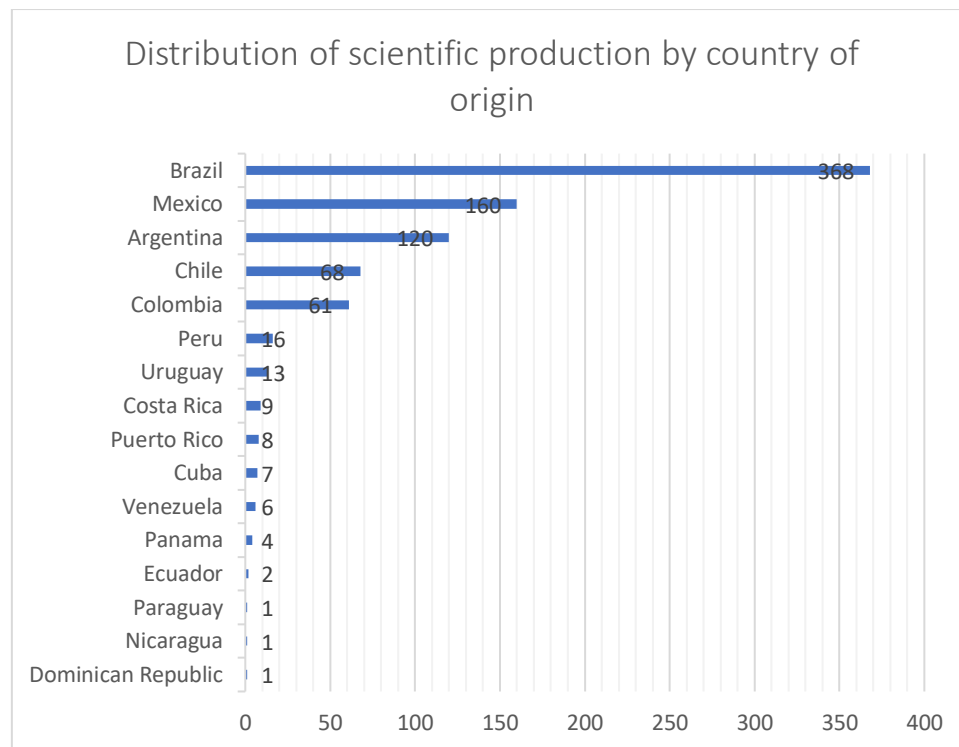


Figure 3. Distribution of scientific production by country of origin.

Source: Own elaboration (2022); based on data provided by Scopus.

Brazil was the Latin American country with the highest number of research papers published in high impact journals indexed in Scopus database, with a total of 368 papers related to the study of new Tyrosine Kinase Inhibitors for use in cancer treatments, among which the article entitled “Kinase inhibition in relapsed/refractory leukemia and lymphoma settings: recent perspectives in clinical research” stands out (Machado et al., 2021), which had as its purpose to carry out a documentary review on the scientific production of relevant clinical trials of the last five years investigating kinase inhibitor in patients suffering from recurrent/refractory hematological malignancies, identifying a trend towards research on the use of kinase inhibitors for the treatment of chronic lymphoid leukemia and acute myeloid leukemia in recurrent/refractory settings.

The article concludes by highlighting the positive results obtained with kinase inhibitors in these types of treatments which are especially effective when combined with tumor genetic profiling, leading to encouraging future prospects for an era in which chemotherapy-free treatment regimens are a reality for many cancer patients.

At this point it should be noted that the production of scientific publications, when classified by country of origin, presents a special characteristic and that is the collaboration between authors with different affiliations to both public and private institutions, and these institutions can be from the same country or of different nationalities, so that the production of an article co-authored by different authors from different countries of origin allows each of the countries to add up as a unit in the overall publications. This is best explained in Figure 4, which shows the flow of collaborative work from different countries.

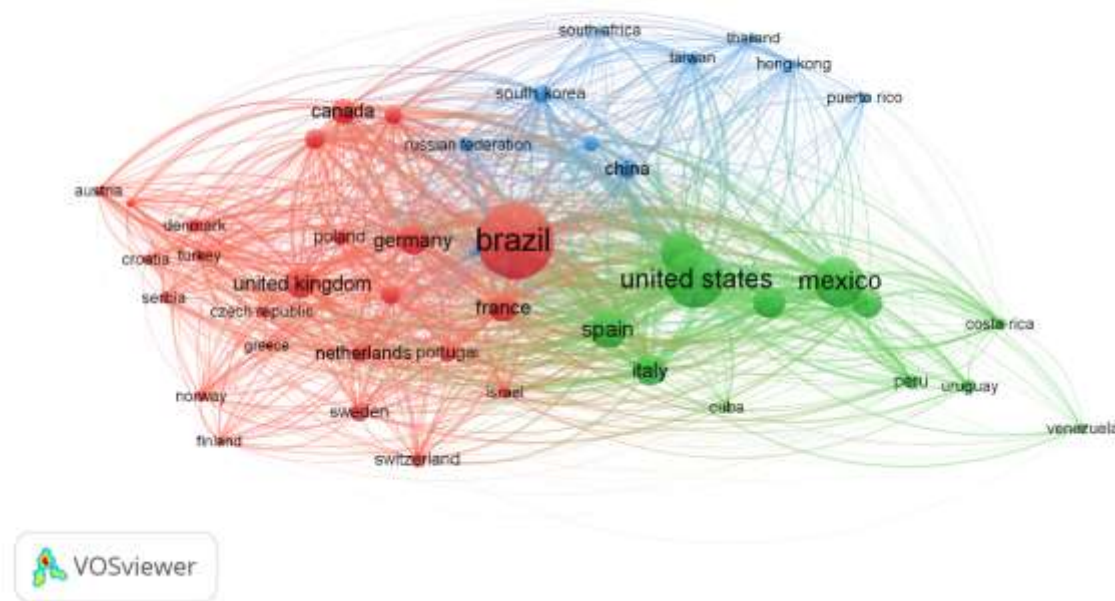


Figure 4. Co-citations between countries.

Source: Own elaboration (2022); based on data provided by Scopus.

Figure 4 shows a large participation in research related to the study of new tyrosine kinase inhibitors in oncological treatments, by authors affiliated to institutions in Brazil, Germany, France, Canada, United Kingdom, among others. Mexico, which occupies the second place in the list of countries with the highest scientific production related to the aforementioned topic with a total of 160 documents, reports, according to Scopus, participation in research works with authors from Spain, Italy, Peru, Uruguay, Cuba, Costa Rica and Venezuela, while Puerto Rico reports 8 publications in Scopus, among which there are research works in co-authorship with researchers from Hong Kong, Thailand, Taiwan, China, among others.

4.4 Distribution of scientific production by area of knowledge.

Figure 4 shows how different areas of knowledge make significant contributions in terms of scientific production of the study, analysis and review of the variables that are the object of this debt. Such is the case of Medicine, which is in first place with a total of 495 publications according to Scopus database records, followed by the area of Biochemistry,

Genetics and Molecular Biology with 352 productions, a figure of great relevance for the required study and also in third place is the area of Pharmacology, Toxicology and Pharmaceutics with 107 publications.

On the other hand, it is important to highlight the review carried out by the area of Biochemistry entitled “*Molecular mechanisms and cellular contribution of pulmonary fibrosis to the development of lung cancer*”, (Samarelli et al., 2021), whose study focused on the review of the studies of the common cellular and molecular mechanisms between Idiopathic Pulmonary Fibrosis (IPF) and lung cancer. Likewise, within its findings, it was evidenced that “*Nintedanib*” is a tyrosine kinase inhibitor, a drug whose first objective was the fight against cancer, but which was finally identified as an antifibrotic agent. This use was given taking into account the differentiation between IPF (Idiopathic Pulmonary Fibrosis) and Lung Cancer (LC), which is that the first is nothing more than an interstitial lung disease caused by risk factors such as smoking and environmental risks, but with the presence of emphysema could put patients at risk of lung cancer, a condition that is configured as one of the leading causes of death in the world.

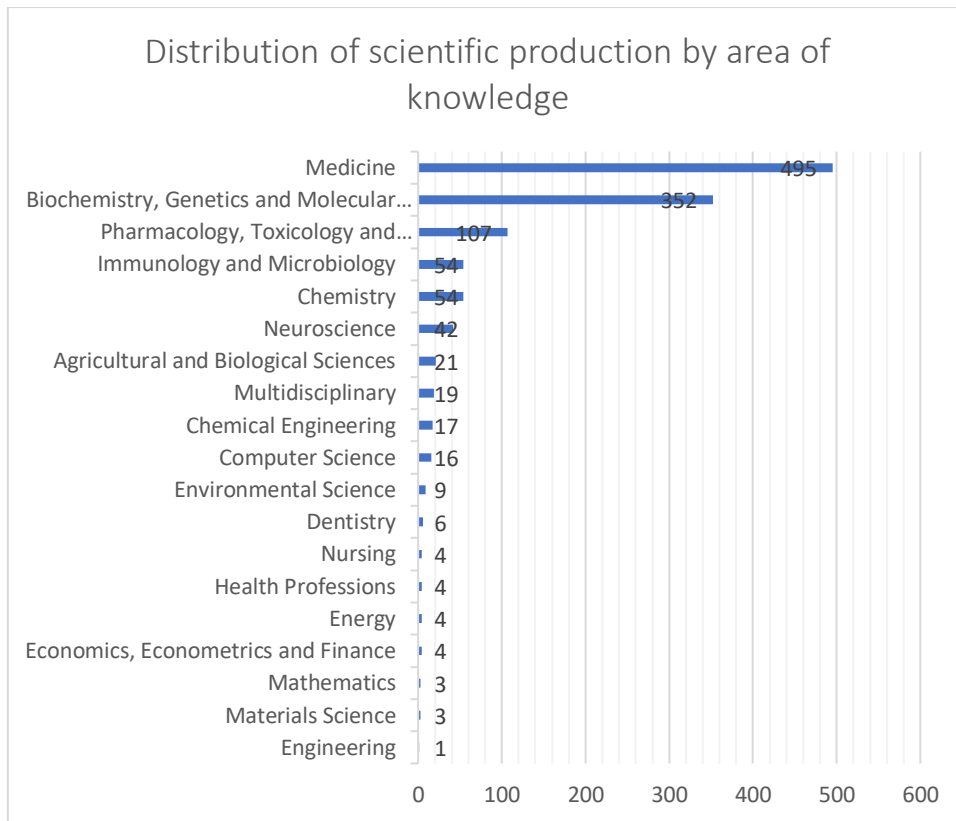


Figure 5. Distribution of scientific production by area of knowledge.

Source: Own elaboration (2022); based on data provided by Scopus.

application of new tyrosine kinase inhibitors for oncological use, as shown in the figure related to this item.

On the other hand, areas such as Chemistry, Computer Science, Economics and even Mathematics, are not alien to the scientific production in the search and analysis of the

4.5 Type of publication

Figure 6 shows how the bibliographic production is distributed according to the type of publication chosen by the authors.

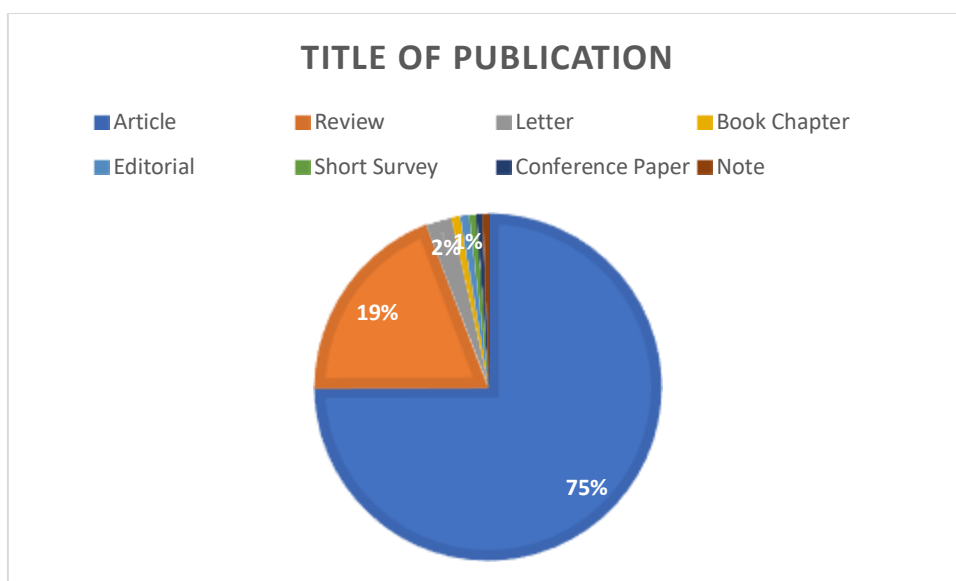


Figure 6. Type of publication.

Source: Own elaboration (2022); based on data provided by Scopus.

Through the scientific production shown by the Scopus database, it can be seen that the different authors of the publications on the variables under study used different types of publication to disseminate information on the content of the same, as shown in Figure 6, with the Scientific Article being the most widely used with 75% of the total, followed by Reviews with 19% and Letter with 2% of the total production.

On the other hand, it is of great relevance to highlight the Review of 2021, entitled “*The role of receptor tyrosine kinase axl kinase in carcinogenesis and the development of therapeutic resistance: An overview of molecular mechanisms and future applications*” (Wium et al., 2021), a review that focused on the benefits of the receptor tyrosine kinase AXL and the fundamental role it plays in the regulation of cellular processes, such as proliferation, motility, survival and immune response in the treatment of some cancers, since resistance to chemotherapeutic agents represents great challenges at the time of successfully defining treatments against cancer, due to various factors that lead to the so-called chemoresistance. Within the review, several reports on the overexpression of AXL as a prognostic biomarker were analyzed, for which it was concluded that its application is positive in the progressive processes of cancer and in the development of drug resistance, even showing the therapeutic potential it has.

Undoubtedly, the types of publication used by the different authors represent important benefits for the scientific-academic community, which immediately allow the reception of different approaches and lead to a change of perspective that from every point of view allows the researcher to go out of his sphere, expand his knowledge, obtain new data and the inclusion of new thoughts that contribute to the research work.

5. Conclusion

Thanks to the bibliometric analysis proposed for the present document, it can be established that Brazil was the Latin American country with the

highest number of publications concerning the study of new tyrosine kinase inhibitors for oncological use with a total of 368 publications in high impact journals indexed in the Scopus database during the period 2016-2021, which allows inferring that research in that country is at a high level regarding the study of the effects produced in cancer treatment by the use of tyrosine kinase enzyme inhibitor drugs.

Research on this topic has presented a uniform volume of publications during the years selected for the development of this study; however, the year in which the most publications were registered in Scopus was 2021, when 166 documents were published. This allows inferring that the trend in the use of new tyrosine kinase inhibitors year after year yields data that constitute important material for the development of new applications and effects derived from the treatment of cancer by means of this type of drugs as well as their dosage, which presents high variability due to the individual characteristics of each patient, which has also been an important subject of study in recent years.

The area of Medicine is the main discipline that develops publications related to the topic proposed in this article due to its nature. 495 publications were made based on theories that frame medicine and its different specializations. It is expected that from research such as the one presented in this paper, more research papers will be generated studying the application, effects and improvements to cancer treatments based on the delivery of tyrosine kinase inhibitor drugs.

References

- [1] Calles, A., Sánchez, E., & Manzo, A. (2019). CÁNCER DE TIROIDES EN ESTADIOS AVANZADOS TRATADOS CON INHIBIDORES DE TIROSINA QUINASA (SORAFENIB). *Revista Venezolana de Oncología*, 2-7.
- [2] Domínguez, L. V. (2019). Monitorización farmacoterapéutica de inhibidores de tirosina quinasa en pacientes oncológicos.
- [3] Higuera-Pulgar, I., Ribed, A., Carrascal-Fabian, M. L., Romero-Jiménez, R. M., Velasco-Gimeno, C., Bretón-Lesmes, I., & García-Peris, P. (2019). Evolución nutricional y de la supervivencia en un

- grupo de pacientes oncológicos en tratamiento con inhibidores de tirosina quinasa. *Endocrinología, Diabetes y Nutrición*, 472-479.
- [4] Machado, C., Pessoa, F., Da Silva, E., Pantoja, L., Ribeiro, R., Filho, M., Moreira-Nunes, C. (2021). Kinase inhibition in relapsed/refractory leukemia and lymphoma settings: Recent prospects into clinical investigations. *Pharmaceutics*.
- [5] Mujica, P., Bustamante, M., Bascuñan, L., & Sanhueza, V. (2021). Effectiveness of treatment of high-grade multiple cutaneous mast cell tumour using tyrosine kinase inhibitor and vinblastine: Case report. *Revista de Investigaciones Veterinarias del Peru*.
- [6] Samarelli, A., Masciale, V., Aramini, B., Coló, G., Tonelli, R., Marchioni, A., Moretti, A. (2021). Molecular mechanisms and cellular contribution from lung fibrosis to lung cancer development. *International Journal of Molecular Sciences*.
- [7] Schneider, T., Abdulrahman, R., Corssmit, E., Morreau, H., Smit, J., & Kapiteijn, E. (2012). Long-term analysis of the efficacy and tolerability of sorafenib in advanced radio-iodine refractory differentiated thyroid carcinoma: Final results of a phase II trial. *Eur J Endocrinol*.
- [8] Wium, M., Ajayi-smith, A., Pancez, J., & Zerbini, L. (2021). The role of the receptor tyrosine kinase axl in carcinogenesis and development of therapeutic resistance: An overview of molecular mechanisms and future applications. *Cancers*.
- [9] Ahmed, T., Vial, M. R., Ost, D., Stewart, J., Hasan, M. A., & Grosu, H. B. (2018). Non-small cell lung cancer transdifferentiation into small cell lung cancer: A case series. *Lung Cancer*, 122, 220-223. doi: 10.1016/j.lungcan.2018.06.024
- [10] Alam, M. M., Sanchez-Azqueta, A., Janha, O., Flannery, E. L., Mahindra, A., Mapesa, K., Tobin, A. B. (2019). Validation of the protein kinase PfCLK3 as a multistage cross-species malarial drug target. *Science*, 365(6456) doi:10.1126/science.aau1682
- [11] Alamón, C., Dávila, B., García, M. F., Sánchez, C., Kovacs, M., Trias, E., Cerecetto, H. (2020). Sunitinib-containing carborane pharmacophore with the ability to inhibit tyrosine kinases receptors FLT3, KIT and PDGFR- β , exhibits powerful in vivo anti-glioblastoma activity. *Cancers*, 12(11), 1-21. doi:10.3390/cancers12113423
- [12] Alcantara, C., Almeida, B. R., Barros, B. C. S. C., Orikaza, C. M., Toledo, M. S., & Suzuki, E. (2020). Histoplasma capsulatum chemotypes I and II induce IL-8 secretion in lung epithelial cells in distinct manners. *Medical Mycology*, 58(8), 1169-1177. doi:10.1093/mmy/myaa006
- [13] Aldaz, A., & Schaiquevich, P. (2017). Individualizing dosage regimens of antineoplastic agents. *Individualized drug therapy for patients: Basic foundations, relevant software and clinical applications* (pp. 281-306) doi:10.1016/B978-0-12-803348-7.00017-4 Retrieved from www.scopus.com
- [14] Alemán, O. R., Mora, N., & Rosales, C. (2021). The antibody receptor fc gamma receptor IIIb induces calcium entry via transient receptor potential melastatin 2 in human neutrophils. *Frontiers in Immunology*, 12 doi:10.3389/fimmu.2021.657393
- [15] Aliev, G., Barreto, G. E., & Cacabelos, R. (2017). Genomics and epigenomics of tumor and aging cells. *Current Genomics*, 18(5), 375-377. Retrieved from www.scopus.com
- [16] Almeida, L. Y. D., Pereira-Martins, D. A., Weinhäuser, I., Ortiz, C., Cândido, L. A., Lange, A. P., Rego, E. M. (2021). The combination of gefitinib with ATRA and ATO induces myeloid differentiation in acute promyelocytic leukemia resistant cells. *Frontiers in Oncology*, 11 doi:10.3389/fonc.2021.686445
- [17] Alonso, C. I., Osycka-Salut, C. E., Castellano, L., Cesari, A., Di Siervi, N., Mutto, A., Perez-Martinez, S. (2017). Extracellular cAMP activates molecular signalling pathways associated with sperm capacitation in bovines. *Molecular Human Reproduction*, 23(8), 521-534. doi:10.1093/molehr/gax030
- [18] Alvau, A., Battistone, M. A., Gervasi, M. G., Navarrete, F. A., Xu, X., Sánchez-Cárdenas, C., Visconti, P. E. (2016). The

- tyrosine kinase FER is responsible for the capacitation-associated increase in tyrosine phosphorylation in murine sperm. *Development (Cambridge)*, 143(13), 2325-2333. doi:10.1242/dev.136499
- [19] Alves-Lopes, R., Neves, K. B., Montezano, A. C., Harvey, A., Carneiro, F. S., Touyz, R. M., & Tostes, R. C. (2016). Internal pudental artery dysfunction in diabetes mellitus is mediated by NOX1-derived ROS-, Nrf2-, and rho kinase-dependent mechanisms. *Hypertension*, 68(4), 1056-1064. doi:10.1161/HYPERTENSIONAHA.116.07518
- [20] Alves-Silva, J. C., de Carvalho, J. L., Rabello, D. A., Serejo, T. R. T., Rego, E. M., Neves, F. A. R., . . . Saldanha-Araujo, F. (2018). GLP overexpression is associated with poor prognosis in chronic lymphocytic leukemia and its inhibition induces leukemic cell death. *Investigational New Drugs*, 36(5), 955-960. doi:10.1007/s10637-018-0613-x
- [21] Aman, J., Duijvelaar, E., Botros, L., Kianzad, A., Schippers, J. R., Smeele, P. J., Bogaard, H. J. (2021). Imatinib in patients with severe COVID-19: A randomised, double-blind, placebo-controlled, clinical trial. *The Lancet Respiratory Medicine*, 9(9), 957-968. doi:10.1016/S2213-2600(21)00237-X
- [22] Amaral, L. S., Ferreira, J. M., Predes, D., Abreu, J. G., Noël, F., & Quintas, L. E. M. (2018). Telocinobufagin and marinobufagin produce different effects in LLC-PK1 cells: A case of functional selectivity of bufadienolides. *International Journal of Molecular Sciences*, 19(9) doi:10.3390/ijms19092769
- [23] Amin, S. B., Anderson, K. J., Boudreau, C. E., Martinez-Ledesma, E., Kocakavuk, E., Johnson, K. C., . . . Verhaak, R. G. W. (2020). Comparative molecular life history of spontaneous canine and human gliomas. *Cancer Cell*, 37(2), 243-257.e7. doi: 10.1016/j.ccell.2020.01.004
- [24] Andrade, S. S., Gouvea, I. E., Silva, M. C. C., Castro, E. D., de Paula, C. A. A., Okamoto, D., Girão, M. J. B. C. (2016). Cathepsin K induces platelet dysfunction and affects cell signaling in breast cancer - molecularly distinct behavior of cathepsin K in breast cancer. *BMC Cancer*, 16(1) doi:10.1186/s12885-016-2203-7
- [25] André, D. M., Calixto, M. C., Sollon, C., Alexandre, E. C., Tavares, E. B. G., Naime, A. C. A., Antunes, E. (2017). High-fat diet-induced obesity impairs insulin signaling in lungs of allergen-challenged mice: Improvement by resveratrol. *Scientific Reports*, 7(1) doi:10.1038/s41598-017-17558-w
- [26] Ángeles-Velázquez, J. L., Hurtado-Monroy, R., Vargas-Viveros, P., Carrillo-Muñoz, S., & Candelaria-Hernández, M. (2016). Imatinib intolerance is associated with blastic phase development in Philadelphia Chromosome-Positive chronic myeloid leukemia. *Clinical Lymphoma, Myeloma and Leukemia*, 16, S82-S85. doi: 10.1016/j.clml.2016.02.028
- [27] Aquino, B., Da Silva, V. C. H., Massirer, K. B., & Arruda, P. (2020). Crystal structure of DRK1, a stress-responsive receptor-like pseudokinase, reveals the molecular basis for the absence of ATP binding. *BMC Plant Biology*, 20(1) doi:10.1186/s12870-020-2328-3
- [28] Aran, V., & Omerovic, J. (2019). Current approaches in NSCLC targeting K-RAS and EGFR. *International Journal of Molecular Sciences*, 20(22) doi:10.3390/ijms20225701
- [29] Aranda, M. L., González Fleitas, M. F., Dieguez, H. H., Milne, G. A., Devouassoux, J. D., Keller Sarmiento, M. I., . . . Rosenstein, R. E. (2019). Therapeutic benefit of environmental enrichment on optic neuritis. *Neuropharmacology*, 145, 87-98. doi: 10.1016/j.neuropharm.2017.12.017
- [30] Aranda-Rivera, A. K., Cruz-Gregorio, A., Aparicio-Trejo, O. E., Ortega-Lozano, A. J., & Pedraza-Chaverri, J. (2021). Redox signaling pathways in unilateral ureteral obstruction (UUO)-induced renal fibrosis. *Free Radical Biology and Medicine*, 172, 65-81. doi: 10.1016/j.freeradbiomed.2021.05.034
- [31] Araujo, J. M., Gomez, A. C., Pinto, J. A., Rolfo, C., & Raez, L. E. (2021). Profile of entrectinib in the treatment of ROS1-positive non-small cell lung cancer: Evidence to date. *Hematology/ Oncology*

- and *Stem Cell Therapy*, 14(3), 192-198. doi: 10.1016/j.hemonc.2020.11.005
- [32] Araujo, L. H., Ferreira, C. G., Baldotto, C. S., Mathias, C., Castro, G., & Coudry, R. (2021). Next-generation sequencing of circulating tumor DNA for metastatic non-small cell lung cancer: A discussion on its implementation in the Brazilian clinical practice. *Future Oncology*, 17(2), 205-213. doi:10.2217/fon-2020-0583
- [33] Arellano-Gutiérrez, G., Martínez-Aldrete, L. F., Pérez-Fabián, A., & Maldonado-García, E. L. (2020). Primary extra-gastrointestinal stromal tumor (EGIST) of the mesentery: Case report and review of literature. *Annals of Medicine and Surgery*, 60, 480-483. doi: 10.1016/j.amsu.2020.11.020
- [34] Armas-López, L., Piña-Sánchez, P., Arrieta, O., Alba, E. G., Ortiz-Quintero, B., Santillán-Doherty, P., . . . Ávila-Moreno, F. (2017). Epigenomic study identifies a novel mesenchyme homeobox 2-GLI1 transcription axis involved in cancer drug resistance overall survival and therapy prognosis in lung cancer patients. *Oncotarget*, 8(40), 67056-67081. doi:10.18632/oncotarget.17715
- [35] Armas-López, L., Zúñiga, J., Arrieta, O., & Ávila-Moreno, F. (2017). The hedgehog-GLI pathway in embryonic development and cancer: Implications for pulmonary oncology therapy. *Oncotarget*, 8(36), 60684-60703. doi:10.18632/oncotarget.19527
- [36] Arriagada, C., Silva, P., Millet, M., Solano, L., Moraga, C., & Torres, V. A. (2019). Focal adhesion kinase- dependent activation of the early endocytic protein Rab5 is associated with cell migration. *Journal of Biological Chemistry*, 294(34), 12836-12845. doi:10.1074/jbc.RA119.008667
- [37] Arrieta, O., Barrón, F., Maldonado, F., Cabrera, L., Corona-Cruz, J. F., Blake, M., De la Garza, J. (2019). Radical consolidative treatment provides a clinical benefit and long-term survival in patients with synchronous oligometastatic non-small cell lung cancer: A phase II study. *Lung Cancer*, 130, 67-75. doi: 10.1016/j.lungcan.2019.02.006
- [38] Arrieta, O., Barrón, F., Padilla, M. -. S., Avilés-Salas, A., Ramírez-Tirado, L. A., Arguelles Jiménez, M. J., . . . Rosell, R. (2019). Effect of metformin plus tyrosine kinase inhibitors compared with tyrosine kinase inhibitors alone in patients with epidermal growth factor receptor-mutated lung adenocarcinoma: A phase 2 randomized clinical trial. *JAMA Oncology*, 5(11) doi:10.1001/jamaoncol.2019.2553
- [39] Arrieta, O., Catalán, R., Guzmán-Vázquez, S., Barrón, F., Lara-Mejía, L., Soto-Molina, H., . . . De La Garza, J. (2020). Cost-effectiveness analysis of first and second-generation EGFR tyrosine kinase inhibitors as first line of treatment for patients with NSCLC harboring EGFR mutations. *BMC Cancer*, 20(1) doi:10.1186/s12885-020-07329-8
- [40] Arrieta, O., Escamilla-López, I., Lira-González, I., Barrón, F., Ramírez-Tirado, L. A., Vergara, E., . . . Jiménez-Fuentes, E. (2019). Radical aggressive treatment among non-small cell lung cancer patients with malignant pleural effusion without extra-thoracic disease. *Journal of Thoracic Disease*, 11(2), 595-601. doi:10.21037/jtd.2019.01.36