e-ISSN: 2980-0463
Anat. J. Pharm. Sci., 2025:4(2)
AJPS
Review Article

# The Vascular Endothelial Growth Factor Receptor (VEGFR) and Cancer

Okan AYKAÇ[1,2], İrem BOZBEY MERDE[3*]

[1] Sivas Cumhuriyet University, Faculty of Pharmacy, Department of Pharmaceutical Chemistry, 58000, Sivas, Turkey

[2] Inonu University, Institute of Health Sciences, Department of Pharmaceutical Chemistry, 44000, Malatya, Turkey

[3] Inonu University, Faculty of Pharmacy, Department of Pharmaceutical Chemistry, 44000, Malatya, Turkey

**ABSTRACT:** Cancer continues to maintain its importance as a pathological condition whose incidence continues to increase. Since the source of pathophysiology is multifaceted, it is one of the popular topics that pharmaceutical and medicinal chemists attach importance to in their studies. Recent studies have highlighted the association between vascular formation mechanisms and the action mechanisms of drugs. As a result, the mechanisms of angiogenesis, as well as the systemic pathways of EGF and VEGF, which play a significant role in angiogenesis, have been elucidated. Inhibition of these systems was targeted while designing drugs and VEGFR emerged. The aim of this study is to compile the types of VEGFR, their relationship with cancer and the mechanisms of action of clinically used drugs approved by various authorities and to enable the readers of this review to recognize the specificities in targets in VEGFR inhibitor design.

**Keywords:** *angiogenesis, cancer, tyrosine kinase inhibitors, VEGFR*

## 1 INTRODUCTION

Cancer remains one of the most significant health complications globally. Many biological mechanisms play a role in the development and spread of this complex disease. One of these mechanisms is the need for the formation of new blood vessels to support cancer cell growth and metastasis. This process is called angiogenesis and vascular endothelial growth factor (VEGF) is one of the key regulators of this process. In recent years, research to understand the role of VEGF in cancer biology has accelerated, and significant progress has been made in treatments targeting this molecule. Recent studies have also highlighted the role of VEGFR2 in cancer stem cell self-renewal, particularly through the VEGFR2/STAT3 signaling pathway, which upregulates oncogenes such as Myc and Sox210. This suggests that VEGFR2 not only contributes to angiogenesis but also to the maintenance of cancer-initiating cells, further underscoring its importance in cancer biology. Understanding the multifaceted role of VEGFR2 in cancer can lead to more effective therapeutic strategies, potentially improving outcomes for patients with various types of cancer. Understanding the multifaceted role of VEGFR2 in cancer can lead to more effective

*Corresponding Author: İrem BOZBEY MERDE
E-mail: irem.bozbey@inonu.edu.tr

Submitted: 06.03.2025 Accepted: 21.04.2025
doi.org/10.71133/anatphar.1652647

therapeutic strategies, potentially improving outcomes for patients with various types of cancer [1].

### 1.1 Role of VEGF in Cancer Biology

VEGF is a growth factor that initiates and regulates angiogenesis. During their rapid growth, cancer cells are exposed to hypoxia due to shortage oxygen and nutrients. In response to hypoxia, VEGF production increases in the tumor microenvironment, leading to the formation of new blood vessels. These vessels supply tumor cells with nutrients and oxygen, allowing them to grow. In addition, these new blood vessels facilitate the entry of cancer cells into circulation, increasing the risk of metastasis [2].

Studies emphasizing the importance of VEGF in cancer have shown that this molecule is present at high levels, especially in metastatic cancer types. For example, overexpression of VEGF in many tumors such as colorectal, lung and kidney, breast cancer has been associated with poor prognosis [3].

The critical role of VEGF in cancer biology has brought treatment approaches targeting this molecule to the forefront. The use of drugs that inhibit VEGF has led to significant results, especially in metastatic cancers. Anti-VEGF monoclonal antibodies such as bevacizumab inhibit angiogenesis and suppress tumor growth by binding VEGF. In addition, tyrosine kinase inhibitors (TKIs) targeting VEGF receptors have also been effective in inhibiting angiogenesis [3]. However, the efficacy of these treatments may remain limited. The resistance mechanisms that develop against anti-angiogenic therapies make the long-term use of these drugs difficult. Especially adaptive changes in the tumor microenvironment and activation of alternative angiogenic pathways play an important role in the development of resistance [4]. Therefore, there are ongoing studies suggesting that VEGF-targeted therapies should be supported by combination therapies.

Recent studies have revealed that VEGF plays a role not only in angiogenesis but also in the regulation of the immune system. High levels of VEGF cause an increase in immunosuppressive cells in the tumor microenvironment and suppress the function of cytotoxic T cells [5]. This has made the combination of immunotherapy and VEGF inhibitors an attractive option. For example, clinical trials using anti $PD_1$/PD-$L_1$ immunotherapies in combination with anti-VEGF therapies have yielded promising results. These combinations both reduce tumor vascularity and enable the immune system to develop a more effective response against the tumor [6]. In addition, studies on genetic and epigenetic regulation of VEGF are increasing. Experimental research on direct modification of VEGF expressions using gene editing technologies such as CRISPR-$_{Cas9}$ is ongoing [7].

therapeutic strategies, potentially improving outcomes for patients with various types of cancer [1].

### 1.1 Role of VEGF in Cancer Biology

VEGF is a growth factor that initiates and regulates angiogenesis. During their rapid growth, cancer cells are exposed to hypoxia due to shortage oxygen and nutrients. In response to hypoxia, VEGF production increases in the tumor microenvironment, leading to the formation of new blood vessels. These vessels supply tumor cells with nutrients and oxygen, allowing them to grow. In addition, these new blood vessels facilitate the entry of cancer cells into circulation, increasing the risk of metastasis [2].

Studies emphasizing the importance of VEGF in cancer have shown that this molecule is present at high levels, especially in metastatic cancer types. For example, overexpression of VEGF in many tumors such as colorectal, lung and kidney, breast cancer has been associated with poor prognosis [3].

The critical role of VEGF in cancer biology has brought treatment approaches targeting this molecule to the forefront. The use of drugs that inhibit VEGF has led to significant results, especially in metastatic cancers. Anti-VEGF monoclonal antibodies such as bevacizumab inhibit angiogenesis and suppress tumor growth by binding VEGF. In addition, tyrosine kinase inhibitors (TKIs) targeting VEGF receptors have also been effective in inhibiting angiogenesis [3]. However, the efficacy of these treatments may remain limited. The resistance mechanisms that develop against anti-angiogenic therapies make the long-term use of these drugs difficult. Especially adaptive changes in the tumor microenvironment and activation of alternative angiogenic pathways play an important role in the development of resistance [4]. Therefore, there are ongoing studies suggesting that VEGF-targeted therapies should be supported by combination therapies.

Recent studies have revealed that VEGF plays a role not only in angiogenesis but also in the regulation of the immune system. High levels of VEGF cause an increase in immunosuppressive cells in the tumor microenvironment and suppress the function of cytotoxic T cells [5]. This has made the combination of immunotherapy and VEGF inhibitors an attractive option. For example, clinical trials using anti $PD_1$/PD-$L_1$ immunotherapies in combination with anti-VEGF therapies have yielded promising results. These combinations both reduce tumor vascularity and enable the immune system to develop a more effective response against the tumor [6]. In addition, studies on genetic and epigenetic regulation of VEGF are increasing. Experimental research on direct modification of VEGF expressions using gene editing technologies such as CRISPR-$_{Cas9}$ is ongoing [7].

tyrosine kinase activity is low compared to other VEGFR types. The primary functions of VEGFR1 are:

Embryonic Development: VEGFR1 plays a critical role in the formation of the vascular network during embryonic development. It is a key regulator especially in the differentiation of endothelial cells.

Negative Regulation: VEGFR1 can negatively regulate angiogenesis by limiting the binding of VEGF to VEGFR2. For this reason, VEGFR1 is often described as a 'trapping receptor'. However, overactivation of VEGFR1 has been associated with some pathological conditions. For example, the soluble form of VEGFR1 (sFlt-1) plays an important role in pregnancy complications such as pre-eclampsia [9].

**VEGFR2 (KDR/Flk-1):** It is considered the most important receptor in angiogenesis. This receptor activates the main signaling pathway that initiates the biological effects of VEGF. The main properties of VEGFR2 are:

Endothelial Cell Activation: VEGFR2 promotes endothelial cell proliferation, migration and tube formation.

Vascular Permeability: Receptor activation leads to an increase in vascular permeability. This is important in both physiological and pathological processes. Overactivation of VEGFR2 is associated with tumor angiogenesis in diseases such as cancer. Therefore, anti-angiogenic therapies targeting VEGFR2 have been developed [10].

**VEGFR3 (Flt-4):** It has a critical role in lymph-angiogenesis and is essential for the development and maintenance of lymphatic vessels. The main functions of this receptor can be summarized as follows:

Lymphatic Vessel Development: Regulates proliferation and migration of lymphatic endothelial cells.

Lymphoedema Pathology: Dysfunction of VEGFR3 has been associated with congenital or acquired lymphoedema diseases. Studies in recent years have also revealed the role of VEGFR3 in cancer metastasis via lymphatic vessels. These findings emphasize the importance of therapeutic strategies targeting lymphangiogenesis [11].

### 1.4 Targeting VEGFR as an Indication

According to the latest data, new findings on the efficacy of anti-VEGF therapies in cancer treatment have been obtained. Monoclonal antibodies such as bevacizumab are widely used in certain types of cancer. However, research on resistance mechanisms emphasizes the importance of combined treatment approaches [12].

In recent years, the use of VEGF inhibitors has increased in diseases such as age-related macular degeneration and diabetic retinopathy. Especially molecules such as aflibercept have given successful results in the treatment of these diseases [13].

Studies on the role of VEGF in

cardiovascular diseases show that this protein can be used in the treatment of myocardial regeneration and ischemia. Especially gene therapy approaches have attracted attention in recent years [4].

Research on VEGF has led to a better understanding of the biological effects of this protein family and has enabled the development of new therapeutic approaches in the treatment of various diseases. The focus of future studies will be to further elucidate the specific roles of different isoforms of VEGF and integrate this knowledge into clinical practice.

### 1.5 Angiogenesis and the Role of VEGF

Angiogenesis is the process of sprouting new blood vessels from existing vascular structures. This is critical for conditions such as surgery, embryogenesis, and wound healing, as well as pathological conditions such as tumor metastasis and growth. The VEGF family is one of the most important growth factors that initiate and regulate angiogenesis. VEGF plays a role in providing the tumor microenvironment with oxygen and nutrients by increasing the proliferation, migration, and vascular permeability of endothelial cells [14]. VEGFR2 plays the most important role in tumor angiogenesis [9, 11]. Activation of VEGFR2 triggers mitogenic signaling pathways in the endothelial lining, expanding proliferation and new vessel formation.

### 1.6 The Importance of VEGF and Its Receptors in Breast Cancer

Breast cancer is one of the most widespread malignancies in women and angiogenesis plays a key role in disease progression (Figure 1). Breast cancer cells increase VEGF expression through Hypoxia-Inducible Factor-1α ($HIF_{1\alpha}$) in response to hypoxia. Increased VEGF levels promote angiogenesis in the tumor microenvironment and increase metastatic potential [14, 15, 16]. The importance of VEGFR2 in breast cancer is particularly striking. Overexpression of this receptor has been associated with more aggressive tumor phenotypes. Furthermore, activation of the VEGFR2 signaling pathway facilitates the metastasis process by increasing cellular migration and invasion. Recent studies suggest that targeting VEGFR2 is a promising approach in the treatment of breast cancer. For example, clinical studies on the inhibition of this pathway using anti-VEGF monoclonal antibodies or tyrosine kinase inhibitors have revealed a reduction in tumor growth [3, 17].

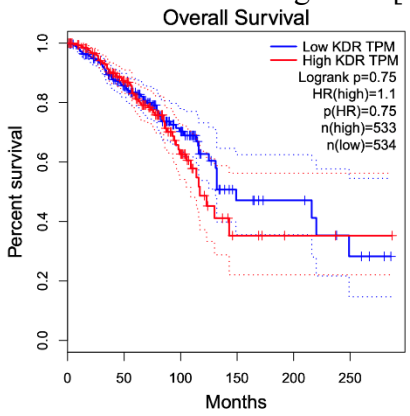


**Figure 1.** Survival graph of VGFR2 inhibition in BRCA gene-related breast cancer studied from GEPIA database.

Therapeutic strategies targeting the VEGF/VEGFR axis have an important place in the treatment of breast cancer. Anti-VEGF antibodies such as bevacizumab or multi-tyrosine kinase inhibitors such as pazopanib aim to reduce tumor vascularity by blocking this axis. However, the efficacy of these therapies is usually limited, and the development of resistance is common. Recent studies suggest that combination therapies (anti VEGF agents and immunotherapies or chemotherapies) may be more effective in overcoming resistance mechanisms [18].

The effects of VEGF on angiogenesis and the role of VEGF receptors in breast cancer emphasize the importance of this molecular pathway in cancer therapy. Recent research has led to a better understanding of the VEGF/VEGFR axis and provided a new perspective on therapeutic strategies targeting this axis. Advances in this field may allow the development of more effective approaches in the treatment of aggressive malignancies such as breast cancer.

## 1.7 Biochemical Mechanisms

The biochemical parameters of VEGF begin with the ligand-receptor agreement. The binding of VEGF-A to VEGFR2 leads to its dimerization and autophosphorylation. This process triggers the activation of the following signals: Vascular endothelial growth factor receptor 2 (VEGFR2) is considered one of the key regulators of the angiogenesis process. VEGFR2 interacts with VEGF-A to trigger endothelial cell proliferation, migration and new vessel formation. This process allows both physiological and pathological angiogenesis to be carried out [5].

1. PI3K/AKT Pathway: Regulates cell survival signaling and suppresses apoptosis.
2. RAS/RAF/MEK/ERK Pathway: Promotes cell proliferation.
3. p38 MAPK Pathway: Plays a role in endothelial cell migration and tubule formation.

These signaling pathways work together to support the basic biological processes of angiogenesis (Figure 2).

### 1.7.1 Relationship between VEGFR2 and Apoptosis: Metabolic Pathways and Mechanisms

VEGFR2 is a tyrosine kinase receptor known for its fundamental role in angiogenesis. It is increasingly recognized that VEGFR2 is an important regulator not only in vessel formation but also in cellular survival and apoptosis processes. In this article, the effects of VEGFR2 on apoptosis and the metabolic pathways involved in this process will be discussed [16].

The role of VEGFR2 in regulating apoptosis is not limited to signaling pathways; it also affects cellular energy metabolism. VEGFR2 activation helping cells meet their energy demands by increasing the rate of glycolysis. Increased glycolysis is an

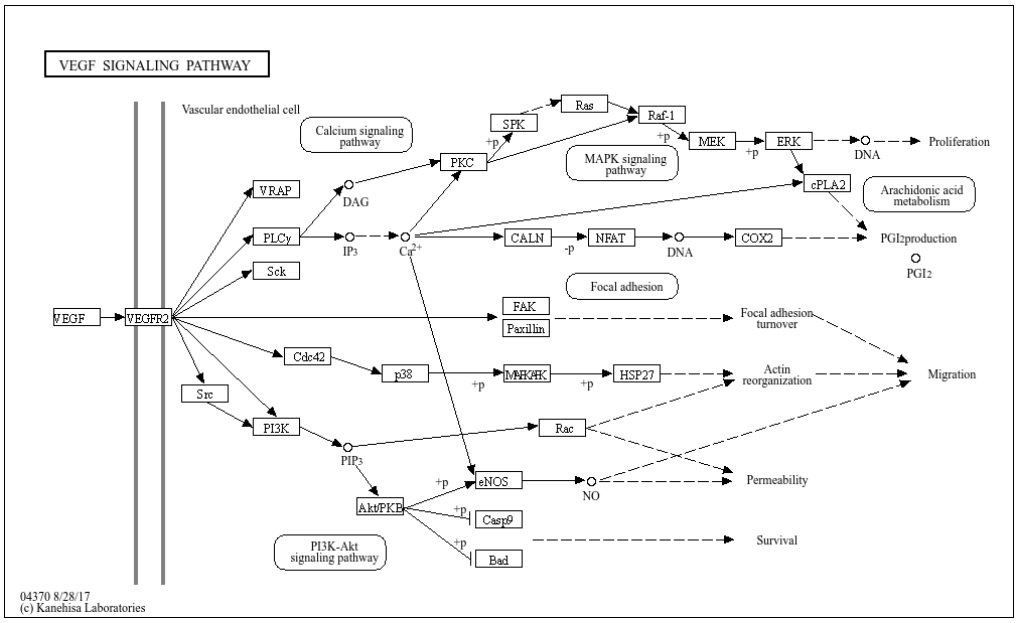


**Figure 2**. VEGF signaling pathway map [6].

important adaptation that supports survival in hypoxic microenvironments such as cancer [18]. It has also been shown that VEGFR2 regulates lipid metabolism and thus maintains membrane stability.

The apoptosis-regulating effects of VEGFR2 have become an important target, especially in cancer therapy. VEGFR2 inhibitors are used to limit tumor growth and direct cancer cells to apoptosis. However, a better understanding of both the pro-apoptotic and anti-apoptotic mechanisms of VEGFR2 is required to minimize the side effects of such therapies. VEGFR2 has a critical role not only in angiogenesis but also in the regulation of apoptosis. Suppressing apoptosis through signaling pathways such as PI3K/Akt, MAPK/ERK and NF-κB, VEGFR2 also supports cellular survival through its effects on energy metabolism [5]. A better understanding of these mechanisms may lead to significant advances in both basic biology and clinical applications.

### 1.8 Structure and Function of VEGFR2

VEGFR2 is activated at the cell surface by interacting with VEGF (Figure 3). This activation leads to autotransphosphorylation of tyrosine residues and initiates intracellular signaling pathways. One of the best-known functions of VEGFR 2 is to promote the formation of new blood vessels by promoting endothelial cell proliferation and migration [7, 10]. However, recent studies show that VEGFR2 also has an important effect on mechanisms that prevent apoptosis.

#### 1.8.1 Apoptosis and VEGFR2

Apoptosis is a programmed process that allows cells to die in a controlled manner. This process is critical for maintaining the homeostasis of the organism and ensuring that damaged or unnecessary cells are eliminated. The question of how VEGFR2 regulates

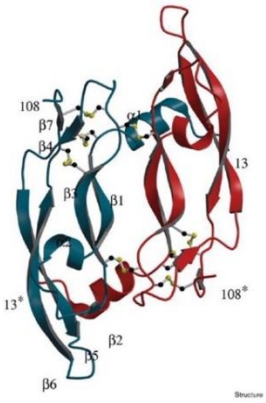


**Figure 3.** VEGFR2 structure in silico demonstration [7].

apoptosis is of great interest, especially in pathological conditions such as cancer. Overexpression of VEGFR2 in cancer cells can lead to suppression of apoptosis and increased cellular survival [11]. The effect of VEGFR2 on apoptosis can be explained through the following main signaling pathways.

**PI3K/Akt Pathway:** Activation of VEGFR2 triggers the phosphatidylinositol 3-kinase (PI3K) pathway, which leads to phosphorylation of Akt. Akt activates several target proteins that suppress apoptosis. For example, Akt inhibits the mitochondrial apoptosis pathway by inactivating the pro-apoptotic protein Bad [3] Akt also activates the mTOR pathway, which regulates the cell cycle and promotes survival.

**MAPK/ERK Pathway:** Activation of VEGFR2 also activates the mitogen-activated protein kinase (MAPK) pathway. ERK1/2, a component of this pathway, promotes cellular survival by increasing the transcription of anti-apoptotic genes. Activation of ERK1/2 protects cells against external factors that trigger apoptosis, especially oxidative stress [21].

**NF-κB Activation:** Another important effect of VEGFR2 signaling is the activation of the nuclear factor kappa B (NF-κB) pathway. NF-κB reduces cellular stress by increasing the expression of anti-apoptotic genes. This mechanism potentiates the apoptosis suppressive effect of VEGFR2, especially in the inflammatory microenvironment [15, 22].

### 1.9 VEGFR2 Inhibitors and Clinical Uses

Vascular endothelial growth factor receptor 2 (VEGFR2) is a tyrosine kinase receptor that plays a key role in angiogenesis. Angiogenesis plays an important role in both physiological and pathological processes [23]. Especially in diseases such as cancer, VEGFR2 signaling pathway is known to be active in the formation of new blood vessels that support the growth and metastasis of tumors. Therefore, VEGFR2 inhibitors have been developed as targeted therapeutic agents in cancer treatment and are widely used in the clinic. In this article, the clinical use of VEGFR2 inhibitors and current literature information in this field are discussed. VEGFR2 inhibitors disrupt the functioning of the VEGF signaling pathway by blocking the activation of the receptor. This prevents new vessel formation and limits the tumor's ability to receive oxygen and nutrients. VEGFR2

inhibitors are generally in the tyrosine kinase inhibitor (TKI) class and can be taken orally. Some inhibitors have been developed as monoclonal antibodies [24].

**VEGFR2 Inhibitors Used in the Clinic**

**Sorafenib:** Sorafenib is a multikinase inhibitor that inhibits both VEGFR2 and other tyrosine kinase receptors (Figure 4). It is used in the remedy of hepatocellular carcinoma (HCC) and renal cell carcinoma (RCC). It has also been shown to be effective in some forms of thyroid cancer [23, 26].

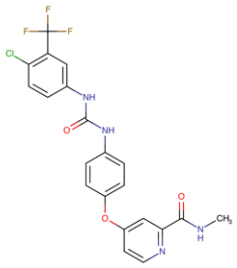

**Figure 4.** Sorafenib 2D

**Sunitinib:** Sunitinib targets VEGFR2 as well as other receptors such as PDGFR and c-Kit (Figure 5). It is widely used in the treatment of renal cell carcinoma and gastrointestinal stromal tumors (GIST) [27, 28].

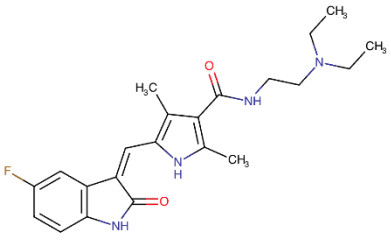

**Figure 5.** Sunitinib 2D

**Pazopanib:** Pazopanib is another tyrosine kinase inhibitor approved for the treatment of renal cell carcinoma and soft tissue sarcoma that acts by inhibiting VEGFR1, VEGFR2, and VEGFR3 [29].

**Axitinib:** Axitinib is a VEGFR2 inhibitor used as 2nd line therapy, especially in metastatic renal cell carcinoma (Figure 6). It is characterized by its high selectivity [30]. Axitinib selectively blocks VEGFR1, VEGFR2 and VEGFR3 tyrosine kinase receptors [31].

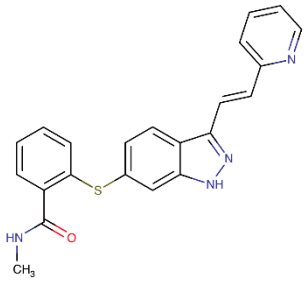

**Figure 6.** Axitinib 2D

**Ramucirumab:** Ramucirumab is a monoclonal antibody that binds to VEGFR2 (Figure 7). This binding prevents the receptor from being activated. It is currently approved for use in various types of cancer (gastric cancer, colon cancer) [32].

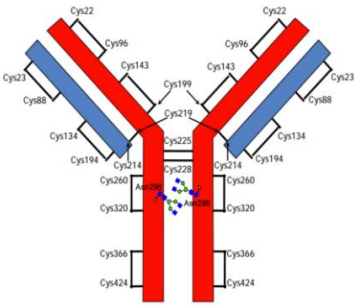

**Figure 7.** Ramucirumab 2D

## 2 CONCLUSION

VEGF plays a critical role in cancer biology and therapies targeting this molecule have an important place in oncology. However, resistance mechanisms and limited efficacy against anti-VEGF therapies require further research in this field. Current studies emphasize the combination of VEGF inhibitors with immunotherapies and genetic editing strategies. In the light of these developments, VEGF-targeted therapies are expected to offer more effective and personalized approaches in the future [33, 34,35].

The VEGF family continues to occupy an important place in biomedical research. The findings obtained in the last five years have provided a better understanding of the biological functions of this protein family and shed light on the development of new therapeutic targets. Understanding the role of VEGF in a wide range of diseases from cancer to cardiovascular diseases will form the basis of future therapeutic strategies [36,37].

VEGFs and VEGFRs are among the most critical pro-angiogenic factors regulating tumor angiogenesis. Therefore, anti-angiogenic therapies targeting VEGF and it signaling pathways are promising in the treatment of various cancers. The VEGF/VEGFR2 system functions as an autocrine/paracrine process required for the proliferation and survival of cancer cells [38]. At the same time, in recent years, significant progress has been made in identifying intracellular signaling cascades specific to VEGFR2. Recent research has also revealed aberrant VEGFR2 expression and signaling activity in cancer cells. Targeting VEGFR2 overexpression has been focused on because it may be an effective way to treat breast cancer and other cancers.

## 3 AUTHOR CONTRIBUTIONS

Hypotesis: O.A., İ.B.M.; Design: O.A., İ.B.M.; Literature review: O.A., İ.B.M.; Data Collection: O.A., İ.B.M.; Manuscript writing: O.A., İ.B.M.

## 5 CONFLICT OF INTEREST

Authors declare that there is no conflict of interest.

## 6 REFERENCES

[1] Dekuang Zhao et al. VEGF drives cancer-initiating stem cells through VEGFR-2/Stat3 signaling to upregulate Myc and Sox2. *Oncogene*, 2014; 3107-3119. https://doi.org/10.1038/onc.2014.257

[2] Ferrara, N. Vascular endothelial growth factor: Basic science and clinical progress. *Endocrinology Reviews*, 2004.

[3] Li, W., Wei, J., Cheng, M., & Liu, M. Unveiling promising targets in gastric cancer therapy: A comprehensive review. *Molecular Therapy: Oncology*, 2004; 32(32), 200857.

[4] Chen, Y., et al. Immunotherapy-based combination strategies for treatment of EGFR-TKI-resistant non-small-cell lung cancer.

*Future Medicine Ltd*, 2024.

[5] Yang, Z., et al. Opportunities and Challenges of Nanoparticles in Digestive Tumors as Anti-Angiogenic Therapies. *Frontiers in Oncology*, 2024.

[6] Hegde, P. S., & Chen, D. S. Top 10 Challenges in Cancer Immunotherapy. *Immunity*, 2024.

[7] Li, B., Jin, J., Guo, D., Tao, Z., & Hu, X. Immune Checkpoint Inhibitors Combined with Targeted Therapy: The Recent Advances and Future Potentials. *Cancers*, 2023; 15(15), 2858.

[8] Song, Z., Tao, Y., Liu, Y., & Li, J. Advances in delivery systems for CRISPR/Cas-mediated cancer treatment: a focus on viral vectors and extracellular vesicles. *Frontiers in Immunology*, 2024.

[9] Zhou, Y., et al. The Role of the VEGF Family in Coronary Heart Disease. *Frontiers in Cardiovascular Medicine*, 2021.

[10] Shah, A. A., Kamal, M. A., & Akhtar, S. Tumor Angiogenesis and VEGFR-2: Mechanism, Pathways and Current Biological Therapeutic Interventions. *Current Drug Metabolism*, 2022; 22(22), 50–59.

[11] Craige, S., Kaur, G., Bond, J., Caliz, A., Kant, S., & Keaney, J. Endothelial Reactive Oxygen Species: Key Players in Cardiovascular Health and Disease. Antioxidants & Redox Signaling.Rosen, L. S. VEGF-Targeted Therapy: Therapeutic Potential and Recent Advances. *The Oncologist*, 2005; 10, 382–391.

[12] Ferrara, N., Gerber, H. P., & LeCouter, J. The biology of VEGF and its receptors. *Nature Medicine*, 2003.

[13] Brown, G. C., Brown, M. M., Rapuano, S. B., & Boyer, D. A Cost-Benefit Analysis of VEGF-Inhibitor Therapy for Neovascular Age-Related Macular Degeneration in the United States. *American Journal of Ophthalmology*, 2021; 223(223), 405–429.

[14] Zhou, Y., et al. The Role of VEGF Family in Lipid Metabolism. *Current Pharmaceutical Biotechnology*, 2022; 24(24), 253–265.

[15] Qi, L., et al. VEGFR-3 signaling restrains the neuron-macrophage crosstalk during neurotropic viral infection. *Cell Reports*, 2023; 42(42).

[16] Huang, Z., et al. Hypoxia makes EZH2 inhibitor not easy—advances of crosstalk between HIF and EZH2. *Life Metabolism*, 2024; 3(3).

[17] Chen, L., et al. How to overcome tumor resistance to anti-PD-1/PD-L1 therapy by immunotherapy modifying the tumor microenvironment in MSS CRC. *Clinical Immunology*, 2024.

[18] Hu, L., Zhang, N., Zhao, C., & Pan, J. Engineering ADSCs by manipulating YAP for lymphedema treatment in a mouse tail model. *Experimental Biology and Medicine*, 2024; 249(249), 10295.

[19] VEGF signaling pathway - Reference pathway. Retrieved from

https://www.kegg.jp/pathway/map04370.

[20] Muller, Y. A., Christinger, H. W., Keyt, B. A., & De Vos, A. M. The crystal structure of vascular endothelial growth factor (VEGF) refined to 1.93 Å resolution: Multiple copy flexibility and receptor binding. *Structure*, 1997; 5(5), 1325–1338.

[21] Cao, J., Chow, L., & Dow, S. Strategies to overcome myeloid cell induced immune suppression in the tumor microenvironment. *Frontiers in Oncology*, 2023.

[22] Abdelnaby, R. M., et al. In Vitro Anticancer Activity Screening of Novel Fused Thiophene Derivatives as VEGFR-2/AKT Dual Inhibitors and Apoptosis Inducers. *Pharmaceuticals*, 2022; 15(15).

[23] Tian, Y., et al. Effect of Electric Fields on the Mechanical Mechanism of Regorafenib–VEGFR2 Interaction to Enhance Inhibition of Hepatocellular Carcinoma. *Biomolecules*, 2025; 15(15).

[24] Iyer, R., Fetterly, G., Lugade, A., & Thanavala, Y. Sorafenib: A clinical and pharmacologic review. *Expert Opinion on Pharmacotherapy*, 2010.

[25] Keating, G. M. Sorafenib: A Review in Hepatocellular Carcinoma. *Drugs*, 2017; 77(77), 583–593.

[26] Keating, G. M., & Santoro, A. Sorafenib: A review of its use in advanced hepatocellular carcinoma. *Drugs*, 2009; 69(69), 2057–2077.

[27] Abd Elhameed, A. A., Ali, A. R., Ghabbour, H. A., Bayomi, S. M., & El-Gohary, N. S. Probing structural requirements for thiazole-based mimetics of sunitinib as potent VEGFR-2 inhibitors. *RSC Medicinal Chemistry*, 2025.

[28] Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. Retrieved from https://go.drugbank.com/articles/A2291.

[29] Podar, K., et al. The small-molecule VEGF receptor inhibitor pazopanib (GW786034B) targets both tumor and endothelial cells in multiple myeloma. *Proceedings of the National Academy of Sciences*, 2006; 103(103), 19478–19483.

[30] Annuryanti, F., et al. Development of axitinib-loaded polymeric ocular implants for the treatment of posterior ocular diseases. *International Journal of Pharmaceutics*, 2025 ;669(669).

[31] Phase I trial of the oral antiangiogenesis agent AG-013736 in patients with advanced solid tumors: pharmacokinetic and clinical results. Retrieved from https://go.drugbank.com/articles/A6910.

[32] Arena, Claudia, et al. Stomatitis and VEGFR-Tyrosine Kinase Inhibitors (VR-TKIs): A Review of Current Literature in 4369 Patients. BioMed Research International, 2018; 5035217.

[33] Luo, D., Liu, Y., Lu, Z., & Huang, L. Targeted therapy and immunotherapy for gastric cancer: rational strategies, novel advancements, challenges, and future perspectives. Molecular Medicine, 2025;

31(31), 52.

[34] Casak, S. J., et al. FDA approval summary: Ramucirumab for gastric cancer. *Clinical Cancer Research*, 2015; 21(21), 3372–3376.

[35] Yang, Haoran, et al. Emerging Gene Therapy Based on Nanocarriers: A Promising Therapeutic Alternative for Cardiovascular Diseases and a Novel Strategy in Valvular Heart Disease. *International Journal of Molecular Sciences,* 2025; 4(4), 1743.

[36] Ahmad, Ajmal, and Mohd Imtiaz Nawaz. Molecular mechanism of VEGF and its role in pathological angiogenesis. *Journal of cellular biochemistry*, 2022; **11**(11), 1938-1965.

[37] Saeed, Anwaar, et al. S2303: phase II/III trial of paclitaxel+ ramucirumab±nivolumab in gastric and esophageal adenocarcinoma (PARAMUNE). *Future Oncology*, 2025; 1-7.

[38] Choi, Dong Kyu. Epigenetic regulation of angiogenesis and its therapeutics. *Genomics & Informatics*, 2025; 1-11.