Potassium Channels as a Target for Cancer Therapy: Current Perspectives

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Abstract: Potassium (K⁺) channels are highly regulated membrane proteins that control the potassium ion flux and respond to different cellular stimuli. These ion channels are grouped into three major families, Kv (voltage-gated K⁺ channel), Kir (inwardly rectifying K⁺ channel) and K2P (two-pore K⁺ channels), according to the structure, to mediate the K⁺ currents. In cancer, alterations in K⁺ channel function can promote the acquisition of the so-called hallmarks of cancer – cell proliferation, resistance to apoptosis, metabolic changes, angiogenesis, and migratory capabilities – emerging as targets for the development of new therapeutic drugs. In this review, we focus our attention on the different K⁺ channels associated with the most relevant and prevalent cancer types. We summarize our knowledge about the potassium channels structure and function, their cancer dysregulated expression and discuss the K⁺ channels modulator and the strategies for designing new drugs.

Keywords: K⁺ channels, potassium channel blockers, K⁺ channels expression, cancer

Introduction

Potassium Channels Structure and Function

K⁺ channels are membrane proteins that facilitate the selective potassium ion flow under an electrochemical gradient. Besides the voltage-dependent gating, K⁺ channels are activated by several intracellular and extracellular stimuli, including extracellular and intracellular pH, kinases, SUMOylation, G protein-coupled receptors, stretch, and lipid regulation among others. These channels can be grouped into three major families according to their subunit structure: the Kv (voltage-gated K⁺ channel), Kir (inwardly rectifying K⁺ channel), and K2P (two-pore K⁺ channels) (see Figure 1A–C). K⁺ channels need four pore-forming domains, which together, generate a functional and selective ion pathway. Thus, the Kv and Kir channels need four subunits to form a functional pore in a tetramer architecture. On the other hand, the K2P family forms a functional channel in a dimer architecture (see Figure 1C). For each K⁺ channel, subunit is also clearly identifiable in this pore-forming P domain, characterized by the amino-acid signature GYG that confers the high selectivity to K⁺ ions observed in potassium channels. The Kv channels present a topology model with six transmembrane domains (TM1-6) and one pore-forming domain (P) (Figure 1A). This Kv family represents the most numerous K⁺ channel group, with 40 genes encoding for K⁺ subunits in humans. The transmembrane domain (TM4) into Kv channels present positive charged amino acids (Arg and Lys) which act as voltage sensors generating the channel opening in response to changes in voltages (Figure 1A).

For the Kir channel family, each subunit has one P domain and two transmembrane domains (Figure 1B), and this family is integrated by 15 different genes grouped into 7 subfamilies (Kir1.x to Kir7.x), identified in mammals. Kir potassium channels present a gating governed by a voltage-dependent blocked process by Mg²⁺ and polyamines. Moreover, the gating voltage-dependence for Kir channels defines their characteristic K⁺ inward rectification (movement into the cell).
K2P family has a two-pore forming domain and four transmembrane domains, whose subunits assemble as dimers (Figure 1C). Fifteen different genes found in mammals encode these family subunits and are grouped into 6 subfamilies according to their homology and functional properties.\textsuperscript{1,5,9,10} The K2P channels are voltage-independent and highly modulated channels, playing key roles in the maintenance of the resting membrane potential in the cells. These channels are recognized as the leak or background potassium channels.\textsuperscript{1,5}

**Potassium Channels in Cancer**

Cancer condition is a major non-infectious public health problem and affects millions of people worldwide. Cancer is also the second most common cause of death after cardiovascular disease, with 10.0 million deaths (9.9 million excluding nonmelanoma skin cancer) in 2020,\textsuperscript{11} with estimated 28.4 million cases in 2040, a 47\% rise from 2020.\textsuperscript{11} The Americas’ accounts 20.9\% of cancer incidence and 14.2\% of mortality worldwide,\textsuperscript{11} and for Latin America and the Caribbean region, it has been estimated that 1.7 million cancer cases will be diagnosed by 2030, whereas more than one million of the cases will die per year.\textsuperscript{12} Currently, more than 100 types of cancer have been identified, being breast (24.5\%), colorectal (9.4\%), lung (8.4\%), cervix (6.5\%), and thyroid (4.9\%) most frequent types of cancer in women.\textsuperscript{11} Meanwhile, lung cancer (14.3\%), prostate (14.1\%), colorectal (10.6\%), stomach (7.1\%) and liver (6.3\%) are the most common type of cancers among men.\textsuperscript{11}

In recent years, ion channels, and particularly potassium (K\textsuperscript{+}) channels, have emerged as relevant molecular targets for the development of cancer treatments.\textsuperscript{13–16} The association between potassium (K\textsuperscript{+}) channels and cancer disease is mainly due to the participation of those proteins in the cancer progression mechanisms.\textsuperscript{13,16–18} Potassium channels are complex proteins that form selective pores for K\textsuperscript{+} conduction in biological membranes, which are critical in K\textsuperscript{+} homeostasis, cell volume regulation, setting of resting membrane potentials, the neurotransmitters release, and regulating the excitability of neurons and muscle tissue.\textsuperscript{1,2,19}

For instance, overexpression of different potassium channels, such as Kv, Ca\textsuperscript{2+} -activated (K\textsubscript{Ca}), ether go-go human (hEag), ATP-sensitive (K\textsubscript{ATP}), and K2P has been reported in prostate cancer cells, colon, lung, breast, and other organs.\textsuperscript{20} It has been hypothesized that there is a relationship between K\textsuperscript{+} channel overexpression and the generation and growth of malignant tumors,\textsuperscript{14,17,18,21} being involved in cell proliferation, apoptosis, and differentiation.\textsuperscript{14,18,21} Studies performed with pharmacological drugs that specifically block K\textsuperscript{+} channels have shown antitumor effects by inhibiting tumor growth directly or enhancing the effectiveness of chemotherapeutics or cytotoxic drugs as a combined therapeutical strategy.\textsuperscript{18,22}

On the other hand, several studies have exhibited the impact of Kv channels (Eag1, HERG, and Kv1.3), Kir (Kir3.1), and Ca\textsuperscript{2+} -activated potassium channels (K\textsubscript{Ca}1.1 and K\textsubscript{Ca}3.1) in cancer cell proliferation and their association with tumorigenesis process in patients and animal models.\textsuperscript{17,18,21–23}
A relatively minor amount of research has focused on the relationship between K2P channels and cancer.\textsuperscript{18,24} Those studies suggested that TASK-3 is involved in tumor formation in several types of human cancer.\textsuperscript{14,18,24,25} Moreover, other investigations showed that breast cancer cells’ metastatic properties depend on TASK-3 expression levels.\textsuperscript{20}

By contrast, the Kir channels have been related to different cancer conditions, such as lung, gastric, prostate, stomach, breast, and choroid plexus.\textsuperscript{26–32}

**Voltage-Gated Potassium Channels Involved in Cancer**

The Kv channel is the most numerous K\textsuperscript{+} channel family, playing relevant functions in various cellular and physiological processes.\textsuperscript{2} Additionally, these channels have been implicated in cancer hallmarks, such as cell proliferation, cancer progression, and migration\textsuperscript{14,15,33–35} (Figure 2 and Table 1).

The Kv1.1 (KCNA1) channel is relevant for potassium transport in the central nervous system and kidney.\textsuperscript{36,37} Moreover, it is overexpressed in cervical cancer tissues and medulloblastoma.\textsuperscript{38,39} Additionally, the Kv1.1 depletion suppressed growth, proliferation, migration and invasion of HeLa cells.\textsuperscript{38}

Kv1.3 channels also have been reported as overexpressed in the breast, lung, colon, prostate, pancreas, smooth muscle, skeletal muscle, and lymph node of some types of cancers.\textsuperscript{40–44} However, its relevance as a therapeutic target has been evidenced in glioblastoma, melanoma, and pancreatic adenocarcinoma models,\textsuperscript{45–47} where Kv1.3 suppression induces apoptosis.

Another related channel is Kv1.5. This channel shows a correlated expression pattern with glioma entities and malignancy grades, with a high expression in astrocytomas, moderate in oligodendrogliomas, and low in glioblastomas.\textsuperscript{48} For the Kv1.5 channel, an overexpression was detected in some gastric cancer cell lines.\textsuperscript{49} Furthermore, Kv1.5 plays a role in the activation and proliferation of cells in the immune system, is remodeled during carcinogenesis, and has shown an abundance that inversely correlates with clinical aggressiveness in human non-Hodgkin lymphomas.\textsuperscript{50} In the same way that Kv1.3, this channel is overexpressed in human smooth muscle tumors.\textsuperscript{40} Kv1.5 has been involved in tumor cell proliferation of gastric cancer cells, where this channel is overexpressed.\textsuperscript{49}

*Figure 2* Roles of K\textsuperscript{+} channels in cancer hallmarks. Cellular processes associated with changes in expression and increased activity of the two-pore domain K\textsuperscript{+} channel (K2P), the inward rectifier K\textsuperscript{+} channel (Kir), and the voltage-gated K\textsuperscript{+} channel (Kv) in cancer. K\textsuperscript{+} channels structure in ribbon representation were generated with the PDB 6RV2, 7s5z and 7wf4.
| Protein (Gene) | Cancer Hallmark                                      | Tumor or Cancer Type                                                                 | Reference |
|---------------|-----------------------------------------------------|--------------------------------------------------------------------------------------|-----------|
| Kv1.1 (KCNA1) | Cell proliferation, apoptosis, migration and invasion | Cervical cancer, medulloblastoma                                                     | [38,39]   |
| Kv1.3 (KCNA3) | Cell proliferation, apoptosis and migration          | Breast, lung, colon, prostate, pancreas, smooth muscle, skeletal muscle, and lymph node cancers, glioblastoma and melanoma | [40–47]  |
| Kv1.4 (KCNA4) | Cell proliferation and cell cycle                   | Neuroblastoma cells                                                                   | [52]      |
| Kv1.5 (KCNA5) | Cell proliferation and apoptosis                     | Glioma, astrocytomas, gastric cancer cells, human non-Hodgkin lymphomas, smooth muscle tumors | [40,48–50]|
| Kv2.1 (KCNB1) | Cell cycle progression and migration                 | Prostate cancer cells, neuroblastoma cells                                            | [51,52]   |
| Kv3.1 (KCNN1) | Proliferation, migration and invasion                | Lung and breast cancer cells                                                          | [55]      |
| Kv3.4 (KCNN4) | Proliferation, migration and invasion                | Oral squamous cell carcinoma, head and neck squamous cell carcinomas, lung and breast cancer models | [53–55]  |
| Kv4.1 (KCNJ1) | Cell cycle progression                               | Breast cancer and gastric cancer cells                                                | [56,57]   |
| Kv4.2 (KCNJ2) | Cell proliferation and cell cycle                    | Neuroblastoma cells                                                                   | [52]      |
| Kv7.1 (KCNQ1) | Cell proliferation                                  | Colon cancer cells, neuroblastoma cells                                              | [52,58,59]|
| Kv9.3 (KCNJ3) | Cell proliferation                                  | Colon carcinoma, lung adenocarcinoma and cervical adenocarcinoma cells               | [60,61]   |
| Kv11.1 (KCNN3) | Cell cycle, apoptosis, migration and cell proliferation | Leukemia, ovarian, lung, pancreatic, colorectal and breast cancer cells              | [74,79–81]|
| KCn1.1 (KCNN1) | Cell proliferation and migration                     | Prostate, glia, breast, pancreas, and endometrium cancer cells                       | [82–87]   |
| KCn2.3 (KCNN3) | Migration                                           | Melanoma cells                                                                       | [96]      |
| Kir2.1 (KCNJ2) | Cell proliferation, invasion, cell cycle and apoptosis | Small-cell lung cancer and gastric cancer                                             | [28,97]   |
| Kir2.2 (KCNJ12) | Cell proliferation and cell cycle                   | Small-cell lung cancer, prostate, stomach, and breast                                | [31,98,99]|
| Kir3.1 (KCNJ3) | Cell proliferation and invasion                      | Pancreatic ductal adenocarcinoma, breast carcinomas, and non-small cell lung cancers | [26,100–102]|
| Kir3.4 (KCNJ5) | Cell proliferation                                  | Adrenal aldosterone-producing adenomas                                               | [29,103]  |
| Kir4.1 (KCNJ10) | Cell proliferation, cell cycle and apoptosis         | Brain tumors, astrocytomas and oligodendrogliomas                                    | [32,104]  |
| Kir6.1 (KCNJ8) | Cell proliferation, invasion, apoptosis and cell cycle | Leiomyoma cells, breast cancer cells (MDA-MB-231) and hepatocellular carcinoma      | [30,105,106]|
| Kir6.2 (KCNJ11) | Cell proliferation, invasion, apoptosis and cell cycle | Leiomyoma cells, breast cancer cells (MDA-MB-231), hepatocellular carcinoma, cervical cancer and glioma cells | [30,105–108]|

(Continued)
The expression of the Kv2.1 channel recently was reported to be higher in the metastatic prostate cancer cells (PC3), and their blockade with stromatoxin-1 or siRNA significantly inhibits the migration of malignant prostate cancer cells.\(^5^1\)

This channel as Kv1.4, Kv4.2, Kv7.1 and large-conductance Ca\(^{2+}\) -activated K\(^+\) channel (BK\(_{\text{Ca}}\)) also showed a high expression in the CD133\(^+\) subpopulation of SH-SY5Y neuroblastoma cells.\(^5^2\)

Increased levels of Kv3.4 channel expression were identified in OSCC (oral squamous cell carcinoma).\(^5^3\) In addition, the expression and clinical significance of this channel in the development and progression of head and neck squamous cell carcinomas was reported.\(^5^4\)

The Kv3.4 and Kv3.1 are known as oxygen sensors, and their function in hypoxia has been well investigated.\(^5^5\) These channels, Kv3.1 and Kv3.4, are tumor hypoxia-related channels involved in cancer cell migration and invasion in A549 and MDA-MB-231 cells (lung and breast cancer models, respectively).\(^5^5\)

Another set of experiments showed a varied expression of Kv4.1 mRNA depending on the tumor stage in human breast cancer tissues.\(^5^6\) Recent studies have demonstrated that Kv4.1 channels are expressed in the human gastric cancer cell lines.\(^5^7\) Moreover, the suppression of Kv4.1 induces a G1-S transition blockade affecting the cell cycle progression.\(^5^7\)

Interestingly, together with the expression profile of Kv7.1 in neuroblastoma cells,\(^5^2\) this channel was also found to be up-regulated in human colonic cancer cells.\(^5^8\) Conversely, Kv7.1 and Kv7.5 expression in vascular cancers was reported to be down-regulated.\(^5^9\) In this case, the proposed role of Kv7 channels is related to cell proliferation rather than controlling vascular tone.\(^5^9\)

A particular case is a Kv9.3 channel, an electronically silent subunit, which forms heterotetramers with Kv2.1.\(^6^0\) The Kv2.1/Kv9.3 heterotetramers are overexpressed in colon carcinoma, lung adenocarcinoma, and cervical adenocarcinoma cells.\(^6^0,6^1\) Moreover, the knockdown of Kv9.3 inhibits proliferation in colon carcinoma and lung adenocarcinoma models.\(^6^0\)

The Ether à go-go (Eag (hERG); Kv10.1) K\(^+\) channel expression is typically restricted to the adult brain and the heart, but it has been detected in several cancer cell lines and tumor tissues from patients,\(^6^2,6^3\) showing it to influence cell proliferation. This channel is overexpressed in 71% of tumors and cancer cell models of neuroblast, glial, liver, lung, breast, ovary, cervix, prostate, gastrointestinal tract, myeloid leukemia, and retinoblastoma.\(^3^4,6^3–6^8\) The Kv10.1 channel suppression generates apoptosis, inhibition of cell proliferation, and decrease in cancer cell migration.\(^6^3,6^9–7^2\)

| Protein (Gene) | Cancer Hallmark | Tumor or Cancer Type | Reference |
|---------------|-----------------|----------------------|-----------|
| Kir7.1 (KCNJ13) | Cell proliferation | Choroid plexus tumors | [27,109–111] |
| TASK-1 (KCNK3) | Cell proliferation, invasion and apoptosis | Medulloblastoma, Ehrlich ascites tumor cells, osteosarcoma, non-small cell lung cancers and adenomas adrenals | [121–123,125] |
| TASK-2 (KCNK5) | Cell proliferation, invasion and apoptosis | Breast cancer, and pancreatic ductal adenocarcinoma | [126–128] |
| TASK-3 (KCNK9) | Cell proliferation, migration, invasion, apoptosis and cell cycle | Melanoma, ovarian carcinoma, breast tumors, colorectal cancers, lung and gastric cancer | [24,117,129–132,135,139,140] |
| TREK-1 (KCNK2) | Cell proliferation, apoptosis and cell cycle | Prostate cancer, osteosarcoma and ovarian cancer | [116,118,141,142,182] |
| TREK-2 (KCNK10) | Cell proliferation and cell cycle | Bladder cancer cells | [119] |
| TWIK-1 (KCNK1) | Cell proliferation | Pancreatic ductal adenocarcinoma | [115] |
| TWIK-2 (KCNK6) | Cell proliferation, invasion and migration | Breast cancer | [120] |
Additionally, the inhibition of Kv10.1 channels sensitizes the mitochondria of tumor cells to antimetabolic treatments, improving the efficacy of the metabolic inhibitors.\textsuperscript{73}

Kv11.1 is overexpressed in leukemia, ovarian, lung, pancreatic, colorectal, and breast cancer cells, among others.\textsuperscript{74–79} The Kv11.1 channels have a key role in the cell cycle, acting as regulators for apoptosis and cell proliferation in cancer cells.\textsuperscript{74,79–81} However, blockers of Kv11.1 channels also retard the cardiac repolarization.\textsuperscript{80}

Another subgroup of potassium channels involved in cancer corresponds to the calcium-activated potassium channels. These channels are activated by rise in cytosolic calcium ions, allowing the K\textsuperscript{+} ion to flow under an electrochemical gradient. As a member of this subgroup, the \(K_{Ca}1.1\) channel is overexpressed in prostate, glia, breast, pancreas, and endometrium cancer cell types.\textsuperscript{82–86} \(K_{Ca}1.1\) channel regulates the proliferation and migration of prostate cancer condition.\textsuperscript{83} In breast cancer, \(K_{Ca}1.1\) channel overexpression has been associated with advanced tumor stage, cell proliferation, and poor prognosis.\textsuperscript{87}

On the other side, the \(K_{Ca}3.1\) (intermediate conductance Ca\textsuperscript{2+}-activated K\textsuperscript{+} channel) is overexpressed in 32\% of glioma patients and correlates with poor patient survival.\textsuperscript{88} In addition, these channels are overexpressed in breast cancer, non-small cell lung cancer, melanoma, leukemia, renal and hepatocellular carcinoma.\textsuperscript{89–94} The inhibition of \(K_{Ca}3.1\) channel activity reduces the cancer cell motility, proliferation and induces apoptosis.\textsuperscript{91,94,95}

A less associated channel to a cancer condition corresponds to \(K_{Ca}2.3\) (SK3), with a report of overexpression in melanoma cell lines, and their knockdown led to plasma membrane depolarization and decreased cell motility.\textsuperscript{96}

### Inward Rectifying Potassium Channels in Cancer

The Kir channel family is integrated by 15 different genes grouped into seven subfamilies. Among these channels, different subunits have been associated with cancer conditions (Kir2.1, 2.2, 3.1, 3.4, 4.1, 6.1, 6.2)\textsuperscript{26,27,29–32,94} (Figure 2 and Table 1).

Kir2.1 (\(KCNJ2\)) is overexpressed in 44.23\% of small-cell lung cancer (SCLC) tissues, and it correlates with the clinical stage and chemotherapy response in SCLC patients. Additionally, the Kir2.1 knockdown in H69AR and H446AR cells inhibited cell growth and was sensitized to chemotherapeutic drugs by increasing cell apoptosis and cell cycle arrest.\textsuperscript{28} Kir2.1 channel also promotes the invasion and metastasis of human gastric cancer by enhancing MEKK2-MEK1/2-ERK1/2 signaling by interaction with Stk38.\textsuperscript{97}

Similarly, Kir2.2 is found in human SCLC cells.\textsuperscript{31} Kir2.2 knockdown induced growth arrest and senescence by a mechanism involving reactive oxygen species (ROS) accumulation in cell lines derived from tissues of the prostate, stomach, and breast.\textsuperscript{98} Kir2.2 plays a role as an unconventional activator of RelA and increases the expression level of NF-\(\kappa\)B targets, including cyclin D1, matrix metalloproteinase (MMP)9, and vascular endothelial growth factor (VEGF)\textsuperscript{99} in cancer cells.

Another inward potassium channel associated with cancer is the Kir3.1 which is found within lymphocytes and in resected human pancreatic ductal adenocarcinoma (PDAC), overexpressed in 80\% of tumor specimens. However, no associations were found between metastasis and Kir3.1 expression.\textsuperscript{26} On the other hand, the gene encoding the Kir3.1 channel was found to be aberrantly overexpressed in invasive breast carcinomas.\textsuperscript{100} In addition, the Kir3.1 overexpression correlates with lymph node metastasis, and this overexpression is greater in tumors with more than one positive lymph node.\textsuperscript{100}

Kir3.1 gene overexpression is detected in tissue specimens from patients with non-small cell lung cancers (NSCLCs).\textsuperscript{101} In addition, the expression of Kir3.1 has been shown in tissue samples from approximately 40\% of primary human breast cancers and in breast cancer cell lines.\textsuperscript{102}

Also, the inwardly rectifying K\textsuperscript{+} channel Kir3.4 (\(KCNJ5\) gene) (or GIRK4 channel) have been identified in adrenal aldosterone-producing adenomas (APAs), where several ion channel gain-of-function mutants are associated with the APA condition.\textsuperscript{29,103}

In human brain tumors (low- and high-grade astrocytomas and oligodendrogliomas), mislocalization (redistribution) of the Kir4.1 channel has been reported and suggests a compromised buffering capacity of glial tumor cells.\textsuperscript{32} Furthermore, in human astrocytic tumors, Kir4.1 channel expression markedly increases with the pathologic grade of cancer\textsuperscript{104} and suggests that Kir4.1 activation could promote proliferation and inhibit apoptosis in the tumors.\textsuperscript{104}

The subunits of ATP-sensitive Kir potassium channels (Kir6.1, Kir6.2) are highly expressed in leiomyoma cells.\textsuperscript{30} The estrogen-induced proliferation of the leiomyoma cells is inhibited by treatment with glibenclamide (\(K\textsubscript{ATP}\)-channel
Two-Pore Domain Potassium Channels in Cancer

The two-pore domain K⁺ channels (K2P), encoded by the KCNK genes, are a family of fifteen members that form the leak or background channels. K2P channels display K⁺ outward rectifying currents, constitutively open, that control the neuronal excitability. Thus, activation of K2P channels stabilizes the cell membrane potential below the firing threshold, whereas the K2P channels inhibition facilitates membrane depolarization and cell excitability.

The K2P family can be divided into six subfamilies based on structural and functional properties. Regarding protein structure, each K2P channel subunit has four transmembrane domains (TM1-TM4) and two pore-forming domains (P1 and P2) (Figure 1C). Moreover, two subunits are required to form a functional channel. Two-Pore Domain Potassium Channels display an exclusive extracellular cap domain formed by the extracellular loop that connects the first transmembrane domain and the first pore-forming sequence (TM1-P1 loop) (Figure 1C). The extracellular cap covers the upper selectivity filter (SF) pore, and this structure is responsible for the poor sensitivity of K2P channels to classical K⁺ channel blockers.

From the K2P family, seven members are confirmed to be involved in cancer (TASK-1, TASK-2, TASK-3, TREC-1, TEREK-2, TWIK-1, and TWIK-2) (Figure 2 and Table 1). Among these, TASK-1 (K2P3, encoded by KCNK3 gene) has been detected in medulloblastoma and Ehrlich ascites tumor cells. Also, in MG63 osteosarcoma cells, the overexpression of TASK-1 was reported. Additionally, TASK-1 is overexpressed in a subset of non-small cell lung cancers, promoting proliferation and inhibiting apoptosis. TASK-1 knockout enhances apoptosis and reduces the proliferation of lung cancer cell-line A549. In these cells, A549, the overexpression of TASK-1 promoted epithelial mesenchymal transition (EMT), a pivotal event in lung cancer cell invasion and metastasis. Moreover, the expression of TASK-1 has been associated with aldosterone production in both aldosterone-producing adenomas and normal adrenals.

The second K2P channel associated with cancer is TASK-2 (K2P5; encoded by KCNK5 gene), a member of the TALK subfamily. TASK-2 plays a role in the proliferation of estrogen α receptor positive breast cancer cells being highly upregulated in response to 17β-estradiol (E2) in MCF-7 and T47D breast cancer cell lines. In these cells, the knockdown of the TASK-2 channel reduces the estrogen-induced proliferation of breast cancer cells. Also, the overexpression of TASK-2 has found in HPAF cells, a human pancreatic ductal adenocarcinoma cell line, but the role in cancer progression has not been further studied.

Among the K2P channels, the most studied in cancer correspond to TASK-3 (TWIK-related acid-sensitive K⁺ channel 3). This channel has been shown to localize in both the plasma membrane and mitochondrial inner membrane. The TASK-3 channel overexpression occurs in several types of cancer, such as melanoma, ovarian carcinoma, and breast cancer.

Also, TASK-3 (KCNK9, located in chromosomal region 8q24.3) gene expression is enhanced by 10–44% in human breast tumors and 35% in lung tumors. Additionally, overexpression of KCNK9 has been reported in over 90% of ovarian tumors. In most cases studied, TASK-3 is associated with the acquisition of malignant characteristics, including hypoxia.
resistance or serum deprivation conditions.\textsuperscript{24,25} Consistently, a monoclonal antibody (Y4) against the cap domain of TASK-3 inhibits the growth of human lung cancer xenografts and breast cancer metastasis in mice.\textsuperscript{133} Further studies showed that TASK-3 gene knockdown in breast cancer cells is associated with an induction of cellular senescence and cell cycle arrest.\textsuperscript{132} Furthermore, TASK-3 is overexpressed in colorectal cancers and gastric cancers.\textsuperscript{134–136} In gastric adenocarcinoma cells, the TASK-3 gene knockdown causes changes in migration and reduces cell proliferation and viability by increasing apoptosis without affecting cell cycle checkpoints.\textsuperscript{136}

TASK-3 is highly expressed in melanoma, being identified in the inner mitochondrial membrane of melanocytes, WM35 and B16F10, and keratinocytes.\textsuperscript{117,129,137} In WM35 and A2058, human melanoma cells, the knockdown of TASK-3 resulted in compromised mitochondrial function, mitochondrial membrane depolarization, and reduced cell survival inducing apoptosis.\textsuperscript{139,140}

Another K2P channel related to cancer is TREK-1 (K2P2, encoded by \textit{KCNK2}). This channel has been shown to play a pro-proliferative role in the human prostate cancer cell-line PC3.\textsuperscript{116} In MG63 osteosarcoma cells, overexpression of TREK-1 was reported\textsuperscript{118} and it is correlated with the proliferation of the osteoblast cells.\textsuperscript{141} TREK-1 is also overexpressed in prostate cancer tissues\textsuperscript{142} and epithelial ovarian cancer.\textsuperscript{130} For TREK-1 channel, the exact role of cancer development is still unclear. However, TREK-1 overexpression is associated with a poor prognosis for patients with prostate cancer.\textsuperscript{142} In prostate cancer, inhibition or knockdown of TREK-1 inhibits proliferation by inducing cell cycle arrest at the G1/S checkpoint.\textsuperscript{142} On the other side, the treatment with TREK-1-blocking agents, such as curcumin, has shown reduced ovarian cancer cells proliferation and increased late apoptosis processes.\textsuperscript{130}

Among the TREK subfamily, the TREK-2 channel (K2P10, encoded by \textit{KCNKI0}) was present in bladder cancer cell lines and contributed to cell cycle-dependent growth.\textsuperscript{119} The sixth K2P channel involved in cancer is TWIK-1 (K2P1, encoded by \textit{KCNK1}). The TWIK-1 was detected as an upregulated channel in pancreatic ductal adenocarcinoma (PDAC) compared to normal tissue.\textsuperscript{115} Recently, TWIK-2 (K2P6, encoded by \textit{KCNK6} gene) was reported as a significantly overexpressed channel in breast cancer.\textsuperscript{120} Moreover, the overexpression of TWIK-2 increases the capacity of proliferation, invasion, and migration of breast cancer cells.\textsuperscript{120}

**Strategies for Designing New K+ Channels Blockers**

The rational design and development of selective blockers is a dynamic field of study that includes diverse methods such as high-throughput screening, bioengineering techniques, and chemical modification, among others.\textsuperscript{143,144} Fortunately, we count on several software and computational tools that allow us to explore innovative approaches based on the molecular interaction of potassium channels structural data from the ligands and molecules, and the physicochemical and pharmacological properties of K\textsuperscript{+} channels interacting with drugs.

Some computational tools used for the rational design of specific modulators (blockers and activators) examine the three-dimensional structure of the target (K\textsuperscript{+} channels, in this case), previously solved by X-ray crystallography, cryoelectron microscopy,\textsuperscript{145} or comparative modeling. Following this, it is necessary to study the binding sites and affinity of the ligand.\textsuperscript{143} This approach has been particularly helpful for the identification of ligands, targeting membrane proteins.\textsuperscript{146,147}

Additionally, the multidisciplinary work among different areas, such as biochemistry, bioinformatics, bioengineering, medical chemistry, genomics, proteomics, and metabolomics, has contributed to the development of new computational tools for the rational design of ion channel modulators.\textsuperscript{143} Thus, the combinatory strategy including docking, virtual screening, de novo drug design, molecular simulations and the experimental validation by electrophysiological measures have allowed the development and a successful search for small modulators.\textsuperscript{146,147} For the K\textsuperscript{+} channels, a three-dimensional structure of representative K\textsuperscript{+} subunits (Kv, K2P, and Kir) has been reported, providing insights into how these channels can be used to design specific modulators for cancer treatment.

Moreover, ion channels with limited background expression in normal tissues and strong overexpression in tumors due to their cell-surface accessibility constitute a preferential target for the development of antibody-based therapies.\textsuperscript{148–152} Antibodies recognizing ion channels represent a strategy effective in modulation of ion channel activity. The mechanisms of action include direct block of ion permeation pathway, modulation of ion channel gating, and internalization and degradation upon surface clustering.\textsuperscript{152–154} For example, systemic administration of specific mouse monoclonal antibodies
generated in the human channel K2P9 (KCNK9) using its M1P1 loop fused into the Fc domain of IgG2a, effectively inhibits the growth of human lung cancer xenografts and murine breast cancer metastasis in mice.\textsuperscript{133} In addition, a specific monoclonal antibody which inhibits the function of highly oncogenic Kv10.1 potassium channel can effectively restrict cancer cell proliferation and reduce tumor growth in animal models with no significant side effects.\textsuperscript{155} However, currently, only one polyclonal antibody (BIL010t; Biosceptre) targeting a non-functional form of P2X7 (nP2X7) has reached the level of clinical trials for the treatment of basal cell carcinoma.\textsuperscript{156,157}

Other developing innovative strategies consist of the rational design of specific short peptides (less than 50 amino acid residues), which have acquired widespread interest as tools to address challenging protein–protein interactions (PPIs).\textsuperscript{158,159} These short peptides can form complexes, and structures, mimicking critical motifs of proteins,\textsuperscript{160} which allow them to inhibit PPIs or functional activities with high specificity and affinity, emerging as a promising alternative to small molecules and biopharmaceuticals (>5000 Da). Furthermore, short peptides are easy to produce and modify\textsuperscript{161} and present low off-target side-effects given their higher specificity and reduced immunogenicity.\textsuperscript{161} All those attractive features make short peptides exceptional candidates to serve as therapeutics, even more considering that more than 100 peptide-based drugs are available in the market for AIDS, Cancer, and other medical conditions.\textsuperscript{162,163} Some examples of therapeutic drug-based peptides include oxytocin (8 aa), calcitonin (32 aa), teriparatide (34 aa), Fuzeon (36 aa, antiretroviral), corticotropin-releasing hormone (41 aa), and growth-hormone-releasing hormone (44 aa).\textsuperscript{159}

Additionally, animal venoms are a natural and affluent source of peptides.\textsuperscript{164–166} These peptide sources (from different animals such as cone snails, scorpions, sea anemones, snakes, spiders, among others) have been widely used as a starting point to develop toxin-based drugs, and some of them have currently reached clinical trials.\textsuperscript{165} Captopril was the first toxin-based drug approved for humans (1981). It is a nonapeptide that acts by blocking the angiotensin-converting enzyme (ACE) activity inhibiting the production of angiotensin II and was developed from Bothrops jararaca snake venom.\textsuperscript{167} Captopril is currently suitable and widely used for hypertension treatment.\textsuperscript{168} Among the different approved toxin-based drugs marketed, the ziconotide is obtained from cone snails, exenatide and lixisenatide are obtained from lizards. Bivalirudin and desirudin from leeches and Batroxobin and cobratide are purified from snake venoms.\textsuperscript{162} Desirudin, on the other hand, is a recombinant peptide derivated from snake. Other drugs (bivalirudin, enalapril, eptifibatide, exenatide, tirofiban, and ziconotide) are synthetic molecules from the same source.\textsuperscript{165}

Currently, a large number of ionic channel blocking peptides (for Ca\textsuperscript{2+}, K\textsuperscript{+} and Na\textsuperscript{+} channels) have been reported and obtained from different origin.\textsuperscript{166,169–173} For instance, some peptides with antitumor effect are κ-hefutoxin 1 and analogues, APETx4, purpurealidin analogs, KAaH1 and KAaH2 among others.\textsuperscript{174–177}

There is no doubt that the specific short peptide blockers can inhibit the functional activity of K\textsuperscript{+} channels and show an antitumor effect, impacting the hallmark of cancer and representing a novel strategy for the rational design of new cancer drugs.

**Conclusion**

Compelling evidence indicates that the upregulation of the majority of K\textsuperscript{+} channels is associated with current cancer hallmarks (Figure 2 and Table 1). Thus, these channels have emerged as alternatives to develop new cancer treatments. K\textsuperscript{+} channel subunits are diverse and highly regulated proteins that respond to different stimuli. In different cancer conditions, where K\textsuperscript{+} channels are overexpressed, K\textsuperscript{+} channel blockers have been shown to reduce the tumorigenic properties and reverse the cancer progression in cell lines and animal models. However, K\textsuperscript{+} channels are critical regulators in several cellular and physiological processes; therefore, the search for selective K\textsuperscript{+} channel blockers becomes restrictive in developing future cancer treatments. Fortunately, the 3D structure of representative K\textsuperscript{+} channels\textsuperscript{178–180} opens new possibilities for the rational design of highly selective K\textsuperscript{+} modulators.

The research for these highly selective potassium channel blockers must also include natural products (eg, plant extracts), bioinformatics search using the database (eg, Zinc\textsuperscript{181}), venom peptides, and the design of cyclic peptides (CPs) as modulators of protein–protein interactions. Indeed, there is no doubt that rational design, search, and development might increase the therapeutic arsenal of drugs against cancer conditions associated with K\textsuperscript{+} channels. Nevertheless, the design, search, and development of selective K\textsuperscript{+} channel blockers remains a challenge that must be addressed in a multidisciplinary manner, including chemistry, bioinformatics, bioengineering, and biophysics groups.
Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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References

1. Goldstein SAN, Bockenhauer D, O’Kelly I, Zilberberg N. Potassium leak channels and the KCNK family of two-P-domain subunits. Nat Rev Neurosci. 2001;2(3):175–184. doi:10.1038/35085574
2. González C, Baez-Nieto D, Valencia I, et al. K+ channels: function-structural overview. Compr Physiol. 2012;2:2087–2149.
3. Hibino H, Imanobe A, Furihata K, et al. Inwardly rectifying potassium channels: their structure, function, and physiological roles. Physiol Rev. 2010;90(1):291–366. doi:10.1152/physrev.00021.2009
4. Cui M, Cantwell L, Zorn A, Logothetis DE. Kir channel molecular physiology, pharmacology, and therapeutic implications. Handb Exp Pharmacol. 2021;267:277–356. doi:10.1007/164_2021_501
5. Zúñiga L, Zúñiga R. Understanding the cap structure in K2P channels. Front Physiol. 2016;7:228. doi:10.3389/fphys.2016.00228
6. Zhou Y, Morais-Cabral JH, Kaufman A, MacKinnon R. Chemistry of ion coordination and hydration revealed by a K+ channel-Fab complex at 2.0 Å resolution. Nature. 2001;414(6859):43–48. doi:10.1038/35102009
7. Bezanilla F. The voltage sensor in voltage-dependent ion channels. Physiol Rev. 2000;80(2):555–592. doi:10.1152/physrev.2000.80.2.555
8. Jiang Y, Lee A, Chen J, et al. X-ray structure of a voltage-dependent K+ channel. Nature. 2003;423(6955):33–41. doi:10.1038/nature01580
9. Lotshaw DP. Biophysical, pharmacological, and functional characteristics of cloned and native mammalian two-pore domain K+ channels. Cell Biochem Biophys. 2007;47:209–256. doi:10.1007/s12013-007-0007-8
10. Enyedi P, Czirjak G. Molecular background of leak K+ currents: two-pore domain potassium channels. Physiol Rev. 2010;90:559–605. doi:10.1152/physrev.00029.2009
11. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209–249. doi:10.3322/caac.21660
12. Goss PE, Lee BL, Badovinac-Crnjevic T, et al. Planning cancer control in Latin America and the Caribbean. Lancet Oncol. 2013;14(5):391–436. doi:10.1016/S1470-2045(13)70048-2
13. Bates E. Ion channels in development and cancer. Annu Rev Cell Dev Biol. 2015;31(1):231–247. doi:10.1146/annurev-cellbio-100814-125338
14. Huang X, Jan LY. Targeting potassium channels in cancer. J Cell Biol. 2014;206(2):151–162. doi:10.1083/jcb.201401436
15. Pardo LA, Stühmer W. The roles of K+ channels in cancer. Nat Rev Cancer. 2014;14(1):39–48. doi:10.1038/nrc3635
16. Prevarskaya N, Skryma R, Shuba Y. Ion channels in cancer: are cancer hallmarks oncochannelopathies? Physiol Rev. 2018;98(2):559–621. doi:10.1152/physrev.00044.2016
17. Ouadid-Ahidouch H, Ahidouch A. K+ channel expression in human breast cancer cells: involvement in cell cycle regulation and carcinogenesis. J Membr Biol. 2008;221(1):1–6. doi:10.1007/s00232-007-9080-6
18. Shen Z, Yang Q, You Q. Researches toward potassium channels on tumor progressions. Curr Top Med Chem. 2009;9(4):322–329. doi:10.2174/15680260878317874
19. Lesage F, Ladzunski M. Molecular and functional properties of two-pore-domain potassium channels. Am J Physiol Renal Physiol. 2000;279:F793–F801. doi:10.1152/ajprenal.2000.279.5.F793
20. Lee G-W, Park HS, Kim E-J, et al. Reduction of breast cancer cell migration via up-regulation of TASK-3 two-pore domain K+ channel. Acta Physiol. 2012;204:513–524. doi:10.1111/j.1748-1716.2011.02359.x
21. Kunzelmann K. Ion channels and cancer. J Membr Biol. 2005;205:159–173. doi:10.1007/s00232-005-0781-4
22. Wang Z. Roles of K+ channels in regulating tumour cell proliferation and apoptosis. Pflugers Arch Eur J Physiol. 2004;448:274–286. doi:10.1007/s00424-004-1258-5
24. Mu D, Chen L, Zhang X, et al. Genomic amplification and oncogenic properties of the KCNK9 potassium channel gene. Cancer Cell. 2003;3:297–302. doi:10.1016/S1535-6108(03)00054-0
25. Pei L, Wiser O, Slavin A, et al. Oncogenic potential of TASK3 (Kcnq9) depends on K+ channel function. Proc Natl Acad Sci USA. 2003;100:7803–7807. doi:10.1073/pnas.1323448100
26. Brevet M, Fucks D, Chatelain D, et al. Deregulation of 2 potassium channels in pancreas adenocarcinomas: implication of Kv1.3 gene promoter methylation. Pancreas. 2009;38(6):649–654. doi:10.1097/MPA.0b013e3181a56ef
27. Hasselblatt M, Böhm C, Tatenhorst L, et al. Identification of novel diagnostic markers for choroid plexus tumors: a microarray-based approach. Am J Surg Pathol. 2006;30(1):66–74. doi:10.1097/01.pas.0000176430.88702.00
28. Liu H, Huang J, Peng J, et al. Uprogulation of the inwardly rectifying potassium channel Kir2.1 (KCNJ2) modulates multidrug resistance of small-cell lung cancer under the regulation of miR-7 and the Ras/MEK pathway. Mol Cancer. 2015;14:59. doi:10.1186/s12943-015-0298-0
29. Murthy M, Azizan EA, Brown MJ, O’Shaughnessy KM. Characterization of a novel somatic KCNJ5 mutation delH157 in an aldosterone-producing adenoma. J Hypertens. 2012;30(9):1827–1833. doi:10.1097/HJH.0b013e282356139f
30. Park S-H, Ramachandran S, Kwon S-H, et al. Uprogulation of ATP-sensitive potassium channels for estrogen-mediated cell proliferation in human uterine leiomyoma cells. Gynecol Endocrinol. 2008;24(5):250–256. doi:10.1080/09513590801893315
31. Sakai H, Shimizu T, Hori K, et al. Molecular and pharmacological properties of inwardly rectifying K+ channels of human lung cancer cells. Eur J Pharmacol. 2002;435(2):125–133. doi:10.1016/s0014-2999(01)01567-9
32. Warth A, Mittelbronn M, Wolburg H. Redistribution of the water channel protein aquaporin-4 and the K+ channel protein Kir4.1 differs in low- and high-grade human brain tumors. Acta Neuropathol. 2005;109(4):418–426. doi:10.1007/s00401-005-0984-x
33. Wulff H, Castle NA. Therapeutic potential of K+ channels in cancer. J Physiol. 2010;588(19):4639–4649. doi:10.1113/jphysiol.2010.199030
34. Ouadid-Ahidouch H, Ahidouch A, Pardo LA. Kv10.1 K+ channels promote BT-474 breast cancer cell migration. Chin J Cancer Res. 2018;30(6):613–622. doi:10.2117/ajrccm.100-9004-2018.06.06
35. Miceli F, Guerrini R, Nappi M, et al. Distinct epilepsy phenotypes and response to drugs in KCNA1 gain- and loss-of-function variants. Epilepsia. 2022;63(1):c7–c14. doi:10.1111/epli.17118
36. van der Wijst J, Konrad M, Verkaart SA, et al. A de novo KCNA1 mutation in a patient with tetany and hypomagnesemia. Nephron. 2018;139:359–366. doi:10.1159/000488954
37. Liu L, Chen Y, Zhang Q, Li C. Silencing of KCNA1 suppresses the cervical cancer development via microtubronia damage. Channels. 2019;13(1):321–330. doi:10.1080/19336950.2019.1648627
38. Taylor MD, Northcott PA, Korshunov A, et al. Molecular subgroups of medulloblastoma: the current consensus. Acta Neuropathol. 2012;123(4):465–472. doi:10.1007/s00401-011-1022-z
39. Bielanska J, Hernández-Losa J, Moline T, et al. Differential expression of Kv1.3 and Kv1.5 voltage-dependent K+ channels in human skeletal muscle sarcomas. Cancer Invest. 2012;30(3):203–208. doi:10.1080/07357900.2012.654872
40. Bielanska J, Hernández-Losa J, Molina T, et al. Increased expression of voltage-dependent K+ channel Kv1.3 and Kv1.5 expression correlates with leiomyosarcoma aggressiveness. Oncol Lett. 2012;4(2):227–230. doi:10.3892/ol.2012.718
41. Comes N, Bielanska J, Vallejo-Gracia A, et al. The voltage-dependent K+ channels Kv1.3 and Kv1.5 in human cancer. Front Physiol. 2013;4:283. doi:10.3389/fphys.2013.00283
42. Teisseye A, Gasiorowska J, Michalak K. Voltage-gated potassium channels Kv1.3 Potentially new molecular target in cancer diagnostics and therapy. Adv Clin Exp Med. 2015;24(3):517–524. doi:10.17219/acem/22339
43. Teisseye A, Pulko-Labau Z, Sroda-Pomianek K, Michalak K. Voltage-gated potassium channel Kv1.3 as a target in therapy of cancer. Front Oncol. 2019;9:933. doi:10.3389/fonc.2019.00933
44. Leanza L, Romio M, Becker KA, et al. Direct pharmacological targeting of a mitochondrion ion channel selectively kills tumor cells in vivo. Cancer Cell. 2017;31(4):516–531. doi:10.1016/j.ccell.2017.03.003
45. Venturini E, Leanza L, Azzolini M, et al. Targeting the potassium channel Kv1.3 kills glioblastoma cells. Neurosignals. 2017;25(1):26–38. doi:10.1159/000480643
46. Chechicotto V, Prosdocimi E, Leanza L. Mitochondrial Kv1.3: a new target in cancer biology? Cell Physiol Biochem. 2019;53(S1):52–62.
47. Preuflat K, Beetz C, Schrey M, et al. Expression of voltage-gated potassium channels Kv1.3 and Kv1.5 in human gliomas. Neurosci Lett. 2003;346(1–2):33–36. doi:10.1016/S0304-3940(03)00562-7
48. Lan M, Shi Y, Han Z, et al. Expression of delayed rectifier potassium channels and their possible roles in proliferation of human gastric cancer cells. Cancer Biol Ther. 2005;4(12):1342–1347. doi:10.4161/cbt.4.12.2175
49. Vallejo-Gracia A, Bielanska J, Hernández-Losa J, et al. Emerging role for the voltage-dependent K+ channel Kv1.5 in B-lymphocyte physiology: expression associated with human lymphoma malignancy. J Leukoc Biol. 2013;94(4):779–789. doi:10.1189/jlb.0213094
50. Park HW, Song MS, Sim HJ, Ryu PD, Lee SY. The role of the voltage-gated potassium channel, Kv2.1 in prostate cancer cell migration. BMB Rep. 2021;54(2):130–135. doi:10.5438/BMBRep.2021.54.2.210
51. Park JH, Park SJ, Chung MK, et al. High expression of large-conductance Ca2+–activated K+ channel in the CD133+ subpopulation of SH-SYSY neuroblastoma cells. Biochem Biophys Res Commun. 2010;396(3):637–642. doi:10.1016/j.bbrc.2010.04.142
52. Chang K-W, Yuan T-C, Fang K-P, et al. The increase of voltage-gated potassium channel Kv3.4 mRNA expression in oral squamous cell carcinoma. J Oral Pathol Med. 2003;32(10):606–611. doi:10.1034/j.1600-0714.2003.00197.x
53. Menéndez ST, Rodrigo JP, Allonza E, et al. Expression and clinical significance of the Kv3.4 potassium channel subunit in the development and progression of head and neck squamous cell carcinomas. J Pathol. 2010;221(4):402–410. doi:10.1002/path.2722
54. Song MS, Park SM, Park JS, et al. Kv3.4 and Kv3.3, are involved in cancer cell migration and invasion. Int J Mol Sci. 2018;19(4):1061. doi:10.3390/ijms19041061
55. Jang SH, Choi C, Hong S-G, et al. Silencing of Kv4.1 potassium channels inhibits cell proliferation of tumorigenic human mammary epithelial cells. Biochem Biophys Res Commun. 2009;384(2):180–186. doi:10.1016/j.bbrc.2009.04.108
57. Kim H-J, Jang SH, Jeong YA, et al. Involvement of Kv4.1 K⁺ channels in gastric cancer cell proliferation. Biol Pharm Bull. 2010;33(10):1754–1757. doi:10.1248/bpb.33.1754
58. Shimizu T, Fujii T, Takahashi Y, et al. Up-regulation of Kv7.1 channels in thromboxane A₂-induced colonic cancer cell proliferation. Pflugers Arch Eur J Physiol. 2014;466(3):541–548. doi:10.1007/s00424-013-1341-x
59. Serrano-Novillo C, Oliveras A, Ferreres JC, Condom E, Felipe A. Remodeling of Kv7.1 and Kv7.5 expression in vascular tumors. Int J Mol Sci. 2020;21(17):6019. doi:10.3390/ijms21176019
60. Lee J-H, Park J-W, Byun JK, et al. Silencing of voltage-gated potassium channel Kᵥ9.3 inhibits proliferation in human colon and lung carcinoma cells. Oncotarget. 2015;6:8132–8143. doi:10.18632/oncotarget.5157
61. Suzuki T, Takimoto K. Selective expression of HERG and Kᵥ2 channels influences proliferation of uterine cancer cells. Int J Oncol. 2004;25(1):153–159.
62. Hemmerlein B, Wesseloh RM. Mello de Queiroz F, et al. Overexpression of Eag1 potassium channels in clinical tumours. Int J Mol Sci. 2006;5:41. doi:10.3390/ijms1054598-5-42
63. Martínez R, Stühmer W, Martin S, et al. Analysis of the expression of Kv10.1 potassium channel in patients with brain metastases and glioblastoma multiforme: impact on survival. BMC Cancer. 2015;15:839. doi:10.1186/s12885-015-1848-y
64. Wang X, Chen Y, Zhang Y, et al. Eag1 voltage-dependent potassium channels: structure, electrophysiological characteristics, and function in cancer. J Membr Biol. 2017;250(2):123–132. doi:10.1007/s00232-016-9944-8
65. Agarwal JR, Griesinger F, Stühmer W, Pardo LA. The potassium channel Ether à go-go is a novel prognostic factor with functional relevance in acute myeloid leukemia. Mol Cancer. 2010;9(1):18. doi:10.1007/s12032-009-0413-5
66. Chávez-López MG, Zúñiga-García V, Castro-Magdonel BE, et al. Eag1 gene and protein expression in human retinoblastoma tumors and its regulation by pRb in HeLa cells. Genes. 2020;11(2):119. doi:10.3390/genes11020119
67. Chávez-López MG, Zúñiga-García V, Castro-Magdonel BE, et al. Eag1 gene and protein expression in human retinoblastoma tumors and its regulation by pRb in HeLa cells. Genes. 2020;11(2):119. doi:10.3390/genes11020119
68. Hemmerlein B, Weseloh RM. Mello de Queiroz F, et al. Overexpression of Eag1 potassium channels in clinical tumours. Int J Mol Sci. 2006;5:41. doi:10.3390/ijms1054598-5-42
69. Hartung F, Stühmer W, Pardo LA. Tumor cell-selective apoptosis induction through targeting of Kᵥ10.1 via bifunctional TRAIL antibody. Mol Cancer. 2011;10:109. doi:10.1186/1476-4598-10-109
70. Pardo LA, Gómez-Varela D, Major F, et al. Approaches targeting Kᵥ10.1 open a novel window for cancer diagnosis and therapy. Curr Med Chem. 2012;19(5):675–682. doi:10.2174/092986712798992011
71. Sales TT, Resende FF, Chaves NL, et al. Suppression of the Eag1 potassium channel sensitizes glioblastoma cells to injury caused by temozolomide. Oncol Lett. 2016;12(4):2581–2589. doi:10.3892/ol.2016.4492
72. Valdés-Abadia B, Morán-Zendejas R, Rangel-Flores JM, Rodríguez-Menchaca AA. Chloroquine inhibits tumor-related Kᵥ10.1 channel and decreases migration of MDA-MB-231 breast cancer cells in vitro. Eur J Pharmacol. 2019;855:262–266.
73. Hernández-Reséndiz I, Pacheu-Grau D, Sánchez A, Pardo LA. Inhibition of Kᵥ10.1 channels sensitizes mitochondria of cancer cells to antimitotic agents. Cancers. 2020;12(4):920.
74. Staudacher I, Jehle J, Staudacher K, et al. HERG K+ channel-dependent apoptosis and cell cycle arrest in human glioblastoma cells. PLoS One. 2014;9(4):e88164. doi:10.1371/journal.pone.0088164
75. Banderali U, Belke D, Singh A, et al. Curcumin blocks Kv11.1 (erg) potassium current and slows proliferation in the infant acute monocytic leukemia cell line THP-1. Cell Physiol Biochem. 2011;28(6):1169–1180. doi:10.1159/0003355850
76. Perez-Neut M, Rao VR, Gentile S. hERG1/Kᵥ11.1 activation stimulates transcription of p21 Rafkip in breast cancer cells via a calcineurin-dependent mechanism. Oncotarget. 2016;7(37):58983–58902. doi:10.18632/oncotarget.3797
77. Lastraioli E, Romoli MR, Iorio J, et al. The hERG potassium channel behaves as prognostic factor in gastric dysplasia endoscopic samples. OncoTargets Ther. 2019;12:9377–9384. doi:10.2147/OTT.S226257
78. Pillozzi S, D’Amico M, Bartoli G, et al. The combined activation of Kᵥ3.1 and inhibition of Kᵥ11.1/hERG currents contribute to overcome Cisplatin resistance in colorectal cancer cells. Br J Cancer. 2018;118(2):200–212. doi:10.1038/bjc.2017.392
79. He S, Moutaoufik MT, Islam S, et al. HERG channel and cancer: a mechanistic review of carcinogenic processes and therapeutic potential. Biochim Biophys Acta Rev Cancer. 2020;1873(2):18855. doi:10.1016/j.bcan.2018.8553
80. Arcangeli A, Beechetti A. Novel perspectives in cancer therapy: targeting ion channels. Drug Resist Updat. 2015;21:11–19. doi:10.1016/j.drup.2015.06.002
81. Jehle J, Schweizer PA, Katus HA, Thomas D. Novel roles for hERG K⁺ channel in cell proliferation and apoptosis. Cell Death Dis. 2011;2(8):e193. doi:10.1038/cddis.2011.77
82. Du C, Chen L, Zhang H, et al. Caveolin-1 limits the suppression of BMCa channel to MCF-7 breast cancer cell proliferation and invasion. Int J Mol Sci. 2014;15(11):20706–20722. doi:10.3390/ijms151120706
83. Du C, Zheng Z, Li D, et al. BCA2 promotes growth and metastasis of prostate cancer through facilitating the coupling between osfβ3 integrin and FAK. Oncotarget. 2016;7(26):40174–40188. doi:10.18632/oncotarget.9559
84. Klumpp L, Szegzin EC, Eckert F, Huber SM. Ion channels in brain metastasis. Int J Mol Sci. 2016;17(9):1513. doi:10.3390/ijms17091513
85. Li N, Liu L, Li G, et al. The role of BCA2 in endometrial cancer HEC-1-B cell proliferation and migration. Gene. 2018;655:42–47. doi:10.1016/j.gene.2018.02.055
86. Noda S, Chikazawa K, Suzuki Y, Imaizumi Y, Yamamura H. Involvement of the γ₁ subunit of the large-conductance Ca²⁺-activated K⁺ channel in the proliferation of human somatostatinoma cells. Biochem Biophys Res Commun. 2020;525(4):1032–1037. doi:10.1016/j.bbrc.2020.02.176
87. Oeggerli M, Tian Y, Ruiz C, et al. Role of KCNMA1 in breast cancer. PLoS One. 2012;7(8):e41664. doi:10.1371/journal.pone.0041664
88. Turner KL, Honasoge A, Robert SM, McFerrin MM, Sontheimer H. A proinvasive role for the Ca²⁺-activated K⁺ channel KCa3.1 in malignant glioma. Glia. 2014;62(6):971–981. doi:10.1002/glia.22655
89. Steudel FA, Mohr CJ, Stegen B, et al. SK4 channels modulate Ca²⁺ signalling and cell cycle progression in murine breast cancer. Mol Oncol. 2011;5(7):1172–1188. doi:10.1016/j.molonc.2011.06.008
90. Gläser F, Hundelhege P, Bulk E, et al. KCa3.1 channel blockers increase effectiveness of the EGF receptor TK inhibitor erlotinib in non-small cell lung cancer cells (A549). Sci Rep. 2021;11(1):18330. doi:10.1038/s41598-021-97406-0
91. Schmidt J, Friebel K, Schönherr R, Coppolino MG, Bosserhoff A-K. Migration-associated secretion of melanoma inhibitory activity at the cell rear is mediated by KCa3.1 potassium channels. Cell Res. 2010;20:1224–1238. doi:10.1038/cr.2010.121

92. Stoneking CJ, Shivakumar O, Thomas DN, Collarde WH, Mason MJ. Voltage dependence of the Ca2+-activated K+ channel Kcα3.1 in human erythroleukemia cells. Am J Physiol Cell Physiol. 2013;304(6):C585–C587. doi:10.1152/ajpcell.00368.2012

93. Rabjerg M, Oliván-Viguer A, Hansen LK, et al. High expression of KCa3.1 in patients with clear cell renal carcinoma predicts high metabolic risk and poor survival. PLoS One. 2015;10(4):e0122992. doi:10.1371/journal.pone.0122992

94. Liu Y, Zhao L, Ma W. et al. The blockage of KCa3.1 channel inhibited proliferation, migration and promoted apoptosis of human hepatocellular carcinoma cells. J Cancer. 2015;6(7):643–651. doi:10.7150/jca.11913

95. Rügieri P, Mangino G, Fioretti B, et al. The inhibition of KCa3.1 channels activity reduces cell motility in glioblastoma derived cancer stem cells. PLoS One. 2012;7(10):e47825. doi:10.1371/journal.pone.0047825

96. Chantome A, Girault A, Potier M. et al. KCa2.3 channel-dependent hyperpolarization increases melanoma cell motility. Exp Cell Res. 2009;315(20):3620–3630. doi:10.1016/j.yexcr.2009.07.021

97. Ji C-D, Wang Y-X, Xiang D-F. et al. Kir2.1 interaction with Stk38 promotes invasion and metastasis of human gastric cancer by enhancing MEKK2–MEK1/2–ERK1/2 signaling. Cancer Res. 2018;78(11):3041–3053. doi:10.1158/0008-5472.CAN-17-3776

98. Lee I, Park C, Kang WK. Knockdown of inwardly rectifying potassium channel Kir2.2 suppresses tumorigenesis by inducing reactive oxygen species-mediated cellular senescence. Mol Cancer Ther. 2010;9(11):2951–2959. doi:10.1158/1535-7163.MCT-10-0511

99. Lee I, Lee S-J, Kang TM, Park C. Conventional role of the inwardly rectifying potassium channel Kir2.2 as a constitutive activator of RelA in cancer. Cancer Res. 2013;73(3):1056–1062. doi:10.1158/0008-5472.CAN-12-2498

100. Stringer BK, Cooper AG, Shepard SB. Overexpression of the G-protein inwardly rectifying potassium channel 1 (GIRK1) in primary breast carcinomas correlates with axillary lymph node metastasis. Cancer Res. 2001;61(2):582–588.

101. Takamani I, Inoue Y, Gika M. G-protein inwardly rectifying potassium channel 1 (GIRK1) gene expression correlates with tumor progression in non-small cell lung cancer. BMC Cancer. 2004;4(1):79. doi:10.1186/1471-2407-4-79

102. Plummer HK, Yu Q, Calik Y, Schuller HM. Expression of inwardly rectifying potassium channels (GIRKs) and beta-adrenergic regulation of breast cancer cell lines. BMC Cancer. 2004;4(1):93. doi:10.1186/1471-2407-4-93

103. Scholl U, Liffon RP. New insights into aldosterone-producing adenomas and hereditary aldosteronism: mutations in the K+ channel KCNJ5. Curr Opin Nephrol Hypertens. 2013;22(2):141–147. doi:10.1097/MNH.0b013e32835acef8

104. Tan G, Sun SQ, Yuan DL. Expression of Kir 4.1 in human astrocytic tumors: correlation with pathologic grade.

105. Núñez M, Medina V, Cricco G, et al. Glibenclamide inhibits cell growth by inducing G0/G1 arrest in the human breast cancer cell line MDA-MB-231. BMC Pharmacol Toxicol. 2013;14(1):6. doi:10.1186/2050-6511-14-6

106. Zhang K, Mu L, Ding M-C, et al. NFκB mediated elevation of KCNJ11 promotes tumor progression of hepatocellular carcinoma through interaction of lactate dehydrogenase A. Biochem Biophys Res Commun. 2018;495(1):246–253. doi:10.1016/j.bbrc.2017.11.011

107. Vázquez-Sánchez AY, Hinojosia LM, Parraguírra-Martínez S, et al. Expression of KATP channels in human cervical cancer: potential tools for diagnosis and therapy. Oncol Lett. 2018;15(5):6302–6308. doi:10.3892/ol.2018.8165

108. Huang L, Li B, Li W, Guo H, Zou F. ATP-sensitive potassium channels control glioma cells proliferation by regulating ERK activity. Carcinogenesis. 2009;30(5):737–744. doi:10.1093/carcin/bgp304

109. Schittenhelm J, Nagel C, Meyermann R, Beschorner R. Atypical teratoid/rhabdoid tumors may show morphological and immunohistochemical features seen in choroid plexus tumors. J Neuropathol Exp Neurol. 2010;69(10):901–912. doi:10.1093/jnnp/nq115

110. Japp AS, Klein-Hitpass L, Denkhaus D, Pietsch T. Unconventional role of the inwardly rectifying potassium channel Kir2.2 in human astrocytic tumors: potential tools for diagnosis and therapy. Oncol Lett. 2018;15(5):6302–6308. doi:10.3892/ol.2018.8165

111. Miller AN, Long SB. Crystal structure of the human two pore domain potassium channel K2P1. J Membr Biol. 2006;200(2–3):93–96. doi:10.1007/s00232-010-9306-x

112. Erzen NJ, Logsdon NJ, McFerrin MB, Sontheimer H, Spiller SE. Biophysical properties of human medulloblastoma cells. J Membr Biol. 2010;237(2–3):59–69. doi:10.1007/s00232-010-9306-x

113. Vološyna I, Besana A, Castillo M, et al. TREK-1 is a novel molecular target in prostate cancer.

114. Vološyna I, Besana A, Castillo M, et al. TREK-1 is a novel molecular target in prostate cancer.

115. Rabjerg M, Oliván-Viguer A, Hansen LK, et al. High expression of KCa3.1 in patients with clear cell renal carcinoma predicts high metabolic risk and poor survival. PLoS One. 2015;10(4):e0122992. doi:10.1371/journal.pone.0122992

116. Liu Y, Zhao L, Ma W. et al. The blockage of KCa3.1 channel inhibited proliferation, migration and promoted apoptosis of human hepatocellular carcinoma cells. J Cancer. 2015;6(7):643–651. doi:10.7150/jca.11913

117. Rügieri P, Mangino G, Fioretti B, et al. The inhibition of KCa3.1 channels activity reduces cell motility in glioblastoma derived cancer stem cells. PLoS One. 2012;7(10):e47825. doi:10.1371/journal.pone.0047825

118. Chantome A, Girault A, Potier M. et al. KCa2.3 channel-dependent hyperpolarization increases melanoma cell motility. Exp Cell Res. 2009;315(20):3620–3630. doi:10.1016/j.yexcr.2009.07.021

119. Ji C-D, Wang Y-X, Xiang D-F. et al. Kir2.1 interaction with Stk38 promotes invasion and metastasis of human gastric cancer by enhancing MEKK2–MEK1/2–ERK1/2 signaling. Cancer Res. 2018;78(11):3041–3053. doi:10.1158/0008-5472.CAN-17-3776

120. Lee I, Park C, Kang WK. Knockdown of inwardly rectifying potassium channel Kir2.2 suppresses tumorigenesis by inducing reactive oxygen species-mediated cellular senescence. Mol Cancer Ther. 2010;9(11):2951–2959. doi:10.1158/1535-7163.MCT-10-0511

121. Lee I, Lee S-J, Kang TM, Park C. Conventional role of the inwardly rectifying potassium channel Kir2.2 as a constitutive activator of RelA in cancer. Cancer Res. 2013;73(3):1056–1062. doi:10.1158/0008-5472.CAN-12-2498

122. Stringer BK, Cooper AG, Shepard SB. Overexpression of the G-protein inwardly rectifying potassium channel 1 (GIRK1) in primary breast carcinomas correlates with axillary lymph node metastasis. Cancer Res. 2001;61(2):582–588.

123. Leithner K, Hirschmugl B, Li Y, et al. TASK-1 regulates apoptosis and proliferation in a subset of non-small cell lung cancers.

124. Leithner K, Hirschmugl B, Li Y, et al. TASK-1 regulates apoptosis and proliferation in a subset of non-small cell lung cancers.

125. Leithner K, Hirschmugl B, Li Y, et al. TASK-1 regulates apoptosis and proliferation in a subset of non-small cell lung cancers.
124. Wang X-G, Yuan N-X, Li X-P, Chen F-F. TASK-1 induces gefitinib resistance by promoting cancer initiating cell formation and epithelial-mesenchymal transition in lung cancer. *Exp Ther Med*. 2018;15(1):365–370. doi:10.3892/etm.2017.4526

125. Nogueira EF, Gerry D, Mantero F, Marinello B, Rainey WE. The role of TASK1 in aldosterone production and its expression in normal adrenal and aldosterone-producing adenomas. *Clin Endocrinol*. 2010;73(1):22–29.

126. Williams C, Edvardsson K, Lewandowski SA, Ström A, Gustafsson J-A. A genome-wide study of the repressive effects of estrogen receptor beta on estrogen receptor alpha signaling in breast cancer cells. *Oncogene*. 2008;27(7):1019–1032. doi:10.1038/sj.onc.1210712

127. Álvarez-Baron CP, Jonsson P, Thomas C, Dryer SE, Williams C. The two-pore domain potassium channel KCNK5: induction by estrogen receptor α and role in proliferation of breast cancer cells. *Mol Endocrinol*. 2011;25(8):1326–1336. doi:10.1210/me.2011-0045

128. Fong P, Argent BE, Guggerino WB, Gray MA. Characterization of vectorial chloride transport pathways in the human pancreatic duct adenocarcinoma cell line HPAF. *Am J Physiol Cell Physiol*. 2003;285(2):C433–C445. doi:10.1152/ajpcell.00509.2002

129. Rusznák Z, Bakondi G, Koszta L, et al. Mitochondrial expression of the two-pore-domain TASK-3 channels in malignantly transformed and non-malignant human cells. *Virchows Arch*. 2008;452(4):415–426. doi:10.1007/s00428-007-0545-x

130. Innamaa A, Jackson L, Asher V, et al. Expression and prognostic significance of the oncogenic K2P potassium channel KCNK9 (TASK-3) in ovarian carcinoma. *Anticancer Res*. 2013;33:1401–1408.

131. Patel AJ, Lazdunski M. The 2P-domain K+ channels: role in apoptosis and tumorigenesis. *Pflugers Arch Eur J Physiol*. 2004;448:261–273. doi:10.1007/s00424-004-1255-8

132. Zúñiga R, Valenzuela C, Concha G, Brown N, Zúñiga L. TASK-3 downregulation triggers cellular senescence and growth inhibition in breast cancer cell lines. *Int J Mol Sci*. 2018;19(4):1033. doi:10.3390/ijms19041033

133. Sun H, Luo L, Lai B, et al. A monoclonal antibody against KCNK9 K+ channel extracellular domain inhibits tumour growth and metastasis. *Nat Commun*. 2016;7:10339. doi:10.1038/ncomms10339

134. Kovács I, Pocsai K, Czifra G, et al. TASK-3 immunoreactivity shows differential distribution in the human gastrointestinal tract. *Virchows Arch*. 2005;446(4):402–410. doi:10.1007/s00424-005-1205-7

135. Kim CJ, Cho YG, Jeong SW, et al. Altered expression of KCNK9 in colorectal cancers. *Int J Mol Med*. 2010;25(8):1326–1336. doi:10.3892/immuno.2011.1033

136. Toczylowska-Maminska R, Olszewska A, Laskowski M, et al. Potassium channel in the mitochondria of human keratinocytes. *J Invest Dermatol*. 2014;134(3):764–772. doi:10.1038/jid.2013.422

137. Checchetto V, Leanza L, De Stefani D, et al. Mitochondrial K+ channel TREK-1 in human osteoblasts. *J Cell Physiol*. 2021;246(8):107874. doi:10.1002/jcp.21074

138. Zúñiga L, Cikutović-Molina R, Herrada AA, González W, Brown N, Zúñiga L. TASK-3 gene knockdown dampens invasion and migration and promotes apoptosis in KATO III and MKN-45 human gastric adenocarcinoma cell lines. *Int J Mol Sci*. 2019;20(23):6077. doi:10.3390/ijms20236077

139. Toczylowska-Maminska R, Olszewska A, Laskowski M, et al. Potassium channel in the mitochondria of human keratinocytes. *J Invest Dermatol*. 2014;134(3):764–772. doi:10.1038/jid.2013.422

140. Nagy D, Görnzi M, Dienses B, et al. Silencing the KCNK9 potassium channel (TASK-3) gene disturbs mitochondrial function, causes mitochondrial depolarization, and induces apoptosis of human melanoma cell lines. *Arch Dermatol Res*. 2014;306(10):885–902. doi:10.1007/s00403-014-1511-5

141. Hughes S, Magnay J, Foreman M, et al. Expression of the mechanosensitive 2PK+ channel TREK-1 in human osteoblasts. *J Cell Physiol*. 2006;206(3):738–748. doi:10.1002/jcp.20536

142. Zhang G-M, Fan F-N, Qin X-J, et al. Prognostic significance of the TREK-1 K2P potassium channels in prostate cancer. *Oncotarget*. 2015;6(21):18460–18468. doi:10.18632/oncotarget.3782

143. Ramirez D. Computational methods applied to rational drug design. *Open Med Chem J*. 2016;10:7–20. doi:10.2174/1874104501610010007

144. Bedoya M, Rühe S, Kiper AK, et al. TASK channels pharmacology: new challenges in drug design. *J Med Chem*. 2019;62(22):10044–10058. doi:10.1021/acs.jmedchem.9b00248

145. Ye D, Wang J, Yu K, et al. Current strategies for the discovery of K+ channel modulators. *Curr Top Med Chem*. 2009;9(4):348–361. doi:10.2174/156802609783187685

146. Ramirez D, Concha G, Arévalo B, et al. Discovery of novel TASK-3 channel blockers using a pharmacophore-based virtual screening. *Int J Mol Sci*. 2019;20(16):4014. doi:10.3390/ijms20164014

147. Toplak Ž, Hendrickx LA, Gubii Š, et al. 3D pharmacophore-based discovery of novel K+1.0 inhibitors with antiproliferative activity. *Cancers*. 2021;13(1):1244. doi:10.3390/cancers13061244

148. Stortelers C, Pinto-Espinoza C, Van Hoorick D, Koch-Nolte F. Modulating ion channel function with antibodies and nanobodies. *Curr Opin Immunol*. 2018;52:18–26. doi:10.1016/j.coi.2018.02.003

149. Haustrate A, Hantute-Ghesquier A, Prevanskaia N, Lehen’kyi V. Monoclonal antibodies targeting ion channels and their therapeutic potential. *Front Pharmacol*. 2019;10:606. doi:10.3389/fphar.2019.00606

150. Hernandez-Resendiz I, Hartung F, Fardo LA. Antibodies targeting Kv potassium channels: a promising treatment for cancer. *Bioelectricity*. 2019;1(3):180–187. doi:10.1089/bioe.2019.0022

151. Hutchings CI, Colussi P, Clark TG. Ion channels as therapeutic antibody targets. *mAbs*. 2019;11(2):265–296. doi:10.1080/19420862.2018.1548232

152. Wulf H, Christophersen P, Colussi P, Chandy KG, Yarov-Yarovoy V. Antibodies and venom peptides: new modalities for ion channels. *Nat Rev Drug Discov*. 2019;18(5):339–357. doi:10.1038/s41573-019-0013-8

153. Sun H, Li M. Antibody therapeutics targeting ion channels: are we there yet? *Acta Pharmacol Sin*. 2013;34(2):199–204. doi:10.1038/aps.2012.202

154. Douthwaite JA, Finch DK, Mustelin T, Wilkinson TC. Development of therapeutic antibodies to G protein-coupled receptors and ion channels: opportunities, challenges and their therapeutic potential in respiratory diseases. *Pharmacol Ther*. 2017;169:113–123. doi:10.1016/j.pharmthera.2016.04.013
155. Gómez-Varela D, Zwick-Wallasch E, Knöttgen H, et al. Monoclonal antibody blockade of the human Eag1 potassium channel function exerts antitumor activity. Cancer Res. 2007;67(15):7343–7349. doi:10.1158/0008-5472.CAN-07-1017

156. Gilbert SM, Oliphant CJ, Hassan S, et al. ATP in the tumour microenvironment drives expression of nP2X7, a key mediator of cancer cell survival. Oncogene. 2019;38(2):192–208. doi:10.1038/s41388-018-0426-6

157. Gilbert SM, Gidley-Baird A, Glazer S, et al. A Phase I clinical trial demonstrates that nP2X7-targeted antibodies provide a novel, safe and tolerable topical therapy for basal cell carcinoma. Br J Dermatol. 2017;177(1):117–124. doi:10.1111/bjd.15364

158. Nevola L, Giralt E. Modulating protein-protein interactions: the potential of peptides. Chem Commun. 2015;51(16):3302–3315. doi:10.1039/C4CC08565E

159. Craik DJ, Fairlie DP, Liras S, Price D. The future of peptide-based drugs. Chem Biol Drug Des. 2013;81(1):136–147. doi:10.1111/cbd.12055

160. Pelay-Gimeno M, Glas A, Koch O, Grossmann TN. Structure-based design of inhibitors of protein-protein interactions: mimicking peptide binding epitopes. Angew Chem Int Ed. 2015;54(31):8896–8927.

161. Fosgerau K, Hoffmann T. Peptide therapeutics: current status and future directions. Drug Discov Today. 2015;20(1):122–128. doi:10.1016/j.drudis.2014.10.003

162. Naiyed F, Angelster J. Peptides in the treatment of AIDS. Curr Opin Struct Biol. 2009;19(4):473–482. doi:10.1016/j.sbi.2009.07.003

163. Schneider JA, Craven TW, Kasper AC, et al. Design of peptoid-peptide macrocycles to inhibit the β-catenin TCF interaction in prostate cancer.

164. Moya AL, Martin C, Delitala E, et al. A new strategy for the design of a novel small molecule peptoid inhibitor of chymase.

165. Gilbert SM, Gidley-Baird A, Glazer S, et al. A Phase I clinical trial demonstrates that nP2X7-targeted antibodies provide a novel, safe and tolerable topical therapy for basal cell carcinoma. Br J Dermatol. 2017;177(1):117–124. doi:10.1111/bjd.15364

166. Díaz-García A, Varela D. Voltage-gated K channels and scorpion venom toxins in cancer. Front Pharmacol. 2020;11:1132. doi:10.3389/fphar.2020.01132

167. Ferreira SH, Greene LJ, Alabaster VA, Bakhle YS, Vane JR. Activity of various fractions of bradykinin potentiating factor against angiotensin converting enzyme. Nature. 1976;225(5230):379–380. doi:10.1038/225379a0

168. Weber MA, Schiffrin EL, White WB, et al. Clinical practice guidelines for the management of hypertension in the community.

169. Tyagi A, Ahmed T, Jian S, et al. Rearrangement of a unique Kv1.3 selectivity filter conformation upon binding of a drug.

170. Rödström KE, Kiper AK, Zhang W, et al. A lower X-gate in TASK channels traps inhibitors within the vestibule.

171. Kalia J, Milescu M, Salvatierra J, et al. From foe to friend: using animal toxins to investigate ion channel function.

172. Oxtoby AD, Childs G, Coverly J, et al. Calcium channel activity in colorectal cancer cells is modulated by scorpion neurotoxins.

173. Chow CY, Absalom N, Biggs K, King GF, Ma L. Venom-derived modulators of epilepsy-related ion channels.

174. Moreels L, Peigneur S, Yamaguchi Y, et al. Expanding the pharmacological profile of κ-hefutoxin 1 and analogues: a focus on the inhibitory antitumor activity.

175. Moreels L, Peigneur S, Yamaguchi Y, et al. Expanding the pharmacological profile of κ-hefutoxin 1 and analogues: a focus on the inhibitory antitumor activity.

176. Díaz-García A, Varela D. Voltage-gated K channels and scorpion venom toxins in cancer. Front Pharmacol. 2020;11:913. doi:10.3389/fphar.2020.00913

177. Ferreira SH, Greene LJ, Alabaster VA, Bakhle YS, Vane JR. Activity of various fractions of bradykinin potentiating factor against angiotensin converting enzyme. Nature. 1976;225(5230):379–380. doi:10.1038/225379a0

178. Rödström KE, Kiper AK, Zhang W, et al. A lower X-gate in TASK channels traps inhibitors within the vestibule.

179. Tyagi A, Ahmed T, Jian S, et al. Rearrangement of a unique Kv1.3 selectivity filter conformation upon binding of a drug.

180. Rödström KE, Kiper AK, Zhang W, et al. A lower X-gate in TASK channels traps inhibitors within the vestibule.

181. Irwin JJ, Shoichet BK. ZINC − a free database of commercially available compounds for virtual screening.

182. Innamaa A, Jackson L, Asher V, et al. Expression and effects of modulation of the K2P potassium channels TREK-1 (KCNK2) and TREK-2 (KCNK10) in the normal human ovary and epithelial ovarian cancer. Clin Transl Oncol. 2013;15:910–918. doi:10.1007/s12094-013-1022-4