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## Targeting ion channels for cancer treatment: current progress and future challenges

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## **Abstract**

Ion channels are key regulators of cancer cell pathophysiology. They contribute to a variety of processes such as maintenance of cellular osmolarity and membrane potential, motility (via interactions with the cytoskeleton), invasion, signal transduction, transcriptional activity and cell cycle progression, leading to tumour progression and metastasis. Ion channels thus represent promising targets for cancer therapy. Ion channels are attractive targets because many of them are expressed at the plasma membrane and a broad range of existing inhibitors are already in clinical use for other indications. However, many of the ion channels identified in cancer cells are also active in healthy normal cells, so there is a risk that certain blockers may have off-target effects on normal physiological function. This review describes recent research advances into ion channel inhibitors as anticancer therapeutics. A growing body of evidence suggests that a range of existing and novel Na<sup>+</sup>, K<sup>+</sup>, Ca<sup>2+</sup> and Cl<sup>-</sup> channel inhibitors may be effective for suppressing cancer cell proliferation, migration and invasion, as well as enhancing apoptosis, leading to suppression of tumour growth and metastasis, either alone or in combination with standard of care therapies. The majority of evidence to date is based on preclinical in vitro and in vivo studies, although there are several examples of ion channel targeting strategies now reaching early phase clinical trials. Given the strong links between ion channel function and regulation of tumour growth, metastasis and chemotherapy resistance, it is likely that further work in this area will facilitate the development of new therapeutic approaches which will reach the clinic in the future.

## Introduction

Traditional chemotherapeutic approaches have been successfully used as cancer treatments for decades, partially due to their generalised, anti-proliferative and cytotoxic activity (DeVita and Chu, 2008). However, the lack of specificity of chemotherapy is a limiting factor in the treatment of more advanced tumours and acquired resistance. This has driven the development of targeted therapies, such as monoclonal antibodies, small molecule pathway inhibitors, immune check-point inhibitors and emerging cellular therapies (Baudino, 2015). The limitations of targeted treatments can come from their specificity, making their effectiveness tumour- or antigen-dependent, and thus potentially only applicable to a relatively small proportion of the population. A relatively underexplored area in cancer research is represented by the therapeutic targeting of ion channels and transporters (Oosterwijk and Gillies, 2014). Plasma membrane ion channels have been shown to contribute to a variety of cellular processes in addition to their role in maintaining membrane potential ( $V_m$ ) and cellular osmolarity (Yang and Brackenbury, 2013, Djamgoz et al., 2014, Leslie et al., 2019). For example, as discussed in detail elsewhere in this series of Special Issues, alterations in ion flux can contribute to cellular motility, cytoskeletal rearrangements and signal transduction underpinning cellular migration (Schwab et al., 2012, Yang et al., 2020), growth and cell cycle progression (Blackiston et al., 2009, Urrego et al., 2014, Humeau et al., 2018), gene expression (Mycielska et al., 2005, Popov et al., 2012), as well as defining the extracellular environment (e.g. pH regulation (Parks et al., 2013, Wu et al., 2017)). In the tumour microenvironment, higher levels of  $K^+$  and  $Na^+$  have been reported, accompanied by a relatively decreased pH and hypoxic environment compared to healthy tissue (Ouwerkerk et al., 2007, Eil et al., 2016, Leslie et al., 2019). Elevated expression of a wide range of ion channels has also been associated with metastasis, reviewed extensively elsewhere (Pardo and Stuhmer, 2014, Brackenbury, 2016, Djamgoz et al., 2019). Together, these findings suggest that ion channels could serve as potential targets for anticancer therapies, particularly given the tumour-specific expression of certain channel types. Ion

channels, particularly those at the plasma membrane, present potentially attractive therapeutic targets due to their location and the fact that a broad range of existing inhibitors are already in clinical use. Given that many blockers of plasma membrane ion channels can act extracellularly, they can be screened relatively easily using electrophysiological approaches. Intracellular ion channels have also been shown to be important regulators of cancer cell metabolism, apoptosis and gene expression (Leanza et al., 2013a, Jang et al., 2015, Peruzzo and Szabo, 2019); these could similarly represent attractive targets for therapeutic inhibition.

On the other hand, given that many of the ion channels identified in cancer cells are expressed in healthy normal cells, there is a risk that these blockers may have off-target effects on normal physiological function. This review describes recent research advances into ion channel inhibitors for cancer treatment. Key Na<sup>+</sup>, K<sup>+</sup>, Ca<sup>2+</sup> and Cl<sup>-</sup> channel inhibitors are covered, followed by details on their use and effectiveness in cancer, as well as considering combining such inhibitors with standard of care therapies (Figure 1).

### **Na<sup>+</sup> Channel Inhibitors**

Several classes of Na<sup>+</sup> channels have been shown to be aberrantly expressed in cancer cells where they regulate cell proliferation, migration, invasion and metastasis (Leslie et al., 2019). In particular, voltage gated Na<sup>+</sup> channels (VGSCs) are upregulated in tumour cells where their activity regulates V<sub>m</sub>, morphological changes and metastatic behaviour (Grimes et al., 1995, Roger et al., 2003, Fraser et al., 2005, Nelson et al., 2014, Nelson et al., 2015, Yang et al., 2020). VGSCs have thus been studied as potential cancer targets (Table 1). VGSCs are important clinical targets for the treatment of epilepsy and cardiac arrhythmia (George, 2005, Mantegazza et al., 2010). Various Class 1B antiarrhythmic drugs, antiepileptic drugs and local anaesthetics have been studied in preclinical in vitro and in vivo cancer models (Martin

et al., 2015). For example, the anticonvulsant phenytoin inhibits breast cancer cell migration, tumour growth, invasion and metastasis (Yang et al., 2012, Nelson et al., 2015). Phenytoin also inhibits migration and secretory activity in prostate and lung cancer cells (Abdul and Hoosein, 2001, Fraser et al., 2003b, Onganer and Djamgoz, 2005). These results are generally supported by other studies using different VGSC-inhibiting drugs in breast cancer and other cancer types, including carbamazepine, riluzole, ranolazine and ropivacaine (Abdul and Hoosein, 2001, Abdul and Hoosein, 2002b, Yip et al., 2009, Speyer et al., 2012, Djamgoz and Onkal, 2013, Baptista-Hon et al., 2014, Driffort et al., 2014, Bugan et al., 2019, Guzel et al., 2019). It should be noted, however, that some compounds may elicit their anticancer effects through other mechanisms in addition to VGSC inhibition. For example, riluzole may prevent migration or promote apoptosis and cell cycle arrest (shown in glioma, neuroblastoma, lung, colon and prostate cancer) and inhibit autophagy (shown in pancreatic cancer) at least in part via its function as a non-competitive inhibitor of the metabolic glutamate receptor 1 (Akamatsu et al., 2009, Zhang et al., 2015, Seol et al., 2016, Lemieszek et al., 2018, Sun et al., 2019). Nonetheless, a number of studies now show that VGSC-inhibiting drugs suppress proliferation, promote apoptosis, and reduce migration, invasion and metastasis (Martin et al., 2015).

A key advantage of Class 1B antiarrhythmic drugs is that they display state-dependent binding and preferentially block VGSCs in the inactivated state (Clare et al., 2000).

Accumulating evidence suggests that cancer cells have a relatively depolarised  $V_m$ , which would mean that VGSCs present in these cells are predominantly in their inactivated state (Yang and Brackenbury, 2013). Importantly, studies have shown that VGSCs expressed in cancer cells, including  $Na_v1.5$ , carry a small persistent  $Na^+$  current in the inactivated state which depolarises the  $V_m$  further and permits cytosolic  $Na^+$  accumulation (Gillet et al., 2009, Brisson et al., 2011, Yang et al., 2012, Campbell et al., 2013, Yang et al., 2020). Further evidence suggests that this persistent  $Na^+$  current is critical for promoting metastatic cell behaviour (Driffort et al., 2014, Nelson et al., 2015). Therefore, state-dependent VGSC

blockers which preferentially bind to VGSCs in the inactivated state are likely to selectively target tumour-expressing VGSCs whilst leaving VGSCs in other cells, e.g. cardiomyocytes and neurons, unaffected. There is, however, currently a lack of clinical data in support of this hypothesis. Although the VGSC-inhibiting drugs valproate and quinidine have been studied in clinical trials, their mode of action via Na<sup>+</sup> current suppression was not investigated (Raderer et al., 1993, Wheler et al., 2014). The therapeutic value of VGSC inhibitors in the context of cancer has been studied retrospectively in several observational cohort data studies (Walker et al., 2011, Fairhurst et al., 2014, Fairhurst et al., 2015, Reddy et al., 2015, Fairhurst et al., 2016, Takada et al., 2016). However, the results are inconsistent, with several studies demonstrating positive associations (Exadaktylos et al., 2006, Biki et al., 2008, Walker et al., 2011, Reddy et al., 2015, Takada et al., 2016) and another study showing a negative association, although the possibility of confounding by indication cannot be excluded (Fairhurst et al., 2015). Thus, prospective clinical trials are required to establish the utility of VGSC inhibition in cancer patients (Djamgoz et al., 2019).

Novel compounds have also been investigated as potential inhibitors of VGSC function in cancer cells. Novel  $\alpha$ -hydroxy- $\alpha$ -phenylamide analogues of phenytoin have been developed in order to improve VGSC subtype specificity and some of these have been shown to inhibit prostate cancer cell proliferation (Anderson et al., 2003, Lenkowski et al., 2004). Additional small molecule VGSC inhibitors have been developed with the aim of increasing selectivity for the neonatal splice variant of Na<sub>v</sub>1.5 expressed in breast cancer cells and these have been shown to inhibit both Na<sup>+</sup> current and invasion (Dutta et al., 2018). The casein kinase 1 inhibitor IC261, which induces cell cycle arrest and apoptosis in cancer cell lines, has also been shown to inhibit Na<sub>v</sub>1.5 currents, suggesting that IC261 may elicit its anti-tumour effects partially through VGSC inhibition (Brockschmidt et al., 2008, Föhr et al., 2017). The mexiletine analogue RS10064, targeted at tetrodotoxin-resistant VGSCs, inhibits oxidative stress induced by tumour development in the DMBA rat breast cancer model (Batcioglu et al., 2012).  $\omega$ -3 polyunsaturated docosahexaenoic acid, which has been shown to improve breast

cancer outcomes, inhibits Na<sub>v</sub>1.5 expression and activity in breast cancer cells via peroxisome proliferator-activated receptor  $\beta$  (PPAR $\beta$ ) (Isbilen et al., 2006, Gillet et al., 2011, Wannous et al., 2015).

Numerous peptide toxins bind to and inhibit VGSCs, and several of these have been explored in the context of cancer treatment. Local injection of the pan-specific VGSC-inhibiting toxin tetrodotoxin directly into subcutaneous prostate tumours in rats significantly reduces lung metastasis, improving survival (Yildirim et al., 2012). Treatment of prostate cancer cells with the tarantula peptide toxin HNTX-III derived from the venom of *Selenocosmia hainana* downregulates Na<sub>v</sub>1.7, decreases RhoA/Rac1 protein expression and inhibits cellular migration, raising the possibility that such isoform-specific toxins may have utility as anti-motility drugs (Chen et al., 2019). However, a potential issue with peptide toxins such as tetrodotoxin is that, unlike Class 1B antiarrhythmic drugs, they do not display state-dependent binding. Thus, it would not be possible to administer such agents systemically without toxic side-effects. Nonetheless, chemical modification of these toxins to aid tumour-specific targeting may be possible. One further issue with the use of VGSC inhibitors in general, including state-dependent blockers, is that they may also inhibit VGSCs present on immune cells, potentially reducing a desirable anti-tumour immune response. For example, Na<sub>v</sub>1.5 is expressed on CD4<sup>+</sup> T cells where it plays a role in positive selection (Lo et al., 2012).

There has also been interest in developing ion-channel targeting monoclonal antibodies. This has proven to be relatively challenging given the complex structure of ion channel proteins, which makes it difficult to identify suitable epitopes, as well as due to the complexity of manufacturing antibodies, compared to small molecule design (Hutchings et al., 2019). A polyclonal antibody directed at the neonatal Na<sub>v</sub>1.5-specific D1:S3/4 linker inhibits Na<sup>+</sup> current with high specificity for neonatal Na<sub>v</sub>1.5 versus the adult splice variant (Chioni et al., 2005). Importantly, this antibody was additionally shown to inhibit migration and invasion of



breast cancer cells (Brackenbury et al., 2007). Although the primary purpose of such antibodies has been to inhibit channel function, an additional possibility is that these antibodies may have utility as diagnostic tools (Yamaci et al., 2017) and/or as vehicles to target cytotoxic therapies to tumours (Arcangeli et al., 2009).

Epithelial Na<sup>+</sup> channels (ENaC) from the ENaC/degenerin family are also important players in metastatic cell behaviour (Yamamura et al., 2008, Bondarava et al., 2009, Del Monaco et al., 2009, Kapoor et al., 2009, Xu et al., 2016). ENaC activity promotes proliferation and inhibits apoptosis of hepatic carcinoma cells, as part of a hypertonicity-induced cationic channel complex (Sparks et al., 1983, Vila-Carriles et al., 2006, Bondarava et al., 2009). More recently, ENaC expression has been associated with increased expression of the achaete-scute homolog 1 (ASCL-1) transcription factor that mediates growth and progression of lung tumours (He et al., 2018). The exact mechanism that connects ENaC and ASCL-1 has not been fully defined, but these findings suggest that ENaC might contribute to tumour growth as a transcriptional target of ASCL-1 (He et al., 2018). Acid-sensing ion channels (ASIC), also members of the ENaC/degenerin family, can enhance invasive behaviour by activating the calcineurin/Nuclear Factor of Activated T Cells 1 (NFAT1) pathway in colorectal cancer cells and treatment with cyclosporin A was shown to block the calcineurin pathway and ASIC2-mediated metastasis (Zhou et al., 2017). ASIC1 and 3 promote epithelial to mesenchymal transition in pancreatic cancer cells in a Ca<sup>2+</sup>-dependent manner (Zhu et al., 2017). The ENaC-inhibiting K<sup>+</sup>-sparing diuretic amiloride has been shown to suppress ENaC-induced chorionic carcinoma cell migration in response to aldosterone (Del Monaco et al., 2009). Together with further studies showing anti-tumour and anti-metastatic effects of amiloride, these data suggest that pharmacological blockade of ENaC/ASIC channels may have therapeutic relevance (Matthews et al., 2011).

The ATP-dependent Na<sup>+</sup>/K<sup>+</sup> pump (also known as the Na<sup>+</sup>/K<sup>+</sup> ATPase) is an important regulator of Na<sup>+</sup>/K<sup>+</sup> homeostasis in cancer cells (Zhang et al., 2008, Schneditz et al.,

2019). This pump is the key membrane protein for transporting  $\text{Na}^+$  out from the cell and maintaining a stable  $V_m$  (Post et al., 1969).  $\text{Na}^+/\text{K}^+$  ATPase expression is elevated in breast cancer cells compared to normal epithelial cells and its activity promotes proliferation, migration and invasion (Li et al., 2017, Khajah et al., 2018). Different  $\text{Na}^+/\text{K}^+$  ATPase  $\alpha$  subunit isoforms have been associated with cancer malignancy:  $\alpha 1$  mostly correlates with early stages of cancer (including prostate, lung and renal tumours), whilst  $\alpha 3$  associates with advanced disease (Felippe Goncalves-de-Albuquerque et al., 2017). Cardiac glycoside digitalis drugs, e.g. ouabain, digoxin, which are potent inhibitors of the  $\text{Na}^+/\text{K}^+$  ATPase (Post et al., 1969, Laursen et al., 2013), have been shown to inhibit proliferation, migration, invasion, inflammation, tumour growth and promote lysis of cancer cells (Zhang et al., 2008, Kepp et al., 2012, Gould et al., 2018, Khajah et al., 2018), reduce risk of certain cancers (Haux et al., 2001) and improve survival (Menger et al., 2012). Inhibition of the  $\text{Na}^+/\text{K}^+$  ATPase by digitalis drugs leads to intracellular accumulation of  $\text{Na}^+$  and subsequent reverse mode operation of the  $\text{Na}^+/\text{Ca}^{2+}$  exchanger (NCX) causing an increase in intracellular  $\text{Ca}^{2+}$ , which may then impact on cell cycle progression and survival (Chen et al., 2014). Interestingly, studies have shown that while the ion transport function of the  $\text{Na}^+/\text{K}^+$  ATPase is inhibited by cardiac glycosides, these can enhance signalling via the pump, inducing activation of an associated kinase – Src, which transactivates the epidermal growth factor receptor (EGFR), forming a signalling complex that induces activation of mitogen-activated kinase (MAPK), thus indicating a complex function of the  $\text{Na}^+/\text{K}^+$  pump in maintaining cellular physiology (Haas et al., 2002). Although the  $\text{Na}^+/\text{K}^+$  ATPase was long thought to be the only target of ouabain and other digitalis drugs, there is emerging evidence suggesting that these compounds modulate additional targets, such as the X-hepatic receptor (Campia et al., 2012) and the steroid receptor co-activators (SRC) 1 and 3 (Wang et al., 2014). Thus, effects on cancer cells following treatment with these drugs might be derived from their impact on other targets.

In summary, a growing body of evidence suggests that pharmacological inhibition of various classes of Na<sup>+</sup> channels and transporters in cancer cells can inhibit proliferative and invasive capacity and may promote cell death. Further work is required to fully delineate the mechanism(s) of action of a number of these compounds in cancer cells and their potential clinical value.

### **K<sup>+</sup> Channel Inhibitors**

Many plasma membrane K<sup>+</sup> channels are aberrantly expressed in cancer cells where their expression is often associated with increased proliferative capacity, and a number of these have been explored as therapeutic targets (Table 2) (Huang and Jan, 2014, Pardo and Stuhmer, 2014). For example, the K<sub>v</sub>1.3 voltage-gated K<sup>+</sup> channel (VGKC) plays a role in regulation of proliferation in brain cell progenitors, but also in cancer cells (Fraser et al., 2000, Chittajallu et al., 2002, Fraser et al., 2003a). In prostate cancer cells, K<sub>v</sub>1.3 was shown to be sensitive to several drugs, including dequalinium, glyburide and amiodarone, which induced growth inhibition and cell death (Abdul and Hoosein, 2002a). In addition, K<sub>v</sub>1.3 currents in prostate cancer cells are sensitive to verapamil, margatoxin, charybdotoxin, 4-aminopyridine and tetraethylammonium (Fraser et al., 2003a). In melanoma cells, treatment with the K<sub>v</sub>1.3 inhibitors tetraethylammonium, verapamil and fampridine was shown to disrupt the interaction between K<sub>v</sub>1.3 channels and β1 integrin, suggesting that integration of VGKCs in macromolecular protein complexes might provide a role in tumour cell adhesion and invasion (Artym and Petty, 2002).

Another VGKC widely studied in the context of cancer is Eag1 (K<sub>v</sub>10.1) (Ouadid-Ahidouch et al., 2016). K<sub>v</sub>10.1 is upregulated in a number of tumour types (Ding et al., 2007, Ousingsawat et al., 2007). K<sub>v</sub>10.1 promotes proliferation in cancer cell lines and over-expression in Chinese hamster ovary cells causes tumorigenesis in vivo (Pardo et al., 1999, Ouadid-

Ahidouch et al., 2001). Direct targeting of K<sub>v</sub>10.1 with monoclonal antibodies inhibits K<sup>+</sup> currents and has an anti-proliferative effect, reducing tumour growth in vivo (Gómez-Varela et al., 2007). Furthermore, development of a bifunctional antibody carrying a human K<sub>v</sub>10.1 recognition site and a human TNF-related apoptosis-inducing ligand (TRAIL) domain was shown to induce selective apoptosis in prostate cancer cells sensitised with cytotoxic drugs (Hartung et al., 2011). Other well-established inhibitors of human Eag1 include astemizole and imipramine (Garcia-Ferreiro et al., 2004). Imipramine was shown to inhibit proliferation and induce apoptotic behaviour in ovarian cancer cells (Asher et al., 2011). Astemizole has also been shown to inhibit proliferation in vitro and tumour growth in vivo (Garcia-Quiroz and Camacho, 2011, de Guadalupe Chavez-Lopez et al., 2015, Bernal-Ramos et al., 2017). In addition, the sea anemone toxin APETx4 inhibits K<sub>v</sub>10.1, although it is cytotoxic in both cancer and non-cancer cell lines (Moreels et al., 2017b). Several novel purpurealidin analogues were also found to inhibit K<sub>v</sub>10.1 current and increase cell death (Moreels et al., 2017a).

HERG (K<sub>v</sub>11.1) is primarily associated with cardiac arrhythmias, but is also upregulated in various cancers (Cherubini et al., 2000, Pillozzi et al., 2002, Lastraioli et al., 2004, Lastraioli et al., 2006). As with K<sub>v</sub>10.1, K<sub>v</sub>11.1-mediated K<sup>+</sup> current has been shown to increase cancer cell proliferation (Bianchi et al., 1998, Wang et al., 2002, Arcangeli, 2005). In addition, K<sub>v</sub>11.1 interacts with β1 integrin, promoting adhesion interactions and adhesion-dependent signalling to regulate cancer cell survival, migration, invasion and chemoresistance (Cherubini et al., 2005, Arcangeli and Becchetti, 2006, Pillozzi et al., 2007, Pillozzi et al., 2011, Crociani et al., 2013). K<sub>v</sub>11.1 has been studied as a potential cancer target and anti-cancer agents, e.g. tamoxifen, have been shown to have an inhibitory effect on channel function (Thomas et al., 2003). The K<sub>v</sub>11.1 inhibitor cisapride has also been shown to inhibit proliferation of gastric cancer cells (Shao et al., 2005). In addition, the K<sub>v</sub>11.1 inhibitor E4031 reduced infiltration of acute lymphoblastic leukaemia cells in a mouse model, increasing survival (Pillozzi et al., 2011). E4031 and another K<sub>v</sub>11.1 inhibitor (WAY123,398) also

suppress gastric and colorectal cancer growth, angiogenesis (by PI3K/  $\beta$ 1-integrin-mediated Akt activation leading to vascular endothelial growth factor (VEGF)-A transcription) and metastasis in mice (Crociani et al., 2013, Crociani et al., 2014). E4031 was also shown to inhibit colon cancer cell proliferation and  $K_v11.1$  was identified as a biomarker of colon cancer in patient samples (Dolderer et al., 2010). E4031 and a second  $K_v11.1$  inhibitor, ergtoxin, were shown to inhibit proliferation of ovarian cancer cells by inhibiting cell cycle progression, but without inducing apoptotic behaviour (Asher et al., 2011). A potential issue with the use of  $K_v11.1$  blockers is the risk of off-target effects, specifically slowed cardiac repolarization and ventricular arrhythmia (Arcangeli et al., 2009). However, this may be overcome by the use of state-dependent blockers targeting  $K_v11.1$  in the open state in cancer cells, whilst leaving cardiac  $K_v11.1$  channels in the inactivated state unaffected (Arcangeli et al., 2009).  $K_v11.1$ -targeting monoclonal antibody-nanoparticle conjugates have also been explored as potential vehicles to deliver photodynamic therapies for pancreatic cancer (Sette et al., 2013) and novel recombinant anti- $K_v11.1$  single chain fragment variable antibodies have been developed and evaluated for cancer molecular imaging (Duranti et al., 2018, Duranti and Arcangeli, 2019).

The  $K^+$  2 pore domain ( $K_{2P}$ ) channels, which contribute to setting the resting  $V_m$ , are also upregulated in a variety of cancers including breast, colon, prostate and lung tumours and have been shown to promote proliferation (Mu et al., 2003, Kim et al., 2004, Voloshyna et al., 2008). However, some members of this family appear to be downregulated in other tumour types, suggesting a complex function of  $K_{2P}$  channels in cancer progression (Williams et al., 2013). A monoclonal antibody against the extracellular domain of  $K_{2P9.1}$  has been shown to inhibit tumour growth and metastasis in mice (Sun et al., 2016).  $Ca^{2+}$ -activated  $K^+$  channels are also expressed in cancer cells (Brackenbury, 2016). The large conductance  $K_{Ca1.1}$  channel promotes proliferation of HeLa cervical cancer cells, and this can be inhibited by treatment with the  $K_{Ca1.1}$  blocker iberiotoxin (Han et al., 2007). In addition, iberiotoxin causes cell cycle arrest and apoptosis in glioma cells (Weaver et al., 2004). The vitamin D receptor

agonists calcitriol and calcipotriol, and the androgen receptor antagonists bicalutamide and enzalutamide inhibit  $K_{Ca}1.1$  expression in breast cancer cells, suggesting that these compounds may also elicit antiproliferative activity via  $K_{Ca}1.1$  inhibition (Khatun et al., 2016, Khatun et al., 2018). The intermediate conductance  $K_{Ca}3.1$  channel blocker TRAM-34 inhibits cell cycle progression of B lymphoma cells induced by serum (Wang et al., 2007). The same study also showed that the CD20-targeting monoclonal antibody rituximab also inhibits  $K_{Ca}3.1$  activity (Wang et al., 2007). Similarly, TRAM-34 inhibits proliferation and migration and promote apoptosis of breast cancer cells (Zhang et al., 2016). TRAM-34 also inhibits  $K_{Ca}3.1$ -mediated glioma cell migration and invasion (Turner et al., 2014). In addition,  $K_{Ca}3.1$  overexpression in breast cancer cells promotes tumour growth and metastasis (Thurber et al., 2017). However, in pancreatic cancer cells, although TRAM-34 inhibited  $K_{Ca}3.1$  currents, it actually promoted migration and invasion, suggesting potential anomalous effects of this compound and/or target (Bonito et al., 2016). Inhibition of small conductance  $K_{Ca}2.3$  channels with tetraethylammonium, apamin and 4-aminopyrimidine decreased breast cancer cell migration in vitro (Potier et al., 2006) and recently new lipophilic pyridine and tetrahydropyridine derivatives have been designed and synthesised which inhibit  $K_{Ca}2.3$  channel activity and cellular migration (Kouba et al., 2020).

Targeting intracellular  $K^+$  channels may also derive benefit. Mitochondrial  $K_v1.3$  is widely expressed in various tissues, and a nuclear  $K_v1.3$  was also identified in some breast, lung and gastric adenocarcinoma cell lines, as well as in lymphocytes and brain cells. Nuclear  $K_v1.3$  functions as a regulator of gene expression by interacting with the cAMP response element-binding protein (CREB) and the c-FOS transcription factors (Jang et al., 2015). Mitochondrial  $K_v1.3$  interacts with the Bcl-2 family protein, Bax, which inhibits the activity of the channel, inducing cytochrome c cytoplasmic release and subsequent apoptosis (Szabó et al., 2008, Szabó et al., 2011). Pharmacological inhibition of intracellular  $K_v1.3$  with Psora-4, clofazimine and 5-(4-Phenoxybutoxy)psoralen (PAP1) induces apoptosis in lymphocyte, fibroblast, bone, skin cancer cell lines in a Bax/Bak-independent manner. Furthermore, the

same inhibitors induce apoptosis in patient-derived leukaemia B cells and clofazimine reduces melanoma tumour growth in vivo (Leanza et al., 2012, Leanza et al., 2013b).

K<sub>v</sub>10.1 is also expressed in the nuclear membrane of malignant brain colon and ovarian cancer cells, as well as leukaemia and fibrosarcoma (Martínez et al., 2015, Peruzzo et al., 2016). Given its location, it has been suggested that K<sub>v</sub>10.1 might also impact on gene expression. However, unlike K<sub>v</sub>1.3 its pro-tumorigenic function seems to occur through changes in channel conformation rather than through K<sup>+</sup> transport (Hegle et al., 2006, Chen et al., 2011). K<sub>Ca</sub>3.1 and VGKCs have also been identified in mitochondria of melanoma, colon and breast cancer cells where they regulate oxidative phosphorylation and proliferation (Kovalenko et al., 2016). Combined activation of membrane and mitochondrial K<sub>Ca</sub>3.1 is associated with breast tumour resistance to radiotherapy in vivo (Mohr et al., 2019). In addition, intracellular K<sub>Ca</sub>3.1 is sensitive to inhibition by TRAM-34 and clotrimazole (De Marchi et al., 2009). Elevated intracellular K<sub>Ca</sub>1.1 has been reported in the endoplasmic reticulum (ER), nucleus and Golgi of pancreatic cancer cells (Singh et al., 2012). Bax-mediated inhibition of mitochondrial K<sub>Ca</sub>1.1 promotes apoptosis by enhancing the formation of the mitochondrial permeability transition pore (Cheng et al., 2011). The mitochondrial acid sensing K<sup>+</sup> channel, TASK3, mediates survival and maintains mitochondrial integrity in melanoma cells (Kosztka et al., 2011, Nagy et al., 2014). Furthermore, inhibition of TASK3 with Zn<sup>2+</sup> or methanandamide slows proliferation of ovarian cancer cells, suggesting that it might serve as a valuable target (Innamaa et al., 2013).

In summary, various classes of plasma membrane and intracellular K<sup>+</sup> channels are upregulated in cancer cells and a number of studies point to pharmacological inhibition of specific subtypes as an effective approach to suppress proliferation, migration and invasion, and increase apoptosis.

## Ca<sup>2+</sup> Channel Inhibitors

A number of different types of plasma membrane Ca<sup>2+</sup> channel have been documented in cancer cells that could be targeted therapeutically (Table 3) (Lee et al., 2011, Prevarskaya et al., 2011, Bong and Monteith, 2018, Gautier et al., 2019). Upregulation of L-type (Ca<sub>v</sub>1.x) and T-type (Ca<sub>v</sub>3.x) voltage-gated Ca<sup>2+</sup> channels promotes differentiation, secretion of mitogenic factors, proliferation and angiogenesis (Bertolesi et al., 2002, Mariot et al., 2002, Sun et al., 2006, Gackiere et al., 2008, Lu et al., 2008). Emerging preclinical evidence suggests that repurposing Ca<sub>v</sub> channel-inhibiting drugs to cancer may be beneficial (Buchanan and McCloskey, 2016). For example, mibefradil and the Ca<sub>v</sub>3.x inhibitor NNC-55-0396 have been shown to reduce cell proliferation and induce cell apoptosis in leukaemia cell lines (Huang et al., 2015). Inhibition of Ca<sub>v</sub>1.3 in endometrial carcinoma cells with nifedipine reduced proliferation and migration and induced autophagy (Bao et al., 2012). Nifedipine has also been shown to inhibit proliferation of breast cancer cells (Squecco et al., 2015). In addition, the Ca<sub>v</sub>3.x blocker KYS05090 has been shown to induce apoptosis and autophagy in lung cancer cells, although the mechanism may be channel independent (Rim et al., 2014).

The store operated Ca<sup>2+</sup> channel proteins also play an oncogenic role (Yang et al., 2009). ORAI1 and ORAI3 heterodimerise to support Ca<sup>2+</sup> influx and promote proliferation (Dubois et al., 2014). Furthermore, the store operated Ca<sup>2+</sup> channel blocker SKF96365 inhibits breast cancer metastasis in mice (Yang et al., 2009). Various transient receptor potential (TRP) channels, activated by extracellular stimuli e.g. pH, mechanical stimuli, are also expressed in cancer cells and can promote proliferation, survival angiogenesis and metastasis (Thebault et al., 2006, Bidaux et al., 2007, Lehen'kyi et al., 2007, Bolanz et al., 2008, Bomben and Sontheimer, 2008, Guilbert et al., 2009, Fiorio Pla et al., 2012). However, there are some exceptions, e.g. TRPM6, which is downregulated in colorectal tumours and associates with improved survival (Xie et al., 2018) and TRPM8, which inhibits migration (Genova et al., 2017). Treatment of breast cancer cells with the TRP channel inhibitor 2-



aminoethoxydiphenyl borate (2-APB) has been shown to decrease proliferation by damaging DNA (Hopkins et al., 2015). The specific TRPM7 inhibitor waixenicin A significantly decreased colon cancer cell proliferation in vitro but had no impact on aberrant crypt foci development in vivo, highlighting the importance of model selection in screening of channel inhibitors (Huang et al., 2017). In addition, given the complex involvement of various TRP channel subtypes in promoting/inhibiting cancer progression, channel inhibition will not be appropriate in certain circumstances. For example, the TRPM8 agonist WS12 suppresses endothelial cell migration and prostate cancer metastasis in mouse models (Genova et al., 2017, Grolez et al., 2019). Nonetheless, TRP channel inhibitors have been studied in the clinical setting. The TRPV6 inhibitor SOR-C13 recently went into first-in-human phase I study in patients with advanced solid tumours and disease stabilisation in the treated cohort suggested potential anti-tumour activity (Fu et al., 2017).

The purinergic P2X7 cation channel has also gained interest in the context of cancer, although conflicting results from different studies have been challenging to interpret (Roger et al., 2015). However, a monoclonal antibody targeting a unique epitope on the cancer-specific variant of P2X7 (nfP2X7) has undergone Phase 1 clinical trial for basal cell carcinoma with promising results including disease stabilisation, partial and complete response (Gilbert et al., 2017, Gilbert et al., 2019).

In colon cancer cells, the cannabinoid cannabigerol suppresses proliferation and promotes reactive oxygen species (ROS) production and apoptosis via TRPM8 inhibition, and slows tumour growth in vivo (Borrelli et al., 2014). In addition, upregulation of TRPV1 has been identified as a key player in cannabinoid-derivative-induced apoptosis of cervical cancer and glioma cells (Contassot et al., 2004a, Contassot et al., 2004b). Other studies, however, propose different mechanisms for the anti-cancer activity of cannabinoids (Hamtiaux et al., 2011), for example, by interacting with the cannabinoid receptor 2 in addition to TRPV1 activation (Ligresti et al., 2006).

Intracellular  $\text{Ca}^{2+}$  channels may also present potential targets. For example, TRPM8 and TRPC1 both play a role in survival and proliferation of tumour cells (Zhang and Barritt, 2004, Shapovalov et al., 2016). TRPM8 inhibition with capsazepine reduces survival of prostate cancer cells, and TRPM8 knockdown slows proliferation of osteosarcoma cells by interfering with  $\text{Ca}^{2+}$ -dependent Akt function (Zhang and Barritt, 2004, Wang et al., 2013). TRPC1 regulates glioma cell division and its inhibition with 2-APB, MRS-1845 and SKF96365 inhibits proliferation in vitro and reduces tumour size in mouse models (Bomben and Sontheimer, 2010). Ryanodine receptors promote breast cancer cell survival and their expression correlates with tumour grade; in addition, the ryanodine receptor inhibitor 4-chloro-m-cresol inhibits breast cancer cell proliferation in vitro (Abdul et al., 2008). Furthermore, treatment of lung cancer cells with the ryanodine receptor inhibitor 20-O- $\beta$ -D-glucopyranosyl-20(S)-protopanaxadiol induces  $\text{Ca}^{2+}$ -dependent apoptosis, supporting the essential role of these channels in cancer cell survival (Shin et al., 2018).

In summary, a number of  $\text{Ca}^{2+}$  channel inhibitors have shown promise in preclinical studies and some of these have now reached clinical trials. Several epidemiological studies show that existing  $\text{Ca}^{2+}$  channel blockers are not associated with increased cancer risk (Grimaldi-Bensouda et al., 2016, Wilson et al., 2016, Brasky et al., 2017), supporting a compelling argument for further exploration of the possibility of repurposing such drugs to treat cancer (Buchanan and McCloskey, 2016). However, the complex opposing roles of some  $\text{Ca}^{2+}$  channels in cancer cells, e.g. certain TRP and P2X7 channels, highlights the importance of fully understanding their diverse physiological roles in order to permit appropriate targeting.

## **Cl<sup>-</sup> Channel Inhibitors**

Several Cl<sup>-</sup> channels have been shown to be aberrantly expressed in cancer cells, contributing to survival and progression and some have been explored as therapeutic targets (Table 4). The ionotropic Cl<sup>-</sup>-permeant GABA<sub>A</sub> receptor is upregulated on metastatic breast cancer cells in the brain (Neman et al., 2014), which themselves promote altered regional excitability (Simon et al., 2020). The voltage-gated Cl<sup>-</sup> channels CLC-2 and CLC-3 are functionally active in glioma cells and the latter is essential for facilitating mitosis and invasion by regulating cell volume (Olsen et al., 2003, Habela et al., 2008, Lui et al., 2010, Watkins and Sontheimer, 2011). CLC-3 also stimulates breast cancer cell proliferation and tumour growth (Zhou et al., 2018) and promotes migration of nasopharyngeal carcinoma cells (Mao et al., 2008). However, other studies have indicated that CLC-3 can also promote apoptosis (Liu et al., 2013), thus cancer-promoting or inhibiting activity of this channel is likely finely tuned and may be context dependent (Hong et al., 2015). CLC-3 is sensitive to non-specific Cl<sup>-</sup> channel inhibitors such as tamoxifen and 4-5-nitro-2-(3-phenylpropylamino) benzoic acids (NPPBs) (Wang et al., 2012), inhibiting cancer cell proliferation (Shen et al., 2000). Similarly, tamoxifen was shown to only have an inhibitory effect on cancer cell migration in the presence of CLC-3, likely as a result of dysregulated cell volume management and therefore cell cycle stagnation (Mao et al., 2013).

Hydrolysis products of 4,4-diisothiocyanatostilbene-2,2'-disulfonic acid (DIDS), which are inhibitors of anion permeability, can inhibit CLC family channels, as can phenylalanine derivatives (stilbenes), clofibric acids, benzofurans, and the newer benzimidazole derivative, BIM1 (Matulef et al., 2008, Koster et al., 2018). However, the broad effect of such compounds on other Cl<sup>-</sup> channels remains a challenge with respect to potential off-target effects (Hong et al., 2015) and applicability in cancer treatment needs to be confirmed through further studies. Specific function-blocking antibodies targeting CLC-3 have been developed (Wang et al., 2003) but their efficacy in cancer models remains to be determined. Chlorotoxin, a scorpion toxin identified as a CLC-3 inhibitor, binds to a membrane-bound matrix metalloproteinase on glioma cells (Deshane et al., 2003). Radiolabelled I<sup>131</sup>-

chlorotoxin has undergone a Phase 1 clinical trial in adult patients with high grade glioma with the aim of improving targeted radiation to the tumour site and demonstrated good tolerability and potential anti-tumoral effects (Mamelak et al., 2006).

The anoctamin  $\text{Ca}^{2+}$ -dependent  $\text{Cl}^-$  channels promote cancer cell proliferation and apoptosis of cancer cells under certain conditions (Kunzelmann et al., 2019). Inhibition of ANO1/TMEM16 with the specific inhibitor CaCCinh-A01 significantly decreased tumour progression, raising the possibility that this channel may be a potential therapeutic target (Britschgi et al., 2013). An important regulator of the  $\text{Cl}^-$  concentration within developing glial cells is the  $\text{Na}^+/\text{K}^+/\text{2Cl}^-$  cotransporter (NKCC1). NKCC1 has been proposed as a key promoter of glioma cell migration, being localized at the tip of the migratory pole of the cell and also influences cell-cell adhesion and  $\text{Cl}^-$ -dependent cell volume regulation (Habela et al., 2009, Garzon-Muvdi et al., 2012). Treatment with the NKCC1 inhibitor bumetanide inhibits migration of metastatic glioma cells both in vivo and in vitro, suggesting that NKCC1 could be a promising target in the treatment of glioma (Haas and Sontheimer, 2010).

In lung cancer cells, the  $\text{Cl}^-$  intracellular channel 1 (CLIC1), which can be found both at the plasma membrane and in the cytosol, suppresses  $\text{Ca}^{2+}$  import via L-type  $\text{Ca}^{2+}$  channels, promoting survival (Lee et al., 2019b). In silico analysis showed a much higher risk of death in breast, pancreatic and liver cancer patients with high CLIC1 expression, while gastric cancer patients with high CLIC1 levels have a survival advantage, suggesting that its function might vary with depending on tumour type (Gururaja Rao et al., 2020). Further work is required to establish the therapeutic value of CLIC1 inhibition, and/or inhibition of other intracellular  $\text{Cl}^-$  channel subtypes, e.g. CLIC4 (Fernández-Salas et al., 2002, Zhong et al., 2012).

In summary, both plasma membrane and intracellular  $\text{Cl}^-$  channels are important regulators of cell cycle, proliferation and migration, making them promising targets for cancer therapies.

Although some inhibitory molecules have been found effective in reducing tumour cell growth and migration, there is a strong potential for developing more specific inhibitors, targeted at both intracellular and extracellular channels.

### **Combinatorial Treatments**

The fact that a number of ion channel-targeting drugs inhibit cellular functions including proliferation, migration and invasion, and that others promote apoptosis, raises the possibility that such compounds may have utility in combination with standard of care therapies, e.g. chemotherapy. Furthermore, perturbation of the ionic balance within tumour cells may provide favourable conditions for the intracellular partitioning of certain cytotoxic drugs, enhancing their effectiveness. For example, in triple negative breast cancer cells,  $\beta$ -adrenergic receptors and  $\text{Na}_v1.5$  colocalise and the  $\beta$ -adrenergic receptor competitive antagonist propranolol and the VGSC inhibitor ranolazine decrease  $\text{Na}^+$  currents, migration and invasion both when administered individually and in combination (Lee et al., 2019a). Downregulation of  $\text{K}_v10.1$  with shRNA or application of the  $\text{K}_v10.1$  inhibitor astemizole to glioblastoma cells sensitises them to treatment with the standard of care chemotherapeutic temozolomide (Sales et al., 2016). Combination of astemizole with gefitinib has been shown to synergistically increase apoptosis of lung cancer cells over treatment with either agent alone (Chavez-Lopez et al., 2017). Another example is the macrolide antibiotics, which have antileukemic activity alone and in combination with chemotherapeutic drugs, and this was shown to be due to  $\text{K}_v11.1$  inhibition (Pillozzi et al., 2016).

Riluzole has been shown to inhibit  $\text{K}_v11.1$  and activate  $\text{K}_{Ca}3.1$  in colon cancer cells, thus contributing to cisplatin uptake (Pillozzi et al., 2018). Combined administration of the  $\text{K}_{Ca}3.1$  activator SKA-31 and E4031 had a similar effect, which was reproducible in mouse models, suggesting a complex interplay between  $\text{K}_{Ca}3.1$  and  $\text{K}_v11.1$  (Pillozzi et al., 2018). Riluzole

has also been shown to activate the  $K_{2P}$  channel (TREK-1), reducing neuropathic pain and depression-like symptoms induced by treatment with oxaliplatin in colon cancer mouse models (Poupon et al., 2018). Another potentially interesting combinatorial treatment is represented by the  $K_{2P3.1}$  and  $K_{2P9.1}$  channel inhibitors anandamide and ruthenium red, which have been shown to additively inhibit  $K^+$  currents in lung cancer cells, although the effect of these compounds on cell proliferation was not determined (Leithner et al., 2016).

Inhibitors of  $Ca^{2+}$  channels have also been investigated for combinatorial therapies. The  $Ca_v3.x$  antagonist mibefradil has been shown to inhibit glioblastoma stem-like cell proliferation in vitro and tumour growth in a glioblastoma mouse model, and sensitises tumours to treatment with temozolomide (Zhang et al., 2017b). Pharmacological inhibition of  $Ca_v3.x$  channel activity with the antagonists mibefradil and pimozide also synergistically suppressed proliferation in several cancer cell lines (Bertolesi et al., 2002). Inhibition of active ion transport may also be beneficial in combinatorial treatments. For example, suppression of plasma membrane  $Ca^{2+}$  ATPase isoform 2 (PMCA2) expression was shown to inhibit proliferation of breast cancer cells on its own, as well as enhancing the cytotoxicity of doxorubicin (Peters et al., 2016). Store operated  $Ca^{2+}$  entry induces expression of the chemotherapy resistance marker MDR1 in breast cancer cells (Babaer et al., 2018). Knock down of ORAI1 or STIM1 thus significantly increases sensitivity to chemotherapeutic drugs including cisplatin, gentamycin and 5-fluorouracyl (Kondratska et al., 2014, Sun et al., 2017, Kischel et al., 2019). Similarly, inhibition of TRPC5, either by siRNA or by treatment with chloroquine or 3-methyladenine, increases sensitivity to doxorubicin in breast cancer cell lines (Zhang et al., 2017a). On the other hand, different studies suggest certain  $Ca^{2+}$  channels render cells more responsive to chemotherapy (Kischel et al., 2019). For example, TRPC1 expression is downregulated in drug-resistant ovarian cancer tissues compared with drug-responsive samples and cisplatin and carboplatin-resistant ovarian cancer cell lines were shown to also have lower levels of TRPC1 (Liu et al., 2016). TRPV2 activation with cannabidiol plays an important role in sensitising glioma cells to doxorubicin, carmustine and

temozolomide (Nabissi et al., 2012). Thus, combination of certain channel-modulating drugs and chemotherapeutic drugs may have value by reducing tumour chemotherapeutic resistance, but the situation is likely channel or cell-type dependent.

Ion channel inhibition may also be advantageous in the context of standard of care radiotherapy. For example, antiepileptic drug use is associated with improved overall survival of breast cancer patients with brain metastasis receiving whole brain radiotherapy (Reddy et al., 2015), raising the possibility that VGSC inhibition may radiosensitise brain metastases. In addition, TRPM8 inhibition has been shown to radiosensitise glioblastoma cells and attenuate DNA repair (Klumpp et al., 2017) and TRPM2 inhibition enhances radiotherapy-induced cell death in leukaemia cells (Klumpp et al., 2016).

By targeting specific ion channels, certain inhibitors may enhance the capacity of the immune system to fight tumours. For example, non-small cell lung cancer patients with low serum salt levels respond poorly to immune check-point inhibitor therapy, illustrating potential interconnection between ionic balance and immune system-mediated tumour clearance (Fuca et al., 2018). Another study showed that an increase in extracellular  $K^+$  caused by tumour cell necrosis has an immunosuppressive impact on effector T cells by increasing intracellular  $K^+$ . Upregulation of  $K_v1.3$  in T cells resulted in  $K^+$  export, counteracting the immunosuppressive action of the tumour-derived  $K^+$  (Eil et al., 2016). Furthermore, high  $K^+$  in the tumour microenvironment maintained T cells in a stem-like state capable of dividing and enhancing tumour destruction (Vodnala et al., 2019). These data suggest manipulation of  $K^+$  flux may be effective in enhancing immunotherapeutic approaches.

In summary, considerable research has been carried out towards combining current cancer therapies and ion channel inhibitors or developing new combinatorial treatments that integrate ionic targeting. Despite significant progress, there is yet much that needs to be

done to optimise and refine existing therapies, as well as to generate new and effective strategies for exploiting ionic imbalances in the tumour microenvironment.

## **Conclusions and Future Perspectives**

The study of ion channel inhibitors in the context of oncology is gaining interest with time, particularly given the limitation of chemotherapy and targeted therapies, and the need for new perspectives on counteracting tumour progression and metastasis. Whilst individual ion channel targeting may be effective on its own in certain circumstances, a combinatorial approach of ion channel-targeting drugs and chemotherapy, radiotherapy and/or emerging immunotherapies may derive greater benefits. However, a key obstacle remains in terms of tumour specificity, given that many of these channels are also expressed in normal cells. Therefore, the use of ion channel blockers can often be accompanied by severe side effects and might even be lethal (Vandenberg et al., 2012).

Engineering antibodies or small molecules that target tumour-specific isoforms/states of various ion channels has been a step forward towards increasing the sensitivity and specificity of ion channel-targeted therapies in cancer (Clare et al., 2000, Chioni et al., 2005, Hartung et al., 2011, Sette et al., 2013, Sun et al., 2016, Gilbert et al., 2017). Yet, the continuous dynamics of the tumour environment could limit the efficacy of these approaches through target mutations. Furthermore, antibody therapies are limited both by the size-dependent tissue penetration and by the manufacturing procedure. Nevertheless, the idea of specifically targeting tumour-associated ion channels is worth investigating for the future. The capacity to distinguish between malignant and healthy ion channels could enable more complex therapeutic approaches such as combining ion channels inhibitors that could suppress tumour growth and ion channel enhancers that would induce activation and proliferation of immune cells, enabling those to clear the malignant tissue (Chiang et al.,



2017). However, before such complex strategies can be designed a more complete understanding of tumour-specific ion channel expression, function and pharmacology is required.

In conclusion, given the strong links between ion channel function and regulation of tumour growth, metastasis and chemotherapy resistance, it is likely that further work in this area will facilitate the development of new, multilateral therapeutic approaches.

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**Table 1.** Na<sup>+</sup> channel/transporter inhibitors in cancer.

Compound	Cancer target	Type of cancer
Amiloride	ENaC, NHE1	In vitro: multiple myeloma (Rojas et al., 2017), trophoblasts (Del Monaco et al., 2009). In vivo: hepatocellular carcinoma breast, gastric, colon, pancreatic (Matthews et al., 2011, Sparks et al., 1983).
Bupivacaine	VGSC, K <sub>v</sub> 11.1	In vitro: breast (Chang et al., 2014, Li et al., 2018), colon (Li et al., 2019), ovarian, prostate (Xuan et al., 2016).
Carbamazepine	VGSC	In vitro: prostate (Abdul and Hoosein, 2001), breast (Teichmann et al., 2014, Meng et al., 2011), neuroblastoma (Lang et al., 1993).
Casein kinase 1 inhibitor IC261	VGSC	In vitro & in vivo: pancreatic cancer (Brockschmidt et al., 2008).
Desipramine	VGSC	In vitro: hepatocellular carcinoma (Yang and Kim, 2017), colon (Arimochi and Morita, 2008), multiple myeloma (Biber et al., 2018).
Diclofenac	VGSC	In vitro and in vivo: colon, ovarian, neuroblastoma fibrosarcoma (Pantziarka et al., 2016). In vivo: breast, lung, connective tissue tumours, prostate, pancreatic, (clinical trials) (Pantziarka et al., 2016).
Digitalis drugs (ouabain, digoxin, bufalin)	Na <sup>+</sup> /K <sup>+</sup> ATPase	In vitro: lung (Pongrakhananon et al., 2013, Lin et al., 2015), breast, colon, prostate, hepatocellular (Gould et al., 2018, Khajah et al., 2018, Shen et al., 2020, Zhang et al., 2008), osteosarcoma (Menger et al., 2012). In vivo: breast (Gould et al., 2018), lymphoma, leukaemia (Zhang et al., 2008, Haux et al., 2001), fibrosarcoma, colon, hepatocellular, head and neck (Menger et al., 2012).
Disopyramide	VGSC	In vitro: breast (Fraser et al., 2005)
Dronedarone	VGSC	In vitro: ovarian (Meléndez et al., 2020). In vitro & in vivo: breast (Elliott et al., 2018).
Imipramine/ chlomipramine/ derivatives	VGSC, K <sub>v</sub> 10.1, K <sub>v</sub> 11.1	In vitro: acute myeloid leukaemia (Xia et al., 1999, Metts et al., 2017), colon (Arimochi and Morita, 2006), melanoma (Gavrilova-Ruch et al., 2002, Parker et al., 2012), multiple myeloma (Biber et al., 2018). In vivo: breast (Rajamanickam et al., 2016).
Lamotrigine	VGSC	In vitro: neuroblastoma (Lang et al., 1993). In vivo: prostate (Stettner et al., 2012), breast (Pellegrino et al., 2018).
Levobupivacaine	VGSC, K <sub>v</sub> 11.1	In vitro: colon (Li et al., 2019), breast (Li et al., 2018), prostate (Jose et al., 2018).
Lidocaine	VGSC	In vitro: breast (Yoon et al., 2011, Chang et al., 2014), colon (Siekmann et al., 2019), lung (Onganer and Djamgoz, 2005). In vivo: breast (Chang et al., 2014).
Mexiletine/ RS100642	VGSC, K <sub>v</sub> 11.1	In vitro: breast (Fraser et al., 2005).
Nortriptyline	VGSC, K <sub>v</sub> 11.1	In vitro: melanoma (Parker et al., 2012), multiple myeloma (Biber et al., 2018). In vivo: bladder (Yuan et al., 2015).
Phenytoin + analogues	VGSC	In vitro: breast (Yang et al., 2012), prostate (Abdul and Hoosein, 2001, Anderson et al., 2003, Fraser

		et al., 2003b), lung (Onganer and Djamgoz, 2005), neuroblastoma (Lang et al., 1993). In vivo: breast (Nelson et al., 2015).
NESOpAb	Neonatal Na <sub>v</sub> 1.5	In vitro: breast (Brackenbury et al., 2007, Chioni et al., 2005).
Propranolol	VGSC	In vitro: breast (Lee et al., 2019a).
Protriptyline	VGSC	In vitro: osteosarcoma (Su et al., 2016), prostate (Chang et al., 2015).
Quinidine	VGSC, VGKC, K <sub>ATP</sub>	In vitro: glioma (Ru et al., 2015), breast (Wonderlin et al., 1995). In vivo: breast (Raderer et al., 1993).
Ranolazine	VGSC	In vitro: breast (Driffort et al., 2014, Lee et al., 2019a), colon (Guzel et al., 2019). In vivo: prostate (Bugan et al., 2019), breast (Driffort et al., 2014).
Riluzole	VGSC, metabotropic glutamate receptor 1, K <sub>v</sub> 11.1, K <sub>2P</sub>	In vitro: prostate (Abdul and Hoosein, 2002b, Akamatsu et al., 2009, Uzun et al., 2017), pancreatic (Sun et al., 2019), neuroblastoma, glioma, lung, colon, leukaemia, myeloma (Lemieszek et al., 2018, Benavides-Serrato et al., 2020, Pillozzi et al., 2018, Poupon et al., 2018). In vivo: breast (Speyer et al., 2012), melanoma (Yip et al., 2009), glioma (Zhang et al., 2015), glioblastoma (Benavides-Serrato et al., 2020) hepatocellular carcinoma (Seol et al., 2016).
Ropivacaine	VGSC, K <sub>v</sub> 11.1	In vitro: colon (Baptista-Hon et al., 2014), breast (Li et al., 2018)
Tarantula peptide toxin HNTX-III	VGSC	In vitro: prostate (Chen et al., 2019).
Tetracaine	VGSC	In vitro: breast (Yoon et al., 2011).
Tetrodotoxin	VGSC	In vitro: prostate (Grimes et al., 1995, Grimes and Djamgoz, 1998). In vivo: prostate (Yildirim et al., 2012).
Topiramate	VGSC	In vitro: ovarian (Xu et al., 2018). In vivo: lung (Ma et al., 2011).
Valproic acid	VGSC	In vitro: prostate (Abdul and Hoosein, 2001, Angelucci et al., 2006) breast (Olsen et al., 2004). In vivo: colon, prostate, gastro-oesophageal (Wheler et al., 2014).
ω-3 polyunsaturated docosahexaenoic acid	VGSC, NHE1	In vitro: breast (Isbilen et al., 2006, Gillet et al., 2011, Wannous et al., 2015).

Abbreviations: ENaC, epithelial Na<sup>+</sup> channel; NHE1, Na<sup>+</sup>/H<sup>+</sup> exchanger-1; VGKC, voltage-gated K<sup>+</sup> channel; VGSC, voltage-gated Na<sup>+</sup> channel.

**Table 2.** K<sup>+</sup> channel inhibitors in cancer.

Compound	Cancer target	Type of cancer
4-aminopyrimidine	VGKC, K <sub>Ca</sub> 2.3	In vitro: breast (Potier et al., 2006), prostate (Fraser et al., 2003a), melanoma (Artym and Petty, 2002), cervical, ovarian (Han et al., 2007).
Amiodarone	K <sub>v</sub> 1.3, K <sub>v</sub> 10.1, VGSCs	In vitro: prostate (Abdul and Hoosein, 2002a), breast (Abdul et al., 2003), glioma (Kim et al., 2011, Chang et al., 2018). In vivo: breast (Lee et al., 2015).
Anandamide	K <sub>2P</sub> 3.1, K <sub>v</sub> 1.2	In vitro: lung (Leithner et al., 2016), breast (De Petrocellis et al., 1998, Laezza et al., 2012), hepatocellular (Xie et al., 2012). In vivo: breast (Grimaldi et al., 2006).
Antibodies	K <sub>v</sub> 10.1, K <sub>v</sub> 11.1, K <sub>2P</sub> 9.1	In vitro: ovarian, neuroblastoma (Gómez-Varela et al., 2007), prostate (Hartung et al., 2011), pancreatic (Sette et al., 2013, Duranti et al., 2018), breast, colon (Duranti et al., 2018), B cell lymphoma (Wang et al., 2007), lung (Sun et al., 2016). In vivo: breast and pancreatic (Gómez-Varela et al., 2007), pancreatic (Duranti et al., 2018), lung (Sun et al., 2016).
Apamine	K <sub>Ca</sub> 2.3	In vitro: breast (Potier et al., 2006).
APETx4	K <sub>v</sub> 10.1	In vitro: neuroblastoma, melanoma, prostate (Moreels et al., 2017b).
Astemizole	K <sub>v</sub> 10.1, K <sub>v</sub> 11.1	In vitro: lung (Chavez-Lopez et al., 2017), prostate (Bernal-Ramos et al., 2017), breast, hepatocellular (García-Quiroz et al., 2012, de Guadalupe Chavez-Lopez et al., 2015). In vivo: breast (García-Quiroz et al., 2014), hepatocellular (de Guadalupe Chavez-Lopez et al., 2015).
Bicalutamide	K <sub>Ca</sub> 1.1	In vitro: breast (Khatun et al., 2018).
Calcitriol/Calcipotriol	K <sub>Ca</sub> 1.1, K <sub>v</sub> 10.1	In vitro: breast (García-Quiroz et al., 2012, Khatun et al., 2016, Khatun et al., 2018) hepatocellular (García-Quiroz et al., 2012). In vivo: breast (García-Quiroz et al., 2014).
Charybdotoxin	K <sub>v</sub> 1.3	In vitro: prostate (Fraser et al., 2003a).
Cisapride	K <sub>v</sub> 11.1	In vitro: gastric (Shao et al., 2005).
Clofazimine	K <sub>v</sub> 1.3	In vitro: melanoma, lymphocytes, (Leanza et al., 2012, Leanza et al., 2013b). In vivo: melanoma (Leanza et al., 2012).
Clotrimazole	K <sub>Ca</sub> 3.1	In vitro: colon (De Marchi et al., 2009), breast (Zhang et al., 2016), pancreatic (Bonito et al., 2016).
Dequalinium	K <sub>v</sub> 1.3	In vitro: prostate (Abdul and Hoosein, 2002a).
Ergtoxin	K <sub>v</sub> 11.1	In vitro: ovarian (Asher et al., 2011).
E4031 and Way123,398	K <sub>v</sub> 11.1	In vitro: breast (Lansu and Gentile, 2013), ovarian (Asher et al., 2011), acute lymphoblastic leukaemia (Pillozzi et al., 2011), gastric (Crociani et al., 2014), colon (Crociani et al., 2013). In vivo: acute lymphoblastic leukaemia (Pillozzi et al., 2011) gastric (Crociani et al., 2014), colon (Crociani et al., 2013).
Enzalutamide	K <sub>Ca</sub> 1.1	In vitro: breast (Khatun et al., 2018)
Glyburide	K <sub>ATP</sub> , K <sub>v</sub> 1.3	In vitro: prostate (Abdul and Hoosein, 2002a).
Iberiotoxin	K <sub>Ca</sub> 1.1	In vitro: cervical, ovarian (Han et al., 2007), glioma (Weaver et al., 2004).

Imipramine	K <sub>v</sub> 10.1	In vitro: ovarian (Asher et al., 2011).
Macrolide antibiotics	K <sub>v</sub> 11.1	In vitro and in vivo: leukaemia (Pillozzi et al., 2016).
Margatoxin	K <sub>v</sub> 1.3	In vitro: prostate (Fraser et al., 2003a).
Methanandamide	K <sub>2P</sub> 9.1	In vitro: ovarian (Innamaa et al., 2013).
Psora-4	K <sub>v</sub> 1.3	In vitro: melanoma, lymphocytes (Leanza et al., 2012, Leanza et al., 2013b).
5-(4-phenoxybutoxy) psoralen	K <sub>v</sub> 1.3	In vitro: melanoma, lymphocytes (Leanza et al., 2012, Leanza et al., 2013b).
Purpurealidin analogues	K <sub>v</sub> 10.1	In vitro: neuroblastoma, prostate, melanoma (Moreels et al., 2017a).
Ruthenium red	K <sub>2P</sub> 9.1	In vitro: lung (Leithner et al., 2016).
Tamoxifen	K <sub>v</sub> 11.1	In vitro and in vivo: breast (Luveta et al., 2020).
Tetraethylammonium	K <sub>Ca</sub> 2.3, K <sub>v</sub> 1.3	In vitro: breast (Potier et al., 2006), prostate (Fraser et al., 2003a), melanoma (Artym and Petty, 2002), cervical, ovarian (Han et al., 2007).
TRAM-34	K <sub>Ca</sub> 3.1	In vitro: lymphoma (Wang et al., 2007), breast (Zhang et al., 2016), pancreatic (Zhang et al., 2016), glioma (Turner et al., 2014), colon (De Marchi et al., 2009), melanoma (Quast et al., 2012).
Verapamil	K <sub>v</sub> 1.3	In vitro: melanoma (Artym and Petty, 2002), prostate (Fraser et al., 2003a).

Abbreviation: VGKC, voltage-gated K<sup>+</sup> channel.

**Table 3.** Ca<sup>2+</sup> channel inhibitors in cancer.

Compound	Cancer target	Type of cancer
2-Aminoethoxydiphenyl Borate (2-APB)	TRP	In vitro: breast (Hopkins et al., 2015), glioma (Bomben and Sontheimer, 2008, Bomben and Sontheimer, 2010).
Bepriidil	VGCC	In vitro: breast (Park et al., 2016, Nguyen et al., 2017) glioma (Kim et al., 2011). In vivo: breast (Park et al., 2016)
Cannabinoids	TRPM8 (inhibited), TRPV1 (activated)	In vitro: colon (Borrelli et al., 2014), cervical, glioma (Contassot et al., 2004a, Contassot et al., 2004b), breast (Ligresti et al., 2006), neuroblastoma (Hamtiaux et al., 2011). In vivo: colon (Borrelli et al., 2014)
Capsazepine	TRPM8	In vitro: prostate (Zhang and Barritt, 2004)
Diltiazem	VGCC	In vitro: prostate (Kaddour-Djebbar et al., 2012), breast (Timar et al., 1992, Roger et al., 2004), pancreatic (Woods et al., 2015)
Felodipine	VGCC	In vitro: melanoma, breast (Honn et al., 1985) In vivo: melanoma (Honn et al., 1985)
Fendiline	VGCC	In vitro: pancreatic (Woods et al., 2015, Alhothali et al., 2019), lung, endometrial, colon (van der Hoeven et al., 2013).
Flunarizine	VGCC	In vitro: melanoma (Sezzi et al., 1985), multiple myeloma, lymphoma (Conrad et al., 2010, Schmeel et al., 2015)
Flusprilene	VGCC	In vitro & in vivo: glioblastoma (Dong et al., 2017), hepatocellular (Shi et al., 2015).
KYS05090	VGCC	In vitro: ovarian (Jang et al., 2013). In vitro and in vivo: lung (Kang et al., 2012, Rim et al., 2014).
Mibefradil	VGCC	In vitro: leukaemia (Huang et al., 2015), breast, retinoblastoma (Bertolesi et al., 2002), colon (Dziegielewska et al., 2014), glioblastoma (Valerie et al., 2013, Zhang et al., 2017b) In vivo: glioma and glioblastoma (Holdhoff et al., 2017, Zhang et al., 2017b)
Monoclonal antibody	nfP2X7	In vivo: basal cell carcinoma (clinical trials) (Gilbert et al., 2017, Gilbert et al., 2019).
Nifedipine	VGCC	In vitro: breast (Timar et al., 1992, Roger et al., 2004, Squecco et al., 2015), melanoma (Honn et al., 1985), pancreatic (Woods et al., 2015) endometrial (Bao et al., 2012). In vivo: melanoma (Honn et al., 1985), colon (Yang and Friedlander, 2001).
Nimodipine	VGCC	In vitro: melanoma, breast (Honn et al., 1984, Honn et al., 1985). In vivo: melanoma (Honn et al., 1984, Honn et al., 1985).
NNC-55-0396	VGCC	In vitro: leukaemia (Huang et al., 2015)
20-O-β-D-glucopyranosyl-20(S)-protopanaxadiol, 4-chloro-m-cresol	Ryanodine receptor	In vitro: lung (Shin et al., 2018). In vivo: breast (Abdul et al., 2008).
Pimozide	VGCC	In vitro: breast, retinoblastoma (Bertolesi et al., 2002).
SKF96365 and MRS-1845	ORAI, TRPC1	In vitro: glioma (Bomben and Sontheimer, 2008, Bomben and Sontheimer, 2010). In vivo: breast (Yang et al., 2009).

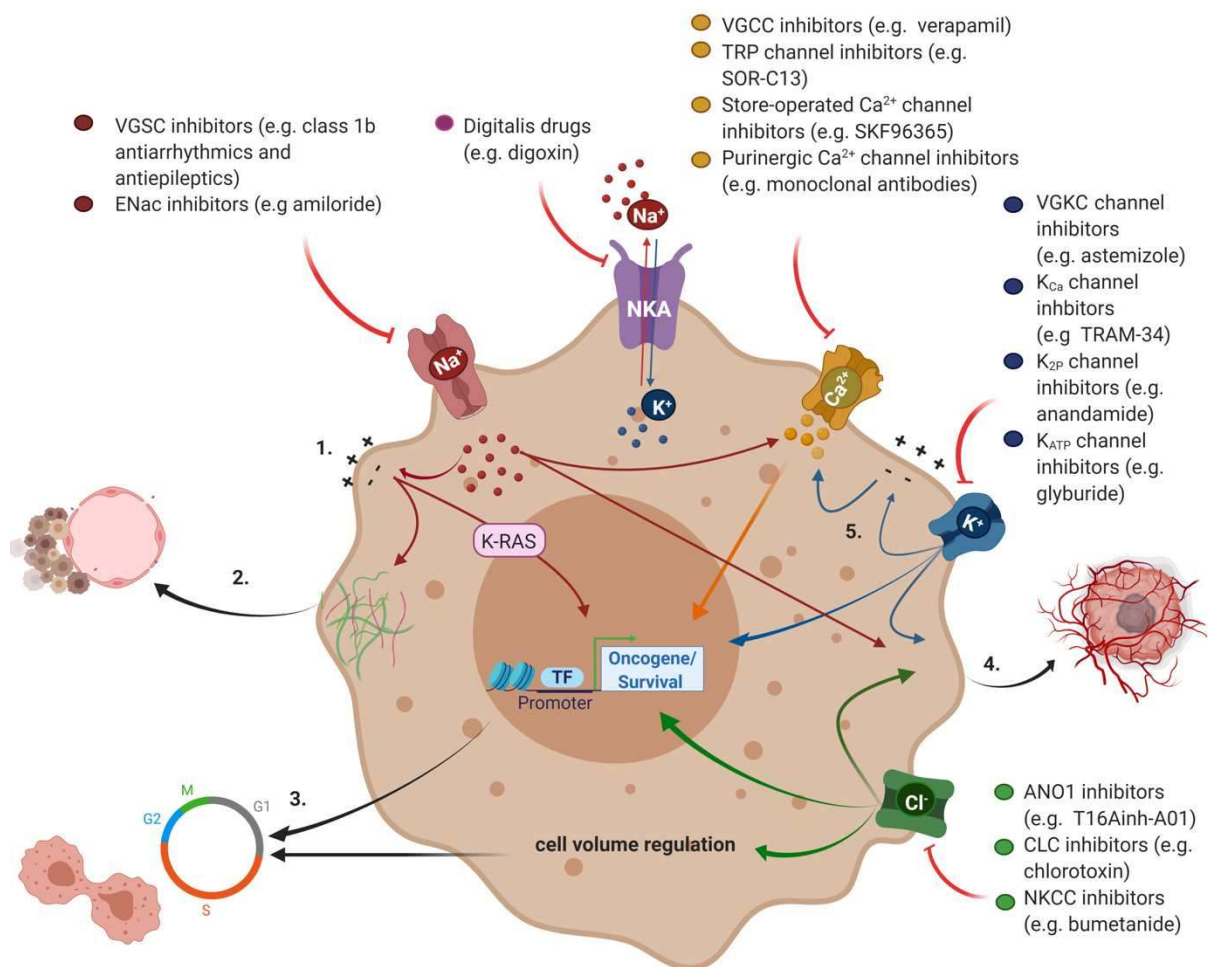
SOR-C13, SOR-C27	TRPV6	In vivo: solid tumours of epithelial origin (Phase I Clinical Trial) (Fu et al., 2017), ovarian (Xue et al., 2018), prostate (Bowen et al., 2013).
Verapamil	VGCC	In vitro: pancreatic (Sato et al., 1994, Zhao et al., 2016), breast (Timar et al., 1992, Roger et al., 2004, Berzingi et al., 2016). In vivo: pancreatic (Sato et al., 1994, Zhao et al., 2016).
Waixenicin A	TRPM7	In vitro and in vivo: colon (Huang et al., 2017).

Abbreviations: TRP, transient receptor potential, VGCC, voltage-gated Ca<sup>2+</sup> channel.

**Table 4.** Cl<sup>-</sup> channel inhibitors in cancer.

Compound	Cancer target	Type of cancer
Ani9 and derivatives	ANO1	In vitro: prostate (Song et al., 2018), pancreatic, breast (Seo et al., 2018).
Bumetanide	NKCC1	In vitro & in vivo: glioma (Haas and Sontheimer, 2010), colon (Malamas et al., 2015).
CaCCinh-A01	ANO1	In vitro: prostate (Song et al., 2018), colon, lung (Guan et al., 2016), breast (Britschgi et al., 2013), oesophageal and pharyngeal squamous carcinoma (Bill et al., 2014), pancreatic (Sauter et al., 2015).
Chlorotoxin	CLC-3	In vitro and in vivo (clinical trials): glioma (Deshane et al., 2003, Mamelak et al., 2006)
DIDS	Acid-induced Cl <sup>-</sup> channels	Nasopharyngeal (Wang et al., 2012)
Digallic Acid and Tannic Acid	ANO1	In vitro: lymphoblastoma (Bhourri et al., 2012), oesophageal and pharyngeal squamous carcinoma (Bill et al., 2014), gingival (Darvin et al., 2015), breast (Nie et al., 2016), prostate (Karakurt and Adali, 2016)
Idebenone	ANO1	In vitro: pancreatic, prostate (Seo et al., 2015)
Luteolin	ANO1	prostate (Seo et al., 2017)
NPPBs	Acid-induced Cl <sup>-</sup> channels	In vitro: cervical (Shen et al., 2000), nasopharyngeal (Wang et al., 2012)
Tamoxifen	Acid-induced Cl <sup>-</sup> channels (CLC-3)	In vitro: hepatocellular (Mao et al., 2013), cervical (Shen et al., 2000), nasopharyngeal (Wang et al., 2012). In vivo: breast (Luveta et al., 2020)
T16Ainh-A01	ANO1	In vitro: pancreatic (Mazzone et al., 2012), prostate (Song et al., 2018), colon, lung (Guan et al., 2016), oesophageal and pharyngeal squamous (Bill et al., 2014), pancreatic (Sauter et al., 2015).





**Figure 1.** Potential anticancer utility of Na<sup>+</sup>, K<sup>+</sup>, Ca<sup>2+</sup> and Cl<sup>-</sup> channel blockers. Principal consequences of ion channel function in cancer cells: (1) Membrane potential depolarisation (Yang and Brackenbury, 2013); (2) invasion and metastasis (Besson et al., 2015); (3) cell cycle progression and proliferation (Becchetti, 2011); (4) angiogenesis (Fiorio Pla et al., 2012); (5) Ca<sup>2+</sup> signalling in response to altered K<sup>+</sup> channel activity (Illek et al., 1992). Na<sup>+</sup>, Ca<sup>2+</sup>, K<sup>+</sup> and Cl<sup>-</sup> channels are represented on the plasma membrane for clarity, but some functions are performed by intracellularly located channels (details in main text). Key inhibitor classes and examples of widely studied compounds are included (see Tables for a complete list). Abbreviations: ENaC – epithelial Na<sup>+</sup> channel, K<sub>Ca</sub> – Ca<sup>2+</sup> dependent K<sup>+</sup> channels, K-

RAS - Kirsten rat sarcoma, NKA - Na<sup>+</sup>/K<sup>+</sup> ATPase, NKCC – Na<sup>+</sup>/ K<sup>+</sup>/Cl<sup>-</sup> co-transporter, TF – transcription factors, VGCC – voltage-gated Ca<sup>2+</sup> channel, VGKC – voltage-gated K<sup>+</sup> channel, VGSC – voltage gated Na<sup>+</sup> channel.