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Voltage-gated Potassium Channels as Therapeutic Drug Targets

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Abstract

The human genome contains 40 voltage-gated potassium channels (K_V) which are involved in diverse physiological processes ranging from repolarization of neuronal or cardiac action potentials, over regulating calcium signaling and cell volume, to driving cellular proliferation and migration. K_V channels offer tremendous opportunities for the development of new drugs for cancer, autoimmune diseases and metabolic, neurological and cardiovascular disorders. This review first discusses pharmacological strategies for targeting K_V channels with venom peptides, antibodies and small molecules and then highlights recent progress in the preclinical and clinical development of drugs targeting $K_V1.x$, $K_V7.x$ (KCNQ), $K_V10.1$ (EAG1) and $K_V11.1$ (hERG) channels.

Introduction

After protein kinases and G-protein coupled receptors, voltage-gated-like ion channels (VGICs) constitute the third largest group of signaling molecules in the human genome¹. With 78 members, potassium channels make up about half of this extended gene superfamily and can be divided into four structural types based on their mode of activation and the number of their transmembrane segments (TM): inwardly rectifying 2 TM K^+ channels (K_{ir}), two-pore 4 TM K^+ channels (K_{2p}), calcium-activated 6 or 7 TM K^+ channels (K_{Ca}), and voltage-gated 6 TM K^+ channels (K_V). This review will focus on the largest gene family within the K^+ channel group, the K_V channels, which in humans are encoded by 40 genes and are divided into 12 subfamilies. Similar to the first cloned K_V channel, the *Drosophila Shaker* channel², all mammalian K_V channels consist of four α -subunits, each containing six transmembrane α -helical segments S1–S6 and a membrane-reentering P-loop (P), which are arranged circumferentially around a central pore as homo- or heterotetramers. This ion-conduction pore is lined by four S5-P-S6 sequences while the four S1–S4 segments, each containing four positively charged arginine residues in the S4 helix, act as voltage-sensor domains and “gate” the pore by “pulling” on the S4–S5 linker^{3,4}. For detailed discussions of the current views on electro-mechanical coupling mechanisms during the gating process interested readers are referred to several excellent reviews^{5,6,7}.

Financial Interest Statement

H.W. is an inventor on the University of California patent claiming PAP-1 and related $K_V1.3$ blockers for immunosuppression. She is a scientific founder of Airmid, a start-up company that is aiming to develop $K_V1.3$ blockers as immunosuppressants. N.A.C. is an employee of Icagen Inc., a company that is currently developing $K_V7.2$ and $K_V7.3$ activators for epilepsy. L.A.P. is a shareholder of iOnGen AG, a company developing ion channel-based diagnostics and therapies in oncology.

All 40 K_V channels in the human genome have been cloned and their biophysical properties characterized in minute detail, but it often remains a challenge to precisely determine what channel underlies a K^+ current in a native tissue. This is because within subfamilies, such as the K_V1 - or K_V7 -family, the α -subunits can heteromultimerize relatively freely resulting in a wide variety of possible channel tetramers with different biophysical and pharmacological properties⁸. The properties of K_V channel α -subunit complexes can be further modified by association with intracellular β -subunits. For example, K_V1 -family channels interact through their N-terminal tetramerization (T1) domain with $K_V\beta1-3$ proteins, which form a second symmetric tetramer on the intracellular surface of the channel (Box 1 figure) and modify the gating of the α -subunits. Another class of so-called “ K^+ channel interacting proteins” (KChIP1–4) enhance surface expression and alter the function of K_V4 channel α -subunits⁸. In addition to this “mixing” and “matching” of α - and β -subunits, K_V channel properties can be further modified by phosphorylation/dephosphorylation, ubiquitinylation, SUMOylation and palmitoylation. In terms of drug discovery, this molecular diversity constitutes a challenge but also provides an opportunity for achieving selectivity by designing modulators that selectively target homotetramers over heteromultimers or *vice versa* or that bind to tissue specific β -subunits⁹.

Because of the concentration gradient for K^+ that exists across cellular membranes, the opening of K_V channels results in an efflux of positive charge, which can serve to repolarize or even hyperpolarize the membrane. In excitable cells such as neurons or cardiac myocytes, K_V channels are therefore often expressed together with voltage-gated Na^+ (Na_V) and/or Ca^{2+} (Ca_V) channels and are responsible for the repolarization after action potential firing. Pharmacological activation of K^+ channels in excitable cells consequently reduces excitability whereas channel inhibition has the opposite effect and increases excitability (Fig. 1). In both excitable and non-excitable cells K_V channels further play an important role in Ca^{2+} signaling, volume regulation, secretion, proliferation and migration. In proliferating cells, such as lymphocytes or cancer cells, K_V channels provide the counterbalancing K^+ efflux for the Ca^{2+} influx through store-operated inward-rectifier Ca^{2+} channels like CRAC (calcium-release activated Ca^{2+} channel)^{10,11} or transient receptor potential (TRP) channels, which is necessary for cellular activation. In this case, K_V channel blockers inhibit proliferation and suppress cellular activation^{10,12}. In fact, it is well established that both migration and metastases require Ca^{2+} influx through CRAC¹³ or TRPV2¹⁴. In this context, potassium channels have been traditionally viewed as modulators of the driving force for Ca^{2+} influx. However, although no K_V channels have been described to possess intrinsic catalytic functions (in the sense of the protein-kinase activity of TRPM channels) they often participate in large supramolecular complexes, whose behavior can be influenced by the channel in the absence of ion flow. Therefore, non-canonical (non-conductive) properties of K_V channels are increasingly found to be important^{15–18}. K_V channels can also be important in preventing depolarization following activation of electrogenic transporters such as Na^+ -coupled glucose and amino acid transporters in cells such as proximal tubule endothelial cells, which have to sustain large fluxes of cations or anions¹⁹. Overall, K_V channels therefore constitute potential drug targets for the treatment of diverse disease processes ranging from cancer over autoimmune diseases to metabolic, neurological and cardiovascular disorders. However, K_V channels, in particular $K_V11.1$ (hERG) with its promiscuous blocker binding pocket and its relevance for cardiac repolarization, also constitute a liability in drug discovery due to drug-induced arrhythmias. The therapeutic potential of K_V channel modulation is further underscored by the phenotypes observed in transgenic mice and various human “channelopathies” which are caused by mutations in K_V channel genes (see Table 1 and later sections). This article will discuss pharmacological strategies for targeting K_V channels with venom peptides, antibodies and small molecules and then review recent progress in the preclinical and clinical development of drugs targeting $K_V1.x$, $K_V7.x$ (KCNQ), $K_V10.1$ (EAG1) and $K_V11.1$ (hERG) channels.

Channels for which there currently is no pharmacology will not be discussed in detail but are listed in Table 1 together with their potential therapeutic significance.

Pharmacological strategies for modulation of K_V channel function

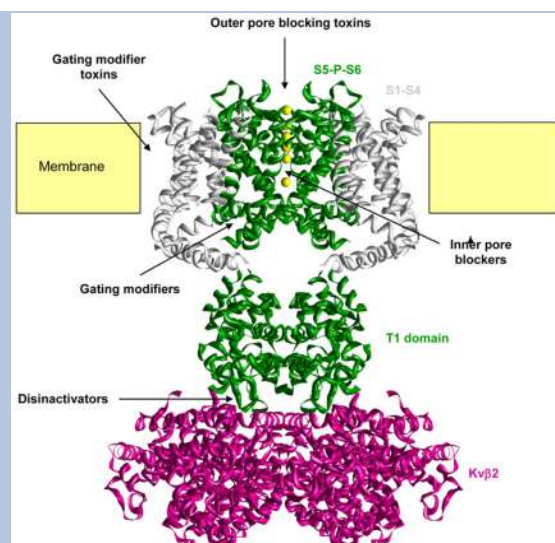
Agents that modulate K_V channels broadly fall into three chemical categories: metal ions, organic small molecules (MW 200–500 Da) and venom-derived peptides (MW 3 to 6 kDa)⁹. These substances affect K_V channel function by blocking the ion-conducting pore from the external or internal side or modifying channel gating through binding to the voltage-sensor domain or auxiliary subunits (Box 1). Similar to other proteins expressed on the cell surface, K_V channels can also be targeted with antibodies (MW 150 kDa), which can either “simply” inhibit channel function, lead to channel internalization or deplete channel-expressing cells by complement or cell-mediated cytotoxicity. Antibodies and toxins can also be engineered to serve as carriers for delivery of active compounds to channel-expressing cells, or can be conjugated to cytotoxic drugs, isotopes or other molecules. In terms of channel inhibition, monoclonal antibodies have been reported in just one case (Kv10.1), although polyclonal antibodies have been obtained in several cases using extracellular parts of the pore loop as antigen²⁰.

Text Box 1

Venom peptides and small molecules can interact with Kv channels in multiple ways

Structure of $K_V1.2^3$ with the S5-P-S6 region colored green, the voltage-sensor domain colored light grey, the tetramerization domain colored green and the intracellular $K_V\beta 2$ subunit magenta. Only two of the four subunits are shown for clarity.

Peptide toxins (see²³⁶ for a systematic nomenclature) typically contain between 18 and 60 amino acid residues and are cross-linked by two to four disulfide bridges forming compact molecules, which are remarkably resistant to denaturation. They can affect K_V channels by two different mechanisms. While toxins from scorpions, sea anemones, snakes and cone snails bind to the outer vestibule of K^+ channels and in most cases insert a lysine side chain into the channel pore to occlude it like a cork a bottle^{237–239}, spider toxins like hanatoxin, interact with the voltage sensor domain of K_V channels and increase the stability of the closed state^{240,241}. The resulting rightward shift in activation voltage and acceleration of deactivation means that the channel is more difficult to open (i.e. membrane requires more depolarization) and closes faster. These so-called “gating-modifier” toxins typically contain a cluster of hydrophobic residues on one face of the molecule and seem to partition into the membrane when they bind to the voltage sensor^{242,243}. In contrast to peptide toxins, which affect K_V channels from the extracellular side, most small molecules bind either to the inner pore, the gating-hinges or the interface between the α - and β -subunit.



Box 1. Venom peptides and small molecules can interact with Kv channels in multiple ways

Structure of Kv1.2³ with the S5-P-S6 region colored green, the voltage-sensor domain colored light grey, the tetramerization domain colored green and the intracellular Kvβ2 subunit magenta. Only two of the four subunits are shown for clarity.

Peptide toxins (see²²³ for a systematic nomenclature) typically contain between 18 and 60 amino acid residues and are cross-linked by two to four disulfide bridges forming compact molecules, which are remarkably resistant to denaturation. They can affect K_V channels by two different mechanisms. While toxins from scorpions, sea anemones, snakes and cone snails bind to the outer vestibule of K⁺ channels and in most cases insert a lysine side chain into the channel pore to occlude it like a cork a bottle^{224–226}, spider toxins like hanatoxin, interact with the voltage sensor domain of K_V channels and increase the stability of the closed state^{227,228}. The resulting rightward shift in activation voltage and acceleration of deactivation means that the channel is more difficult to open (i.e. membrane requires more depolarization) and closes faster. These so-called “gating-modifier” toxins typically contain a cluster of hydrophobic residues on one face of the molecule and seem to partition into the membrane when they bind to the voltage sensor^{229,230}. In contrast to peptide toxins, which affect K_V channels from the extracellular side, most small molecules bind either to the inner pore, the gating-hinges or the interface between the α- and β-subunit.

While peptide toxins typically bind either to the outer vestibule or the voltage-sensor of K_V channels, small molecules, as exemplified by the hydrophobic cations tetrabutylammonium (**1**, Fig. 2), *d*-tubocurarine (**2**), and verapamil (**3**), block K_V channels by physically occluding the inner pore and inserting their ammonium group into the ion permeation pathway (Box 1). The inner pore of K_V channels can also be targeted by nucleophilic molecules like the K_V1 channel blocker correolide (**11**), which “snuggles” into the hydrophobic surface of the S6 helix with its lipophilic part and chelates a permeating potassium ion with its polar acetyl groups²¹. Typical blockers of K_V11.1 enter the channel from the intracellular side and appear to reside in a pocket in the inner mouth, where they interact mostly with two aromatic residues²². The large variety of drugs that this pocket can accommodate might be attributable to the lack of a cluster of prolines that induces a kink in the inner mouth of K_V channels, in contrast to other families²³. This leaves a broader opening in K_V11.1 that allows entry of a wide range of molecules of varying sizes and shapes²⁴. In addition to the inner pore, small molecules can further bind to the “gating-hinges” as in the case of the K_V7 channel activator retigabine, which has been found by mutagenesis to bind to a putative hydrophobic pocket formed upon channel opening between the cytoplasmic parts of S5 and S6²⁵. Another

interesting mechanism of action for channels with β -subunits are the so-called disinactivators that disrupt the interaction between α - and β -subunits and modify channel behavior in this way^{26,27}. However, rational design of K_V channel modulators is extremely difficult because there are currently no crystal structures for medically important K_V channels like $K_V1.5$, $K_V7.2$ or $K_V11.1$. Overall, the K_V channel field only has two structures, the bacterial $KvAP$ and the mammalian $K_V1.2$ channels (both in the open state) and no structure of a channel with a drug molecule bound. K_V channel modulators are therefore typically identified through high-throughput-screening (See Box 2) or serendipity and then optimized through classical medicinal chemistry. Lead identification is usually performed by ion flux assays (mostly using isotopes and/or atomic absorption spectroscopy) or fluorescent dye assays²⁸, and more recently through automated electrophysiology, which can offer quality levels comparable to manual patch-clamp with a reasonable throughput. Detailed studies on functional drug-target interactions can be achieved through patch-clamping, which allows the behavior of a single ion channel to be studied on the microsecond time scale.

Text Box 2

Ion channel screening technologies

Implementing successful drug discovery campaigns against K_V channels has been, and continues to be challenging. One of the reasons for this is that the traditional technologies used to measure ion channel function have not always been translatable to the high throughput world of drug discovery. Electrophysiology such as cellular voltage-clamp, and in particular the patch-clamp variant of this technique, has been the “gold standard” for measuring ion channel function for nearly three decades²⁴⁴. It is a high fidelity, but low throughput platform that requires skilled operators. While this technology can teach much about the biophysical properties and modulation of ion channels in general and K_V channels in particular, it can only be used to examine a few compounds per day and is impractical in modern drug discovery, where hundreds of thousands, and sometime times millions of compounds need to be tested for activity. In order to enable drug discovery against ion channels, a number of technologies have been developed. As with many drug target classes, radioligand binding studies have been employed with some success to identify modulators of K_V channels. Radioiodinated venom toxins like margatoxin²⁴⁵ or tritiated natural products like correolide²⁴⁶ have been used to look for modulators of $K_V1.3$ channels; radiolabeled dofetilide is used regularly in assays to look for potential modulators of $K_V11.1$ (hERG)²⁴⁷. While radioligand binding assays can be very high throughput, ligands identified by this technique do not always have functional activity. Examining K_V channel function more directly in flux assays can get around this issue. Historically, radiolabelled⁸⁶ rubidium ions have been used as a surrogate for potassium in high throughput flux assays for a variety of potassium channel targets²⁴⁸. Radioactive rubidium can also be replaced by unlabelled rubidium and then be detected by atomic absorption spectroscopy²⁴⁹. More recently, thallium, which is also permeant through potassium channels, has been used successfully in high throughput screening assays, where upon fluxing through open channels it interacts with a preloaded intracellular fluorescent dye²⁵⁰. Membrane potential-sensitive fluorescent dyes have also been used successfully to examine compound interactions with K_V channels²⁵¹. However, perhaps the biggest impact on ion channel drug discovery in recent years has been the development of higher throughput electrophysiological platforms. These range from the medium throughput systems like the high fidelity PatchXpress (Molecular Devices)²⁵², Qpatch (Sophion)^{253,254} or PatchLiner (Nanion)²⁵⁵, which can test up to a 100 compounds per day to higher throughput platforms like IonWorks HT and Quattro (Molecular Devices)^{256,257} and more recently Qpatch HTX (press release from Sophion) that can test thousands of compounds per day. While not truly high throughput, when used in conjunction with other screening technologies, these new

electrophysiology platforms have allowed for a higher fidelity and a more direct approach to K_V channel drug discovery. More detailed discussions of screening for ion channel modulators can be found in the following recent reviews^{28,258,259}.

K_V -1-Family Channels

Channels belonging to the K_V 1.x or mammalian *Shaker*-family are widely expressed throughout the nervous system. Of the eight known pore forming subunits of this family (K_V 1.1- K_V 1.8), most have been shown to form heteromultimers in the CNS. Therefore, the exact composition of neuronal K_V 1.x channels remains to be fully elucidated. However, in general, most forms of neuronal K_V 1.x channels are believed to contain at least one K_V 1.1 and/or K_V 1.2 subunit²⁹ and these two channels are therefore regarded as targets for various CNS disorders. K_V 1.x family channels are further found in peripheral tissues such as the heart, the vasculature and the immune system, where K_V 1.5 and K_V 1.3 are pursued respectively as targets for atrial fibrillation and immunosuppression. The therapeutic relevance of K_V 1.4, K_V 1.6, K_V 1.7 and K_V 1.8 is currently not clear.

K_V 1.1 and K_V 1.2

The importance of K_V 1.1 and K_V 1.2 in controlling neuronal excitability has been demonstrated by the observation that K_V 1.x channel inhibiting venom toxins like dendrotoxin produce seizures in rodents³⁰. Furthermore, K_V 1.1^{-/-} transgenic knockout mice exhibit spontaneous seizures and CNS structural changes³¹. Similarly, knockout of K_V 1.2 in mice is also associated with increased susceptibility to seizures³². In humans, several loss-of-function mutations in K_V 1.1 have been linked to partial seizures, episodic ataxia and myokymia disorders³³. Moreover, loss-of-function mutations in a protein called LGI1, which is co-expressed with K_V 1.1, have been associated with temporal lobe epilepsy³⁴. While normal LGI1 protein functions to inhibit $K_V\beta$ 1 subunit mediated inactivation of K_V 1.1/ K_V 1.4 heteromultimeric channels, increasing potassium current and lessening neuronal excitability, mutated LGI1 lacks the ability to abrogate β -subunit mediated inactivation³⁴.

Researchers at Wyeth have identified several small molecule agents that functionally behave like LGI1 and reverse or prevent $K_V\beta$ 1 mediated inactivation of K_V 1.1. Using a variety of techniques including a yeast two hybrid based screen they identified inhibitors (termed “disinactivators”) of protein/protein interactions between β - and pore forming α -subunits^{26, 27}. Several structural classes of compounds (see Fig. 2 for examples) have been reported to interact directly with the $K_V\beta$ 1 N-terminus or its receptor site on K_V 1.1, preventing inactivation of the channel. In addition to increasing current flow, these K_V 1.1 disinactivators effectively reduce pentylentetrazole and maximal electric shock induced seizures in mice²⁷. Accordingly, compounds acting by this mechanism have the potential to reduce neuronal hyperexcitability in epilepsy and pain disorders. However, the current development status of this therapeutic strategy is unknown. Utilizing a different screening strategy termed Leptics™ technology³⁵, investigators at Lectus Therapeutics have recently identified both activators and inhibitors of K_V 1.1 function that modulate β -subunit protein-protein interactions with K_V 1.x pore forming α -subunits³⁶.

While activation of K_V 1.1/1.2 channels is expected to reduce neuroexcitability (Fig. 2), there are physiological and pathophysiological situations where electrical signaling in the nervous system is reduced and needs to be amplified. Damage to nerves caused by trauma (i.e. spinal cord injury) or disease (i.e. multiple sclerosis) is often associated with a decreased ability to generate and propagate action potentials^{37,38}. Neuronal damage is typically manifested as a loss of myelin, resulting in the exposure of juxtapanodal K_V 1.1 and K_V 1.2 channels and their redistribution along damaged axons^{37,39}. The presence of newly exposed K_V channels slows

and sometimes prevents conduction of electrical signals along the axon. Studies have shown that inhibition of these axonal $K_V1.1$ and $K_V1.2$ channels by the non-selective potassium channel inhibitor 4-AP (4-aminopyridine, **4**) improves impulse conduction in damaged nerve fibers. This resulted in speculation that 4-AP might provide a treatment opportunity for spinal cord injury³⁷, a hypothesis tested by Acorda Therapeutics. However, despite encouraging phase-II clinical data with a slow release formulation of 4-AP, Fampridine-SR, two subsequent larger Phase-3 clinical studies in patients with spinal cord injury (SCI), failed to produce any statistically significant reduction in spasticity³⁸. However, Acorda Therapeutics has continued to evaluate 4-AP, and recently reported on phase-III clinical studies where Fampridine-SR was found to improve walking ability in patients with multiple sclerosis (MS)^{40,41}. While these results represent significant progress in treating the symptoms of MS, the impact of Fampridine-SR on actual disease progression remains to be determined.

Although typically considered a neuronal channel, $K_V1.1$ has recently been linked to human autosomal dominant hypomagnesemia⁴². A loss-of-function mutation in $K_V1.1$ reduces TRPM-6 mediated magnesium reabsorption in the kidney, which depends on $K_V1.1$ setting a negative membrane potential⁴³. Because of its fundamental role in many cellular functions, abnormalities in magnesium levels can result in widespread organ dysfunction, which can precipitate potentially fatal complications (e.g. ventricular arrhythmia, coronary artery vasospasm, seizures). Pharmacological enhancement of available $K_V1.1$ channel activity might provide a therapeutic opportunity for treating hypomagnesemia.

$K_V1.3$

$K_V1.3$ was discovered in human T cells in 1984^{10,44,45} and proposed as a target for immunosuppression based on the fact that non-selective K^+ channel blockers like 4-AP (**4**) inhibit T cell proliferation and IL-2 secretion⁴⁴. Investigators at Merck later confirmed these findings with the more $K_V1.3$ -selective scorpion toxin margatoxin⁴⁶ and also provided the first evidence that $K_V1.3$ blockade can inhibit immune responses *in vivo* by demonstrating that continuous infusion of margatoxin suppressed delayed type hypersensitivity in mini-pigs⁴⁷. $K_V1.3$ blockers exert their immunosuppressive effect by depolarizing the T cell membrane⁴⁶ and thus reducing the driving force for Ca^{2+} entry through the calcium-release activated Ca^{2+} (CRAC) channel¹⁰, which consists of the ER Ca^{2+} -sensor STIM1 and the pore forming protein Orai1^{11,48–50}. Since T cells are small and have no significant intracellular calcium stores, this Ca^{2+} influx through the inward-rectifier CRAC is absolutely necessary for the translocation of NFAT (nuclear factor of activated T cells) to the nucleus and the ultimately resulting cytokine secretion and T cell proliferation. The T cell must therefore retain a negative membrane potential through a counterbalancing K^+ efflux through $K_V1.3$ and/or the other T cell K^+ channel, the Ca^{2+} -activated channel $K_{Ca3.1}$, in order to be fully activated.

In the mid-1990s, Merck and Pfizer initiated small molecule $K_V1.3$ discovery programs but failed to identify compounds that were selective enough for *in vivo* use⁵¹. The Pfizer compounds CP-339818 (**9**, Fig. 2) and UK-78282 (**10**) lacked selectivity over Na^+ channels or $K_V1.4$, while the molecular complexity of Merck's nor-triterpene correolide (**11**) was too great for successful analogue development. Interest in $K_V1.3$ as a target for immunosuppression subsequently waned, partially because species differences in T cell K^+ channel expression between mice and humans made it impossible to use the well-established mouse models of autoimmune diseases to evaluate $K_V1.3$ blockers. Interestingly, mice express additional K_V channels like $K_V1.1$, $K_V1.6$ and $K_V3.1$ in their T cells^{47,52,53} and do not rely on $K_V1.3$ to set their resting membrane potential. However, interest in $K_V1.3$ as a drug target recently revived considerably with the discovery that $K_V1.3$ blockers selectively inhibit the Ca^{2+} -signaling, proliferation and *in vivo* migration of $CCR7^-$ effector memory T cells^{54–56} and therefore rather constitute immunomodulators instead of general immunosuppressants⁵⁷. So-called effector

memory T cells (T_{EM}) are a memory T cell subset that is negative for the chemokine receptor CCR7 and which has been implicated in the pathogenesis of T cell-mediated autoimmune diseases such as MS, type-1 diabetes, rheumatoid arthritis (RA) and psoriasis^{55,58–61}. In keeping with this observation, myelin antigen reactive T cells in the blood from MS patients, islet antigen reactive T cells from new onset type-1 diabetic children as well as synovial fluid T cells from patients with RA and brain infiltrating T cells in postmortem brain sections from MS patients have all been demonstrated to be $K_V1.3^{high} CCR7^- T_{EM}$ cells^{54,55,61}. [Similar to humans, rats, pigs, and primates up-regulate $K_V1.3$ in their effector memory T cells making it possible to evaluate the immunosuppressive effects of $K_V1.3$ blockers in these species.]

The possibility that $K_V1.3$ could serve as a target for T_{EM} specific immunosuppression has led to the recent development of both peptidic and small molecule $K_V1.3$ blockers. After demonstrating that the sea anemone peptide ShK effectively treats adoptive-transfer experimental autoimmune encephalomyelitis (EAE) in rats⁶², George Chandy's group more recently described ShK-L5⁶³, a ShK derivative with improved selectivity over $K_V1.1$, and showed that it treats pristane-induced arthritis and chronic-relapsing EAE in rats^{55,56}. A close-structural analog of ShK-L5 is currently in preclinical development for MS by Airmid and Kineta Inc., while Amgen Inc. is making efforts to prolong the short half-life of venom peptides like ShK or the scorpion peptide OSK1 by conjugating them to Fc antibody fragments or polyethylenglycol (PEG)⁶⁴.

Starting from two natural products, the psoralen 5-methoxypsoralen from the rue plant and the benzofuran khellinone from the toothpickweed, academic laboratories at the Universities of California, Davis and Melbourne have developed several classes of nanomolar to low micromolar $K_V1.3$ inhibitors^{65–67}. The most potent of these compounds, the psoralen PAP-1 (**12**), inhibits $K_V1.3$ with an IC_{50} of 2 nM and has been shown to effectively treat rat allergic contact dermatitis⁶⁸, a simple animal model for psoriasis, and to prevent spontaneous autoimmune diabetes in diabetes-prone Biobreeding Worchester rats⁵⁵. The khellinone-type $K_V1.3$ blockers (as exemplified by the chalcone (**13**) and the 4-substituted khellinone (**14**)) are currently being further optimized by the Australian Biotech company Bionomics, which has entered into an agreement with Merck-Serono to develop this class of compounds for MS. $K_V1.3$ was recently further corroborated as a target for immunosuppression in humans by the finding that clofazimine (**15**), a drug that is marketed as Lamprene® by Novartis and which has been clinically used since the 1960s for leprosy, pustular psoriasis, skin graft-versus-host-disease and discoid lupus erythematosus, inhibits $K_V1.3$ with an IC_{50} of 400 nM and prevents the rejection of transplanted human foreskin in immunodeficient mice reconstituted with human T cells⁶⁹. Clofazimine could therefore either be used as a template for the design of $K_V1.3$ blockers of a different chemotype or could directly enter clinical trials after careful consideration of its benefit versus its known risks such as gastrointestinal intolerance and skin discolorations. Results obtained with clofazimine should of course be interpreted with caution since the compound has multiple activities on other targets and pathways such as stimulation of phospholipases, increasing phagocytosis by macrophages or interactions with DNA.

Based on experiments with $K_V1.3^{-/-}$ mice, these channels have also been suggested as a target for the treatment of type-2 diabetes and obesity⁷⁰. $K_V1.3^{-/-}$ mice were reported to gain less weight on a high-fat diet than $K_V1.3^{+/+}$ littermates and to exhibit increased insulin sensitivity due to increased glucose uptake into adipose tissue and skeletal muscle. In these tissues in normal mice, blockade of $K_V1.3$ with margatoxin facilitates the translocation of the glucose transporter, GLUT4, to the plasma membrane and thus improves insulin sensitivity⁷¹. Intriguingly, deletion of $K_V1.3$ can also reduce adiposity and increase lifespan in a genetic model of obesity. Double $K_V1.3$ and melanocortin-4 receptor (MC4R) knockout mice exhibited a lower bodyweight, an increased lifespan and reproductive success compared to $MC4R^{-/-}$ mice⁷². However, while it is certain that mouse adipocytes express $K_V1.3$ protein,

electrophysiological studies performed with neonatal brown fat cells^{73,74} and white adipocytes from rats and adult humans^{75,76} show K_V currents with properties that do not fit the pharmacological and biophysical characteristics of a current that is carried by $K_V1.3$ channel homotetramers. It therefore remains to be seen whether or not $K_V1.3$ constitutes a target for the improvement of insulin sensitivity and weight reduction in type-2 diabetes in humans.

$K_V1.5$

Although $K_V1.5$ is expressed in a variety of tissues in humans^{77–79}, its functional expression in atrial but not ventricular muscle in heart⁷⁷ has made this channel the focus of great interest within the pharmaceutical industry. Studies by Nattel and colleagues in the early 1990s demonstrated that $K_V1.5$ was the primary molecular component of the ultra rapid delayed rectifier (IKur)^{80,81}, a human atrial specific potassium conductance that plays an important role in the early phases of atrial action potential repolarization⁸² (Fig. 3a). This mechanism, and its regiospecific localization, suggested $K_V1.5$ as an attractive target for the development of safer pharmacological interventions for atrial arrhythmias, particularly atrial fibrillation (AF). The absence of functional $K_V1.5$ expression in human ventricle reduces the potential risk of serious ventricular arrhythmias that can occur with treatments targeting channels with broader expression within the heart^{83,84}. Given the ubiquitous expression of other $K_V1.x$ channels, there has been a desire to identify and develop $K_V1.5$ selective agents. Development has been complicated by the fact that the importance of IKur, or the contribution of $K_V1.5$ to IKur-like currents to atrial action potential repolarization in the hearts of mice, rats, rabbits and dogs may differ from humans, making it difficult to evaluate anti-arrhythmic efficacy in these species^{84,85}.

Despite these challenges, a number of pharmaceutical companies have attempted to develop $K_V1.5$ inhibitors for AF (Fig. 3b). Over 50 patent applications for $K_V1.5$ inhibitors have been submitted (see⁸⁵ for a comprehensive review). One of the earliest attempts was by Icagen Inc., who in collaboration with Eli Lilly and then with Bristol Myers Squibb (BMS), identified a number of potent $K_V1.5$ inhibitors from multiple chemotypes including arylsulphonamidoindanes⁸⁶ (**16**) and later tetrahydronaphthalenes, but ultimately abandoned them because of poor pharmacokinetic profiles. Other compounds from the Icagen/BMS collaboration entered human clinical trials although they were not progressed beyond phase-I. Bristol Myers Squibb⁸⁷, Sanofi-Aventis^{83,88–90}, Merck^{91–93}, Procter and Gamble^{94,95}, Cardiome/Astellas^{96–98}, and Wyeth⁹⁹ have also developed $K_V1.5$ inhibitors (**17–22**), demonstrating varying degrees of validation with regard to atrial-specific modulation of action potential repolarization, but the majority of these compounds have not progressed beyond animal efficacy testing due to pharmacodynamic or pharmacokinetic issues. However, the bisaryls AVE0118 (**17**) and AVE1231 from Sanofi-Aventis^{89,90,100,101}, although at best weakly selective for $K_V1.5$, have progressed into human testing, with AVE0188 reaching phase-IIa trials before development ceased. Canadian based Cardiome, in collaboration with Merck, is currently in the final development stages of vernakalant (**18**) after a completed Phase-III study gained conditional FDA approval for intravenous conversion of AF. This compound has previously been shown to reduce AF in a variety of animal models^{97,98}. Although $K_V1.5$ has been argued to be the primary target of vernakalant, its mechanism of action probably involves blockade of several ion channels including I_{to} , and I_{Na} ⁹⁷ (see Fig. 3a). Xention has recently reported the development of a selective $K_V1.5$ inhibitor, XEN-D0101⁸⁵, which was effective in two preclinical canine models of AF^{102,103} and is currently undergoing Phase-I evaluation as an intravenous treatment to terminate AF.

$K_V2.1$

$K_V2.1$ encodes a classical delayed rectifier current involved in neuronal repolarization and its function can be diversified through heteromultimerization with the so-called “silent” K_V5 ,

K_V6, K_V8 and K_V9 subunits (Table 1), which modify inactivation, trafficking, drug sensitivity and expression^{104,105}. K_V2.1 has been recently implicated in exocytic processes both in neurons and in pancreatic β-cells. In β-cells, inhibition of K_V2.1 enhances insulin secretion, suggesting a potential therapeutic strategy for type-2 diabetes mellitus^{106,107}. This effect apparently occurs (at least in part) through non-conducting functions, namely a physical interaction with syntaxin (a component of the SNARE complex) that facilitates vesicle fusion^{108,109}.

K_V3.4

Of the *Shaw*-related family of mammalian K_V channels, so far only K_V3.4 has been proposed as a drug target. K_V3.4 co-assembles with KCNE3 (MIRP2) to give rise to a fast inactivating (A-type) K_V current in skeletal muscle and neurons¹¹⁰. In muscle, alterations in the function of the complex, through mutations in the accessory subunit KCNE3, are associated with periodic paralysis¹¹¹. Additionally, in nervous tissue, K_V3.4 has been related to neuronal death induced by β-amyloid peptides in Alzheimer's disease^{112,113}. Potassium depletion through hyperactivity of K_V channels contributes to apoptotic neuronal death¹¹⁴, while blockade of K⁺ channels has neuroprotective effects¹¹⁵. The expression of K_V3.4 is increased in the early stages of Alzheimer's disease and increases further as the disease advances¹¹². Together with higher expression levels, the current carried by K_V3.4 is enhanced by β-amyloid peptide, while the K_V3.4-blocking anemone toxin BDS simultaneously abolishes current increase and neuronal death¹¹³. Hence, blockade of K_V3.4 in the context of Alzheimer's disease could reduce neuronal loss and thereby cognitive impairment.

K_V4.2/K_V4.3

The *Shal*-type K_V4.2 and K_V4.3 channels are expressed at relatively high levels in the brain and the heart, where they contribute to the transient A-type or I_{to} current (Fig. 3a). One remarkable feature of K_V4 channels is the complexity of their association with various ancillary subunits or scaffolding proteins and their extensive posttranslational modification¹¹⁶. In terms of drug discovery, atrial and ventricular K_V4.3 channels could potentially constitute targets for antiarrhythmic therapy and inhibition of I_{to}, which in humans consists of a K_V4.3 homotetramer¹¹⁷, seems to be one of the mechanisms of action of the class III antiarrhythmic tedisamil. However, in addition to I_{to} tedisamil, which is being developed by Solvay also inhibits I_{Kr}, I_{Ks}, I_{Kur} and I_{K-ATP}¹¹⁸. The FDA recently rejected an application for the use of tedisamil for the treatment of atrial arrhythmias. Future development of this compound remains unclear. Based on the important role of K_V4.2 in pain plasticity in dorsal horn neurons in the spinal cord¹¹⁹ K_V4.2 activators might be useful for the treatment of inflammatory pain.

K_V7-Family Channels

The K_V7.x or KCNQ family comprises five members: K_V7.1 to K_V7.5. While K_V7.1 (KCNQ1) is predominantly found in peripheral tissues, K_V7.2–7.5 (KCNQ2–5) appear to be most widely expressed in the nervous system^{120,121}.

K_V7.1

K_V7.1 is present in cardiac muscle where it is coexpressed with the auxiliary subunits KCNE1, KCNE2 and KCNE3 to form the functional channel responsible for the slow delayed rectifier current I_{Ks}^{120,122}. This current plays an important role in controlling repolarization, and thus duration, of the cardiac action potential (Fig. 4a). In humans, numerous loss-of-function mutations of K_V7.1 or KCNE (resulting in reduced current flow and prolongation of cardiac action potentials) have been identified in potentially life threatening cardiac abnormalities such as Long QT syndrome^{120,123}. Several of these loss-of-function mutations in K_V7.1 are also associated with Jervell and Lange-Nielsen Syndrome¹²⁴, a condition with auditory

abnormalities in addition to cardiac rhythm defects. Gain-of-function mutations in $K_V7.1$ increase current flow and lead to shortening of the cardiac action potential and are associated with cardiac rhythm disorders such as Short QT syndrome¹²⁵ and atrial fibrillation¹²⁶.

For more than a decade, IKs has remained a target of interest for the development of anti-arrhythmic drugs. Some marketed anti-arrhythmic agents (i.e. amiodarone) may produce their clinical effects in part through modulation of $K_V7.1/KCNE$ activity¹²⁷. Azimilide (**23**, Fig. 4b), a mixed inhibitor of $K_V7.1$ (IKs) and $K_V11.1$ (IKr) developed by Procter & Gamble has exhibited efficacy in a variety of animal arrhythmia models^{128,129}. However, when assessed in human clinical trials, only limited efficacy in the conversion of atrial fibrillation has been observed^{130–132}. The current development status of azimilide is unknown. Selective inhibitors of $K_V7.1$ like the chromanol HMR1556 (**24**) from Sanofi-Aventis^{133,134} and L-768,673 (**25**) from Merck have also been reported to prolong cardiac action potentials and reduce the incidence of arrhythmias in animal models. HMR1556 - which has greater than 1000-fold selectivity for IKs over IKr, restores sinus rhythm and prevents heart failure in pigs with persistent atrial fibrillation^{135,136}. However, in a canine model of vagal AF, HMR1556 prolonged the atrial effective refractory period, but exerted only a modest effect on the duration of induced AF¹³⁷. The acyl benzodiazepine, L-768,673 developed by Merck has been reported to increase ventricular refractoriness in conscious dogs¹³⁸. Despite their activities in animal models, neither of these selective $K_V7.1$ inhibitors appears to have been assessed for clinical efficacy in humans.

In addition to inhibitors, several pharmacological activators of $K_V7.1$ (\pm KCNE1) channels have been reported. Niflumic acid (**26**) and structurally related mefenamic acid (**27**) increase current flow through $K_V7.1/KCNE1$ by inducing hyperpolarizing shifts in the voltage-dependence of activation¹³⁹. Investigators at Merck have demonstrated that the benzodiazepine L-364,373 (**28**) potently activates homomeric $K_V7.1$ channels but is considerably weaker when $K_V7.1$ coexpresses with the auxiliary subunit KCNE1 (as occurs in the heart)^{140,141}. The utility of $K_V7.1$ activators in a therapeutic setting remains to be evaluated.

Although most well characterized in the heart, $K_V7.1$ is found in the inner ear and epithelial tissues of the kidney, lung and gastrointestinal tract¹²⁰. In contrast to the heart, $K_V7.1$ channels in epithelial cells appear to primarily coexpress with KCNE3 to form a conductance that exhibits little time dependence with regard to activation and only weak sensitivity to membrane potential¹⁴². Gating of the channel is modulated via a variety of second messenger pathways including cyclic AMP^{143,144}. Epithelial $K_V7.1$ channels play an important role in maintaining the driving force for proximal tubular and intestinal Na^+ absorption, gastric acid secretion, and cAMP-induced jejunal Cl^- secretion^{120,145}. Recent studies have also revealed an association of $K_V7.1$ with the susceptibility to type-2 diabetes mellitus¹⁴⁶. $K_V7.1$ activity seems to neutralize the stimulation of cellular K^+ uptake into liver by insulin and thereby influences K^+ -dependent insulin signaling¹⁴⁷. The therapeutic utility of targeting $K_V7.1$ for diabetes or epithelia fluid transport disorders is an area that remains to be explored.

$K_V7.2$ – $K_V7.5$

Over the past decade there has been considerable interest within the pharmaceutical industry to develop modulators of the neuronal potassium conductance referred to as the M-current, because of its sensitivity to inhibitory modulation by a variety of G-protein coupled receptor ligands, most notably muscarinic acetylcholine receptor agonists¹⁴⁸. This current was first identified in the late 1970's and subsequently demonstrated to modulate synaptic plasticity and neuronal excitability in many areas of the brain^{121,148}. The molecular nature of the M-current only became evident following the characterization of loss-of function mutations in a rare hereditary human epilepsy called benign familial neonatal convulsions (BFNC)¹⁴⁹. Around the time of these studies, Wang and colleagues demonstrated for the first time that a

heteromultimeric combination of $K_V7.2$ and $K_V7.3$ were the molecular components of at least one form of the neuronal M-current¹⁵⁰. Subsequent studies have indicated that heteromultimeric combinations of $K_V7.3$ and $K_V7.5$ may also underlie M-currents in some areas of the brain¹⁵¹. The contribution of $K_V7.4$ to the M-current is less clear although it is evident that $K_V7.4$ is important in auditory physiology because of its expression in hair cells of the cochlea and loss-of-function mutations or SNPs associated with congenital deafness DFNA2 (deafness, autosomal dominant nonsyndromic sensorineural 2) and age-related hearing impairment^{152,153}.

Given the importance of $K_V7.2-5$ in a wide variety of neuronal processes it is perhaps not surprising that considerable effort has been directed towards developing therapeutic agents that target these channels. More than 20 patents for novel $K_V7.2-7.5$ modulators have been issued and over 100 US patent applications are currently at various stages of approval. Early studies with M-current ($K_V7.x$) inhibitors like linopirdine (**29**, Fig. 5) demonstrated improvements in learning and memory performance in animals¹⁵⁴. However clinical trials only provided equivocal results for treating cognitive disorders¹⁵⁵. While second generation inhibitors like XE-991 (**30**) and DMP-543 (**31**) were developed¹⁵⁶, no further clinical efficacy studies investigating improvement of cognitive function have been reported.

In contrast to the abandoned inhibitors, there remains widespread interest in the pharmaceutical industry to develop M-current activators. The first agent proven to enhance M-current activity was retigabine (**32**). Retigabine's activation of recombinant $K_V7.2/K_V7.3$ was confirmed independently by a number of investigators, who demonstrated current enhancement by retigabine resulted from a profound hyperpolarizing shift in the voltage-dependence of channel activation¹⁵⁷⁻¹⁵⁹. When examined *in vivo*, retigabine exhibited anticonvulsant activity in a broad range of seizure models including PTZ, maximal electric shock, audiogenic seizures in DBA/2J mice as well as seizures produced by amygdala-kindling¹⁶⁰. Based on these findings retigabine has been the subject of a number of clinical studies assessing its anticonvulsant activity in humans. Phase-II^{161,162} and more recently Phase-III efficacy trials^{163,164} have been successfully completed and retigabine is currently awaiting FDA approval as a new first-in-class epilepsy therapy.

A number of other pharmaceutical companies are at various stages in the development of $K_V7.2-7.5$ activators. For example, Icagen Inc. has developed benzanilide $K_V7.2/7.3$ openers, exemplified by ICA-27243 (**34**), which exhibits >30-fold selectivity for $K_V7.2/7.3$ over $K_V7.3/7.5$ heteromultimeric, or $K_V7.1$, $K_V7.4$ and $K_V7.5$ homomultimeric channels¹⁶⁵. Like retigabine, ICA-27243 shows efficacy in a variety of animal seizure models¹⁶⁶ providing evidence that selective activation of $K_V7.2/7.3$ is sufficient to achieve anticonvulsant activity. Despite the promising *in vivo* activity of ICA-27243 (and a more advanced related compound ICA-69673) in animal models, this class of agents has not been developed beyond Phase-I. However, Icagen is currently developing a new structurally distinct $K_V7.2/7.3$ activator chemotype, exemplified by ICA-105665, which recently successfully completed Phase-I clinical trials¹⁶⁷.

The clear role of K_V7 channels in controlling neuronal excitability, combined with expression of $K_V7.x$ channels in sensory and central neurons involved in nociceptive signaling^{168,169}, has further prompted the exploration of $K_V7.2-7.5$ activators for the treatment of pain^{170,171}. Both retigabine and its structural analog flupirtine (**33**) produce analgesic activity in rat models of neuropathic pain¹⁷²⁻¹⁷⁴. Flupirtine has been in clinical use as an analgesic in Europe since 1984 and is currently in Phase-II clinical trials in the United States for the treatment of fibromyalgia (press release from Pipex Pharmaceuticals, Inc.). However, a recently completed Phase-IIa clinical trial of retigabine in patients with postherpetic neuralgia failed to demonstrate significant antinociceptive activity. Furthermore, the $K_V7.2/7.3$ selective activator ICA-27243

has shown significant oral anti-nociceptive activity in animal models of inflammatory, chronic and neuropathic pain^{175,176}, and a number of different K_V7.2–7.5 activator chemotypes (**35**, **36**) developed by Bristol Myers Squibb (BMS) have been reported to be effective in diabetic neuropathy and other rodent neuropathic pain models following intravenous administration^{170,177,178}. BMS has also sought patent approval for the use of K_V7.2–7.5 activators for the treatment of migraine pain¹⁷⁹. Interestingly, diclofenac (**37**), an “old” non-steroidal anti-inflammatory drug used clinically to treat inflammation and pain associated with arthritis, activates K_V7.2 channels, as do a number of related compounds (i.e. meclofenamic acid)¹⁸⁰. Structural analogs of diclofenac such as NH6 (**38**), which retain K_V7.2 channel opening activity, but lack cyclooxygenase inhibitory activity, have recently been synthesized¹⁸¹ and may allow assessment of the contribution of K_V7.x opening to the analgesic activity of this class of agents.

Both selective and non-selective K_V7.2/7.3 activators further exhibit efficacy in animal models of neuropsychiatric disorders such as anxiety, ADHD, mania, bipolar disease and schizophrenia¹⁸². Investigators at Neurosearch A/S in Denmark have shown that retigabine and ICA-27243 but not the K_V7.4/7.5 preferring activator BMS-204352 (Maxipost), are effective in an amphetamine and chlordiazepoxide induced hyperactivity model of mania¹⁸³. Similar findings with retigabine were reported by researchers at Lundbeck A/S, who demonstrated in a conditioned avoidance response paradigm model of antipsychotic activity, that retigabine could inhibit avoidance responses, an effect blocked by the K_V7.x inhibitor XE-991¹⁸⁴. Furthermore, retigabine was able to inhibit hyper-locomotor responses in phencyclidine-sensitized animals, which is often considered as a disease model for schizophrenia¹⁸⁴. Lundbeck has reproduced these findings with their own proprietary compounds (**39**)^{185,186}.

While most of the interest in developing K_V7.2–5 activators as therapeutic agents has focused on neurological or psychological disorders, the presence of these channels in bladder and other urologic tissues, in combination with the finding that K_V7.2–7.5 activators can modulate bladder contraction and micturition responses in animal models, has resulted in speculation that these agents may also find utility in the treatment of incontinence and related disorders¹⁸⁷.

K_V10.1 (EAG1)

K_V10.1 (EAG1) gives rise to a slowly activating, non-inactivating K⁺ current in heterologous systems. Abundant message^{12,188,189} and protein¹⁹⁰ are found in the brain, but peripheral tissues show protein expression only in restricted cell populations¹⁸⁸. Paradoxically, the only characterized physiological role of K_V10.1 is in skeletal muscle development, where it is expressed during a limited time window when myoblasts exit the cell cycle and fuse¹⁹¹. Deletion of exon 1 in mice results in a mild increase in sensitivity to seizures, but no more severe phenotype (Menke, H, Dissertation 1998, University Göttingen). Most of the interest in K_V10.1 stems from its expression in up to 70% of tumor cell lines and human cancers, such as colon carcinoma^{192,193} (where amplification of the gene has been detected by FISH in 3.5% cases and correlates with poor prognosis), gastric¹⁹⁴ and mammary tumors¹⁸⁸ and sarcomas¹⁹⁵ (in some of which channel expression also correlates with a poor outcome). Efforts to determine the mechanism underlying this expression pattern have been largely unsuccessful, although it has been reported that K_V10.1 expression is initiated after immortalization by papillomavirus oncogenes¹⁹⁶. K_V10.1 expression might offer an advantage to tumors through increased vascularization and resistance to hypoxia¹⁸. However, this does not explain the observation that the proliferation of cell lines, derived from all mentioned tumor types, is reduced by inhibition of the expression or function of K_V10.1¹⁹⁷. Additionally, K_V10.1

expression appears to also affect cytoskeletal organization, which might influence proliferation and other properties of tumor cells such as migration and metastasis¹⁹⁸.

Two potent blockers of K_V10.1, astemizole (**40**, Fig. 6) and imipramine (**41**) have been shown to decrease tumor cell proliferation *in vitro*, and, in the case of astemizole, also *in vivo*^{195, 199–201}. In mouse models, oral doses of astemizole well below the toxic range reduced the progression of established subcutaneous tumors (melanoma, pancreas and mammary carcinomas) and the frequency of metastasis in lung carcinoma models with a potency comparable to the maximal tolerable dose of the established chemotherapeutic agent cyclophosphamide¹⁸. As is always the case in oncology, only tests in humans will clarify the predictive value of these observations. Additionally, both imipramine and astemizole block also K_V11.1 (hERG) and therefore pose cardiac risks (e.g. Ref.202); in fact, the antihistamine astemizole was withdrawn from the market in 2000 because of this risk. However, as we will describe below for K_V11.1, the risk to benefit ratio for these drugs might need to be reconsidered for repositioning. The inner mouths of K_V10.1 and K_V11.1 are very similar, although not identical²⁰³. Nevertheless, all known K_V10.1 blockers are also effective blockers of K_V11.1 and therefore share their cardiac safety problems. This has prompted the search for biological modulators able to differentiate between the two channel classes. As of yet, no specific peptide toxin has been reported and only a monoclonal antibody (mAb56) specifically blocks K_V10.1 without affecting K_V11.1 or the close relative K_V10.2²⁰⁴. The antibody showed efficacy *in vitro* against several tumor cell lines, and *in vivo* in certain tumor models, but the doses required were high, and the reduction of tumor growth was modest. The experiments were performed in immunodeficient mice, so that the antibody could in principle act exclusively as a channel blocker. Interestingly, the role of K_V10.1 in tumor biology is not exclusively mediated by potassium permeation, since a non-conducting mutant still preserves part of the pro-neoplastic properties of the wild type channel¹⁸.

K_V11.1 (hERG)

K_V11.1 (hERG) plays a crucial role in cardiac repolarization (Fig. 4a), especially in the later phases of the action potential based on its unique kinetics. Upon depolarization, i.e. in the ascending phase of the action potential, K_V11.1 opens rapidly, but potassium flux is quickly terminated by channel inactivation. Upon repolarization, release of inactivation is fast and is followed by slow deactivation. In this way, the channel is active during the depolarization of the action potential and during part of the diastolic phase of the cardiac cycle. In the later phase the potential is set at values where the driving force for potassium is very low, but potassium conductance buffers incoming depolarizations^{202,205}. Thus, K_V11.1 has a pivotal role in setting the duration of the effective refractory period. K_V11.1 mutations cause Long QT syndrome (LQTS) type-2 because deficient K_V11.1 function reduces repolarization and increases the possibility of torsade de pointes, ventricular fibrillation and sudden death^{24,206}. The enormous interest of the pharmaceutical industry in K_V11.1 is due to its involvement in drug-induced or acquired Long QT syndrome (aLQT). K_V11.1 blockers like dofetilide (**42**) have been used for many years as class III antiarrhythmics²⁰⁷. This class of drugs is very efficacious in preventing and reverting atrial fibrillation and flutter, but their intrinsic arrhythmogenic activity largely restricts their use (often to stationary therapies). As mentioned earlier, K_V11.1 can be blocked by a large variety of structurally diverse compounds and regulatory agencies request that all new drug candidates are tested for this possibility.

The large number of compounds identified as channel modulators has made it possible to identify several K_V11.1 activators in recent years (Fig. 6). Of these, six are small molecules (NS1643²⁰⁸, NS3623²⁰⁹ (Neurosearch A/S) RPR260243²¹⁰ (Sanofi-Aventis), PD307243²¹¹ (GlaxoSmithKline) and A935142²¹² (Abbott)), and one is a natural toxin (mallotoxin²¹³). Due to its complex kinetics, the activity of K_V11.1 can be increased by altering activation,

inactivation, or deactivation, and all these properties are actually modified by the various $K_V11.1$ activators. NS1643 (**43**) and NS3623 (**44**) reduce inactivation, RPR260243 (**45**) delays deactivation, while PD307243 (**46**) and A935142 (**47**) alter all three. These activators have two potential therapeutic applications: First, they could be used to rescue aLQT. Additionally, $K_V11.1$ activators could become a novel class of anti-arrhythmics, since they have been reported to reduce electrical heterogeneity in the myocardium and thereby the possibility of re-entry²⁰⁵. However, a recently described cardiac condition exhibiting faster repolarization resulting in a shorter QT interval and therefore termed Short QT (SQTS)²¹⁴, raises concerns about the feasibility of such an anti-arrhythmic approach although experimental models show that shortening of the QT interval appears to pose low risk of arrhythmia²⁰⁵.

Of the 300 different LQT-inducing mutations described in $K_V11.1$, a large fraction results in defective channel trafficking²¹⁵. Interestingly, $K_V11.1$ blockers also increase surface expression. However, there is no direct relationship between channel blocking efficiency and trafficking increase, since compounds that do not block the channels, like thapsigargin or fexofenadine, also increase surface expression²¹⁶. Compounds like these could directly improve membrane targeting of the channel by acting as molecular chaperones. It is therefore conceivable to use modifiers of $K_V11.1$ trafficking to ameliorate LQTS originating from surface expression defects of $K_V11.1$ ²¹⁷.

Besides its relevance in cardiac physiology, relative overexpression of a primate-specific, brain isoform of $K_V11.1$ (*KCNH2-3.I*), which lacks an N-terminal domain crucial for slow deactivation and therefore induces high-frequency, non-adaptive firing patterns in cultured cortical neurons, has recently been linked to an increased risk of schizophrenia²¹⁸. The authors of this study speculate that isoform-specific inhibitors might be useful for the treatment of schizophrenia. $K_V11.1$ has also been extensively characterized in tumors²¹⁹. As discussed for $K_V10.1$, the expression of $K_V11.1$ seems to be required for tumor cell proliferation, and $K_V11.1$ blockers impair the proliferation of tumor cells. $K_V11.1$ also interacts with integrins to regulate survival and migration, and is implicated in the regulation of apoptosis^{220–226}. Thus, available data suggests $K_V11.1$ as a target for cancer therapy, but the concomitant inhibition of IKr would initially seem a severe hurdle for such an approach. Several considerations should be made in this regard. Obviously, the risk/benefit profile of an antioncogenic drug is radically different from that of compounds for the treatment benign conditions. Additionally, there exist at least three alternative transcripts or $K_V11.1$ ^{227,228}, with different expression in the heart and in tumor cells, which opens the possibility to selectively inhibit the channel in tumors while preserving heart function, in a similar way as previously mentioned for schizophrenia.

Finally, it has been recently shown that an anticancer compound (the CDK inhibitor roscovitine), in phase-II clinical trials²²⁹ is actually an efficient blocker of $K_V11.1$, but does not induce arrhythmia, probably due to its low affinity for the closed and inactivated states of the channel. However, $K_V11.1$ inhibition could not only directly contribute to the prevention of tumor progression but might also treat some collateral effects of neoplasia. For example, $K_V11.1$ expression is required for muscle wasting related to inactivity and neoplasia²³⁰ presumably through its role in the activation of massive ubiquitin-dependent protein degradation.

Outlook and challenges of K_V channel drug discovery

Since the cloning of the first K_V channel more than 20 years ago, remarkable progress has been made in our understanding of the diverse physiological and pathophysiological roles of this class of channels. However, due to the difficulties of targeting ion channels in general, medicinal chemistry efforts in this area have considerably lagged behind drug development in the G-protein coupled receptor and the protein kinase field. K_V channel drug discovery is of

course plagued by the same general problems as all other target fields, namely that transgenic approaches can be misleading for target evaluation. Although heterozygous $K_V7.2^{+/-}$ and $K_V7.2$ transgenics, where channel expression was drastically reduced^{231,232}, validated $K_V7.2$ as a target for anticonvulsive therapy, many other transgenic approaches have been disappointing. The reasons for this can be multiple and range from developmental compensation to different physiological roles of a particular K_V channels in different species. Striking examples of the later are the lack of importance of $K_V1.3$ in mouse T cell function (see $K_V1.3$ section) or the different roles of $K_V1.4$, $K_V1.5$, $K_V4.2$ and $K_V4.3$ in the cardiac action potential of different species²³³. Another aspect that has made K_V channel drug discovery difficult is the fact that traditional methods developed for high-throughput screening of ion channels, such as binding assays or voltage-sensitive fluorescent probes, measure ion channel activity indirectly and thus can miss compounds that interact with a particular conformational (gating) state of the channel. Furthermore, these assays can be susceptible to potentially misleading actions of compounds with poor physiochemical properties (i.e. low solubility “sticky” hydrophobic compounds) that can result in the identification of false actives or can miss some truly active compounds [see Box 2 for an overview of screening technologies]. However, with the recent advent of high- or at least medium-throughput electrophysiology, which measures K_V channel function directly and is able to identify state-dependent modulators, this situation is currently changing and pharmaceutical companies and academic screening centers are becoming increasingly successful at identifying potent and selective K_V channel modulators.

The discovery of K^+ channel modulating drugs is also increasingly assisted by structural information. The X-ray structures of K^+ channels in the open and closed states have revolutionized our knowledge about how drugs target K^+ channels and although a co-crystal of the bacterial KcsA channel with tetrabutyl ammonium currently is the only visualized example of a ligand bound in the inner pore of a K^+ channel, results of mutational, electrophysiological, and ligand-binding experiments are increasingly interpreted in structural terms using homology modeling and ligand docking. However, as impressive as this progress has been, true channel structure-based drug design is currently not possible for K_V channel modulators and it is to be hoped that co-crystals for medically important channels such as $K_V1.5$, $K_V7.2$ or $K_V11.1$ with drug molecules bound, will eventually be obtained. At present, it remains a challenge to decide which of the available structures to use for homology modeling since the inner-pore geometry varies substantially between the KcsA, K_VAP and $K_V1.2$ structures⁹. Other critical issues are the possible coexistence of multiple drug-binding modes and the general lack of concepts that include the influence of protein dynamics on high-affinity drug binding. Like all ion channels, K_V channels are “moving targets” that undergo large conformational changes switching between open, closed and inactivated states on a millisecond time scale. These changes in “gating state” are often accompanied by drastic changes in the conformation of drug binding sites resulting in a phenomenon referred to as “state-dependent inhibition”. The possible “trapping” of the channel in one of its many possible conformations is at present impossible to model.

Based on the current status of the K_V channel field, it is to be expected that drugs modulating the channels discussed here ($K_V1.1$, $K_V1.3$, $K_V1.5$, $K_V7.2-7.5$, $K_V10.1$ and $K_V11.1$) will reach the clinic within the next few years. Non-selective K_V channel modulators like Fampridine (4-AP) may have already found a niche in the potential treatment of multiple sclerosis. The $K_V7.2/7.3$ activator retigabine has completed phase-III clinical trials for the treatment of epilepsy and currently represents the most advanced novel K_V channel modulator. Next generation modulators of $K_V7.2/7.3$ channels are only a few years behind retigabine in their development. However, it is also sobering to contemplate, that despite more than 20 years of work no K_V channel modulator specifically designed for a particular target has reached the market yet. Other K_V channels like $K_V2.1$ or $K_V3.4$ may offer attractive therapeutic

opportunities in the future, but need to be explored further before they can be regarded as valid drug targets. It will also be interesting to see whether any repositioning of existing marketed drugs will take place in the K_V channel field. For example, could an “old” drug like clofazimine find new life as a $Kv1.3$ inhibitor-based immunosuppressant? Clearly, development of K_V channel targeting drugs is at an early stage and certainly a challenging endeavor, but the opportunities for future success are extensive.

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References

1. Harmar AJ, et al. IUPHAR-DB: the IUPHAR database of G protein-coupled receptors and ion channels. *Nucleic Acids Res* 2009;37:D680–685. [PubMed: 18948278]
2. Papazian DM, Schwarz TL, Tempel BL, Jan YN, Jan LY. Cloning of genomic and complementary DNA from Shaker, a putative potassium channel gene from *Drosophila*. *Science* 1987;237:749–753. [PubMed: 2441470] Study describing the cloning of the first K_V channel.
3. Long SB, Campbell EB, Mackinnon R. Crystal structure of a mammalian voltage-dependent Shaker family K^+ channel. *Science* 2005;309:897–903. [PubMed: 16002581] First description of the crystal structure of a voltage-gated mammalian K^+ channel with its associated β -subunit.
4. Long SB, Campbell EB, Mackinnon R. Voltage sensor of $Kv1.2$: structural basis of electromechanical coupling. *Science* 2005;309:903–908. [PubMed: 16002579] Companion paper to Ref. 3 describing the structural basis of voltage-sensor and pore-domain coupling.
5. Swartz KJ. Towards a structural view of gating in potassium channels. *Nat Rev Neurosci* 2004;5:905–916. [PubMed: 15550946]
6. Bezanilla F. Ion channels: from conductance to structure. *Neuron* 2008;60:456–468. [PubMed: 18995820]
7. Bezanilla F. How membrane proteins sense voltage. *Nat Rev Mol Cell Biol* 2008;9:323–332. [PubMed: 18354422]
8. Gutman GA, et al. International Union of Pharmacology. LIII Nomenclature and molecular relationships of voltage-gated potassium channels. *Pharmacol Rev* 2005;57:473–508. [PubMed: 16382104]
9. Wulff H, Zhorov BS. K^+ channel modulators for the treatment of neurological disorders and autoimmune diseases. *Chem Rev* 2008;108:1744–1773. [PubMed: 18476673]
10. Chandy KG, et al. Potassium channels as targets for specific immunomodulation. *Trends Pharmacol Sci* 2004;25:280–289. [PubMed: 15120495]
11. Feske S, et al. A mutation in *Orai1* causes immune deficiency by abrogating CRAC channel function. *Nature* 2006;441:179–185. [PubMed: 16582901] Study describing the cloning of CRAC (calcium-release activated Ca^{2+} channel) from patients with a rare form of SCID (severe combined immunodeficiency).
12. Pardo LA, et al. Oncogenic potential of EAG K^+ channels. *EMBO J* 1999;18:5540–5547. [PubMed: 10523298] Study demonstrating the oncogenic potential of $K_V10.1$ and suggesting it as potential target for cancer therapy.
13. Yang S, Zhang JJ, Huang XY. *Orai1* and *STIM1* are critical for breast tumor cell migration and metastasis. *Cancer Cell* 2009;15:124–134. [PubMed: 19185847]
14. Monet M, et al. Lysophospholipids stimulate prostate cancer cell migration via TRPV2 channel activation. *Biochim Biophys Acta* 2009;1793:528–539. [PubMed: 19321128]
15. Hegle AP, Marble DD, Wilson GF. A voltage-driven switch for ion-independent signaling by ether-a-go-go K^+ channels. *Proc Natl Acad Sci USA* 2006;103:2886–2891. [PubMed: 16477030]
16. Feinshreiber L, Singer-Lahat D, Ashery U, Lotan I. Voltage-gated potassium channel as a facilitator of exocytosis. *Ann New York Acad Sci* 2009;1152:87–92. [PubMed: 19161379]

17. Kaczmarek LK. Non-conducting functions of voltage-gated ion channels. *Nat Rev Neurosci* 2006;7:761–771. [PubMed: 16988652]
18. Downie BR, et al. Eag1 expression interferes with hypoxia homeostasis and induces angiogenesis in tumors. *J Biol Chem* 2008;283:36234–36240. [PubMed: 18927085]
19. Hebert SC, Desir G, Giebisch G, Wang W. Molecular diversity and regulation of renal potassium channels. *Physiol Rev* 2005;85:319–371. [PubMed: 15618483]
20. Zhou BY, Ma W, Huang XY. Specific antibodies to the external vestibule of voltage-gated potassium channels block current. *J Gen Physiol* 1998;111:555–563. [PubMed: 9524138]
21. Bruhova I, Zhorov BS. Monte Carlo-energy minimization of correolide in the Kv1.3 channel: possible role of potassium ion in ligand-receptor interactions. *BMC Struct Biol* 2007;7:5. [PubMed: 17261195]
22. Sanchez-Chapula JA, Navarro-Polanco RA, Culberson C, Chen J, Sanguinetti MC. Molecular determinants of voltage-dependent human ether-a-go-go related gene (HERG) K⁺ channel block. *J Biol Chem* 2002;277:23587–23595. [PubMed: 11960982]
23. del Camino D, Holmgren M, Liu Y, Yellen G. Blocker protection in the pore of a voltage-gated K⁺ channel and its structural implications. *Nature* 2000;403:321–325. [PubMed: 10659852]
24. Sanguinetti MC, Tristani-Firouzi M. hERG potassium channels and cardiac arrhythmia. *Nature* 2006;440:463–469. [PubMed: 16554806] Excellent review describing the role of K_V11.1 in arrhythmias.
25. Wuttke TV, Seeböhm G, Bail S, Maljevic S, Lerche H. The new anticonvulsant retigabine favors voltage-dependent opening of the Kv7.2 (KCNQ2) channel by binding to its activation gate. *Mol Pharmacol* 2005;67:1009–1017. [PubMed: 15662042]
26. Zhang ZH, Rhodes KJ, Childers WE, Argentieri TM, Wang Q. Disinactivation of N-type inactivation of voltage-gated K channels by an erbstatin analogue. *J Biol Chem* 2004;279:29226–29230. [PubMed: 15136567]
27. Lu Q, et al. Disruption of Kv1.1 N-type inactivation by novel small molecule inhibitors (disinactivators). *Bioorg Med Chem* 2008;16:3067–3075. [PubMed: 18226531]
28. Dabrowski MA, et al. Ion channel screening technology. *CNS & Neurological Disorders Drug Targets* 2008;7:122–128. [PubMed: 18537641]
29. Coleman SK, Newcombe J, Pryke J, Dolly JO. Subunit composition of Kv1 channels in human CNS. *J Neurochem* 1999;73:849–858. [PubMed: 10428084]
30. Bagetta G, Nistico G, Dolly JO. Production of seizures and brain damage in rats by alpha-dendrotoxin, a selective K⁺ channel blocker. *Neurosci Lett* 1992;139:34–40. [PubMed: 1357602]
31. Smart SL, et al. Deletion of the K(V)1.1 potassium channel causes epilepsy in mice. *Neuron* 1998;20:809–819. [PubMed: 9581771] Study describing that K_V1.1 knock-out induces epilepsy in mice.
32. Brew HM, et al. Seizures and reduced life span in mice lacking the potassium channel subunit Kv1.2, but hypoexcitability and enlarged Kv1 currents in auditory neurons. *J Neurophysiol* 2007;98:1501–1525. [PubMed: 17634333]
33. Zuberi SM, et al. A novel mutation in the human voltage-gated potassium channel gene (Kv1.1) associates with episodic ataxia type 1 and sometimes with partial epilepsy. *Brain* 1999;122:817–825. [PubMed: 10355668]
34. Schulte U, et al. The epilepsy-linked Lgi1 protein assembles into presynaptic Kv1 channels and inhibits inactivation by Kvbeta1. *Neuron* 2006;49:697–706. [PubMed: 16504945]
35. Hogg DS, Ryan R, Kozlowski RZ. Ion channels and protein-protein interactions: novel approaches to mining validated targets. *Drug Discovery⁺ International* 2007;20–22.
36. Lawton G. Potassium channel modulators and uses thereof. *Lectus Therapeutics Limited WO* 28149163. 2008
37. Nashmi R, Fehlings MG. Mechanisms of axonal dysfunction after spinal cord injury: with an emphasis on the role of voltage-gated potassium channels. *Brain Res* 2001;38:165–191.
38. Hayes KC. The use of 4-aminopyridine (fampridine) in demyelinating disorders. *CNS Drug Reviews* 2004;10:295–316. [PubMed: 15592580]

39. Karimi-Abdolrezaee S, Eftekharpour E, Fehlings MG. Temporal and spatial patterns of Kv1.1 and Kv1.2 protein and gene expression in spinal cord white matter after acute and chronic spinal cord injury in rats: implications for axonal pathophysiology after neurotrauma. *Eur J Neurosci* 2004;19:577–589. [PubMed: 14984408]
40. Korenke AR, Rivey MP, Allington DR. Sustained-release fampridine for symptomatic treatment of multiple sclerosis. *Ann Pharmacother* 2008;42:1458–1465. [PubMed: 18780812]
41. Goodman AD, et al. Sustained-release oral fampridine in multiple sclerosis: a randomised, double-blind, controlled trial. *Lancet* 2009;373:732–738. [PubMed: 19249634]
42. Browne DL, et al. Episodic ataxia/myokymia syndrome is associated with point mutations in the human potassium channel gene, KCNA1. *Nature Genetics* 1994;8:136–140. [PubMed: 7842011]
43. Glaudemans B, et al. A missense mutation in the Kv1.1 voltage-gated potassium channel-encoding gene KCNA1 is linked to human autosomal dominant hypomagnesemia. *J Clin Invest* 2009;119:936–942. [PubMed: 19307729] Paper linking Kv1.1 mutations to human hypomagnesemia.
44. DeCoursey TE, Chandy KG, Gupta S, Cahalan MD. Voltage-gated K⁺ channels in human T lymphocytes: a role in mitogenesis? *Nature* 1984;307:465–468. [PubMed: 6320007]
45. Matteson DR, Deutsch C. K channels in T lymphocytes: a patch clamp study using monoclonal antibody adhesion. *Nature* 1984;307:468–471. [PubMed: 6320008]
46. Lin CS, et al. Voltage-gated potassium channels regulate calcium-dependent pathways involved in human T lymphocyte activation. *J Exp Med* 1993;177:637–645. [PubMed: 7679705]
47. Koo GC, et al. Blockade of the voltage-gated potassium channel Kv1.3 inhibits immune responses in vivo. *J Immunol* 1997;158:5120–5128. [PubMed: 9164927]
48. Zhang SL, et al. STIM1 is a Ca²⁺ sensor that activates CRAC channels and migrates from the Ca²⁺ store to the plasma membrane. *Nature* 2005;437:902–905. [PubMed: 16208375]
49. Vig M, et al. CRACM1 is a plasma membrane protein essential for store-operated Ca²⁺ entry. *Science* 2006;312:1220–1223. [PubMed: 16645049]
50. Feske S. Calcium signalling in lymphocyte activation and disease. *Nat Rev Immunol* 2007;7:690–702. [PubMed: 17703229]
51. Wulff H, Beeton C, Chandy KG. Potassium channels as therapeutic targets for autoimmune disorders. *Curr Opin Drug Discovery & Development* 2003;6:640–647.
52. Liu QH, et al. Modulation of Kv channel expression and function by TCR and costimulatory signals during peripheral CD4⁺ lymphocyte differentiation. *J Exp Med* 2002;196:897–909. [PubMed: 12370252]
53. Beeton C, Chandy KG. Potassium channels, memory T cells and multiple sclerosis. *Neuroscientist* 2005;11:550–562. [PubMed: 16282596]
54. Wulff H, et al. The voltage-gated Kv1.3 K⁺ channel in effector memory T cells as new target for MS. *J Clin Invest* 2003;111:1703–1713. [PubMed: 12782673]
55. Beeton C, et al. Kv1.3 channels are a therapeutic target for T cell-mediated autoimmune diseases. *Proc Natl Acad Sci USA* 2006;103:17414–17419. [PubMed: 17088564] Study validating Kv1.3 as a target for the treatment of multiple sclerosis, rheumatoid arthritis and type-1 diabetes.
56. Matheu MP, et al. Imaging of effector memory T cells during a delayed-type hypersensitivity reaction and suppression by Kv1.3 channel block. *Immunity* 2008;29:602–614. [PubMed: 18835197]
57. Wulff H, Pennington M. Targeting effector memory T-cells with Kv1.3 blockers. *Curr Opin Drug Discov Devel* 2007;10:438–445.
58. Markovic-Plese S, Cortese I, Wandinger KP, McFarland HF, Martin R. CD4⁺CD28⁻ costimulation-independent T cells in multiple sclerosis. *J Clin Invest* 2001;108:1185–1194. [PubMed: 11602626]
59. Viglietta V, Kent SC, Orban T, Hafler DA. GAD65-reactive T cells are activated in patients with autoimmune type 1a diabetes. *J Clin Invest* 2002;109:895–903. [PubMed: 11927616]
60. Kivisakk P, et al. Expression of CCR7 in multiple sclerosis: Implications for CNS immunity. *Ann Neurol* 2004;55:627–638. [PubMed: 15122702]
61. Rus H, et al. The voltage-gated potassium channel Kv1.3 is highly expressed on inflammatory infiltrates in multiple sclerosis brain. *Proc Natl Acad Sci USA* 2005;102:11094–11099. [PubMed: 16043714]

62. Beeton C, et al. Selective Blockade of T lymphocyte K⁺ channels ameliorates experimental autoimmune encephalomyelitis, a model for multiple sclerosis. *Proc Natl Acad Sci USA* 2001;98:13942–13947. [PubMed: 11717451]
63. Beeton C, et al. Targeting effector memory T cells with a selective peptide inhibitor of Kv1.3 channels for therapy of autoimmune diseases. *Mol Pharmacol* 2005;67:1369–1381. [PubMed: 15665253]
64. Sullivan JK, et al. Fusion proteins of toxin peptides with linkers and IgG and their use as therapeutic agents. *Amgen WO* 200611616156 . 2006
65. Schmitz A, et al. Design of PAP-1, a Selective Small Molecule Kv1.3 Blocker, for the Suppression of Effector Memory T Cells in Autoimmune Diseases. *Mol Pharmacol* 2005;68:1254–1270. [PubMed: 16099841]
66. Baell JB, et al. Khellinone derivatives as blockers of the voltage-gated potassium channel Kv1.3: synthesis and immunosuppressive activity. *J Med Chem* 2004;47:2326–2336. [PubMed: 15084131]
67. Harvey AJ, Baell JB, Toovey N, Homerick D, Wulff H. A new class of blockers of the voltage-gated potassium channel Kv1.3 via modification of the 4- or 7-position of khellinone. *J Med Chem* 2006;49:1433–1441. [PubMed: 16480279]
68. Azam P, Sankaranarayanan A, Homerick D, Griffey S, Wulff H. Targeting Effector Memory T Cells with the Small Molecule Kv1.3 Blocker PAP-1 Suppresses Allergic Contact Dermatitis. *J Invest Dermatol* 2007;127:1419–1429. [PubMed: 17273162]
69. Ren YR, et al. Clofazimine inhibits human Kv1.3 potassium channel by perturbing calcium oscillation in T lymphocytes. *PLoS ONE* 2008;3:e4009. [PubMed: 19104661]
70. Xu J, et al. The voltage-gated potassium channel Kv1.3 regulates energy homeostasis and body weight. *Hum Mol Gen* 2003;12:551–559. [PubMed: 12588802]
71. Xu J, et al. The voltage-gated potassium channel Kv1.3 regulates peripheral insulin sensitivity. *Proc Natl Acad Sci USA* 2004;101:3112–3117. [PubMed: 14981264] Study suggesting that Kv1.3 is involved in determining peripheral insulin sensitivity and proposing Kv1.3 as a target for the treatment of obesity.
72. Tucker K, Overton JM, Fadool DA. Kv1.3 gene-targeted deletion alters longevity and reduces adiposity by increasing locomotion and metabolism in melanocortin-4 receptor-null mice. *Int J Obes* 2008;32:1222–1232.
73. Lucero MT, Pappone PA. Voltage-gated potassium channels in brown fat cells. *J Gen Physiol* 1989;93:451–472. [PubMed: 2467964]
74. Pappone PA, Ortiz-Miranda SI. Blockers of voltage-gated K channels inhibit proliferation of cultured brown fat cells. *Am J Physiol* 1993;264:C1014–1019. [PubMed: 8476010]
75. Ramirez-Ponce MP, Mateos JC, Carrion N, Bellido JA. Voltage-dependent potassium channels in white adipocytes. *Biochem Biophys Res Commun* 1996;223:250–256. [PubMed: 8670268]
76. Ramirez-Ponce MP, Mateos JC, Bellido JA. Human adipose cells have voltage-dependent potassium currents. *J Membr Biol* 2003;196:129–134. [PubMed: 14724749]
77. Tamkun MM, et al. Molecular cloning and characterization of two voltage-gated K⁺ channel cDNAs from human ventricle. *FASEBJ* 1991;5:331–337.
78. Overturf KE, et al. Cloning and characterization of a Kv1.5 delayed rectifier K⁺ channel from vascular and visceral smooth muscles. *Am J Physiol* 1994;267:C1231–1238. [PubMed: 7977686]
79. Archer SL, et al. Molecular identification of the role of voltage-gated K⁺ channels, Kv1.5 and Kv2.1, in hypoxic pulmonary vasoconstriction and control of resting membrane potential in rat pulmonary artery myocytes. *J Clin Invest* 1998;101:2319–2330. [PubMed: 9616203]
80. Wang Z, Fermini B, Nattel S. Sustained depolarization-induced outward current in human atrial myocytes: evidence for a novel delayed rectifier K⁺ current similar to Kv1.5 cloned channel currents. *Cir Res* 1993;73:1061–1076.
81. Fedida D, et al. Identity of a novel delayed rectifier current from human heart with a cloned K⁺ channel current. *Cir Res* 1993;73:210–216. Ref. 80 and 81 demonstrated that Kv1.5 underlies the atrial specific ultra-rapid delayed rectifier.
82. Wettwer E, et al. Role of IK_{ur} in controlling action potential shape and contractility in the human atrium: influence of chronic atrial fibrillation. *Circulation* 2004;110:2299–2306. [PubMed: 15477405]

83. Brendel J, Peukert S. Blockers of the Kv1.5 channel for the treatment of atrial arrhythmias. *Curr Med Chem* 2003;1:273–287.
84. Tamargo J, Caballero R, Gomez R, Delpon E. I(K_{ur})/Kv1.5 channel blockers for the treatment of atrial fibrillation. *Expert Opin Investig Drugs* 2009;18:399–416.
85. Ford JW, Milnes JT. New drugs targeting the cardiac ultra-rapid delayed-rectifier current (I_{Kur}): rationale, pharmacology and evidence for potential therapeutic value. *J Cardiovas Pharmacol* 2008;52:105–120.
86. Gross MF, et al. Aryl sulfonamido indane inhibitors of the Kv1.5 ion channel. *Bioorg Med Chem Lett* 2007;17:2849–2853. [PubMed: 17350840]
87. Lloyd J, et al. Benzopyran sulfonamides as KV1.5 potassium channel blockers. *Bioorg Med Chem Lett* 2007;17:3271–3275. [PubMed: 17462888]
88. Knobloch K, et al. Electrophysiological and antiarrhythmic effects of the novel I(K_{ur}) channel blockers, S9947 and S20951, on left vs. right pig atrium in vivo in comparison with the I(K_r) blockers dofetilide, azimilide, d,l-sotalol and ibutilide. *Naunyn-Schmiedeberg's Arch Pharmacol* 2002;366:482–487.
89. Wirth KJ, et al. Atrial effects of the novel K⁺-channel-blocker AVE0118 in anesthetized pigs. *Cardiovasc Res* 2003;60:298–306. [PubMed: 14613859]
90. Gogelein H, et al. Effects of the atrial antiarrhythmic drug AVE0118 on cardiac ion channels. *Naunyn-Schmiedeberg's Arch Pharmacol* 2004;370:183–192.
91. Trotter BW, et al. Design and synthesis of novel isoquinoline-3-nitriles as orally bioavailable Kv1.5 antagonists for the treatment of atrial fibrillation. *J Med Chem* 2006;49:6954–6957. [PubMed: 17125248]
92. Lagrutta A, Wang J, Fermini B, Salata JJ. Novel, potent inhibitors of human Kv1.5 K⁺ channels and ultrarapidly activating delayed rectifier potassium current. *J Pharmacol Exp Ther* 2006;317:1054–1063. [PubMed: 16522807]
93. Regan CP, et al. Atrial antifibrillatory effects of structurally distinct I_{Kur} blockers 3-[(dimethylamino)methyl]-6-methoxy-2-methyl-4-phenylisoquinolin-1(2*H*)-one and 2-phenyl-1,1-dipyridin-3-yl-2-pyrrolidin-1-yl-ethanol in dogs with underlying heart failure. *J Pharmacol Exp Ther* 2008;324:322–330. [PubMed: 17967939]
94. Fluxe A, et al. Discovery and synthesis of tetrahydroindolone-derived carbamates as Kv1.5 blockers. *Bioorg Med Chem Lett* 2006;16:5855–5858. [PubMed: 16942878]
95. Wu S, et al. Discovery and in vitro/in vivo studies of tetrazole derivatives as Kv1.5 blockers. *Bioorg Med Chem Lett* 2006;16:6213–6218. [PubMed: 17010606]
96. Eldstrom J, et al. The molecular basis of high-affinity binding of the antiarrhythmic compound vernakalant (RSD1235) to Kv1.5 channels. *Mol Pharmacol* 2007;72:1522–1534. [PubMed: 17872968]
97. Fedida D. Vernakalant (RSD1235): a novel, atrial-selective antifibrillatory agent. *Expert Opin Investig Drugs* 2007;16:519–532.
98. Naccarelli GV, et al. Vernakalant: pharmacology electrophysiology, safety and efficacy. *Drugs Today* 2008;44:325–329. [PubMed: 18548135]
99. Janusz JM, et al. Kv1.5 potassium channel inhibitors Wyeth. US 7504517. 2009
100. Wirth KJ, et al. In vitro and in vivo effects of the atrial selective antiarrhythmic compound AVE1231. *J Cardiovasc Pharmacol* 2007;49:197–206. [PubMed: 17438404]
101. Ehrlich JR, et al. Characterization of human cardiac Kv1.5 inhibition by the novel atrial-selective antiarrhythmic compound AVE1231. *J Cardiovasc Pharmacol* 2008;51:380–387. [PubMed: 18427281]
102. Rivard L, et al. Electrophysiological and atrial antiarrhythmic effects of a novel I_{Kur}/Kv1.5 blocker in dogs. *Heart Rhythm* 2005;2:S180.
103. Shiroshita-Takeshita A, Maltais C, Ford J, Madge D, Nattel S. Electrophysiological and atrial antiarrhythmic effects of a novel I_{KUR}/Kv1.5 blocker in dogs with atrial tachycardia remodeling. *Heart Rhythm* 2005;3:S183–S183.
104. Salinas M, Duprat F, Heurteaux C, Hugnot JP, Lazdunski M. New modulatory alpha subunits for mammalian Shab K⁺ channels. *J Biol Chem* 1997;272:24371–24379. [PubMed: 9305895]

105. Ottschytch N, Raes A, Van Hoorick D, Snyders DJ. Obligatory heterotetramerization of three previously uncharacterized Kv channel alpha-subunits identified in the human genome. *Proc Natl Acad Sci USA* 2002;99:7986–7991. [PubMed: 12060745]
106. Jacobson DA, et al. Kv2.1 ablation alters glucose-induced islet electrical activity, enhancing insulin secretion. *Cell Metabol* 2007;6:229–235.
107. Dai XQ, Kolic J, Marchi P, Sipione S, Macdonald PE. SUMOylation regulates Kv2.1 and modulates pancreatic β -cell excitability. *J Cell Sci* 2009;122:775–779. [PubMed: 19223394]
108. Leung YM, Kwan EP, Ng B, Kang Y, Gaisano HY. SNAREing voltage-gated K^+ and ATP-sensitive K^+ channels: tuning beta-cell excitability with syntaxin-1A and other exocytotic proteins. *Endocr Rev* 2007;28:653–663. [PubMed: 17878408]
109. Zhuang GQ, et al. SNAP-25(1–180) enhances insulin secretion by blocking Kv2.1 channels in rat pancreatic islet beta-cells. *Biochem Biophys Res Commun* 2009;379:812–816. [PubMed: 19103161]
110. Veh RW, et al. Immunohistochemical localization of five members of the Kv1 channel subunits: contrasting subcellular locations and neuron-specific co-localizations in rat brain. *Eur J Neurosci* 1995;7:2189–2205. [PubMed: 8563969]
111. Abbott GW, et al. MiRP2 forms potassium channels in skeletal muscle with Kv3.4 and is associated with periodic paralysis. *Cell* 2001;104:217–231. [PubMed: 11207363]
112. Angulo E, et al. Up-regulation of the Kv3.4 potassium channel subunit in early stages of Alzheimer's disease. *J Neurochem* 2004;91:547–557. [PubMed: 15485486]
113. Pannaccione A, et al. Up-regulation and increased activity of KV3.4 channels and their accessory subunit MinK-related peptide 2 induced by amyloid peptide are involved in apoptotic neuronal death. *Mol Pharmacol* 2007;72:665–673. [PubMed: 17495071]
114. Yu HB, Li ZB, Zhang HX, Wang XL. Role of potassium channels in Abeta(1–40)-activated apoptotic pathway in cultured cortical neurons. *J Neurosci Res* 2006;84:1475–1484. [PubMed: 17022037]
115. Ogita K, et al. In vivo treatment with the K^+ channel blocker 4-aminopyridine protects against kainate-induced neuronal cell death through activation of NMDA receptors in murine hippocampus. *Neuropharmacology* 2005;48:810–821. [PubMed: 15829253]
116. Birnbaum SG, et al. Structure and function of Kv4-family transient potassium channels. *Physiol Rev* 2004;84:803–833. [PubMed: 15269337]
117. Dixon JE, et al. Role of the Kv4.3 K^+ channel in ventricular muscle. A molecular correlate for the transient outward current. *Circ Res* 1996;79:659–668. [PubMed: 8831489]
118. Hohnloser SH, Dorian P, Straub M, Beckmann K, Kowey P. Safety and efficacy of intravenously administered tedisamil for rapid conversion of recent-onset atrial fibrillation or atrial flutter. *J Am Col Cardiol* 2004;44:99–104.
119. Hu HJ, et al. The Kv4.2 potassium channel subunit is required for pain plasticity. *Neuron* 2006;50:89–100. [PubMed: 16600858] Study demonstrating that Kv4.2 channels important for pain plasticity.
120. Jespersen T, Grunnet M, Olesen SP. The KCNQ1 potassium channel: from gene to physiological function. *Physiology* 2005;20:408–416. [PubMed: 16287990]
121. Brown DA, Passmore GM. Neural KCNQ (Kv7) channels. *Br J Pharmacol*. 2009 Epub ahead of print
122. Sanguinetti MC, et al. Coassembly of K(V)LQT1 and minK (IsK) proteins to form cardiac I(Ks) potassium channel. *Nature* 1996;384:80–83. [PubMed: 8900283] Demonstration that Kv7.1 and KCNE1 underlie IKs.
123. Peroz D, et al. Kv7.1 (KCNQ1) properties and channelopathies. *J Physiol (Lond)* 2008;586:1785–1789. [PubMed: 18174212]
124. Duggal P, et al. Mutation of the gene for IsK associated with both Jervell and Lange-Nielsen and Romano-Ward forms of Long-QT syndrome. *Circulation* 1998;97:142–146. [PubMed: 9445165]
125. Belloq C, et al. Mutation in the KCNQ1 gene leading to the short QT-interval syndrome. *Circulation* 2004;109:2394–2397. [PubMed: 15159330]
126. Chen YH, et al. KCNQ1 gain-of-function mutation in familial atrial fibrillation. *Science* 2003;299:251–254. [PubMed: 12522251]

127. Lai L, Su M, Tseng Y, Lien W. Sensitivity of the slow component of the delayed rectifier potassium current (IKs) to potassium channel blockers: implications for clinical reverse use-dependent effects. *J Biomed Sci* 1999;6:251–259. [PubMed: 10420082]
128. Nattel S, Liu L, St-Georges D. Effects of the novel antiarrhythmic agent azimilide on experimental atrial fibrillation and atrial electrophysiologic properties. *Cardiovasc Res* 1998;37:627–635. [PubMed: 9659446]
129. Gerlach U. Blockers of the slowly delayed rectifier potassium IKs channel: potential antiarrhythmic agents. *Curr Med Chem* 2003;1:243–252.
130. Pritchett EL, Marcello SR. Azimilide for atrial fibrillation: clinical trial results and implications. *Card Electrophysiol Rev* 2003;7:215–219. [PubMed: 14739716]
131. Pritchett EL, et al. Antiarrhythmic efficacy of azimilide in patients with atrial fibrillation. Maintenance of sinus rhythm after conversion to sinus rhythm. *Am Heart J* 2006;151:1043–1049. [PubMed: 16644334]
132. Viswanathan MN, Page RL. Pharmacological therapy for atrial fibrillation: current options and new agents. *Expert Opin Investig Drugs* 2009;18:417–431.
133. Gogelein H, Bruggemann A, Gerlach U, Brendel J, Busch AE. Inhibition of IKs channels by HMR 1556. *Naunyn-Schmiedeberg's Arch Pharmacol* 2000;362:480–488.
134. Thomas GP, Gerlach U, Antzelevitch C. HMR 1556, a potent and selective blocker of slowly activating delayed rectifier potassium current. *J Cardiovasc Pharmacol* 2003;41:140–147. [PubMed: 12500032]
135. So PP, Hu XD, Back PH, Puglisi JL, Dorian P. Blockade of IKs by HMR 1556 increases the reverse rate-dependence of refractoriness prolongation by dofetilide in isolated rabbit ventricles. *Br J Pharmacol* 2006;148:255–263. [PubMed: 16565733]
136. Bauer A, et al. The new selective I(Ks)-blocking agent HMR 1556 restores sinus rhythm and prevents heart failure in pigs with persistent atrial fibrillation. *Basic Res Cardiol* 2005;100:270–278. [PubMed: 15795798]
137. Nakashima H, Gerlach U, Schmidt D, Nattel S. In vivo electrophysiological effects of a selective slow delayed-rectifier potassium channel blocker in anesthetized dogs: potential insights into class III actions. *Cardiovasc Res* 2004;61:705–714. [PubMed: 14985067]
138. Lynch JJ Jr, et al. Antiarrhythmic efficacy of selective blockade of the cardiac slowly activating delayed rectifier current, I(Ks), in canine models of malignant ischemic ventricular arrhythmia. *Circulation* 1999;100:1917–1922. [PubMed: 10545437]
139. Busch AE, et al. Positive regulation by chloride channel blockers of IsK channels expressed in *Xenopus* oocytes. *Mol Pharmacol* 1994;46:750–753. [PubMed: 7969055]
140. Magyar J, et al. L-364,373 fails to activate the slow delayed rectifier K⁺ current in canine ventricular cardiomyocytes. *Naunyn-Schmiedeberg's Arch Pharmacol* 2006;373:85–89.
141. Salata JJ, et al. A novel benzodiazepine that activates cardiac slow delayed rectifier K⁺ currents. *Mol Pharmacol* 1998;54:220–230. [PubMed: 9658209]
142. Schroeder BC, et al. A constitutively open potassium channel formed by KCNQ1 and KCNE3. *Nature* 2000;403:196–199. [PubMed: 10646604]
143. Bleich M, Warth R. The very small-conductance K⁺ channel KvLQT1 and epithelial function. *Pflugers Arch* 2000;440:202–206. [PubMed: 10898519]
144. Mall M, et al. Role of K(V)LQT1 in cyclic adenosine monophosphate-mediated Cl⁽⁻⁾ secretion in human airway epithelia. *Am J Respir Cell Mol Biol* 2000;23:283–289. [PubMed: 10970817]
145. Vallon V, et al. KCNQ1-dependent transport in renal and gastrointestinal epithelia. *Proc Natl Acad Sci USA* 2005;102:17864–17869. [PubMed: 16314573]
146. Yasuda K, et al. Variants in KCNQ1 are associated with susceptibility to type 2 diabetes mellitus. *Nature Genetics* 2008;40:1092–1097. [PubMed: 18711367]
147. Boini KM, et al. Enhanced insulin sensitivity of gene targeted mice lacking functional KCNQ1. *Am J Physiol* 2009;296:R1695–1701.
148. Marrion NV. Control of M-current. *Ann Rev Physiol* 1997;59:483–504. [PubMed: 9074774]
149. Biervert C, et al. A potassium channel mutation in neonatal human epilepsy. *Science* 1998;279:403–406. [PubMed: 9430594] Study demonstrating that K_V7.2 mutations cause neonatal epilepsy.

150. Wang HS, et al. KCNQ2 and KCNQ3 potassium channel subunits: molecular correlates of the M-channel. *Science* 1998;282:1890–1893. [PubMed: 9836639] Paper showing that Kv7.2/Kv7.3 heteromultimers underlie the neuronal M current.
151. Schroeder BC, Hechenberger M, Weinreich F, Kubisch C, Jentsch TJ. KCNQ5, a novel potassium channel broadly expressed in brain, mediates M-type currents. *J Biol Chem* 2000;275:24089–24095. [PubMed: 10816588]
152. Kubisch C, et al. KCNQ4, a novel potassium channel expressed in sensory outer hair cells, is mutated in dominant deafness. *Cell* 1999;96:437–446. [PubMed: 10025409]
153. Van Eyken E, et al. KCNQ4: a gene for age-related hearing impairment? *Human Mutation* 2006;27:1007–1016. [PubMed: 16917933]
154. Fontana DJ, Inouye GT, Johnson RM. Linopirdine (DuP 996) improves performance in several tests of learning and memory by modulation of cholinergic neurotransmission. *Pharmacol Biochem Behav* 1994;49:1075–1082. [PubMed: 7886078]
155. Borjesson A, Karlsson T, Adolfsson R, Ronnlund M, Nilsson L. Linopirdine (DUP 996): cholinergic treatment of older adults using successive and non-successive tests. *Neuropsychobiol* 1999;40:78–85.
156. Zaczek R, et al. Two new potent neurotransmitter release enhancers, 10,10-bis(4-pyridinylmethyl)-9(10H)-anthracenone and 10,10-bis(2-fluoro-4-pyridinylmethyl)-9(10H)-anthracenone: comparison to linopirdine. *J Pharmacol Exp Ther* 1998;285:724–730. [PubMed: 9580619]
157. Wickenden AD, Yu W, Zou A, Jegla T, Wagoner PK. Retigabine, a novel anticonvulsant, enhances activation of KCNQ2/Q3 potassium channels. *Mol Pharmacol* 2000;58:591–600. [PubMed: 10953053]
158. Rundfeldt C, Netzer R. The novel anticonvulsant retigabine activates M-currents in Chinese hamster ovary-cells transfected with human KCNQ2/3 subunits. *Neurosci Lett* 2000;282:73–76. [PubMed: 10713399]
159. Main MJ, et al. Modulation of KCNQ2/3 potassium channels by the novel anticonvulsant retigabine. *Mol Pharmacol* 2000;58:253–262. [PubMed: 10908292]
160. Blackburn-Munro G, Dalby-Brown W, Mirza NR, Mikkelsen JD, Blackburn-Munro RE. Retigabine: chemical synthesis to clinical application. *CNS Drug Reviews* 2005;11:1–20. [PubMed: 15867950]
161. Plosker GL, Scott LJ. Retigabine: in partial seizures. *CNS Drugs* 2006;20:601–610. [PubMed: 16800718]
162. Porter RJ, Nohria V, Rundfeldt C. Retigabine. *Neurotherapeutics* 2007;4:149–154. [PubMed: 17199031]
163. French, J.; Mansbach, H. 1200 mg/day retigabine as adjuvantive therapy in adults with refractory partial-onset seizures. American Epilepsy Society Meeting; Seattle, Washington. 2008;
164. Brodie, M.; Mansbach, H. Retigabine 600 or 900 mg/day as adjunctive therapy in adults with partial-onset seizures. American Epilepsy Society Meeting; Seattle, Washington. 2008;
165. Wickenden AD, et al. *N*-(6-chloro-pyridin-3-yl)-3,4-difluoro-benzamide (ICA-27243): a novel, selective KCNQ2/Q3 potassium channel activator. *Mol Pharmacol* 2008;73:977–986. [PubMed: 18089837]
166. Roeloffs R, et al. In vivo profile of ICA-27243 [*N*-(6-chloro-pyridin-3-yl)-3,4-difluoro-benzamide], a potent and selective KCNQ2/Q3 (Kv7.2/Kv7.3) activator in rodent anticonvulsant models. *J Pharmacol Exp Ther* 2008;326:818–828. [PubMed: 18577704]
167. Rigdon, GC. Results of phase I program for ICA-105665, drug candidate for the treatment of epilepsy and neuropathic pain. Antiepileptic Drug Trials X Conference Coral Gables; Florida. 2009.
168. Passmore GM, et al. KCNQ/M currents in sensory neurons: significance for pain therapy. *J Neurosci* 2003;23:7227–7236. [PubMed: 12904483]
169. Gerlach, A.; Stoehr, S.J.; Rigdon, GC. Sub-type selective activation of KCNQ2/3 channels modulates the excitability of nociceptive dorsal root ganglion neurons. Society of Neuroscience Meeting; San Diego, California. 2007;
170. Munro G, Dalby-Brown W. Kv7 (KCNQ) channel modulators and neuropathic pain. *J Med Chem* 2007;50:2576–2582. [PubMed: 17489574]
171. Wickenden AD, McNaughton-Smith G. Kv7 channels as targets for the treatment of pain. *Curr Pharm Des* 2009;15:1773–1798. [PubMed: 19442190]

172. Ilyin, V.; Carlin, KP.; Hodges, DD.; Robeldo, S.; Woodward, RM. Flupirtine: A positive modulator of heteromeric KCNQ2/Q3 channels. Society of Neuroscience Meeting; Orlando, Florida. 2002;
173. Blackburn-Munro G, Jensen BS. The anticonvulsant retigabine attenuates nociceptive behaviours in rat models of persistent and neuropathic pain. *Eur J Pharmacol* 2003;460:109–116. [PubMed: 12559370]
174. Hirano K, et al. Kv7.2–7.5 voltage-gated potassium channel (KCNQ2–5) opener, retigabine, reduces capsaicin-induced visceral pain in mice. *Neurosci Lett* 2007;413:159–162. [PubMed: 17184917]
175. Leventhal, L., et al. Activity of a KCNQ2/3 opener in rat models of inflammatory pain. Society of Neuroscience Meeting; San Diego, California. 2007;
176. Mark, L., et al. Activity of a KCNQ2/3 opener in rat models of neuropathic pain. Society of Neuroscience Meeting; San Diego, California. 2007;
177. Wickenden AD, Roeloffs R, McNaughton-Smith G, Rigdon GC. KCNQ potassium channels: drug targets for the treatment of epilepsy and pain. *Expert Opin Therapeutic Patents* 2004;14:1–13.
178. Wua YJ, Dworetzky SI. Recent developments on KCNQ potassium channel openers. *Curr Med Chem* 2005;12:453–460. [PubMed: 15720253]
179. Dworetzky, SI.; Gribkoff, VK.; Kinney, GG.; Hewawasam, P. 3-Fluoro-2-oxindole modulators of KCNQ potassium channels and use thereof in treating migraine and mechanistically related disease. Bristol-Myers-Squibb Company; US 6855829: 2005.
180. Peretz A, et al. Meclofenamic acid and diclofenac, novel templates of KCNQ2/Q3 potassium channel openers, depress cortical neuron activity and exhibit anticonvulsant properties. *Mol Pharmacol* 2005;67:1053–1066. [PubMed: 15598972]
181. Peretz A, et al. A tale of switched functions: from cyclooxygenase inhibition to M-channel modulation in new diphenylamine derivatives. *PLoS ONE* 2007;2:e1332. [PubMed: 18159230]
182. Hansen HH, et al. Kv7 channels: interaction with dopaminergic and serotonergic neurotransmission in the CNS. *J Physiol (Lond)* 2008;586:1823–1832. [PubMed: 18174210]
183. Redrobe JP, Nielsen AN. Effects of neuronal Kv7 potassium channel activators on hyperactivity in a rodent model of mania. *Behav Brain Res* 2009;198:481–485. [PubMed: 19162078]
184. Sotty F, et al. Antipsychotic-like effect of retigabine [*N*-(2-Amino-4-(fluorobenzylamino)-phenyl) carbamic acid ester], a KCNQ potassium channel opener, via modulation of mesolimbic dopaminergic neurotransmission. *J Pharmacol Exp Ther* 2009;328:951–962. [PubMed: 19098162]
185. Husum Bak-Jensen, H., et al. Use of KCNQ-openers for treating or reducing the symptoms of schizophrenia. H. Lundbeck A/S; WO 27090409: 2007.
186. Bak-Jensen, HH.; Hertel, KP. Use of KCNQ potassium channel openers for reducing symptoms or treating disorders or conditions wherein the dopaminergic system is disrupted. H. Lundbeck A/S; WO 29015667: 2009.
187. Argentieri, TM.; Sheldon, JH. Methods of selecting compounds for modulation of bladder function. Wyeth; US 7160684: 2007.
188. Hemmerlein B, et al. Overexpression of Eag1 potassium channels in clinical tumours. *Mol Can* 2006;5:41.
189. Occhiodoro T, et al. Cloning of a human ether-a-go-go potassium channel expressed in myoblasts at the onset of fusion. *FEBS Lett* 1998;434:177–182. [PubMed: 9738473]
190. Martin S, et al. Eag1 potassium channel immunohistochemistry in the CNS of adult rat and selected regions of human brain. *Neurosci* 2008;155:833–844.
191. Bijlenga P, et al. An ether-a-go-go K⁺ current, ih-eag, contributes to the hyperpolarization of human fusion-competent myoblasts. *J Physiol (Lond)* 1998;512:317–323. [PubMed: 9763622]
192. Ousingsawat J, et al. Expression of voltage-gated potassium channels in human and mouse colonic carcinoma. *Clin Cancer Res* 2007;13:824–831. [PubMed: 17289873]
193. Ding XW, Yan JJ, An P, Lu P, Luo HS. Aberrant expression of ether a go-go potassium channel in colorectal cancer patients and cell lines. *World J Gastroenterol* 2007;13:1257–1261. [PubMed: 17451210]
194. Ding XW, Luo HS, Jin X, Yan JJ, Ai YW. Aberrant expression of Eag1 potassium channels in gastric cancer patients and cell lines. *Med Oncol* 2007;24:345–350. [PubMed: 17873312]

195. Mello de Queiroz F, Suarez-Kurtz G, Stuhmer W, Pardo LA. Ether a go-go potassium channel expression in soft tissue sarcoma patients. *Mol Cancer* 2006;5:42. [PubMed: 17022811]
196. Diaz L, et al. Estrogens and human papilloma virus oncogenes regulate human ether-a-go-go-1 potassium channel expression. *Cancer Res* 2009;69:3300–3307. [PubMed: 19351862]
197. Weber C, et al. Silencing the activity and proliferative properties of the human Eag1 potassium channel by RNAi. *J Biol Chem* 2006;281:13033–13037.
198. Toral C, et al. Effect of extracellular matrix on adhesion, viability, actin cytoskeleton and K⁺ currents of cells expressing human ether a go-go channels. *Life Sci* 2007;81:255–265. [PubMed: 17586530]
199. Gavrilova-Ruch O, et al. Effects of imipramine on ion channels and proliferation of IGR1 melanoma cells. *J Membr Biol* 2002;188:137–149. [PubMed: 12172639]
200. Ouadid-Ahidouch H, et al. Changes in the K⁺ current-density of MCF-7 cells during progression through the cell cycle: Possible involvement of a h-ether. a-gogo K⁺ channel. *Recept Channels* 2001;7:345–356. [PubMed: 11697078]
201. Roy J, Vantol B, Cowley EA, Blay J, Linsdell P. Pharmacological separation of hEAG and hERG K⁺ channel function in the human mammary carcinoma cell line MCF-7. *Oncol Rep* 2008;19:1511–1516. [PubMed: 18497958]
202. Hancox JC, McPate MJ, El Harchi A, Zhang YH. The hERG potassium channel and hERG screening for drug-induced torsades de pointes. *Pharmacol Ther* 2008;119:118–132. [PubMed: 18616963]
203. Gomez-Varela D, et al. Different relevance of inactivation and F468 residue in the mechanisms of hEag1 channel blockage by astemizole, imipramine and dofetilide. *FEBS Lett* 2006;580:5059–5066. [PubMed: 16949586]
204. Gomez-Varela D, et al. Monoclonal antibody blockade of the human Eag1 potassium channel function exerts antitumor activity. *Cancer Res* 2007;67:7343–7349. [PubMed: 17671204]
205. Grunnet M, Hansen RS, Olesen SP. hERG1 channel activators: a new anti-arrhythmic principle. *Prog Biophys Mol Biol* 2008;98:347–362. [PubMed: 19351523]
206. Sanguinetti MC, Jiang C, Curran ME, Keating MT. A mechanistic link between an inherited and an acquired cardiac arrhythmia: HERG encodes the IKr potassium channel. *Cell* 1995;81:299–307. [PubMed: 7736582]
207. Kamath GS, Mittal S. The role of antiarrhythmic drug therapy for the prevention of sudden cardiac death. *Prog Cardiovasc Dis* 2008;50:439–448. [PubMed: 18474286]
208. Hansen RS, et al. Activation of human ether-a-go-go-related gene potassium channels by the diphenylurea 1,3-bis-(2-hydroxy-5-trifluoromethyl-phenyl)-urea (NS1643). *Mol Pharmacol* 2006;69:266–277. [PubMed: 16219910]
209. Hansen RS, et al. Biophysical characterization of the new human ether-a-go-go-related gene channel opener NS3623 [N-(4-Bromo-2-(1H-tetrazol-5-yl)-phenyl)-N'-(3'-trifluoromethylphenyl)urea]. *Mol Pharmacol* 2006;70:1319–1329. [PubMed: 16825484]
210. Kang J, et al. Discovery of a small molecule activator of the human ether-a-go-go-related gene (HERG) cardiac K⁺ channel. *Mol Pharmacol* 2005;67:827–836. [PubMed: 15548764]
211. Zhou J, et al. Novel potent human ether-a-go-go-related gene (hERG) potassium channel enhancers and their in vitro antiarrhythmic activity. *Mol Pharmacol* 2005;68:876–884. [PubMed: 15976038]
212. Su Z, et al. Electrophysiologic characterization of a novel hERG channel activator. *Biochem Pharmacol* 2009;77:1383–1390. [PubMed: 19426677]
213. Zeng H, et al. Mallotoxin is a novel human ether-a-go-go-related gene (hERG) potassium channel activator. *J Pharmacol Exp Ther* 2006;319:957–962. [PubMed: 16928897]
214. Gussak I, Antzelevitch C. Early repolarization syndrome: clinical characteristics and possible cellular and ionic mechanisms. *J Electrocardiol* 2000;33:299–309. [PubMed: 11099355]
215. Anderson CL, et al. Most LQT2 mutations reduce Kv11.1 (hERG) current by a class 2 (trafficking-deficient) mechanism. *Circulation* 2006;113:365–373. [PubMed: 16432067]
216. Zhou Z, Gong Q, January CT. Correction of defective protein trafficking of a mutant HERG potassium channel in human long QT syndrome. *J Biol Chem* 1999;274:31123–31126. [PubMed: 10531299]
217. Dennis A, Wang L, Wan X, Ficker E. hERG channel trafficking: novel targets in drug-induced long QT syndrome. *Biochem Soc Trans* 2007;35:1060–1063. [PubMed: 17956279]

218. Huffaker SJ, et al. A primate-specific, brain isoform of KCNH2 affects cortical physiology, cognition, neuronal repolarization and risk of schizophrenia. *Nat Med* 2009;15:509–518. [PubMed: 19412172] Study showing that overexpression of a primate specific splice variant of Kv11.1 is associated with an increased risk of schizophrenia.
219. Arcangeli A. Expression and role of hERG channels in cancer cells. *Novartis Found Symp* 2005;266:225–232. [PubMed: 16050271]
220. Bianchi L, et al. HERG encodes a K⁺ current highly conserved in tumors of different histogenesis - a selective advantage for cancer cells? *Cancer Res* 1998;58:815–822. [PubMed: 9485040]
221. Cherubini A, et al. HERG potassium channels are more frequently expressed in human endometrial cancer as compared to non-cancerous endometrium. *Br J Cancer* 2000;83:1722–1729. [PubMed: 11104572]
222. Pillozzi S, et al. HERG potassium channels are constitutively expressed in primary human acute myeloid leukemias and regulate cell proliferation of normal and leukemic hemopoietic progenitors. *Leukemia* 2002;16:1791–1798. [PubMed: 12200695]
223. Lastraioli E, et al. hERG1 gene and HERG1 protein are overexpressed in colorectal cancers and regulate cell invasion of tumor cells. *Cancer Res* 2004;64:606–611. [PubMed: 14744775]
224. Masi A, et al. hERG1 channels are overexpressed in glioblastoma multiforme and modulate VEGF secretion in glioblastoma cell lines. *Br J Cancer* 2005;93:781–792. [PubMed: 16175187]
225. Lastraioli E, et al. hERG1 channels in human esophagus: evidence for their aberrant expression in the malignant progression of Barrett's esophagus. *J Cell Physiol* 2006;209:398–404. [PubMed: 16883575]
226. Pillozzi S, et al. VEGFR-1 (FLT-1), beta1 integrin, and hERG K⁺ channel form a macromolecular signaling complex in acute myeloid leukemia: role in cell migration and clinical outcome. *Blood* 2007;110:1238–1250. [PubMed: 17420287]
227. Crociani O, et al. Cell cycle-dependent expression of HERG1 and HERG1B isoforms in tumor cells. *J Biol Chem* 2003;278:2947–2955. [PubMed: 12431979]
228. Guasti L, et al. Identification of a posttranslational mechanism for the regulation of hERG1 K⁺ channel expression and hERG1 current density in tumor cells. *Mol Cell Biol* 2008;28:5043–5060. [PubMed: 18559421]
229. Ganapathi SB, Kester M, Elmslie KS. State-dependent block of HERG potassium channels by Roscovitine: implications for cancer therapy. *Am J Physiol Cell Physiol* 2009;296:C701–710. [PubMed: 19244476]
230. Wang X, et al. Merg1a K⁺ channel induces skeletal muscle atrophy by activating the ubiquitin proteasome pathway. *FASEB J* 2006;20:1531–1533. [PubMed: 16723379]
231. Watanabe H, et al. Disruption of the epilepsy KCNQ2 gene results in neural hyperexcitability. *J Neurochem* 2000;75:28–33. [PubMed: 10854243]
232. Peters HC, Hu H, Pongs O, Storm JF, Isbrandt D. Conditional transgenic suppression of M channels in mouse brain reveals functions in neuronal excitability, resonance and behavior. *Nat Neurosci* 2005;8:51–60. [PubMed: 15608631]
233. Nerbonne JM. Studying cardiac arrhythmias in the mouse - a reasonable model for probing mechanisms? *Trends Cardiovasc Med* 2004;14:83–93. [PubMed: 15121155]
234. Fadool DA, et al. Kv1.3 channel gene-targeted deletion produces "Super-Smeller Mice" with altered glomeruli, interacting scaffolding proteins, and biophysics. *Neuron* 2004;41:389–404. [PubMed: 14766178]
235. Koni PA, et al. Compensatory anion currents in Kv1.3 channel-deficient thymocytes. *J Biol Chem* 2003;278:39443–39451. [PubMed: 12878608]
236. Tytgat J, et al. A unified nomenclature for short-chain peptides isolated from scorpion venoms: alpha-KTx molecular subfamilies. *Trends Pharmacol Sci* 1999;20:444–447. [PubMed: 10542442]
237. MacKinnon R, Miller C. Mutant potassium channels with altered binding of charybdotoxin, a pore-blocking peptide inhibitor. *Science* 1989;245:1382–1385. [PubMed: 2476850]
238. MacKinnon R, Heginbotham L, Abramson T. Mapping the receptor site for charybdotoxin, a pore-blocking potassium channel inhibitor. *Neuron* 1990;5:767–771. [PubMed: 1702643]
239. Chandy KG, et al. Potassium channels in T lymphocytes: toxins to therapeutic immunosuppressants. *Toxicon* 2001;39:1269–1276. [PubMed: 11384714]

240. Swartz KJ, MacKinnon R. Hanatoxin modifies the gating of a voltage-dependent K⁺ channel through multiple binding sites. *Neuron* 1997;18:665–673. [PubMed: 9136774]
241. Swartz KJ. Tarantula toxins interacting with voltage sensors in potassium channels. *Toxicol* 2007;49:213–230. [PubMed: 17097703]
242. Phillips LR, et al. Voltage-sensor activation with a tarantula toxin as cargo. *Nature* 2005;436:857–860. [PubMed: 16094370]
243. Lee SY, MacKinnon R. A membrane-access mechanism of ion channel inhibition by voltage sensor toxins from spider venom. *Nature* 2004;430:232–235. [PubMed: 15241419]
244. Hamill OP, Marty A, Neher E, Sakmann B, Sigworth FJ. Improved patch-clamp techniques for high-resolution current recording from cells and cell-free membrane patches. *Pflugers Arch* 1981;391:85–100. [PubMed: 6270629]
245. Helms LM, et al. Margatoxin binds to a homomultimer of K(V)1.3 channels in Jurkat cells. Comparison with K(V)1.3 expressed in CHO cells. *Biochemistry* 1997;36:3737–3744. [PubMed: 9132027]
246. Felix JP, et al. Identification and biochemical characterization of a novel nortriterpene inhibitor of the human lymphocyte voltage-gated potassium channel, Kv1.3. *Biochemistry* 1999;38:4922–4930. [PubMed: 10213593]
247. Finlayson K, Turnbull L, January CT, Sharkey J, Kelly JS. [³H]dofetilide binding to HERG transfected membranes: a potential high throughput preclinical screen. *Eur J Pharmacol* 2001;430:147–148. [PubMed: 11698075]
248. Hanson DC, et al. UK-78,282, a novel piperidine compound that potently blocks the Kv1.3 voltage-gated potassium channel and inhibits human T cell activation. *Br J Pharmacol* 1999;126:1707–1716. [PubMed: 10372812]
249. Wang K, et al. Validation of an atomic absorption rubidium ion efflux assay for KCNQ/M-channels using the Ion Channel Reader 8000. *Assay Drug Dev Technol* 2004;2:525–534. [PubMed: 15671650]
250. Weaver CD, Harden D, Dworetzky SI, Robertson B, Knox RJ. A thallium-sensitive, fluorescence-based assay for detecting and characterizing potassium channel modulators in mammalian cells. *J Biomol Screen* 2004;9:671–677. [PubMed: 15634793]
251. Wolff C, Fuks B, Chatelain P. Comparative study of membrane potential-sensitive fluorescent probes and their use in ion channel screening assays. *J Biomol Screen* 2003;8:533–543. [PubMed: 14567780]
252. Ghatti A, Guida A, Xu J. Automated voltage-clamp technique. *Methods Mol Biol* 2007;403:59–69. [PubMed: 18827987]
253. Mathes C, Friis S, Finley M, Liu Y. QPatch: the missing link between HTS and ion channel drug discovery. *Combinatorial Chemistry & High Throughput Screening* 2009;12:78–95. [PubMed: 19149494]
254. Korsgaard MP, Strobaek D, Christophersen P. Automated planar electrode electrophysiology in drug discovery: examples of the use of QPatch in basic characterization and high content screening on Na(v), K(Ca)2.3, and K(v)11.1 channels. *Combinatorial Chemistry & High Throughput Screening* 2009;12:51–63. [PubMed: 19149491]
255. Farre C, et al. Port-a-patch and patchliner: high fidelity electrophysiology for secondary screening and safety pharmacology. *Combinatorial Chemistry & High Throughput Screening* 2009;12:24–37. [PubMed: 19149489]
256. Jow F, et al. Validation of a medium-throughput electrophysiological assay for KCNQ2/3 channel enhancers using IonWorks HT. *J Biomol Screen* 2007;12:1059–1067. [PubMed: 18087070]
257. Dale TJ, Townsend C, Hollands EC, Trezise DJ. Population patch clamp electrophysiology: a breakthrough technology for ion channel screening. *Mol Biosyst* 2007;3:714–722. [PubMed: 17882333]
258. Lu Q, An WF. Impact of novel screening technologies on ion channel drug discovery. *Combinatorial Chemistry & High Throughput Screening* 2008;11:185–194. [PubMed: 18336212]
259. Southan A, Clark G. Recent advances in electrophysiology-based screening technology and the impact upon ion channel discovery research. *Methods Mol Biol* 2009;565:187–208. [PubMed: 19551363]

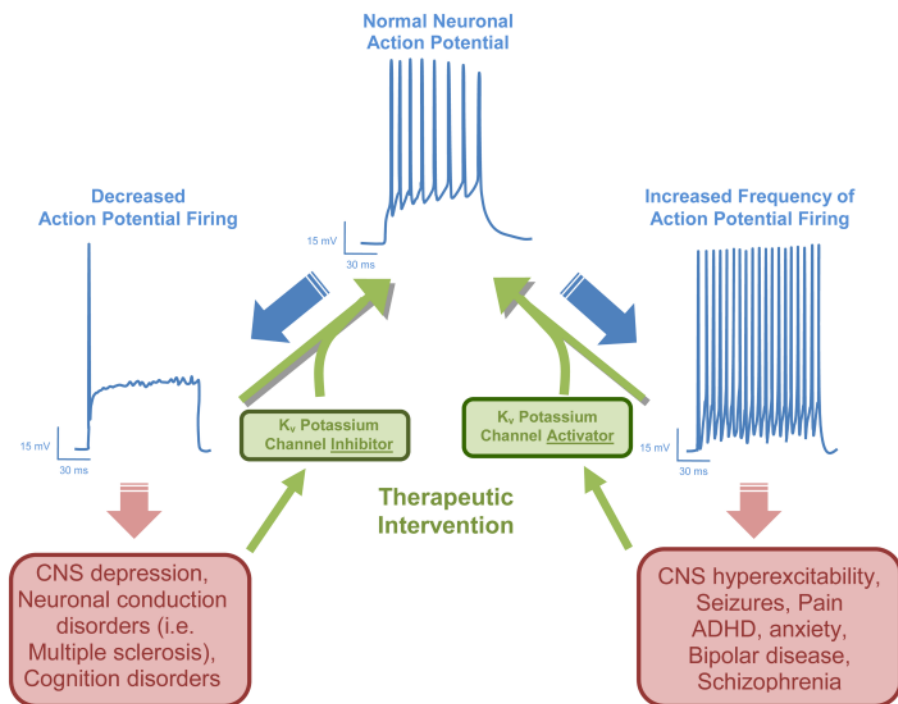


Figure 1. Theoretical effects of K_V channel inhibitors and activators on pathologically altered neuronal activity

Transmission of information within the nervous system is encoded in the frequency of electrical action potential firing in nerve fibers. Pathological changes in action potential firing frequency within the nervous system can lead to a variety of neurological and psychological disorders. Since K_V channels play important roles in defining the action potential waveform, modulators of these channels are expected to have therapeutic utility in these disorders. For example, under conditions where action potential firing is decreased (i.e. depression, cognitive dysfunction) K_V channel blockers should be able to restore normal firing. K_V channel activators in contrast should be useful to reduce pathological hyperexcitability (i.e. epilepsy, pain) by reducing action potential firing.

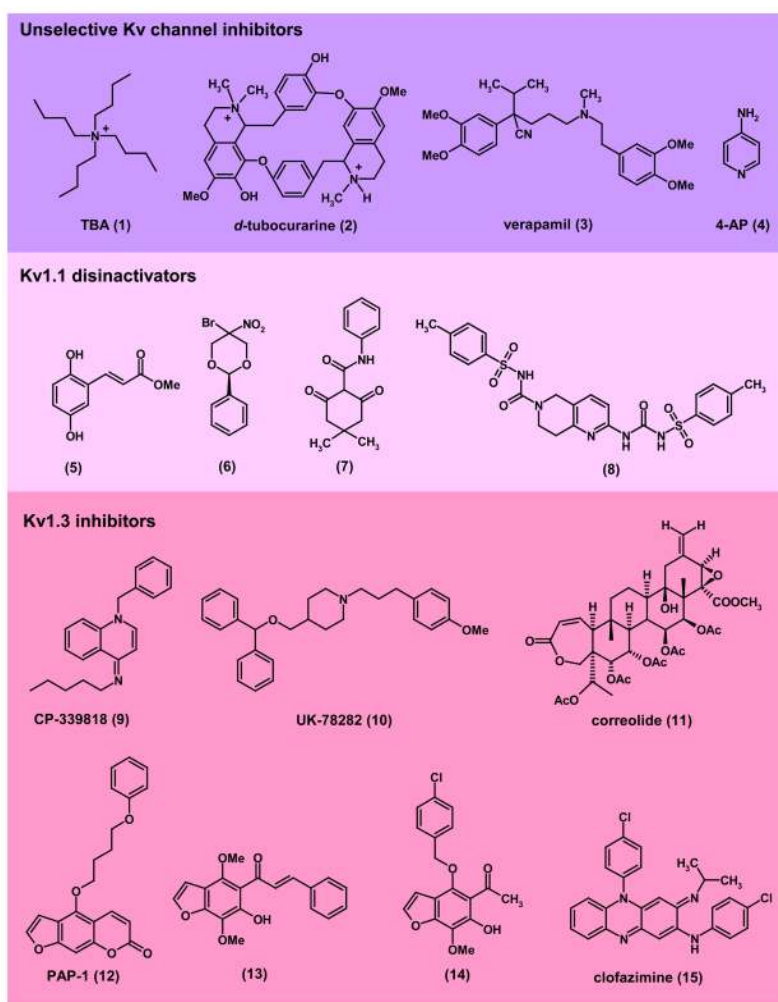


Figure 2. Structures of unselective Kv channel blockers and Kv1-family channel modulators.

Unselective Kv channel inhibitors:

(1), TBA (tetrabutyl ammonium); (2), *d*-tubocurarine; (3), verapamil; (4), 4-AP (4-aminopyridine). 4-AP recently completed Phase-3 clinical trials for multiple sclerosis^{40,41}.

Kv1.1 disinactivators: (5), methyl 2,5-dihydroxycinnamate²⁶; (6), cylohexadione compound-5 (Wyeth)²⁷; (7) 1,3-dione-2-carboxamide compound-2 (Wyeth)²⁷; (8) *N*-tosyl-2-(3-tosylureido)-7,8-dihydro-1,6-naphthyridine-6(5*H*)-carboxamide compound-6 (Lectus Therapeutics)³⁶. Kv1.1 disinactivators prevent seizures in mice and have been suggested for the treatment of epilepsy and pain.

Kv1.3 inhibitors: (9), CP-339818 (Pfizer); (10), UK-78282 (Pfizer); (11), correolide (Merck); (12), PAP-1 (UC Davis)⁶⁵; (13), khellinone chalcone (University of Melbourne)⁶⁶; (14), 4-substituted khellinone (University of Melbourne)⁶⁷; (15), clofazimine⁶⁹. Kv1.3 blockers effectively treat autoimmune disease models in rats and pigs and are therefore regarded as promising new immunosuppressants.

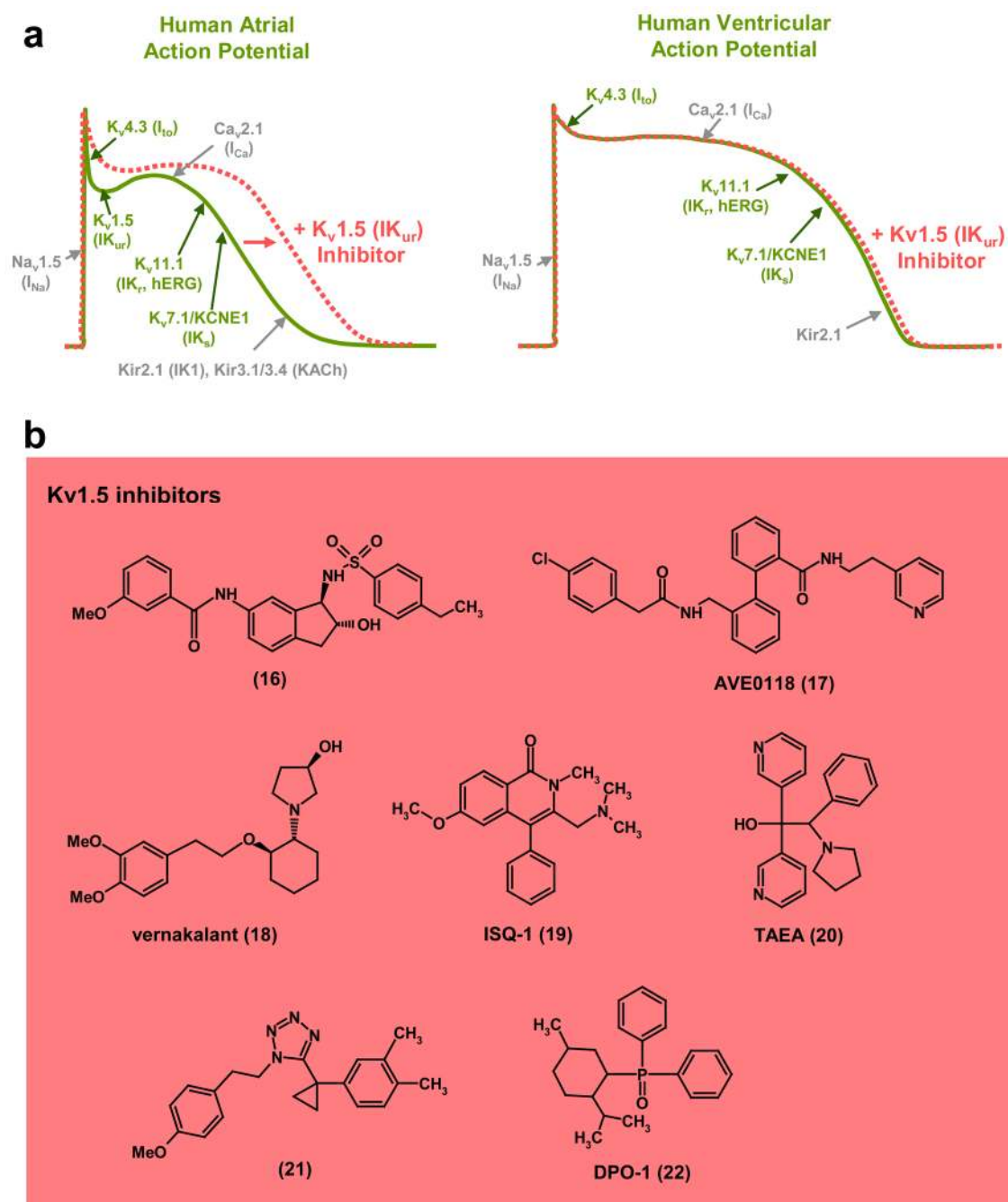


Figure 3. $K_v1.5$ inhibitors as atrial selective antiarrhythmic agents

a, Schematic of a human atrial and ventricular action potential and the underlying ionic conductances (voltage-gated potassium (K_v) channels shown in green; other classes of ion channel shown in grey) that define the waveform. $K_v1.5$ ($I_{K_{ur}}$) is only expressed in atrial myocytes and $K_v1.5$ blockers therefore selectively prolong the action potential duration in the atrium. **b**, **Structures of $K_v1.5$ inhibitors**: (16), arylsulphonamidoindane (Icagen/Lilly)⁸⁶; (17), AVE0118 (Sanofi-Aventis)^{89,90}; (18), vernakalant (Cardiome)^{96,97}; (19), ISQ-1 (Merck)⁹³; (20), TAEA (Merck)⁹³; (21), tetrazole derivative (Procter & Gamble)⁹⁵; (22), DPO-1 (Merck)⁹². Several $K_v1.5$ blockers have been or are in clinical trials for the treatment of atrial fibrillation.

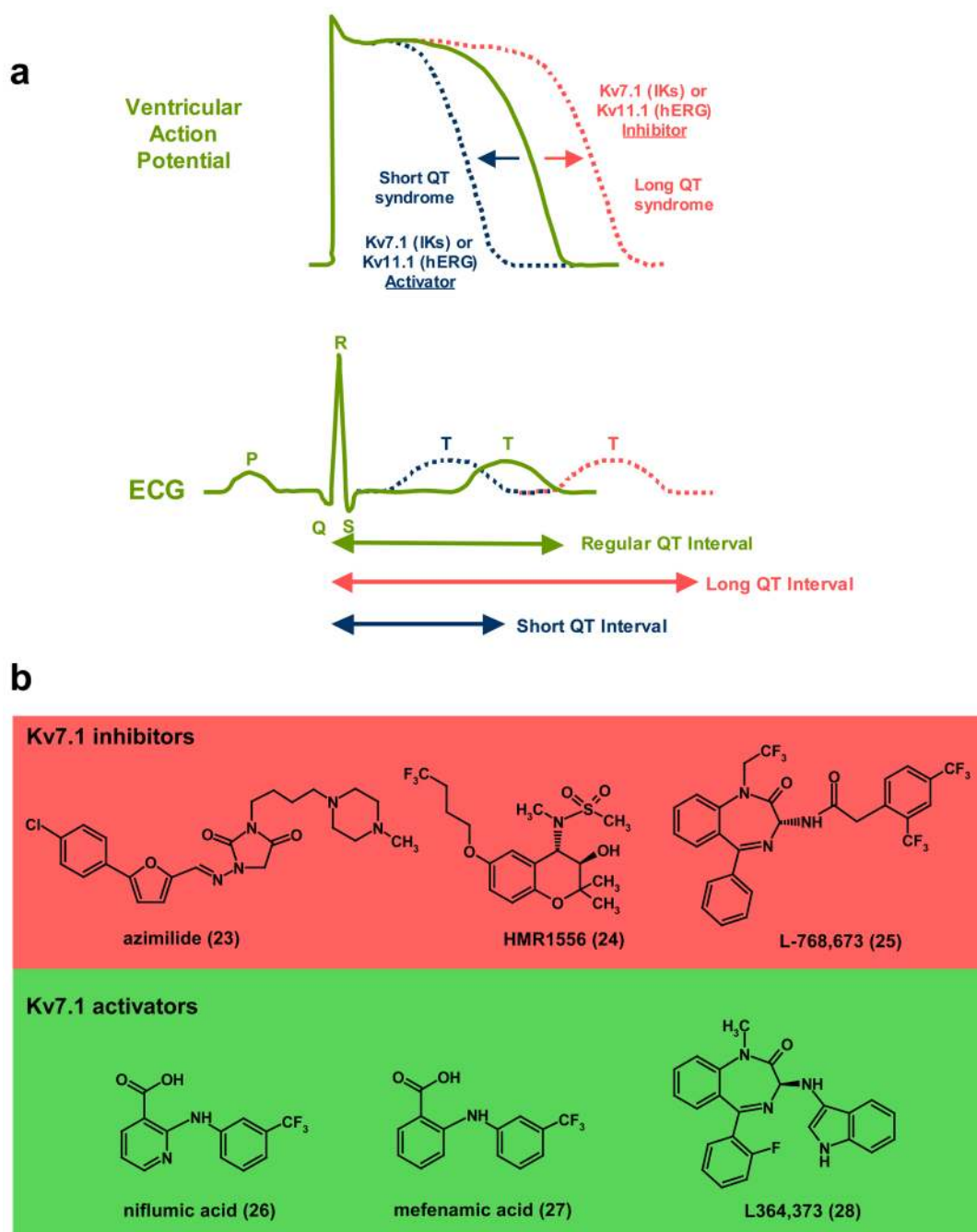
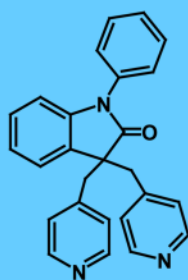
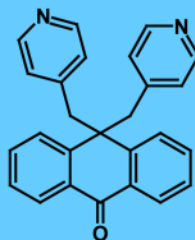


Figure 4. $K_V7.1$ and $K_V11.1$ are crucial for determining the length of the cardiac action potential
a, Illustration of ventricular action potential (AP) and electrocardiogram (ECG) showing effects of Long- and Short-QT syndrome as well as pharmacological modulators of $K_V7.1$ (IKs) or $K_V11.1$ (hERG) on AP duration and length of QT interval. Inhibition of $K_V7.1$ and $K_V11.1$ produces prolongation of ventricular AP duration which is similar to what occurs in acquired or hereditary Long QT syndrome. Activators of $K_V7.1$ or $K_V11.1$ reduce the duration of cardiac action potential which is manifested as a shorter QT interval **b**, ***K_V7.1 inhibitors:*** (23), azimilide (Procter & Gamble)^{128,129}; (24), HMR1556 (Sanofi-Aventis)¹³⁴; (25), L768,673 (Merck)¹³⁸. Azimilide has been shown to reduce atrial fibrillation (AF) in clinical

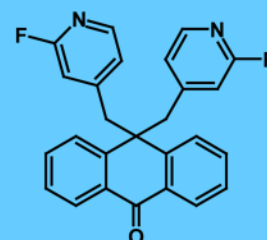
trials^{128,129}, while HMR1556 and L768,673 are effective in dog models of AF. **K_v7.1 activators: (26)**, niflumic acid¹³⁹; **(27)**, mefenamic acid¹³⁹; **(28)**, L384,373 (Merck)¹⁴¹.

Kv7.2-7.5 inhibitors

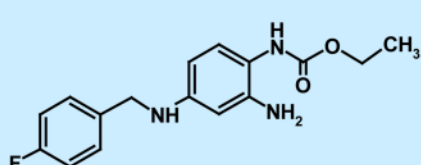
linopirdine (29)



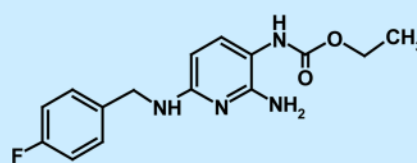
XE-991 (30)



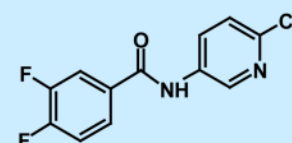
DMP-543 (31)

Kv7.2-7.5 activators

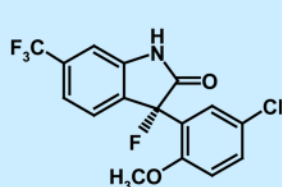
retigabine (32)



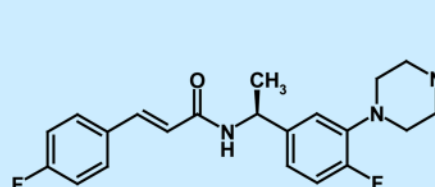
flupirtine (33)



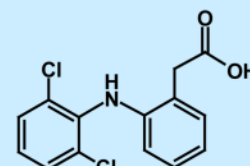
ICA-27243 (34)



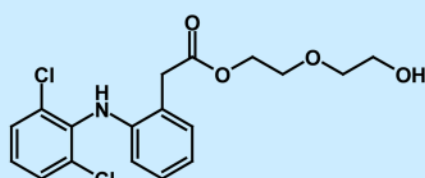
Maxiprost/BMS-204352 (35)



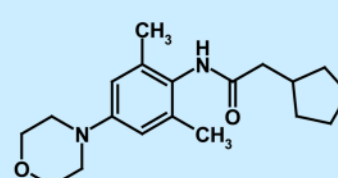
(36)



diclofenac (37)



NH6 (38)



(39)

Figure 5. Structures of Kv7.2–7.5 channel modulators

Kv7.2–7.5 inhibitors: (29), linopirdine¹⁵⁴; (30), XE-991¹⁵⁶; (31), DMP-543¹⁵⁶. Kv7 channel activators had been proposed to improve learning and memory but failed in clinical trials. **Kv7.2–7.5 activators:** (32), retigabine (Valeant/GSK)^{157–159}; (33), flupirtine^{173,174}; (34), ICA-27243 (Icagen)^{165,166}; (35), Maxiprost/BMS-204352^{170,178}; (36), acrylamide compound-24 (BMS)^{170,178}; (37), diclofenac¹⁸⁰; (38), NH6 (Tel-Aviv University)¹⁸¹; (39), 2-cyclopentyl-*N*-(2,6-dimethyl-4-morpholin-4-yl-phenyl)-acetamide (Lundbeck)^{185,186}. Kv7.2/7.3 activators are effective anticonvulsants in rodent models and clinical trials and have been proposed for the treatment of neuropathic pain, anxiety disorders, mania, migraine, ADHD and schizophrenia based on rodent data.

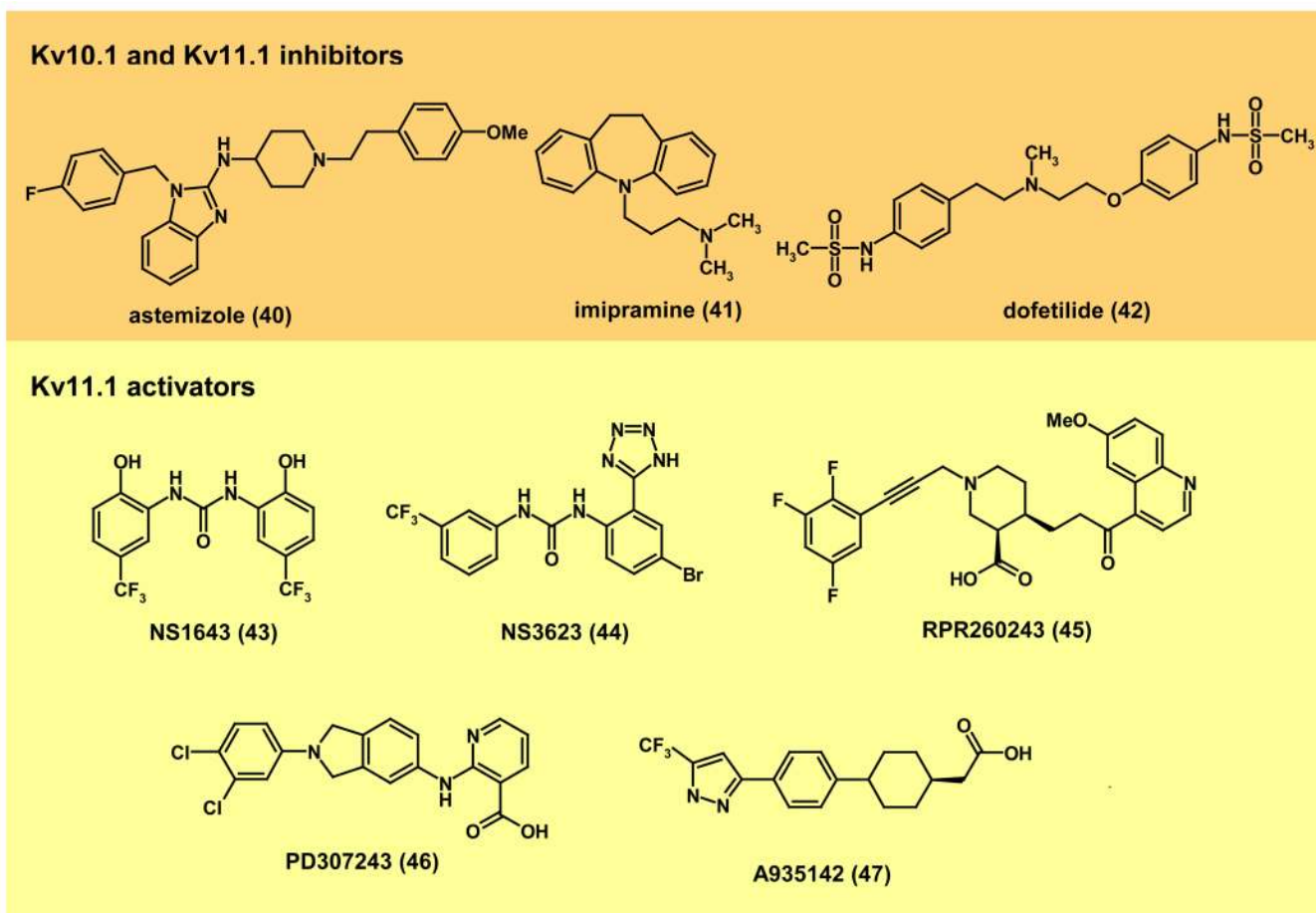


Figure 6. Modulators of $K_v10.1$ and $K_v11.1$

$K_v10.1$ and $K_v11.1$ inhibitors: (40), astemizole^{199–202}; (41), imipramine¹⁹⁹; (42) dofetilide. $K_v10.1$ inhibitors have been proposed for the treatment of cancer^{9,179}. $K_v11.1$ (hERG) inhibitors prolong the QT interval and can be both antiarrhythmic and proarrhythmic (e.g. recall of the antihistamine astemizole). **$K_v11.1$ activators:** (43) NS1643 (Neurosearch)²⁰⁸; (44) NS3623 (Neurosearch)²⁰⁹; (45), RPR260243 (Sanofi-Aventis)²¹⁰; (46), PD307243 (GlaxoSmithKline)²¹¹; (47), A935143 (Abbott Laboratories)²¹². $K_v11.1$ activators have been proposed as potential antiarrhythmics²⁰⁵.

Table 1

Major expression, known channelopathies, phenotypes of transgenic mice and therapeutic significance of the 40 K_V channels.

Channel	Expression	Channelopathy	Phenotype transgenic mice	Therapeutic Significance
$K_V1.1$ (KCNA1)	CNS (medulla, pons, cerebellum, midbrain, hippocampus, auditory nuclei), Node of Ranvier Kidney	Missense mutations cause episodic ataxia ³³ and primary hypomagnesemia ⁴³	$K_V1.1^{-/-}$: epilepsy with spontaneous seizures ³¹ ; hyperalgesia; fail to follow high-frequency amplitude-modulated sound	$K_V1.1$ disinactivators reduce PTZ induced seizures ²⁷ ; suggested for epilepsy and neuropathic pain; $K_V1.1$ blockers in clinical trials for MS ^{40,41} and spinal cord injury ³⁸
$K_V1.2$ (KCNA2)	CNS (pons, medulla, cerebellum, hippocampus, thalamus, cerebral cortex), spinal cord	Not reported	$K_V1.2^{-/-}$: die on P17 from generalized seizures ³² ; reduced NREM sleep	$K_V1.2$ activators or disinactivators might be useful for seizure disorders
$K_V1.3$ (KCNA3)	T and B cells, macrophages, microglia, osteoclasts, platelets, CNS (prominent in olfactory bulb), testis	Variant in the promoter associated with impaired glucose tolerance and lower insulin sensitivity	$K_V1.3^{-/-}$: increase sense of smell ("Supersmellers") ²³⁴ , increased insulin sensitivity, lower bodyweight ^{70 71} [no immune phenotype ²³⁵]	$K_V1.3$ blockers preferentially inhibit $CCR7^{-}$ effector memory T cells ⁵⁴ , treat rat models of MS, RA, type-1 diabetes ⁵⁵ , contact dermatitis ⁶⁸ and periodontal bone resorption
$K_V1.4$ (KCNA4)	CNS (olfactory bulb, corpus striatum, hippocampus), heart, skeletal and smooth muscle, pancreatic islets	Not reported	$K_V1.4^{-/-}$: occasionally spontaneous seizures; no changes in cardiac I_{to}	Not determined
$K_V1.5$ (KCNA5)	cardiac myocytes (I_{Kur}), CNS (hippocampus, cortex, pituitary), microglia, Schwann cells, macrophages vascular smooth muscle	No human mutations reported; $K_V1.5$ expression reduced in chronic AF	$K_V1.5^{-/-}$: no LPS induced NO release in microglia SWAP mice (m $K_V1.5$ replaced with r $K_V1.1$): resistant to drug-induced prolongation of QT interval	$K_V1.5$ blockers in development as anti-arrhythmics for atrial fibrillation (AF) ⁸⁵
$K_V1.6$ (KCNA6)	Spinal cord, CNS, oligodendrocyte progenitor cells, astrocytes, pulmonary artery smooth muscle	Not reported	$K_V1.6^{-/-}$ mice commercially available; phenotype not characterized	Not determined
$K_V1.7$ (KCNA7)	Heart, skeletal muscle, liver, lung, placenta, CNS	Not reported	$K_V1.7^{-/-}$ mice commercially available; phenotype not characterized	Might be a target for atrial fibrillation similar to $K_V1.5$
$K_V1.8$ (KCNA10)	Kidney, CNS, heart, skeletal muscle	Not reported	Not reported	Not determined
$K_V2.1$ (KCNB1)	CNS (cerebral cortex, hippocampus, cerebellum), pancreatic beta cells, insulinomas, gastric cancer cell	Not reported	$K_V2.1^{-/-}$: reduced fasting blood glucose levels and elevated serum insulin levels ¹⁰⁶	$K_V2.1$ blockers suggested as hypoglycemic agents for type-2 diabetes
$K_V2.2$ (KCNB2)	CNS (olfactory bulb, cortex, hippocampus, cerebellum), pancreatic delta cells	Not reported	Not reported	Not determined
$K_V3.1$ (KCNC1)	CNS (cerebellum, substantia nigra, cortical and hippocampal interneurons, inferior colliculi, cochlear and vestibular nuclei), skeletal muscle, mouse $CD8^{+}$ T cells	Not reported	$K_V3.1^{-/-}$: reduced body weight, impaired motor skills, sleep loss [K _V 3.1/K _V 3.3 double knockout: severe myoclonus and hypersensitivity to ethanol]	Not determined
$K_V3.2$ (KCNC2)	CNS (fast spiking GABAergic interneurons), pancreatic islets, Renshaw cells (spinal interneurons), pancreatic beta cells	Not reported	$K_V3.2^{-/-}$: Alterations in cortical electroencephalographic patterns and increased seizure susceptibility	Not determined
$K_V3.3$ (KCNC3)	CNS (brainstem, cerebellum, forebrain, Purkinje cells, motoneurons, auditory brainstem)	Missense mutations cause SCA13 (spinocerebellar ataxia 13)	$K_V3.1/K_V3.3$ double knockout: severe myoclonus and hypersensitivity to ethanol ($K_V3.3^{-/-}$: no overt phenotype)	Not determined
$K_V3.4$ (KCNC4)	CNS (brainstem, hippocampal granule cells), skeletal muscle	Missense mutation in the beta-subunit KCNE3 (MiRP2) causes periodic paralysis ¹¹¹	Not reported	$K_V3.4$ blockers suggested for Alzheimer's disease ^{112,113}

Channel	Expression	Channelopathy	Phenotype transgenic mice	Therapeutic Significance
K_v4.1 (KCND1)	CNS, heart, liver, kidney, thyroid gland, pancreas	Not reported	Not reported	Not determined
K_v4.2 (KCND2)	CNS (cerebellum, hippocampus, thalamus, forebrain, dorsal horn neurons), heart [rodents]	Truncation mutations cause temporal lobe epilepsy	K _v 4.2 ^{-/-} : Enhanced sensitivity to tactile and thermal stimuli; I _{to,f} eliminated [in mice I _{to,f} is a heteromultimer of K _v 4.2 and K _v 4.3]	K _v 4.2 activators might be useful for inflammatory pain ¹¹⁹
K_v4.3 (KCND3)	Heart, CNS (cortex, cerebellum), atrial and ventricular myocytes (I _{to}) smooth muscle	Not reported	Not reported	K _v 4.3 blockers might be useful as antiarrhythmics [in humans I _{to,f} is a K _v 4.3 homotetramer ¹¹⁷]
K_v5.1 (KCNF1)				
K_v6.1 (KCNG1)				
K_v6.2 (KCNG2)				
K_v6.3 (KCNG3)				
K_v6.4 (KCNG4)				
K_v7.1 (KCNQ1)	Heart, ear, skeletal muscle, liver, epithelia in kidney, lung, gastrointestinal tract	Loss-of-function mutations lead to Type 1 Long QT Syndrome ¹²³ or Jervell and Lange-Nielsen Syndrome ¹²⁴ ; Gain-of-function mutations lead to Familial Atrial Fibrillation ¹²⁶ , short QT Syndrome ¹²⁵ or type-2 diabetes mellitus ¹⁴⁶	K _v 7.1 ^{-/-} mice are deaf and have abnormal cardiac ECG T- and P-wave morphologies and prolongation of QT interval	K _v 7.1 inhibitors in development for treating atrial arrhythmias ¹³⁴ K _v 7.1 openers suggested for treatment of Long QT syndrome
K_v7.2 (KCNQ2)	CNS (hippocampus, cortex, thalamus, cerebellum, brain stem, nodes of Ranvier); sympathetic and dorsal root ganglia	Loss of function mutations lead to benign familial neonatal convulsions (BFNC) ¹⁴⁹	Homozygous (K _v 7.2 ^{-/-}) die within a few hours after birth; heterozygous K _v 7.2 ^{+/-} mice show hypersensitivity to pentylenetetrazole induced seizures	K _v 7.2/7.3 inhibitors historically developed for treatment of learning and memory disorders ^{154, 155}
K_v7.3 (KCNQ3)	CNS (hippocampus, cortex, thalamus, cerebellum, brain stem), nodes of Ranvier; sympathetic and dorsal root ganglia	Loss of function mutations lead to benign familial neonatal convulsions (BFNC)	Mouse models of human K _v 7.3 (and K _v 7.2/7.3) mutations for BFNC exhibit seizures	K _v 7.2/7.3 activators in development for the treatment of epilepsy ^{160,162,166} and pain ¹⁶⁸ . Suggested for treatment of migraine, ADHD, bipolar disease, schizophrenia ¹⁸² and bladder contractility disorders
K_v7.4 (KCNQ4)	Outer hair cells and neurons of auditory system, vascular smooth muscle	Loss of function mutations leading to deafness autosomal dominant 2a (DFNA2A) ^{152, 153}	K _v 7.4 ^{-/-} mice have a degenerative loss of outer hair cells and accompanying loss of hearing	K _v 7.4 activators may have therapeutic utility in the treatment of hearing disorders
K_v7.5 (KCNQ5)	CNS (hippocampus, cortex, thalamus), skeletal muscle, vascular smooth muscle	Not reported	Phenotype not reported	Not determined
K_v8.1 (KCNV1)				
K_v8.2 (KCNV2)				
K_v9.1 (KCNS1)				
K_v9.2 (KCNS2)				
K_v9.3 (KCNS3)				
K_v10.1 (KCNH1, eag-1)	CNS	Aberrantly expressed in cancer ^{12,188}	Slight tendency to seizures	K _v 10.1 inhibitors for cancer ²⁰⁴
K_v10.2 (KCNH5, eag-2)	CNS, muscle, heart, placenta, lung, liver, kidney, pancreas	Not reported	Not reported	Not determined
K_v11.1 (KCNH2, erg-1, HERG)	Heart, CNS, endocrine cells, lymphocytes	K _v 11.1 mutations cause Type 2 LQT ^{24,206}	Paroxysmic bradycardia (HERGB); N629D lethal due to cardiac malformation	K _v 11.1 blockers suggested for arrhythmia (liability for drug-induced LQT) and cancer treatment
K_v11.2 (KCNH6, erg-2)	CNS, endocrine cells	Not reported	Not reported	None reported
K_v11.3 (KCNH7, erg-3)	CNS	Not reported	Not reported	None reported
K_v12.1 (KCNH8, elk-1)	CNS	Not reported	Not reported	None reported
K_v12.2 (KCNH3, elk-2)	CNS	Not reported	Not reported	None reported
K_v12.3 (KCNH4, elk-3)	CNS	Not reported	Not reported	None reported

For a complete reference list containing gene and protein accession numbers, chromosomal location, splice variants, expression, physiological role, mutations and pharmacology please see the IUPHAR database of voltage-gated potassium channels at <http://www.iuphar-db.org/PRODIC/FamilyMenuForward?familyId=16>