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Voltage gated sodium channels as drug discovery targets

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Abbreviations: Na_V, Voltage-gated sodium channel; TTX, Tetrodotoxin; TTX-S, Tetrodotoxin sensitive; TTX-R, Tetrodotoxin resistant; PEPD, Paroxysmal extreme pain disorder; CIP, Congenital insensitivity to pain; FDA, Food and Drug Administration.

Voltage-gated sodium (Na_V) channels are a family of transmembrane ion channel proteins. They function by forming a gated, water-filled pore to help establish and control cell membrane potential *via* control of the flow of ions between the intracellular and the extracellular environments. Blockade of Na_Vs has been successfully accomplished in the clinic to enable control of pathological firing patterns that occur in a diverse range of conditions such as chronic pain, epilepsy, and cardiac arrhythmias. First generation sodium channel modulator drugs, despite low inherent subtype selectivity, preferentially act on over-excited cells which reduces undesirable side effects in the clinic. However, the limited therapeutic indices observed with the first generation demanded a new generation of sodium channel inhibitors. The structure, function and the state of the art in sodium channel modulator drug discovery are discussed in this chapter.

Voltage-gated sodium (Na_V) channels are crucial in the initiation and propagation of electrical signals (action potentials) in excitable neuronal cells, muscles, and heart tissues. This has led to the successful clinical exploitation of Na_V channel inhibitors as anticonvulsants, antiarrhythmics and local anesthetics e.g. lamotrigine, flecainide and lidocaine.[1-3] The Na_V channel family has nine members ($Na_V1.1$ to $Na_V1.9$) with a high degree of sequence homology between the nine subtypes. A number of natural toxins such as tetrodotoxin (TTX) block the sodium channel extracellular pore, and the sensitivity of the sodium channel subtypes to blockade by TTX has been used to divide the family into two classes: (i) TTX-S (sensitive), TTX $IC_{50}<30$ nM against $Na_V1.1$, 1.2, 1.3, 1.4, 1.6, 1.7 and (ii) TTX-R (resistant), TTX IC_{50} >30 nM against $Na_V1.5$, 1.8 and $Na_v1.9$. The selectivity difference is believed to be explained by the presence of a key cysteine residue in the TTX binding site.[4] The Na_X channel has also been classified as a subtype of voltage-gated sodium channels although the primary structure of Na_X is markedly different from the other Na_V channels. Na_X is thought to have a physiological role in maintaining body fluid homeostasis through the regulation of sodium concentration (**Table 1**).

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Structure and Function

Na_V channels are heteromeric complexes comprised of an α subunit, having an approximate mass of 260 kDa, and one or more β subunits of lower molecular weight (**Fig. 1**). Each α subunit has four homologous domains (D1–D4), with each domain containing six transmembrane segments (S1–S6). The S4 segment of each domain contains positively charged arginine and lysine residues which allow them to act as voltage sensors of cell membrane depolarisation and repolarisation. In combination, the S5 and S6 transmembrane helices from each domain form the sodium channel pore and the p-loop creates the Na^+ ion selectivity filter. **Figure 1** shows a 3-dimensional representation of a voltage-gated sodium channel and highlights common regions that have been reported to support ligand binding.[4] A significant proportion of this evidence has been gathered via site directed mutagenesis. However, there are now several published apo crystal structures of bacterial Na_V channels that highlight key structural features.[4-8] Moreover, the first co-crystal structures of ligands bound in a Na_V channel have been recently generated.[9]

Na_V channels exist in essentially three states: open, closed (resting) and inactivated (**Fig. 2**). Under resting membrane potential the channels are in their non-conducting closed state. Upon depolarization (decrease in membrane voltage) it is believed that the S4 voltage sensors move outward, allowing the pore to open briefly (<1 millisecond), before several processes termed fast and slow inactivation occur that move the channel into a non-conducting inactivated state. The inactivation gate between D3 and D4 is thought to be responsible for fast inactivation. Upon cell membrane hyperpolarisation (increase in membrane voltage) the sodium

Table 1. Sodium channel distribution and classification based on sensitivity to tetrodotoxin (TTX) block

Type	Type Symbol	Primary Tissue	TTX Sensitivity
NaV1.1	SCN1a	CNS, PNS	+
NaV1.2	SCN2a	CNS, PNS	+
NaV1.3	SCN3a	CNS, PNS	+
NaV1.4	SCN4a	skeletal muscle	+
NaV1.5	SCN5a	heart	—
NaV1.6	SCN8a	CNS, PNS	+
NaV1.7	SCN9a	PNS	+
NaV1.8	SCN10a	PNS	—
NaV1.9	SCN11a	PNS	—
NaX	SCN7a	Glia	NA

CNS or PNS = central or peripheral nervous system.
Useful websites for clinical trial information 101 http://clinicaltrials.gov/.

channel is reprimed back into the resting state ahead of the next depolarization. Many Na_V channel blockers have different affinities for each state, often with a preference for the open and/or inactivated state. Since the proportion of channels populating different states is controlled by cell membrane voltage, this **state dependence** is also termed voltage dependence. Many compounds additionally demonstrate a phenomenon called **use dependence** which occurs when the compound potency increases upon higher Na_V channel firing frequency stimulation. As damaged nerve Na_V channels move more rapidly through the three states than a sodium channel in the heart, this phenomenon has been exploited to preferentially target diseased cells and derive an improved therapeutic index over cardiovascular side effects. The improved therapeutic index is accomplished because use dependence imparts functional selectivity over sodium channels in heart.

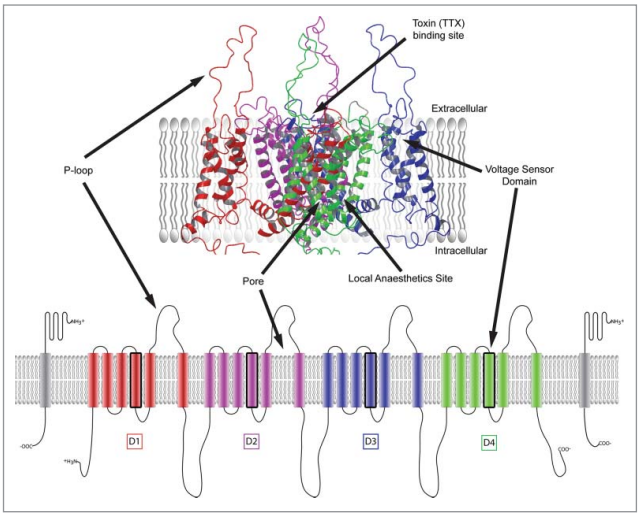

Figure 1. Na_V channel structural topology, highlighting common ligand binding sites and significant structural features. Domains D1-D4 are represented in different colors while β subunits are shown in gray.

Genetic Link to Disease State

A number of channelopathies linked to sodium channels have been identified which has helped to identify their physiological role. This data has been used to classify sodium channel subtypes as potential drug targets and anti-targets. Expression of the mutant sodium channels in transfected cells and biophysical characterization indicate a diverse range of gain- and loss-of-function properties. In addition to measuring mRNA and protein expression levels from ex vivo studies, mice with knock-in, knock-out or conditional expression of sodium channel genes have also been used to better understand the role of the sodium channel subtypes.[2,4,10] From the various studies, $Na_V1.1$ and $Na_V1.2$ mutations have a genetic link to epilepsy and related CNS disorders whilst $Na_V1.5$ mutations have significant relation to cardiac arrhythmias. Periodic paralyses are caused by mutations in $Na_V1.4$, while the $Na_V1.6$ channel has been associated with cerebellar atrophy, behavioural deficits and ataxia.[11] Due to their differential expression and presence in sensory neurons in humans and animals $Na_V1.3$, 1.7, 1.8 and 1.9 are of interest for their potential role in pain transmission.[12,13] There is compelling genetic evidence for the role of $Na_V1.7$ as a key contributor to pain perception in humans. Gain-of-function mutations in $Na_V1.7$ can lead to paroxysmal extreme pain disorder (PEPD) an inherited disease that is characterized by severe rectal, ocular, or sub-mandibular pain and primary erythromelalgia,[14] typified by burning pain in the extremities accompanied with hyperemia and inflammation.[15] Conversely, congenital insensitivity to pain (CIP) can result from several loss-of-function mutations in $Na_V1.7$ characterized by a complete inability to sense pain.[16] While no human loss-of–function mutation of *SCN10A*, the gene which codes Nav1.8, have been reported gain-of-function mutations which increase the likelihood of depolarization and which are associated with painful neuropathies are known.[17] Finally, different gain-of–function mutations of *SCN11A,* the gene coding for $Na_v1.9$, have recently demonstrated a genetic link to pain.[18,19]

Toxins Which Act Through Sodium Channels

A number of natural toxins are known to exert their effect through sodium channels. Some neurotoxins such as TTX (**1**), saxitoxin (**2**) are known to be blockers of Na_V channels whereas other toxins such as batrachotoxin (**3**) and natural pyrethroid insectisides are conversely known to activate Na_V channels (**Fig. 3**). TTX (**1**) is considered to be a true ion channel current blocker as it has been established to physically occlude the extracellular channel pore.[20] In addition to these polar small molecule toxins, a variety of peptide-based venom toxins have been isolated from spider, snail, scorpion and centipede venoms and have been shown to modulate sodium channel function.[20] These include protoxins (ProTx), huwentoxins (HwnTx) e.g. HwnTx IV (**4**) and a variety of other cysteine knot peptides, many of which have been reported to display Na_V subtype

selective modulation *via* binding to the extracellular portion of the channel.[21,22] Na_V toxins have also been taken into clinical trials for use as therapeutic treatments; Wex Pharmaceuticals is currently progressing TTX in Phase III trials for the treatment of cancer pain.

Small Molecule Blockade of Sodium Channels

Sodium channels have been implicated as biological targets for some antiarrhythmic, anticonvulsant and local anesthetic medications, but many of these classical clinical agents were discovered prior to appreciating their full pharmacology profiles. Whilst many of these drugs are known to be weak and subtype unselective sodium channel blockers, they also modulate other ion channels. Over the past two decades, based on a more detailed understanding of biology and genetics, Na_V channels have been confirmed to be therapeutically desirable targets, leading to a resurgence of medicinal chemistry work in this area. Much of this work has focussed on delivering safer variants of subtype unselective blockers. However, there have also been some recent examples of subtype selective modulators.

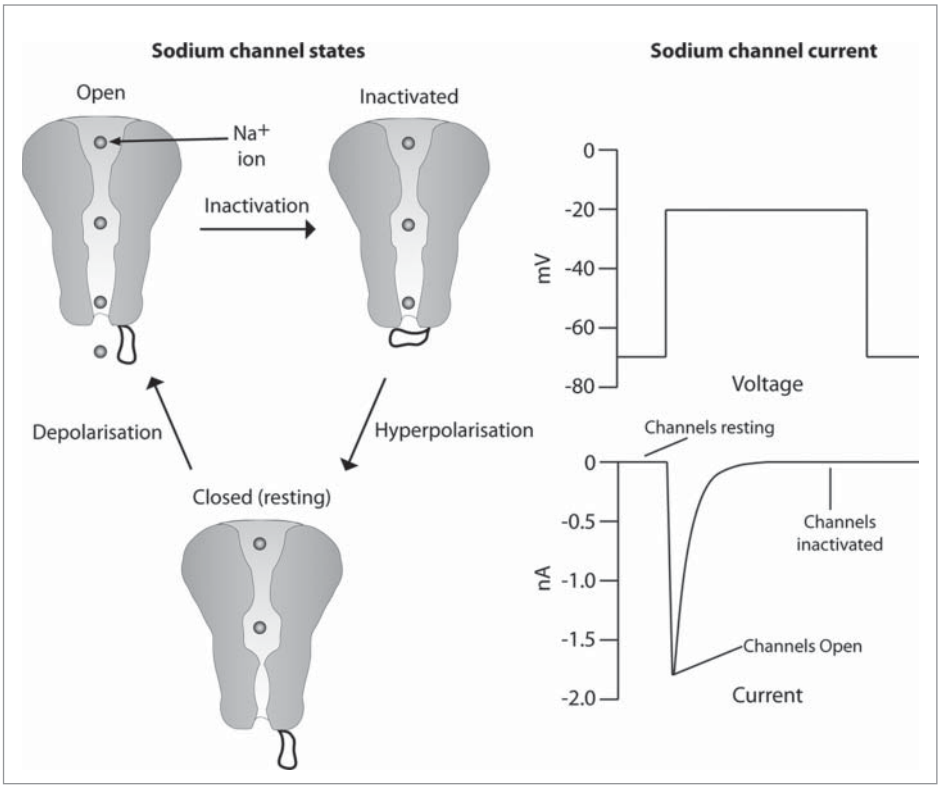

Figure 2. Sodium channel states: Na_V channels cycle between 3 states: open, closed (resting) and inactivated. They cycle from the closed (resting) state to the open state upon membrane depolarisation. The channel is open for less than a millisecond prior to inactivation. The inactivated state reprimes to the resting state when the cell membrane potential has returned to a hyperpolarised resting potential. Sodium channel current: The current associated with the cycling of sodium channels through the resting, open and inactivated state.

First Generation Sodium Channel Modulators

A variety of sodium channel modulating drugs have been applied to the treatment of clinical conditions caused by abnormal cell excitability.[2] In particular they have been applied to CNS conditions such as anti-convulsants e.g. carbamazepine (**5**), and epilepsy therapy e.g. phenytoin (**6**) via modulation of sodium channels expressed in the brain (**Fig. 4**). Antiarrhythmics such as mexiletine (**7**) and flecainide (**8**) rectify cardiac rhythm by acting on Na_V channels in the heart. Finally, local anesthetics e.g. lidocaine (**9**) and bupivacaine (**10**) are established injectable or topical agents for the treatment of pain via the blockade of Na_V channels in peripheral nerves. These compounds are largely subtype unselective within the sodium channel family leading to the potential for undesirable side effects which limit their application for certain chronic indications. Physicochemically, all of these compounds are either weakly basic or neutral and structurally it has been suggested that they to bind to an intracellular site within the channel pore that is commonly referred to as the local anesthetic binding site (**Fig. 1**).[23] Due to a high degree of amino acid sequence conservation in the channel pore across the Na_V subtypes, it is not surprising that imparting subtype selectivity via binding to this site has proven challenging.

Second Generation Sodium Channel Modulators

Recent research efforts have focused on the purposeful identification of molecules with known sodium channel pharmacology (as opposed to characterisation subsequent to their use in the clinic) with minimal off-target related activity. The main focus of interest has been directed towards identifying molecules that block $Na_V1.3$, $Na_V1.7$, $Na_V1.8$ and $Na_V1.9$. These subtypes are predominately expressed in sensory neurons with a link to nociception and therefore provide strong rationale as targets for the development of novel pain therapeutics.[2,10] Whilst subtypes $Na_V1.1$ and $Na_V1.2$ have been associated with the treatment of a variety of disorders they are also implicated in CNS mediated side effects, resulting in a narrow therapeutic index for many of the modulators. Furthermore, pro-arrhythmic effects resulting

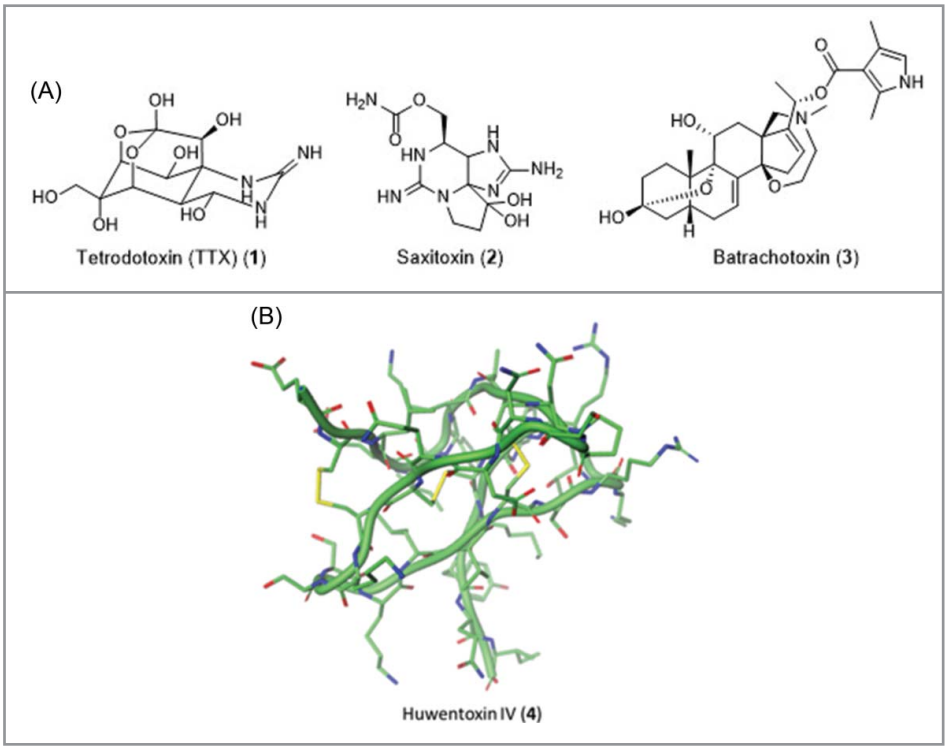

Figure 3. Selected toxin modulators.

from block of $Na_V1.5$ channels presents a potential cardiac liability. This increased understanding for the functional roles of sodium channel subtypes, coupled with dramatic advances in automated screening technologies, provided the necessary impetus for the pharmaceutical industry to undertake high-throughput screening campaigns in an effort to identify second generation inhibitors with improved selectivity and side effect profile compared to first generation molecules. However, whilst this has led to the discovery of a diverse array of chemotypes, relatively few have been disclosed with data to support them being subtype selective, implying that delivering subtype selectivity still presents a significant challenge.

Molecules with sodium channel activity that bridge the gap between first and second generation modulators have been taken into clinical development (**Fig. 5**). Ralfinamide (**11**), a state and use dependent Na_V modulator from Newron, is also reported to act through N-type calcium channels and N-methyl-D-aspartic acid (NMDA) receptors.[24] Lacosamide (**12**) which also possesses a benzylamino headgroup, is suggested to bind to a novel site that enhances slow inactivation with some selectivity towards TTX-S channels. Lacosamide (**12**) was approved in 2008 as an anticonvulsant and for the treatment of diabetic neuropathic pain.[25]

Recently, the number of sodium channel modulators disclosed in the scientific literature has increased substantially with many examples spanning a broad range of chemotypes and physicochemistry. Selected examples described below.[2,3,26-28]

Patents from Vertex based on TTX-S channel modulators containing a weakly acidic N-heterocylic sulfonamide suggest $Na_V1.1$ and $Na_V1.3$ to be the preferred targets with compound **13** exhibiting IC_{50} <2 μM at both $Na_V1.1$ and $Na_V1.3$ (**Fig. 6**). Icagen and a collaboration between Pfizer and Icagen have also reported compounds containing acidic N-heterocyclic sulfonamides which have been reported to modulate TTX-S channels with compound **14** having $Na_V1.3$ IC_{50} 30 nM and examples reported to possess >1000-fold selectivity over cardiac channel $Na_V1.5$.

The high confidence in target rationale for $Na_V1.7$ provided by genetic data has sparked an industry-wide search for $Na_V1.7$ preferring modulators for the treatment of pain resulting in the publication of a diverse array of chemotypes with several lead compounds moving forward into clinical trials.[2,3] Convergence and Xenon have both entered clinic trials with chemotypes represented

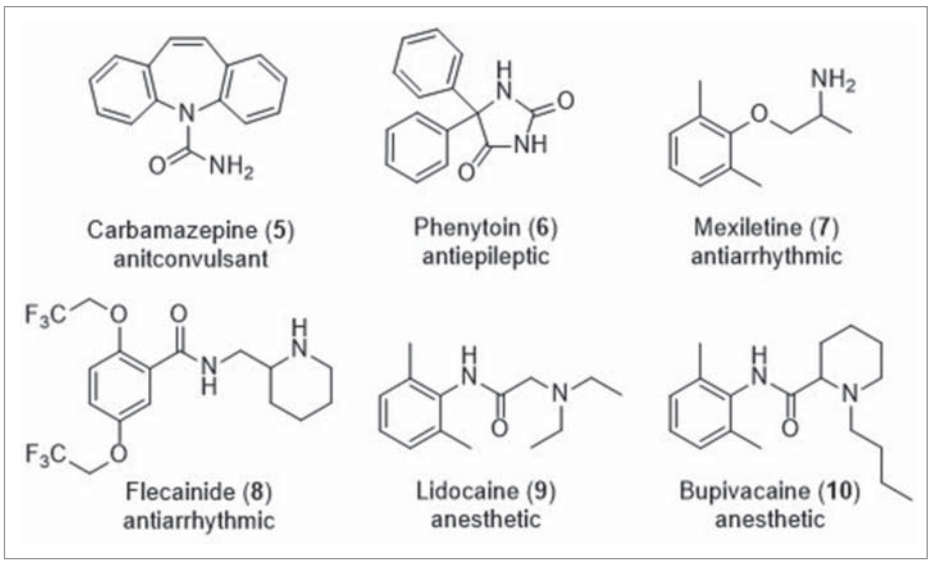

Figure 4. Selected first generation sodium channel modulator drugs.

by a weakly basic proline **15**,[29] and a neutral spiro-oxindole **16**,[30] respectively. AstraZeneca have also published several patents which cover a diversity of chemical series including chromane **18**, reporting $Na_V1.7$ IC_{50} 66 nM, $Na_V1.5$ IC_{50} 13 μM and $Na_V1.2$ IC_{50} >33 μM. Benzazepinone **19** has been reported by Merck to be a state dependent inhibitor of $Na_V1.7$ (IC_{50} 90 nM) and $Na_V1.8$ (IC_{50} 680 nM) whilst displaying ~10-fold use dependent selectivity over $Na_V1.5$.[31] Pfizer, in collaboration with Icagen, have published several patents based on acidic and zwitterionic series (represented here by compound **17**) with numerous examples reported to have $Na_V1.7$ potency in the single digit nanomolar range and a molecule currently in clinical trials. Recently, Icagen and Pfizer have also described a unique binding site on the voltage sensor domain away from the pore region for related chemotypes.[32] Amgen have described a novel series of triazine derivatives as $Na_V1.7$ modulators and have also determined that **20** binds to a distinct site from that of local anesthetics.[33] Modulation of this subtype remains a competitive area and multiple pharmaceutical companies have recently published patents for chemical series with activity against $Na_V1.7$ that cover diverse structures and physicochemistry including basic, neutral and acidic series.

Pfizer has described a series of 6,6-biaryl derivatives optimised for $Na_V1.8$ activity whilst retaining selectivity over the related TTX-R $Na_V1.5$ cardiac channel.[34] For example, compound **21** has a whole cell electrophysiology $Na_V1.8$ IC_{50} of 260 nM and selectivity of >20-fold over $Na_V1.1$, $Na_V1.5$ and $Na_V1.7$. A collaboration between Abbott and Icagen has also discovered 6,6 and 6,5 biaryl lead matter with an alternative amide geometry. Substituted pyrazine **22** showed $Na_V1.8$ IC_{50} of 30 nM and good selectivity over TTX-S channel $Na_V1.2$ and TTX-R channel $Na_V1.5$. Alternative cores were also tolerated and had similar profiles such as the furan derivative A-803467 (**23**).[35]

Despite the recent compelling genetic evidence for $Na_v1.9$ as an analgesic target, development of modulators for this subtype has been hampered by the difficulty of expressing this subtype in recombinant systems and to date no modulators of $Na_v1.9$ have been described.

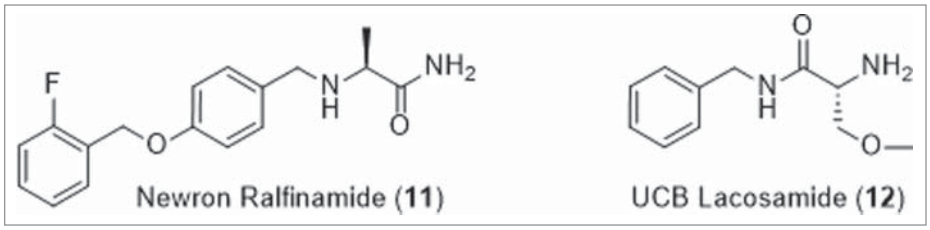

Figure 5. Early examples of second generation sodium channel modulators.

Compounds in Clinical Development and Outlook

Despite significant interest in sodium channel blockers as pain therapies, only a few second generation compounds have been reported to have entered clinical trials. AstraZeneca has reported the effects of intradermal administration of AZD-3161 in a Phase I UVIH burn study. Xenon Pharmaceuticals reported a positive Phase II readout in acute pain with a compound targeting $Na_V1.7$ where topical application of XEN402 (**16**) reduced pain

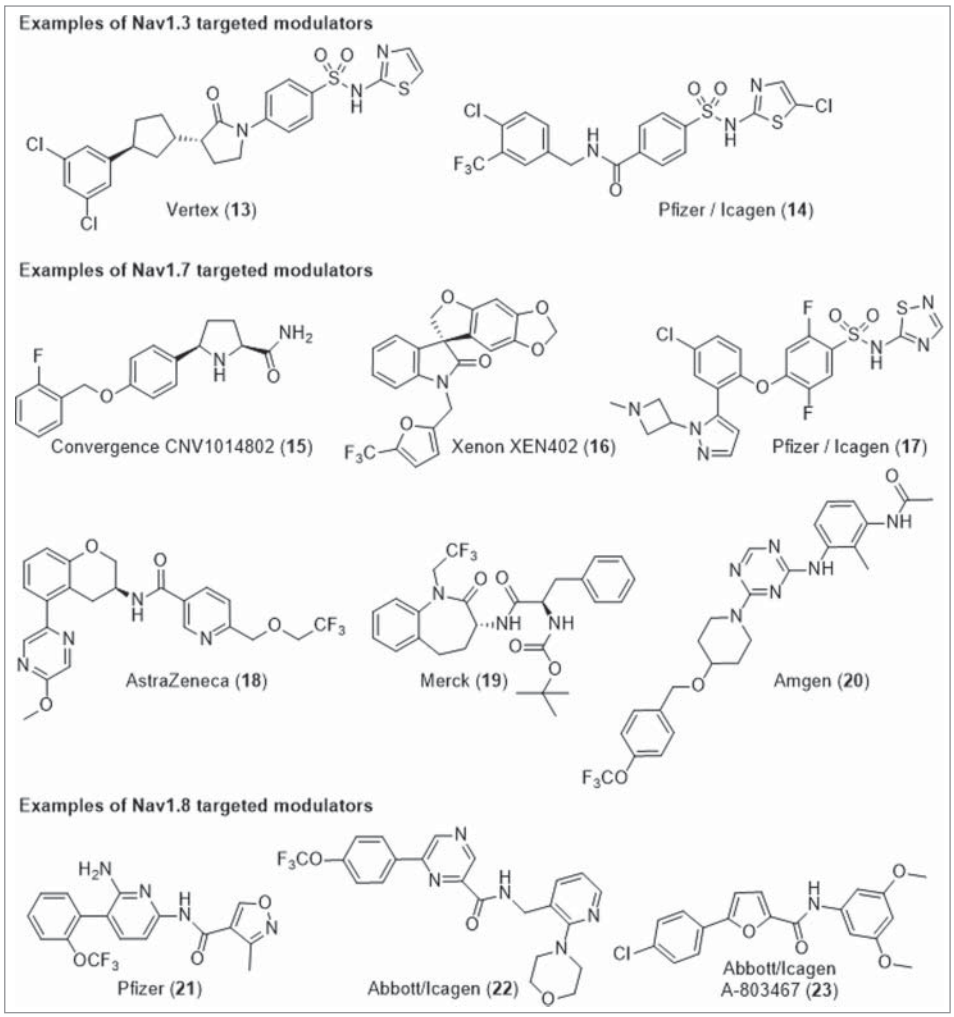

Figure 6. Examples of Na_V subtype selective targeting modulators.

in postherpetic neuralgia (PHN). Results from an oral Phase II study with XEN402 (**16**) suggested positive effects in patients suffering from primary erythromelalgia.[30] Xenon recently partnered XEN402 (TV-45070, **16**) with Teva and have been granted orphan drug designation by the FDA for the treatment of erythromelalgia. Pfizer have advanced a $Na_V1.7$ compound PF-05089771 into Phase II clinical trials of third molar extraction and primary inherited erythromelalgia.[36] Pfizer has also reported advancing selective $Na_V1.8$ blockers into the clinic. Convergence have conducted Phase II trials for lumbosacral radiculopathy and trigeminal neuralgia with their most advanced sodium channel modulator CNV1014802 (**15**), which is reported to be a highly state dependent subtype preferring $Na_V1.7$ blocker. Convergence also announced that CNV1014802 (**15**) has been granted orphan drug status by the FDA for the treatment of trigeminal neuralgia. Dainippon Sumitomo has advanced a $Na_V1.7/Na_V1.8$ compound DSP-2230 into Phase II for neuropathic pain. Although the second generation sodium channel modulators are making their way through efficacy based clinical trials, the isoform selectivity and biophysical characteristics of many of these clinical compounds have not been disclosed. The hope is that new agents with greater subtype selectivity will achieve therapeutic utility with decreased cardiovascular and CNS side effects.

In conclusion, there have been major advances in sodium channel drug discovery over the last decade. Sodium channels have been implicated in a variety of disease states through both genetic data and a greater understanding of the pharmacology of marketed drugs. Moreover, knowledge around the role of specific sodium channel subtypes has led to an increase in drug discovery efforts for the identification of subtype or functionally selective agents. Advances in screening technology, coupled with the use of sodium channel co-crystal structures in the various sodium channel states for structure based drug design, should further enable future efforts.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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