Sodium Channel Blockers

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I. Introduction

Like many other currently marketed pharmaceutical agents, the therapeutic use of sodium channel blockers can be traced in history to a time even before their pharmacological target(s) had been mechanistically identified or cloned. For example, cocaine **1** (Table 1) was introduced in 1884 as the first local anesthetic drug useful in clinical surgery but it was quickly realized that its use also led to undesirable side effects.[1] The involvement of sodium channel blockade in cocaine's mechanism of action was not realized for many decades afterward. Synthetic chemistry efforts were subsequently initiated in many laboratories and were aimed at the identification of analogues of cocaine with the goal of creating a better local anesthetic, i.e., one with less abuse liability and improved pharmacological, pharmaceutical, and side effect profile. This work led ultimately to the "caine" class of local anesthetics, which can be broadly divided into two categories on the basis of the chemical structures. The aminoester category includes cocaine itself as well as benzocaine **2** and procaine **3**. The aminoamide category includes bupivacaine **4** and lidocaine **5**. Lidocaine today is still the subject of dozens of research publications per year and is used routinely in hospitals as well as in many exploratory clinical trials.

Starting in the 1960s a parallel line of research led to the serendipitous observation that certain known anticonvulsants, antidepressants, and antiarrythmics were highly efficacious in certain painful conditions in man including neuropathic pain.[2−5] Since then, evidence has emerged that shows their analgesic action is partly mediated by sodium channel blockade, possibly quite different from the mechanism by which they address the clinical indications they were originally designed to serve. One such drug, carbamazepine **6**, remains today as one of the drugs of choice for treating pain associated with trigeminal neuralgia.

Most recently, sodium channel subtypes and various subunits have been identified and cloned, thus creating an opportunity, for the first time, to obtain precise measurements and insight at the molecular and biophysical level about the structure of the channels and the way(s) in which the various channel blockers interact to produce their pharmacological effects. The field is arguably rich with known ligands that have unique sodium channel pharmacology, and by combining them with recent molecular biological and electrophysiological advances, further developments toward the discovery of novel sodium channel blockers are easily envisioned.

II. Structure, Classification, and Function

The voltage-gated sodium channels are heteromeric integral membrane proteins. The major α-subunit is folded in such a way as to form a Na^+ selective pore across the plasma membrane.[6] The presumed arrangement of the α-subunit is such that six α-helical transmembrane segments (numbered 1−6) are repeated in the sequence four times, thus creating four domains numbered I, II, III, and IV (Figure 1). Within each of the four domains, there is a relatively short and nonhelical segment between S5 and S6 known as the P-segment. In the context of a correctly folded channel, these four P-segments are spatially positioned in a way that creates the ion pathway. The primary sequence of the fourth transmembrane segment (colored red in Figure 1) contains several polar amino acid residues that are involved in the voltage-sensing of the channel gate. Residues contained in the S6 segment are known by mutagenesis to contribute significantly to local anesthetic binding to sodium channels.[7,8]

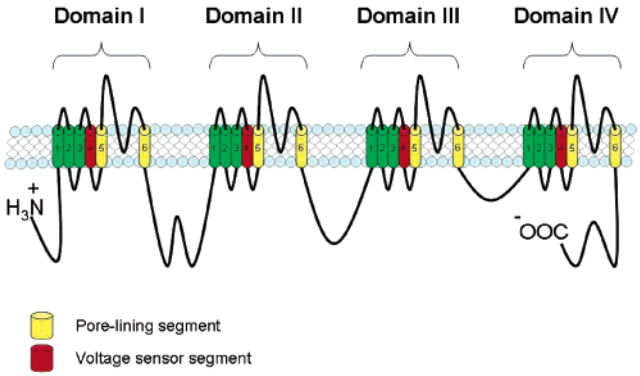

Figure 1. Illustrative schematic of the presumed arrangement for the α-subunit of the voltage-gated sodium channel. The pore-lining segments are colored yellow, and the segment containing the voltage-sensing amino acid residues are colored red.

Although still a matter of debate, a sliding helix model has been proposed to describe the mechanics of how this polar helix "unscrews" from the membrane, causing conformational changes to occur in the loop region between domains III and IV (the gate region) to activate the channel.[9] The α-subunit is also ionically associated with one or more auxiliary β-subunits, each of which is of lower relative molecular weight. These β-subunits typically have a large N-terminal domain that is extracellular and immunoglobulin-like, a single transmembrane region, and a relatively short C-terminal segment that is intracellular. Viewed from the extracellular perspective, domains I−IV are proposed to be arranged roughly in a circular pattern, forming the pore in the center.[6]

Thus far, nine functional α-subunits ($Na_v1.1$−$Na_v1.9$) and four β-subunits (β1−β4) have been cloned.[10,11] A tenth α-subunit, lacking the amino acids needed for proper voltage gating, has also recently been identified and is proposed to play a role in the regulation of salt intake in animals.[12] This unique α-subunit is known as Na_x and has been shown to be gated by extracellular sodium concentration. $Na_v1.1$, $Na_v1.2$, and $Na_v1.6$−$Na_v1.9$ are all present in adult rat and mouse dorsal root ganglion (DRG^a) neurons and are typically coexpressed in various combinations in functionally different neurons. Coexpression patterns have not been correlated with functional class of

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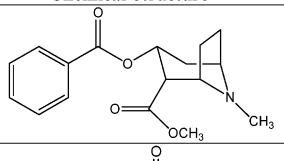
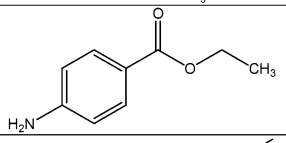
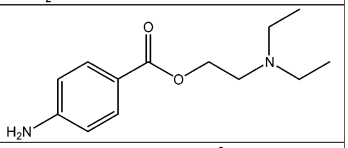
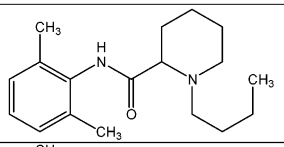
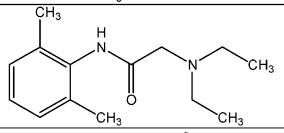
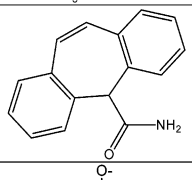
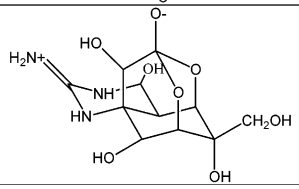
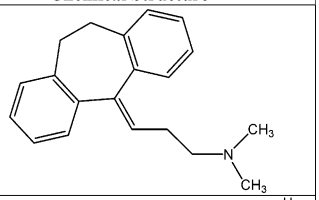
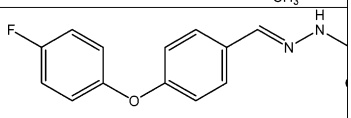
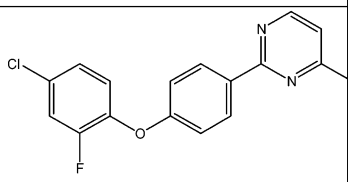
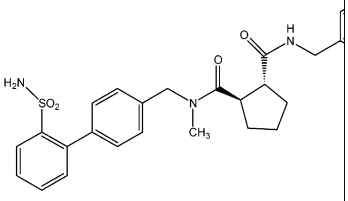
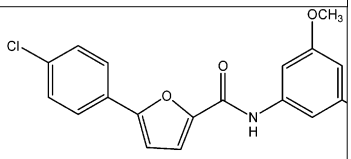
Table 1.

Compound Number	Chemical Structure
1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	

primary afferent neuron.[13] $Na_v1.3$ and $Na_v1.5$ are present only in the embryonic DRG.[14] $Na_v1.3$ is up-regulated following nerve injury in adult rats.[15−17]

The voltage-gated sodium channels and the currents they mediate were historically classified into two groups on the basis of sensitivity to the puffer fish toxin tetrodotoxin (TTX) **7**. As described previously, DRG neurons express multiple sodium channels, some of which are TTX-sensitive and some of which are TTX-resistant. The sodium currents associated with nociceptive primary afferent neurons contain significant TTX-resistant component and are thought to be mediated predominantly by $Na_v1.8$ and $Na_v1.9$ and to some extent by $Na_v1.5$, all of which are resistant up to micromolar concentrations of TTX. On the other hand, $Na_v1.1$, $Na_v1.4$, $Na_v1.6$, and $Na_v1.7$ are sensitive to nanomolar concentrations of TTX.

The schematic of functional-state transitions of the voltage-gated sodium channel, all governed by membrane voltage V_m, is presented in Figure 2. Upon membrane depolarization, the sodium channel becomes "open", allowing a rapid influx of Na^+ into the cell. Within a few milliseconds, the channel undergoes a conformational state change that involves isoleucine, phenylalanine, and methionine between domains III and IV that closes the channel to the "inactive" state. Repriming of the channel is another conformational state change that requires repolarization of the membrane. As a result, the channel returns to the "resting" state where it is once again ready to open.

Electrophysiological analysis of many known sodium channel blockers has revealed subtle kinetic and thermodynamic differences in the way they interact with the channel. It is now understood that many of the original local anesthetics, anticonvulsants, and tricyclic antidepressants have preferential affinity for the open and/or inactivated state of the channel, compared to its resting state, thus exhibiting state-dependent sodium channel blockade. In addition, each compound also has specific kinetics of interaction with the channel that may affect the inhibition patterns depending on the duration of firing episodes, especially when steady-state drug binding is not reached. Abnormal neuronal firing rates (such as occurs following nerve injury or as a consequence of certain degenerative diseases) result in the presentation of a higher population of "open" or "inactive" channels such that the inhibition of the channel is more effective for a state-dependent drug. Consideration of these

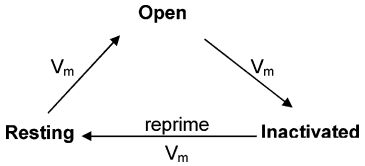


Figure 2. Simplified functional state diagram. V_m refers to the membrane voltage necessary to affect transitions between resting, open, and inactivated states of the voltage-gated Na^+ channel.

[a] Abbreviations: DRG, dorsal root ganglion; CCI, chronic constriction injury; PEPD, paroxysmal extreme pain disorder; FCA, Freund's complete adjvant; GPCR, G-protein-coupled receptor; TTX, tetrodotoxin.

mechanistic subtleties may be important during the design of inhibitors with optimal side effect profiles because they would be expected to preferentially block sodium channels in rapidly misfiring neurons.

III. Sodium Channels in Neuropathic Pain

Peripheral nerve injury often leads to neuropathic pain that typically is associated with symptoms including allodynia and hyperalgesia. The injured afferent neurons have altered membrane properties and abnormal responses to various stimuli. In animal models of sciatic nerve injury, electrophysiological measurements demonstrate that hyperexcitabilty and spontaneous nerve firing occurs at the DRG and also at the site of injury. Results from animal pain models using a variety of sodium channel blockers support an important role for this target in neuropathic pain.[18,19] For example, Abdi et al. has reported that either 10 mg/kg lidocaine (iv) or 1.5 mg/kg amitriptyline **8** (ip) is effective in increasing the threshold for mechanical allodynia in the rat spinal nerve ligation model.[20] The author showed further that lidocaine and amitriptyline caused a reduction in the ectopic discharges of the injured afferent neurons. Of further interest is the author's conclusion that primary site of action for lidocaine is in the periphery.

Further evidence for an important role of sodium channels in neuropathic pain can be obtained from human clinical trial results. Eight different randomized, placebo-controlled human clinical trials have been published that test iv lidocaine against the symptoms of neuropathic pain.[21−28] Five of these reports indicate that lidocaine was effective in the setting of peripheral neuropathic pain. The results of one study was negative (possible because of the use of a very low dose (2.5 mg/kg) of lidocaine), and the results of another study were positive in evoked pain only. In one of the remaining two studies, lidocaine was shown to be effective in central neuropathic pain, while in the other study it had no statistical effect against phantom pain. Anticonvulsants, antiarrhythmics, and tricyclic antidepressants, which share with local anesthetics common mechanism of inhibition of voltage-gated sodium channels, all have therapeutic utility in human neuropathic pain settings.[4,5,29] Taken together, there is a substantial human trial evidence that is supportive of an important role of voltage-gated sodium channels in certain types of neuropathic pain.

$Na_v1.3$ is expressed in brain and sensory neurons, but the expression is up-regulated in DRG following axotomy or chronic constriction injury (CCI) of the sciatic nerve in adult rats, heightening its possible role in pathological pain states. The $Na_v1.3$ channels are also known to be rapidly repriming such that their increased number following nerve injury may partly account for the abnormal high-frequency activity in the DRG neurons. In rat, up-regulation of $Na_v1.3$ in thalamic neurons has been demonstrated following spinal cord injury. It has recently been shown that the cell adhesion molecule contactin may participate in the delivery of $Na_v1.3$ to the cell surface because it too is up-regulated in axotomized DRG neurons and accumulates similarly.[30] Peripheral nerve injury has been linked to abnormal expression of $Na_v1.3$, which, because of its rapidly repriming character, contributes to the hyper-responsiveness of second-order dorsal horn neurons.[31] Specifically, intrathecal delivery of antisense oligodeoxynucleotides targeting $Na_v1.3$ reduced the hyper-responsiveness of dorsal horn neurons and attenuated pain-related behaviors after CCI.

$Na_v1.7$ sodium channels are normally expressed on sensory neurons and exhibit slow repriming and slow closed-state inactivation, meaning they respond to slow membrane depolarization.[32] As a result, $Na_v1.7$ might amplify small excitatory inputs that are otherwise close to the resting potential, thus participating in the spontaneous action of DRG neurons during pathological firing.[33] Convincing human evidence for an important role of the $Na_v1.7$ sodium channel in nociception was recently published by Cox et al.[34] The authors described human relatives with a phenotype showing the inability to perceive any form of pain; yet all other sensory modalities were normal. The authors correlated the condition to mutations in the SCN9A gene of chromosome 2q24.3 that encodes the α-subunit of the $Na_v1.7$ sodium channel. The analysis revealed three distinct nonsense mutations that led to a loss of function of $Na_v1.7$ when expressed in HEK293 cells and compared to human wild-type $Na_v1.7$. Previous studies in $Na_v1.7$ knockout mice had revealed similar changes to behavior including profound deficits on behavior associated with inflammatory pain.[35,36]

Adding to this evidence is work published recently by Fertleman et al. that describes certain mutations in the $Na_v1.7$ sequence that can cause impaired inactivation of $Na_v1.7$ sodium channels that is associated with paroxysmal extreme pain disorder (PEPD).[37] Eight mutations of $Na_v1.7$ are known to be associated with PEPD, and all of them result in poorly inactivating sodium currents on $Na_v1.7$ channels. This alteration of the normal state changes for the sodium channel results in repetitive firing in the peripheral nerves, even in the absence of external painful stimuli, and is thus proposed to underpin the burning rectal, ocular, and submandibular pain and flushing typically associated with PEPD.

$Na_v1.8$ and $Na_v1.9$ are two extensively studied TTX-resistant sodium channels in DRG neurons and have recently been reviewed.[11,38] $Na_v1.8$ is primarily expressed in nociceptive afferents and is localized in the cell body, peripheral terminals, and central terminals of the dorsal horn. The intrathecal administration of antisense oligonucleotide to $Na_v1.8$ has been shown to inhibit tactile allodynia and thermal hyperalgesia in a rat model of neuropathic pain and in a Freund's complete adjuvant (FCA) induced inflammatory pain model.[39] Following peripheral nerve injury, the mRNA for $Na_v1.8$ and $Na_v1.9$ channels are down-regulated in the DRG but aggregate at the distal tips of the injured neurons.[40] Moreover, this mRNA is up-regulated in nearby uninjured neurons following nerve injury in animal models.[41] Similarly in humans with peripheral nerve injury, they are down-regulated in the DRG but accumulate at the site of injury.[42] On the other hand, mRNA for $Na_v1.8$ and $Na_v1.9$ are up-regulated in DRG in the setting of chronic inflammatory pain models.[43] Inflammatory mediators including prostaglandins have also been shown to potentiate the $Na_v1.8$ current via a PKA-dependent mechanism.[44]

$Na_v1.9$ has a low threshold for activation and may even be active at resting membrane potentials. $Na_v1.9$ is primarily restricted to Aδ- and C-fibers and, because of its very slow inactivation rate, may contribute to subthreshold oscillations and so-called "burst" discharge.[45]

IV. Mechanism-Based Sodium-Channel Blockers

Since the first use of cocaine as a local anesthetic in man, significant advances have been made toward the development of improved molecules. These newer drugs are typically administered topically, intrathecally, or locally in the vicinity of an injury in part because they are not orally bioavailable but also because of adverse side effects (i.e., convulsions and cardiovascular collapse) observed upon systemic administration. Often times, they are coformulated or coadministered with a vasoconstrictor such as adrenaline to ensure minimal tissue uptake and distribution away from the site of administration.

Lidocaine, introduced in 1944 as the first member of a new chemical class of local anesthetics, is one of the few local anesthetics to be well tolerated in humans following systemic administration. As a result, it has been tested in a wider array of human pain states and efficacy has been demonstrated against pain associated with peripheral nerve damage, spinal cord injury, diabetic neuropathy, and postherpetic neuralgia. The exposure levels required to get the antihyperalgesic and antiallodynic effects for lidocaine in neuropathic pain states are significantly lower than those needed for local anesthesia,[46] indicating that blunt blockade of nerve conduction is not required in pain settings.

The long history of serendipity continued in the sodium channel field when, in 1993, Dimmock et al. described a new class of molecules with potent anticonvulsant activity in both the maximal electroshock- and pentozocine-induced seizure models in rats.[47] These molecules, generally comprised of a substituted phenoxyphenyl group and a semicarbazone, do not resemble previously described local anesthetics or other known sodium channel blockers. Although interactions with GABA-gated Cl^- channels were initially proposed, Ilyin et al. later demonstrated that several members of the series were potent voltage-gated sodium blockers.[48]

One specific member of this series, originally known as Co102862 (but later renamed to V102862, **9**) was discovered to have an impressive state-dependent mechanism with broad spectrum action.[48] By use of HEK-293 cells stably expressing rat brain type II sodium channels ($rNa_v1.2$), the dissociation constant for the inactivated state of the channel (K_I) was ~400 nM while the corresponding dissociation constant from the resting state (K_R) was ~30 μM for V102862. Binding to inactivated channels was relatively slow with a rate constant $k_+ \approx 1.7\ \mu M^{-1}\ s^{-1}$. The steady-state inactivation curve was shifted in the hyperpolarizing direction, reducing the fraction of channels available for activation at physiologically relevant membrane voltages. In addition, **9** significantly retarded the recovery of the channels from inactivation. By biophysical parameters of interaction with the sodium channels, **9** was superior to classical local anesthetics, antiarrhytmics, and anticonvulsants. The authors concluded that **9** has significant binding preference for the inactivated state of the channel versus either the resting or open state. **9** was also shown to be a broad spectrum sodium channel inhibitor, binding to most of the known sodium channel isoforms. Given the unique pharmacological profile of this compound, it was advanced into human clinical trials, the results of which have not been published, such that any mechanistically derived advantages of this "next generation" sodium channel blocker in man remain unknown.

Attempts to improve the pharmaceutical profile of **9** led to the discovery of several other series of sodium channel blockers, one of which is known as PPPA **10**.[49] This molecule is also a broad spectrum sodium channel blocker with a faster on-rate kinetics and a higher degree of state dependency than existing drugs. Tested on $rNa_v1.2$ channels and on native channels in cultured rat DRG neurons, **10** was shown to be nearly 1000-fold more potent with 2000-fold faster on-rate and >30-fold higher levels of state dependency than either lamotrigine or carbamazepine, clinically relevant comparators. The important impact on the hyperalgesic potential of **10** can arise from the fact that it blocks the native TTX-resistant current in rat DRG neurons ~2,000-fold more potently than carbamazepine and lamotrigine. In rat pain models (partial sciatic nerve ligation, Freund's complete adjuvant, and postincisional pain), the compound was reported to be highly effective against a mechanical endpoint with minimal effective doses in the range of 1−3 mg kg^{-1} (oral dosing). Significantly, the authors further demonstrated that **10** did not produce motor deficits in the accelerating rotarod assay of ataxia. The experimentally determined therapeutic index was >10, superior to both carbamazepine and lamotrigine. Taken together, the data are supportive of a hypothesis that a potent, broad-spectrum, state-dependent sodium channel blocker might be an effective agent for treating pain in humans while also providing a more satisfactory side effect profile. **10** entered human clinical trials in 2004 at Purdue Pharma L.P.

An alternative strategy is to look for a subtype-selective inhibitor (either state-dependent or not state-dependent) of a specific, preferably peripheral voltage-gated sodium channel, for example, $Na_v1.8$ or $Na_v1.7$.[34,50] This latter approach has proven to be quite difficult, and in spite of significant and sustained research during the past 7−8 years, very few reports describing subtype-selective molecules have appeared. Although a prominent role for certain channel subtypes such as $Na_v1.7$ appears to be emerging, there are still questions about whether or not the selective inhibition of a single isoform of Na^+ channels will be sufficient to produce a robust analgesic effect across diverse pain states.[51,52]

Nonetheless, progress toward the discovery of such a molecule is occurring, as evidenced by the recent publication of CDA54, **11**.[53] The authors describe this molecule as being peripherally restricted and a potent blocker of both $Na_v1.7$ and $Na_v1.8$ (K_i = 0.25 and 0.18 μM, respectively). When it was dosed in rats at 10 mg kg^{-1} (po), the authors observed significant reduction in the behavioral signs of neuropathic pain in conventional nerve injury models. At the same dose, the molecule did not affect acute nociception or motor coordination, and in anesthetized dogs plasma concentrations of 6.7 μM had no effect on various cardiac electrophysiological parameters.

A second example of a subtype-selective molecule has recently been described by scientists at Abbott Laboratories and is known as A-803467, **12**.[54] This small molecule has been described as a state-dependent, $Na_v1.8$ selective blocker. The reported IC_{50} values against the inactivated state of $hNa_v1.8$, $hNa_v1.2$, $hNa_v1.3$, $hNa_v1.5$, and $hNa_v1.7$ are 0.008, 7.18, 2.45, 7.44, and 6.74 μM, respectively. Following ip administration to rodents, the ED_{50} values in the Chung and CCI models of neuropathic pain were 47 and 86 μM, respectively. Of interest are the ED_{50} values in the locomotor and rotarod tests, which were >300 μM in both experiments, suggesting some improvement in the therapeutic window over what is typically observed for sodium channel blockers.

A third possible approach to the design of new modulators of various sodium channels might take advantage of emerging evidence that some local anesthetics, including lidocaine, may have a pharmacological mechanism that is broader than state-dependent blockade of voltage-gated sodium channels.[11] It has been proposed that some of these molecules may also act directly upon certain GPCRs and on the neuroimmune interactions that contribute to pain hypersensitivity in addition to their actions upon sodium channels. If true, it could open another dimension to the design of molecules aimed at the treatment of neuropathic pain.

V. Perspective

The sodium channels and drugs that act upon them have been the subject of direct and indirect research for over a century. Key contributions to our current understanding have been made through careful research, by technology advancement, by design,

and even serendipity. It is clear that neuronal injury causes changes in the excitability of neurons as well as changes in sodium channel expression over the cell body and their neurites. These changes underpin abnormal, repetitive neuronal firing that is typically associated with human neuropathic pain conditions.

Unlike many newer pain targets, the sodium channel field has the benefit of a long history, many emerging or already known and well-characterized ligands, and molecular level understanding of the channel biophysics. It seems probable that through the consideration of this broad collection of information one might still imagine new hypotheses leading to new opportunities for the design of superior molecules to treat human pain. Abrogating abnormal activity of voltage-gated sodium channels while leaving normal sensation intact might represent a promising approach to pain relief in humans.

Biographies

Donald J. Kyle received his B.S. degree in Chemistry from Colorado State University in 1982 and a Ph.D. in Synthetic Organic Chemistry from Texas Tech University in 1986. He then joined Nova Pharmaceutical Corporation and Scios, Inc., where he was the Director of Chemistry and Structural Biology. In 1998, he joined Purdue Pharma L.P. and is currently the Vice President of Discovery Research. His team at Purdue Pharma L.P. is focused on pain research and the discovery of small molecules whose actions are via ion channels and cell surface receptors.

Victor I. Ilyin received a M.S. (Highest Honors) in Bionics from the Kazan State University (USSR) in 1972 and his Ph.D. in Biophysics from the Institute of Biological Physics, USSR Academy of Sciences, Pushchino, USSR, in 1977 under the guidance of Professor Boris N. Veprintsev, Dr. Peter D. Bregestovski, and Dr. Catherine A. Vulfius. Following 22 years in academia, Dr. Ilyin joined the pharmaceutical industry in 1993 where he has been instrumental in the discovery of novel therapeutics for central nervous system disorders and pain. Dr. Ilyin has worked for such neuroscience-focused companies as ACEA Pharmaceuticals, Inc. (Irvine, CA), CoCensys, Inc. (Irvine, CA), and Purdue Pharma L.P. (Cranbury, NJ). Dr. Ilyin's recent discovery and development efforts have been directed toward state-dependent blockers of voltage-gated sodium channels.

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