ION CHANNEL DRUG TARGETS
unlocking the potential

A striking number of drugs targeting ion channels have reached blockbuster status, generating $ billion revenues. In spite of the historical success of ion channels as therapeutic targets and the considerable investment in this target class by the industry, not a single novel, small molecule ion channel drug has been approved by the FDA in the past 10 years. This article will provide an overview of the current status of ion channel drug discovery and the technologies currently available to the industry for undertaking ion channel R&D programmes. In addition, this review will highlight emerging discovery approaches to this valuable target class that may initiate a paradigm shift in ion channel drug discovery.

By Dr Dayle S. Hogg, Dr Philip Boden, Dr Geoff Lawton and Dr Roland Z. Kozlowski

Despite billions of dollars of research spend, the pharmaceuticals industry has been unable to replicate the early success of compounds such as the calcium antagonists, sulphonylureas and local anaesthetics. Indeed, since the approval of Posicor (mibefradil) in 1997, and its subsequent withdrawal, a paucity of ion channel therapeutics have been approved by the US Food and Drug Administration (FDA). Despite this poor success the pharmaceutical industry continues to invest vast resources in ion channel research. This research targets many different therapeutic indications with a combined market value of more than $24 billion and also provides a key filter in safety pharmacology. In addition to the fully integrated pharmaceutical companies, a number of biotechnology companies are also active in this field (see **Table 1**).

In light of the significant historical success of ion channel therapeutics, that were largely identified prior to the genomic bubble of the early 1990s, the global scientific community has generated huge quantities of biological data in relation to ion channels as therapeutic targets. Indeed 400+ ion channel genes have been identified. The potential validation of these as drug targets provides an enormous market opportunity for the re-emergence of ion channels as key targets in drug discovery. However, to realise the potential of this target class, an understanding of the validation of these targets as well as development of suitable screening technologies that reflect the complexity of ion channel structure and function remain key drivers for exploitation of this opportunity.

Ion channel therapeutics

A history of success

Historically, drugs targeting ion channels have been well represented as important therapeutics for a number of key indications including cardiovascular disorders such as angina, hypertension and cardiac arrhythmias; metabolic disorders such as type II diabetes; and neurological disorders such as pain and stroke; in addition to their use as local anaesthetics.

Table 1: Ion channel focused biotechnology companies

COMPANY	LOCATION	WEBSITE
Cardiome Pharma Corp	Vancouver, BC, Canada	www.cardiome.com
Icagen, Inc	Durham, NC, USA	www.icagen.com
Lectus Therapeutics Ltd	Cambridge, UK	www.lectustherapeutics.com
Neurion Pharmaceuticals, Inc	Pasadena, CA, USA	www.neurionpharma.com
NeuroMed Pharmaceuticals, Inc	Vancouver, BC, Canada	www.neuronmed.com
NeuroSearch A/S	Ballerup, Denmark	www.neurosearch.com
Newron Pharmaceuticals SpA	Milan, Italy	www.newron.com
Xention Discovery Ltd	Cambridge, UK	www.xention.com

A number of these ion channel drugs have reached blockbuster status such as Pfizer's calcium channel blocker Norvasc® (amlodipine besylate). Indeed, the L-type calcium channel as a target for antihypertensive and/or anti-anginal therapies has been the subject of intense interest which is directly reflected in the number of calcium channel antagonists that have been approved by the FDA. These can be broadly divided into three distinct classes: the dihydropyridine calcium channel blockers (eg, Plendil®, AstraZeneca; Norvasc®, Pfizer; and Adalat®, Bayer), the phenylalkylamine calcium channel blockers (eg, Calan®, Pfizer; Verelan®, Elan) and the benzothiazepine calcium channel blockers (eg, Cardizem®, Aventis/Biovail; Tiazac®, Forest Laboratories). Calcium channel antagonists still form a significant proportion of the global cardiovascular market and as a target class, despite the expiry of key patents currently generate ~$6.5 billion in annual sales.

Anti-epileptic drugs (AEDs) also include a significant number of blockers of sodium ion channels such as Novartis' Tegretol® (carbamazepine) indicated for control of partial seizures. The 1990s saw the introduction of newer ion channel AEDs such as Ortho-McNeil Pharmaceuticals' Topamax® (topiramate), a sodium channel blocker which received FDA approval in 1997 as an adjunctive therapy for control of partial onset seizures. More recently in 2005, Topamax® also received FDA approval as initial monotherapy in people aged >10 with partial onset or primary generalised tonic-clonic seizures. Lamotrigine (marketed as Lamictal® by GlaxoSmithKline) a different sodium channel blocker, is also currently used in the treatment of partial seizures, primary and secondary tonic-clonic seizures, and seizures associated with Lennox-Gastaut syndrome.

An ion channel blocker with an entirely novel mode of action, Pfizer's Neurontin® (gabapentin), was approved by the FDA in 1993 for adjunctive therapy in the treatment of partial seizures in adults and paediatric patients. Gabapentin is a compound that was originally designed as a GABA mimetic, however, it has since been shown that gabapentin may exert its efficacy through a novel mechanism of action; through binding to an accessory protein of a calcium channel (see below for further details). Gabapentin has also more recently (2002) been approved for pain management of postherpetic neuralgia in adults. However, off-label use of gabapentin for indications such as panic disorder, migraine prophylaxis, social phobia, mania, bipolar disorder and alcohol withdrawal may have also significantly contributed to the commercial success of this drug[1-3].

In addition to L-type calcium channels and voltage-gated sodium channels, ATP-regulated potassium channels have also received focus as key ion channel therapeutic targets for the treatment of type II diabetes[4]. The sulphonylurea potassium channel blockers exemplify this success. These include Aventis's Amaryl® (glimepiride), which binds to sulphonylurea receptor-1. This receptor forms a multimeric complex with the Kir6.2 potassium channel on pancreatic beta cells that regulate insulin release.

Ligand-activated anion channels such as the $GABA_A$-receptor chloride channel complex have also been successfully targeted for the treatment of

Insomnia. In 1999, Wyeth received approval of Sonata® (zaleplon), for short-term treatment (7-10 days) of insomnia in adults.

Thus, the pharmaceutical industry has successfully developed a wealth of therapeutics targeted at selected calcium, potassium, sodium and chloride channel targets. Given the number of genes identified in the human genome project it would appear that there remains a significant pool of unexploited space within the ion channel field for this clearly pharmacologically tractable target class.

Recent developments

Given the historical success of targeting ion channels in drug discovery, the development of new screening technologies and a greater understanding of the genetics, structure and function of ion channels, expectations of ion channel drugs have remained high. It is therefore interesting to note that since 1997, the number of entirely ion channel drugs approved by the FDA has been limited. However, in this period, discounting new formulation and incremental improvements to existing therapies, there have been a few notable developments that expand the diversity of clinically validated therapeutic ion channel targets.

Recent approvals include Prialt® (ziconotide) from Elan Corporation in 2004. Prialt® is a synthetic equivalent of a naturally occurring conopeptide found in a marine snail known as *Conus magus*, which selectively blocks N-type calcium channels on sensory neurones. This drug is administered intrathecally via a surgically implanted catheter, and is indicated for the management of severe chronic pain in patients for whom intrathecal therapy is warranted, and who are intolerant of or refractory to other treatment, such as systemic analgesics, adjunctive therapies or intratheal morphine. Prialt® represents development of the first clinically approved N-type calcium channel blocker and provides a clinical exemplification of a new mechanistic approach for this target for the treatment of serve pain syndromes. However, given the limitations afforded by a peptide-based drug and intrathecal administration, significant opportunities for the next-generation of orally available small molecule N-type calcium channel blockers exist. Indeed these opportunities can be can be further exemplified by the recent research and in-licensing deal signed between Neuromed, Inc and Merck which includes Neuromed's lead drug candidate, NMED-160, an N-type calcium channel blocker which is in midstage testing for chronic pain. Under the terms of the agreement, Merck has made an initial payment of $25 million to Neuromed and will pay an additional $450 million in milestone payments based on the success of its experimental products for pain and other neurological disorders. Thus considerable commercial opportunities exist for the novel modulators of ion channels in areas of unmet medical need.

In a further significant advancement in ion channel drug discovery, FDA approval has also been given for the first therapeutic use of a selective chloride channel activator (non-ligand gated chloride channel). Anionic channels, which appear relatively underexploited compared with their cationic channel counterparts are emerging as key therapeutic targets as their role in physiological and pathophysiological functions advances[5]. In early 2006, Sucampo Pharmaceuticals, Inc announced that the FDA had approved the new drug application for AMITIZA™ (lubiprostone), a CLC-2 chloride channel activator capsules, for chronic idiopathic constipation in adults.

An example of an ion channel drug which exerts its effects through a novel mechanism of action (through binding to ion channel accessory proteins) Pfizer's Neurontin® (gabapentin), lost its product exclusivity in mid-2005. Consequently, Pfizer introduced Lyrica® (pregabalin), an analogue of gabapentin, which gained FDA approval in late 2004 for use in neuropathic pain associated with diabetic peripheral neuropathy and postherpetic neuralgia; making it the first FDA-approved treatment for both of these neuropathic pain states and further exemplifying the role of calcium channels as important therapeutic targets in neuropathic pain states.

Additional recent developments have also seen Novartis receive FDA approval in 2001 for its oral therapeutic agent Starlix® (nateglinide) for the management of type II diabetes. Nateglinide is a non-sulphonylurea ATP-regulated potassium channel blocker.

Noticeably, since 2000, only Prialt® and Amitiza™ address 'new' ion channel targets indicating perhaps an underlying difficulty in progressing ion channel modulators though development and on to the market and also highlighting a void of new ion channel drugs.

Ion channel discovery

Multimeric ion channel complexes as therapeutic targets

Ion channels are a complex scaffold of multimeric proteins which display differential cellular and tissue specific expression patterns. The core membrane spanning domains of ion channels form the channel 'pore'. These pore-forming domains

References

1 Mathew, NT, Rapoport, A, Saper, J, Magnus, L, Klapper, J, Ramadan, N, Stacey, B and Tepper, S. Efficacy of gabapentin in migraine prophylaxis. Headache, 41, 119-28, (2001).

2 Chouinard, G. The search for new off-label indications for antidepressant, antianxiety, antipsychotic and anticonvulsant drugs. J Psychiatry Neurosci., 31, 168-176, (2006).

3 Hamer, AM, Haxby, DG, McFarland, BH and Ketchum, K. Gabapentin use in a managed medicaid population. J. Manag. Care Pharm., 8, 266-71, (2002).

4 Proks, P and Lippiat, JD. Membrane ion channels and diabetes. Curr. Pharm. Des., 12, 485-501, (2006).

5 Kozlowski RZ (Ed): Chloride channels. Publ: ISIS Medical Media, Oxford (1999).

6 Birch, PJ, Dekker, LV, James, IF, Southan, A, Cronk, D. Strategies to identify ion channel modulators: current and novel approaches to target neuropathic pain. Drug Discov. Today., 9, 410-8, (2004).

7 Xu, J, Wang, X, Ensign, B, Li, M, Wu, L, Guia, A and Xu J. Ion-channel assay technologies: quo vadis? Drug Discov. Today., 6, 1278-1287, (2001).

8 Townsend, C. Population patch-clamp: an enabling technology for the discovery of potassium channel openers. 2006 Automated Electrophysiology Users Meeting, Salt Lake City (2006).

9 Yu, FH and Catterall, WA. Overview of the voltage-gated sodium channel family. Genome Biol., 4, 207, (2003).

10 Hockerman, GH, Johnson, BD, Abbott, MR, Scheuer, T and Catterall, WA. Molecular determinants of high affinity phenylalkylamine block of L-type calcium channels. J. Biol. Chem., 270, 22119-22122, (1995).

11 Levitan, IB. Signaling protein complexes associated with neuronal ion channels. Nat. Neurosci., 9, 305-10, (2006).

Continued on page 89

Table 2: Key high-throughput electrophysiology providers

INSTRUMENT	SUPPLIER	WEBSITE
CytoPatch™ Automat	Cytocentrics AG	www.cytocentrics.com
Dynaflow 16	Cellectricon AB	www.cellectricon.com
Flyscreen® 8500	Flyion GmbH	www.flyion.com
Ion Works® HT	Molecular Devices Corp	www.moleculardevices.com
IonWorks® Quattro™	Molecular Devices Corp	www.moleculardevices.com
OpusExpress® 6000A	Molecular Devices Corp	www.moleculardevices.com
PatchExpress® 7000A	Molecular Devices Corp	www.moleculardevices.com
NPC-1 Port-a-Patch	Nanion Technologies GmbH	www.nanion.de
QPatch 16	Sophion Bioscience A/S	www.sophion.dk

(PFDs) control the flow of sodium, calcium, potassium or chloride ions in response to a number of stimuli such as voltage, ligand binding and pH which subsequently regulate the conformational state of ion channels (eg, open state, closed state and inactivated state)[6].

Ion channel screening

Electrophysiology is the 'gold standard' methodology for ion channels research, which allows detailed kinetic and pharmacological analysis of potential drug molecules in real time. This information is of critical importance in attempts to optimise compounds as they progress though the hit to lead stages of a drug discovery programme. However, the key limitation of classical resource-intensive electrophysiology is throughput. To address these limitations, a number of high-throughput assays have been developed for ion channel screening. These include radioactive flux assays and also non-radioactive flux assays such as atomic absorption spectroscopy, fluorescence assays and colorimetric assays. This area has been reviewed recently[6,7] and provides key tools for screening large compound collections in hit identification programmes. However, such methodologies possess some limitations associated with physiological correlation and temporal resolution[6,7] which are central to driving medicinal chemistry programmes though the hit to lead process.

More recently, advances in high-throughput electrophysiological techniques have been introduced which go some way to circumventing these problems. Key providers of currently available high-throughput electrophysiology systems are summarised in **Table 2**. Nanion Technologies GmbH has successfully established its entry level device for automated patch clamp, the NPC©-1 port-a-patch©, and is now launching its second generation instrumentation, the NPC©-16 patchliner©. The patchliner© is a robotic multi-channel patch clamp workstation for high quality cellular electrophysiology with increased throughput capabilities. Nanion claims good success with gigaseal formation (60-80%). Molecular Devices Corp has incorporated population patch clamp technology™ in its IonWorks® Quattro™. This uses multiple recording sites within each well to improve success rate and thus reduce the need for sampling in quadruplicate which was a requirement for its original IonWorks® HT. Seal resistances are still only in the order of a hundred megaohm at best, however, and one group from Glaxosmithkline reported that the seal resistance using population patch clamp technology™ was actually worse than that for the single hole system in its studies of KCNQ2/3 activators[8]. The technology clearly is now able to provide a greater degree of quantification and reproducibility than with the earlier high-throughput electrophysiology systems but it is still the case that the methodology is best suited at present to screening strategies based around cloned ion channel targets expressed in cell lines rather than study of native cell systems.

Given the limitations of these systems for use with native cells, compared with cell-lines or cloned ion channels expressed in cell systems, the issues of physiological relevance need to be clearly

understood. Cloning efforts have identified a diverse range of ion channels with further diversity being apparent as a consequence of alternative spicing of gene products and/or heteromeric assembly. Such genetic variation occurs both with the principal pore-forming subunits and their accessory proteins. Despite this diversity, it has been possible to use molecular correlates of native channels to identify compounds that bind to the pore-forming domains of ion channels. Compounds identified using such models have been shown to retain predictable activity in native tissues and, as such, high-throughput screening utilising these technologies offers a significant opportunity. However, to identify compounds that interact at modulatory sites of ion channels, or their accessory proteins, an enhanced temporal resolution of channel kinetics and a good understanding of their molecular physiology in native tissues is required. The development of new screening strategies for the identification of ion channel modulators therefore requires development of a strategy for understanding the selectivity of potential ion channel drugs across related target channels. This strategy must encapsulate (i) an understanding of the mode of compound binding to ion channels (open state, closed state, inactivated state); and (ii) an understanding of the physiological correlation between the composition of ion channel protein-complexes and their cytoplasmic signalling pathways in the desired target tissue.

Such factors are particularly important to achieve channel-specific or sub-type selective modulators when working with ion channels that possess a high degree of homology between pore-forming domains. The homologous nature of pore-forming domains of ion channels[9] – the region which retains the binding site for many ion channel blockers[10] – is perhaps one of the key hurdles that has contributed to the recent failings in discovery of selective ion channel drugs (see **Figure 1**). As a consequence of this, alternative mechanisms for modulating ion channel function are being exploited in order to increase the subtype selectivity of potential ion channel drugs.

Emerging screening strategies – ion channel accessory protein drug discovery

Given the paucity of new drugs arising from targeting of the pore-forming domain of ion channels, strategies have been developed to consider modulatory sites on the ion channel complex. There is a plethora of accessory proteins whose role is to fine tune the total current flowing through the ion channel and this is achieved predominantly by regulation of either the kinetics of the current or the chaperoning of pore-forming subunits to the cell membrane[11]. To illustrate this further, two examples will be considered.

Calcium channels

Voltage-activated calcium channels are modulated by a number of accessory proteins which include the α2, β, γ, and δ subunits[12]. Cavβ subunits modulate the biophysical characteristics of Cav currents[13]. The Cavβ subunits of voltage-dependent calcium channels also play an important role in controlling the surface expression of α1 subunits in mammalian cells by binding to a site known as the alpha interaction domain (AID) present in the intracellular linker between domains I and II of the α1 subunits[13]. Interestingly, trafficking of Cavα1 subunits is also under the control of the α2δ subunit[14] and this appears to be the binding site for Pfizer's Neurontin® (gabapentin)[15].

Gabapentin was originally designed as a GABA mimetic and found to be useful as an adjunct for partial seizures. It has now been shown to have efficacy in a wide range of disease states including postherpetic neuralgia[16] and painful diabetic neuropathy[17]. Four members of the α2δ subunit have been identified so far and gabapentin binds with the highest affinity to the α2δ-1 subunit[18]. This subunit is also up-regulated in gabapentin-sensitive animal models of neuropathy[19].

Given the important roles accessory proteins play in regulating ion channel function, Lectus Therapeutics Limited (Lectus) has developed a proteomics-based approach to identifying ion channel modulators that exhibits its pharmacological effects through such proteins. Lectus uses its LEPTICS® technology to immobilise folded, functional ion channel accessory proteins on screening substrates. These are then interrogated with fluorescently labelled interaction domains of the pore-forming domain of the ion channels themselves in the presence of test compounds. LEPTICS® has already been used to identify novel Cav channel modulators following immobilisation of Cav, accessory protein subunits which were interrogated with the alpha interaction domain (AID) of the α1 subunit of the Cav2.2 channel[20]. Older less efficient technologies have also been used to similar effect. Young et al[21] developed a counterselection yeast-two hybrid assay, based on the intracellular linker between domain I and II of the α1 subunit of Cav2.2 and the Cavβ3 subunit, to detect compounds that would inhibit this interaction. Subsequently, hit compounds were also shown to

Continued from page 86

12 Catterall, WA. Structure and regulation of voltage-gated Ca^{2+} channels. Annu. Rev. Cell Dev. Biol., 16, 521-55, (2000).
13 Dolphin, AC. Beta subunits of voltage-gated calcium channels. J. Bioenerg. Biomembr., 35, 599-620, (2003).
14 Canti, C, Davies, A and Dolphin, AC. Calcium Channel α2δSubunits: Structure, Functions and Target Site for Drugs. Current Neuropharmacology. 1, 209-217 (2003).
15 Gee, NS, Brown, JP, Dissanayake, VU, Offord, J, Thurlow, R and Woodruff, GN. The novel anticonvulsant drug, gabapentin (Neurontin), binds to the alpha2delta subunit of a calcium channel. J. Biol. Chem., 271, 5768-76, (1996).
16 Rice, AS and Maton, S. Gabapentin in postherpetic neuralgia: a randomised, double blind, placebo controlled study. Pain, 94, 215-24, (2001).
17 Rowbotham, M, Harden, N, Stacey, B, Berntein, P and Magnus-Miller, L. Gabapentin for the treatment of postherpetic neuralgia: a randomized controlled trial. JAMA, 280, 1837-42, (1998).
18 Marais, E, Klugbauer, N and Hofmann, F. Calcium channel alpha(2)delta subunits-structure and Gabapentin binding. Mol.Pharmacol., 59,1243-8, (2001).
19 Li, CY, Song, YH, Higuera, ES and Luo, ZD. Spinal dorsal horn calcium channel α2δ-1 subunit upregulation contributes to peripheral nerve injury induced tactile allodynia. J. Neurosci., 24, 8494-8499, (2004).
20 Kanumilli, S, Ginham, R, Stafford, S, Hogg, D and Kozlowski, R. In vitro assay for identifying modulators of Cav channel α1–β subunit interactions. J. Physiol., 568P,PC16,(2005).

Continued on page 90

Continued from page 89

21 Young, K, Lin, S, Sun, L, Lee, E, Modi, M, Hellings, S, Husbands, M, Ozenberger, B and Franco, R. Identification of a calcium channel modulator using a high throughput yeast two-hybrid screen. Nat. Biotechnol., 16, 946-50, (1998).
22 Rettig, J, Heinemann, SH, Wunder, F, Lorra, C, Parcej, DN, Dolly, JO and Pongs, O. Inactivation properties of voltage-gated K^+ channels altered by presence of beta-subunit. Nature, 369, 289-294, (1994).
23 Heinemann, SH, Rettig, J, Graack, HR and Pongs, O. Functional characterization of Kv channel beta-subunits from rat brain. J. Physiol., 493, 625-633, (1996).
24 Morales, MJ, Castellino, CR, Crews, AL, Rasmusson, RL and Strauss, HC. A novel beta subunit increases rate of inactivation of specific voltage-gated potassium channel alpha subunits. J. Biol. Chem., 270, 6272-6277, (1995).
25 Gulbis, JM, Zhou, M, Mann, S and MacKinnon, R. Structure of the cytoplasmic beta subunit-T1 assembly of voltage-dependent K^+ channels. Science, 289, 123-7, (2000).
26 Stafford, S, Ginham, R, Davies, ARL, Lawton, G, Boden, PR and Kozlowski, RZ. In vitro assay for identifying modulators of Kv channel α-β subunit interactions. J. Physiol., 567P, C89, (2005).
27 Zhang, ZH, Rhodes, KJ, Childers, WE, Argentieri, TM and Wang, Q. Disinactivation of N-type inactivation of voltage-gated K channels by an erbstatin analogue. J. Biol. Chem., 279, 29226-30, (2004).
28 Decher, N, Pirard, B, Bundis, F, Peukert, S, Baringhaus, KH, Busch, AE, Steinmeyer, K and Sanguinetti, MC. Molecular basis for Kv1.5 channel block: conservation of drug binding sites among voltage-gated K^+ channels. J. Biol. Chem., 279, 394–400, (2004).

Continued on page 92

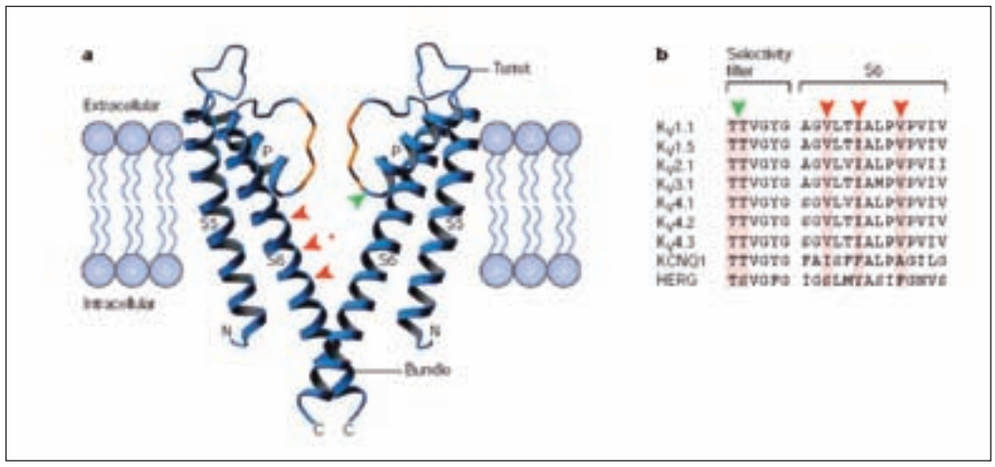

Figure 1: Homology of the K^+ channel pore region presents a hurdle in the design of channel-specific blockers
a) Typical structure of the pore region of a voltage-gated K^+ (Kv) channel elucidated by the X-ray crystal structure of KcsA3 (Only two of the four identical subunits are shown.) The pore helices are labelled P, and the central cavity is indicated by a red asterisk. The green triangle points to the position of the two threonine residues located at the base of the pore helix. The side chains of these threonine residues and a few residues (red triangles) of the S6 helices face the central cavity and are common sites of interaction with pore blockers
b) The sequence alignment of key regions near the selectivity filter and S6 domains of several Kv channels are shown. Residues that face the central cavity of the channel are shaded in red. Blockers of Kv1.5[28], KCNQ1[29] and human ether-a-go-go-related gene HERG[30] channels have been reported to interact with these residues. The key residues of Kv1-Kv4 channels are identical, illustrating the difficulty in discovering specific drugs for these channels. Drugs that effect channel gating or block through alternative mechanisms, such as (i) binding to variable domains of the outer pore region of the channel, (for example, the turret structure in part a) or (ii) binding to ion channel accessory proteins; may lead to greater selectivity for target channels
 Part a) modified, with permission, from Jiang et al[31]

inhibit N-type calcium channels in superior cervical ganglion (SCG) neurones and display selectivity over structurally-related sodium channels in SCG neurones and cloned Kv1.2 and Kv2.1 potassium channels expressed in mammalian cells, suggestive of channel selectivity.

The modulatory nature of compounds which act by disrupting the interaction between the pore-forming domain and accessory proteins may indeed provide the basis for an enhanced selectivity profile. However the additional complexity introduced by the protein-protein interaction necessitates the use of native cells in conjunction with classical electrophysiology for detailed analysis of the often subtle effects mediated via ion channel accessory proteins.

Potassium channels

The second example is one of the most widely studied ion channel accessory proteins, the Kvβ subunit of the delayed rectifier (Kv1.x) potassium channels. Currents measured through the α subunit Kv1.x channels show an increased rate of inactivation when co-expressed with the Kvβ1 subunits in Xenopus[22,23]. These alterations in the kinetics of the potassium currents would appear to be Kvβ-subunit specific. For example, co-expression of either the Kvβ2 or Kvβ3 subunits with Kvα pore forming domain does not alter inactivation rates[24]. On this basis, Lectus, using LEPTICS®, has immobilised Kvβ accessory protein subunits on a screening substrate and interrogated them with different T1 domains (the corresponding Kv1.x channel interaction sites located on the N-terminus of the α subunit[25]) to identify novel inhibitors of this interaction[26].

In an alternative approach to this same target, using a high-throughput yeast-two-hybrid screen, Zhang et al[27] have also identified small molecules which inhibit the interaction domain between the inactivation region of either Kvβ1 subunits or the intrinsic inactivation region of Kv1.4 channels with a putative acceptor site located on the S4-S5 intracellular loop of the channel α subunit.

These approaches demonstrate significant advancement in developing alternative strategies for modulation of ion channel function and collectively offer a differentiated approach to existing screening technologies for the identification of new classes of ion channel modulators.

Continued from page 90

29 Seebohm, G, Chen, J, Strutz, N, Culberson, C, Lerche, C and Sanguinetti, MC. Molecular determinants of KCNQ1 channel block by a benzodiazepine. Mol. Pharmacol., 64, 70–77, (2003).
30 Mitcheson, JS, Chen, J, Lin, M, Culberson, C and Sanguinetti, MC. A structural basis for drug-induced long QT syndrome. Proc. Natl Acad. Sci. USA, 97, 12329–12333, (2000).
31 Jiang, Y. et al. The open pore conformation of potassium channels. Nature 417, 523–526 (2002).

Conclusions

Advancements in structural and molecular biology coupled with those in screening technology should help overcome the present hiatus in development of novel ion channel therapeutics. Additionally, alternative approaches to the targeting of ion channels, via modulation of their accessory proteins, will also add to the repertoire of strategies available for identifying compounds differentiated from those that have so far experienced limited success in development. Given the current investment in this field, the next decade has the potential to yield therapeutics targeting ion channels in a broad range of disease indications that remain ineffectively treated including overactive bladder, pain, autoimmune disorders, osteoporosis and COPD. DDW

Dr Dayle S. Hogg *is the Commercial Manager at Lectus Therapeutics Limited. Dayle plays a key role in developing strategic alliances, pursuing partnering/collaborative opportunities, evaluating new commercial opportunities and securing commercial deals with service providers. Dayle was part of the team that secured the strategic investment from Takeda Research Investment and also the recent Series A financing for the company. Dayle previously worked within Business Development at Sense Proteomic Ltd, whose core business was the development and sale of functional protein array products. Dayle received a BSc degree from the University of Leeds and a DPhil from the University of Oxford. At a research level, Dayle trained as an electrophysiologist where his interests centred the role of ion channels in regulating pulmonary blood flow.*

Dr Philip Boden *worked for Warner-Lambert (now part of Pfizer) from 1984 to 1999. In that time he established the electrophysiology laboratories in Cambridge UK which pioneered the use of brain slices for drug testing. Dr Boden also served on project teams for many neuropeptide programmes and established a group with a research focus on molecular mechanisms underlying neuropeptide receptor/ion channel interaction in the central nervous system. Studies on Glucose Responsive neurons were reported from Dr Boden's laboratory in 1990 and he collaborated with members of the Pharmacology Department at the University of Cambridge, UK in further studies of these, leading to the first reports of the existence of ATP-K channels in rat brain. Dr Boden left his position as Senior Group Leader in Molecular Neurobiology at Warner-Lambert to establish his own company, NeuroServe, in 2000. Having been actively involved in the management of Lectus Therapeutics since 2004, he became full-time Director of Biology in April 2006 following the acquisition of NeuroServe by Lectus.*

Dr Geoff Lawton *is Research Director of Lectus Therapeutics Limited. Dr Lawton has extensive experience in drug discovery across many therapeutic areas with Roche and is co-inventor of a marketed drug (Cilazapril). His roles at Roche included Head of Medicinal Chemistry and Director of Chemistry within Roche UK, and Vice-president Chemistry and Preclinical Sciences within Roche Bioscience, Palo Alto, USA. Prior to joining Lectus, Dr Lawton provided evaluation and advice on drug discovery projects as an independent consultant for a number of different companies.*

Dr Roland Z. Kozlowski *is the principal founder and CEO of Lectus Therapeutics Limited. He has led the company through both seed and a recent £8.2 million series A financing round. As part of the financing strategy of the business he executed a strategic alliance with Takeda Research Investment, the investment arm of Takeda Pharmaceutical Company. Roland was until December 2002 CEO and principal founder of Sense Proteomic Limited. At Sense he raised a total of £5.75 million from private equity sources and grew the business from a virtual start-up to a company operating with 30 staff. Under his leadership the company produced the world's first functional proteomics array product. Having developed the strategy for the business he led the Sense team to conclude a sale of the company to Procognia Limited as part of a $4 million financing of the combined businesses in December 2002. Before that, he was pivotal to the initiation and success of Oxford Molecular's Drug Discovery Division where he conducted business development for the company and won its cornerstone drug discovery deal with Yamanouchi Pharmaceutical Corp (Japan). Roland is on the Main Board of the Bio Industry Association and is a member of the faculty of the University of Bristol where he advises on enterprise strategy. Roland is an inventor on six patent applications in the proteomics arena and has more than 50 peer reviewed scientific publications in the ion channels field. He holds a First Class Honours Degree in Pharmacology from the University of Bath and a PhD in Pharmacology from the University of Cambridge. He formerly ran a research group in the Pharmacology Department at the University of Oxford and was a fellow of Brasenose College.*