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The Role of Sodium Channels in Disease

by Alan M. Palmer and Nick Carter

The September 2001 symposium focused on the role of sodium channels in disease. Native sodium channels exist as polypeptide multimers of an α-subunit (260kD) and subsidiary and smaller β-subunits (generally three different subunits: β_1, β_2 and β_3). The α-subunits are structurally diverse, arising from multiple sodium channel genes and alternative splicing events. Recent progress has led to a good understanding of the molecular structure of sodium channels, how they work and the significance of their expression in particular cell types. This, coupled with experimental studies linking particular isoforms with particular disease states and the discovery of distinct human sodium channelopathies (specific mutations in specific isoforms that cause a variety of diseases, including paralysis, long QT syndrome and epilepsy), is beginning to reveal how particular sodium channel subtypes underlie specific pathologies. All this provides great potential for the development of new therapies. The first generation of sodium channel blockers has led to a broad-spectrum anti-convulsant that is now used widely (lamotrigine) and an impressive neuro-protective agent that is in clinical trials for stroke (sipatrigine). The development of the next generation of sodium channel blockers will be greatly facilitated by an elaboration of the pharmacology of the various isoforms, which itself is dependent upon the existence of reliable, rapid and high-throughput assays for sodium channel activity.

Introduction

Sodium channel activity is intrinsic to neurotransmission and therefore has a central role in normal neuronal function. Sodium channels are highly selective molecular pores, the opening and closing of which shape membrane potential changes and give rise to characteristic action potentials. Over-activation of sodium channels can lead to neuronal dysfunction. Thus, the depolarisation of plasma membranes that occurs in acute brain injury (such as stroke and traumatic brain injury) or over-stimulation of certain neurones (such as that occurring in chronic pain

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Malcolm Duckworth: New SMR Chairman

Dr Malcolm Duckworth has taken over as the Chairman of the Society for Medicines Research. All his industrial life has been spent in research in the pharmaceutical industry. He started as a medicinal chemist with Beecham Pharmaceuticals in the late 1970s at the Walton Oaks Research Site in Surrey and continued in that discipline with SmithKline Beecham where he gained experience in metabolic, anti-infective and CNS disease areas. His emerging interest in genomics led to him to move into Bioinformatics in 1997. He is currently head of a bioinformatics group in Glaxo-SmithKline with responsibility for supporting the European Centres of Excellence for Drug Discovery, and is based at Harlow in Essex.

Dr Duckworth has always been a strong supporter of the SMR. He joined the Committee in 1995 and became the Honorary Secretary in 1998.•

Case Histories Meeting

by the SMR Committee

The Society for Medicines Research (SMR) held a one-day meeting on Case Histories in Drug Discovery on 6 December 2001 at the National Heart and Lung Institute in London. These meetings have been organised by the SMR biannually for many years and this latest meeting of the series attracted over 100 registrants. The purpose of these meetings is educational: it allows those interested in drug discovery to hear succinct accounts of recent successes. There was no overall linking theme between the talks other than that each success story has led to the introduction of a new and improved product for therapeutic use. The drug discovery stories covered in the meeting were extremely varied and, put together, emphasised that each successful story is individual and special. This meeting is also special for the SMR in that it presents its 'SMR Award for Drug Discovery' in recognition of outstanding achievement and contribution in the area. These successes were considered in the context of the high risk of failure in drug discovery and the rarity of successful new product introduction.

The programme included two unrelated talks on chiral drugs both of which have a currently marketed racemate — single isomer switches. **Dr Sverker von Unge (AstraZeneca, Sweden)** related the account of the development of nexium (esomeprazole) (2), the S-enantiomer of the proton pump inhibitor, Losec (omeprazole) (1), the top-selling anti-ulcer drug. To understand why esomeprazole was developed, it was important to know the origin and mechanism of action of the racemate. Omeprazole was discovered in the late 1970s as a blocker of gastric-acid secretion and came from a medicinal chemistry programme based on a

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SMR Committee

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pyridine-based thioamide. Elucidation of the mechanism of action of omeprazole showed that it was a prodrug which relies on a protonated form of the compound reacting with the enzyme H^+/K^+ ATPase. The basicity of the pyridine is important. While the free base is acid labile, if present in sufficient quantity, it can penetrate the parietal cells of the gastric mucosa wherein the protonated form made inside the cells accumulates, because of much-reduced permeability. In a reversible process, a reactive intermediate is formed from the protonated omeprazole, which reacts with a mercapto group of the enzyme. Omeprazole, therefore, has a fast mode of action at the target, which leads to high selectivity and a long duration of action. However, improvements were sought in pharmacokinetic profile, in terms of less inter-individual variability and greater resistance to gastric juice.

Several hundred compounds were synthesised in the search but none could surpass omeprazole. An ongoing project was to test fully both enantiomers since either might meet the requirements for a backup compound. With improved methods for synthesising large quantities of each isomer, it was shown that both isomers have identical enzyme inhibitor potency *in vitro*, but *in vivo*, in rats, the R-isomer was more potent and had higher bioavailability compared with the S-isomer. Alkaline salts of the isomers were found to be crystalline which was also advantageous for future clinical studies. Surprisingly, in man, there was a reversal of isomer superiority with the S-isomer showing 90% inhibition of stimulated acid secretion compared with 25% for the R-isomer after 15mg p.o., day 7. In addition, the clearance of the S-isomer was slower by approximately one-third of the R-isomer. Individual differences were explained by variations in the metabolic enzyme CYP2C19. This form of the enzyme does not exist in the rat. In summary, nexium is superior to omeprazole because of advantageous metabolism, acid control is greater, faster, more sustained and more predictable, thus improving the clinical efficacy. To give some idea of the time scale, the omeprazole project first began in 1972 and nexium was launched in Sweden in 2000.

The second isomer talk was given by **Dr Robert Gristwood (Arachnova Ltd)** who described the story behind Chirocaine™ (levobupivacaine) (3), the single-levo enantiomer of the racemic drug bupivacaine (4), currently the leading long-acting local anaesthetic. Chirocaine was developed through to registration by Chiroscience Ltd (now part of Celltech Group) and is currently marketed in 11 countries (the first in 2000), including the US. It represented the first new chemical entity from a 'UK biotech company' to be approved in the US by the FDA in 1999. Dr Gristwood gave some background to single-isomer switches and reasons why they should be considered. Some advantages may be to give drugs that are less toxic, or more potent, or that have cleaner pharmacokinetic profiles. Over 500 drugs currently exist as racemates but possibly only 5% are suitable. Unfortunately, the properties of the enantiomers are not predictable from the racemates, for example, liver toxicity is seen with an enantiomer of labetalol and QT prolongation is observed for R-fluoxetine.

The story behind Chirocaine provided an interesting strategic contrast to the nexium story. Adopting a systematic evaluation of racemic drug opportunities, bupivacaine was identified as a candidate for a single isomer switch. The decision to proceed with development in 1993 was based on Chiroscience's expertise in single-isomer synthesis and development, the hypothesis that levobupivacaine had similar local anaesthetic activity to the racemate but lower cardiotoxicity in man, and the ability to protect the product commercially through use-and-process patents despite the absence of a substance-of-matter patent. In order to evaluate data clearly the metabolism of chiral drugs has to be considered as it can often lead to racemisation or chiral inversion, which would negate the advantages. In the case of levobupivacaine, the compound is metabolised to inactive species rather than to the dextro isomer. Evidence from animal species showed that Chirocaine is less toxic than the racemate, e.g. less effective in isolated hearts, less active on myocardial

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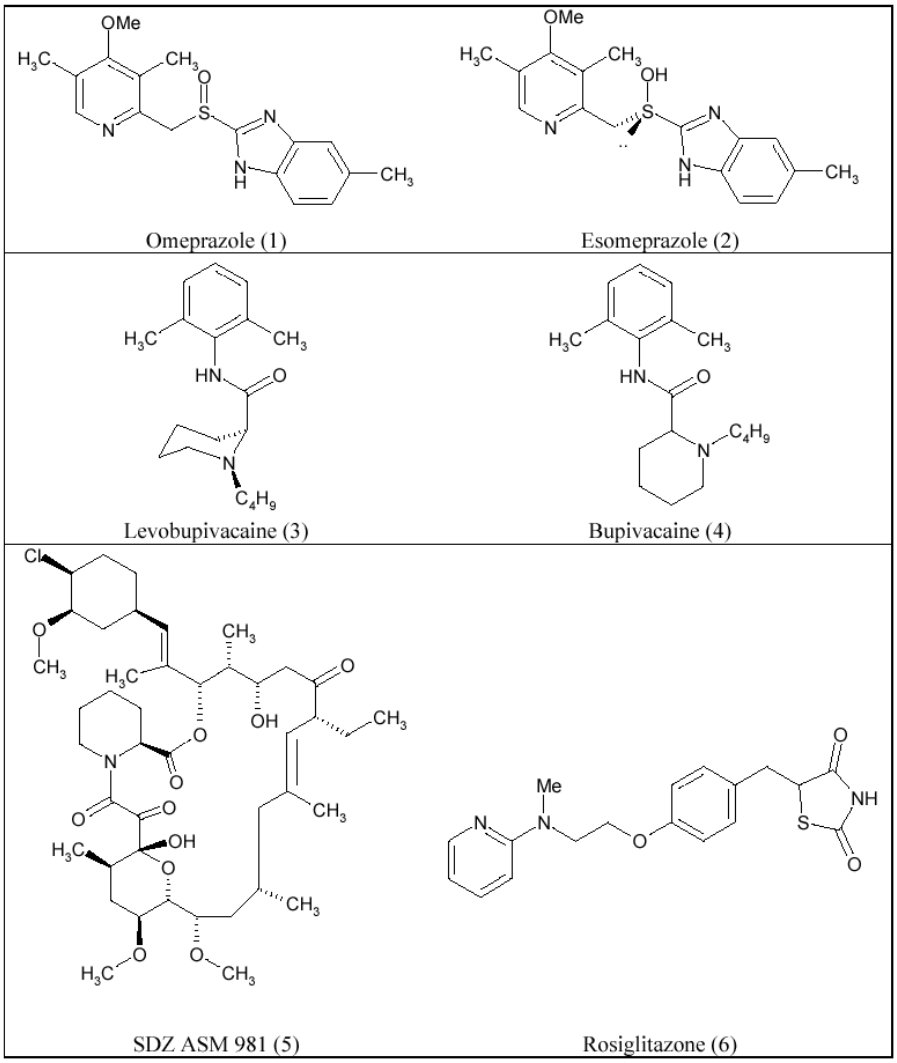

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sodium and potassium channels. Phase I studies in humans (clinical proof-of-principle studies) looking at cardiovascular parameters after intravenous administration confirmed the preclinical evidence that the levo isomer was less toxic than the racemate while in an efficacy study (ulnar nerve blockage) there were no differences in anaesthetic potency. Following successful Phase II studies, Chirocaine was licensed for a number of routes of clinical administration (e.g., epidural, intrathecal, peripheral block). Phase III efficacy studies were completed in 1996. Chirocaine was approved by the FDA without the black box warning regarding cardiovascular liability then associated with bupivacaine. It has not, however, totally displaced bupivacaine. It does cost approximately 50% more than the racemate in the UK so increased usage will depend on perceived cost-benefit considerations and perceived risks with bupivacaine.

Professor Anton Stuetz (Novartis Research Institute, Vienna) described the discovery and development of pimecrolimus (Elidel, SDZ ASM 981) (5), a new skin-selective option for topical and oral treatment of inflammatory skin diseases. Current treatments for inflammatory skin diseases such as corticosteroids, cyclosporin-A or tacrolimus (FK 506), have a number of deficiencies, most notably induction of skin atrophy, a lack of topical effect or systemic side-effects. Pimecrolimus was the successful outcome of a structure–activity relationship study of the natural product macrolactam ascomycin. It binds in low nanomolar concentrations to macrophilin-12 and inhibits calcineurin, a phosphatase, preventing phosphorylation of a transcription factor ultimately leading to a down regulation of inflammatory cytokines in T-cells, such as IL4.

Elidel is cell selective and highly effective in animal models of skin inflammation, such as the pig model of allergic contact dermatitis. This is predictive for humans as the skins of the two species are very similar. Unlike corticosteoids, Elidel does not induce skin atrophy. With respect to tacrolimus, Elidel is more lipophilic with a higher affinity for skin. Thus, it distributes more preferentially in skin, but because it permeates through it only slowly, it has a reduced systemic side-effect profile. It is much less immuno-suppressive and overall has an improved therapeutic window of anti-inflammatory to immuno-suppressive profile. There is minimal systemic absorption, regardless of age, and Elidel cream 1% shows rapid relief of atopic dermatitis and pruritus, suitable for short- and long-term treatment in adults, children and babies. Treatment success is maintained over six months.

Orally, pimecrolimus has also been shown to be effective, safe and well tolerated in patients with moderate to severe plaque psoriasis. By integrating disease knowledge with pharmaco-genomic gene expression technology, it was possible to link mRNA expression with therapeutic progress, and also find potential indicators of side-effects, by profiling blood samples following oral Elidel treament. One hundred and sixty-three genes were identified with consistent behaviour related to psoriasis pathophysiology, such as down-regulation of genes associated with leucocyte activation, lymphocyte infiltration and inflammatory process. No changes in gene expression were observed that might be linked to drug-related side-effects. Currently Elidel cream is under review for registration worldwide for topical treatment and is undergoing further evaluation as an oral treatment.

The 2001 SMR Award for Drug Discovery was presented to the key members of the team that led to the discovery of rosiglitazone (Avandia, BRL 49653) (6), which was developed for the treatment of type 2 diabetes. **Michael Cawthorne, Stephen Smith, Barrie Cantello, Richard Hindley and David Haigh, scientists from the original Beecham Pharmaceuticals**

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states) leads to excessive sodium channel activity.

The pharmacology of sodium channels is currently very rudimentary, since they are distinguished on the basis of sensitivity to a toxin derived from puffer fish, tetrodotoxin. It is now known that native sodium channels exist as polypeptide multimers, comprising a large (260kD) α-subunit and smaller (33–36kD) modulatory β-subunits (there are at least three different subtypes: β_1, β_2 and β_3). The α-subunits are structurally diverse, arising from multiple sodium channel genes and alternative splicing events (see Table 1). Recent progress has led to a good understanding of the molecular structure of sodium channels, how they work and the significance of their expression in particular cell types. This, coupled with the therapeutic utility of sodium channel blockers for a number of disorders and the elucidation of distinct sodium channelopathies, is beginning to reveal how particular sodium-channel subtypes are linked to different disease states. All this provides great potential for the development of new therapies and underlines the attractiveness of this under-exploited class of compounds.

The discovery of compounds that block over-activated sodium channels, while permitting normal currents of sodium ions, has provided the basis to develop sodium channel blockers for the treatment of CNS disorders, such as stroke, traumatic brain injury and pain; sodium channel blockers may also be useful in treating other disorders. The ability of sodium channel blocking drugs to attenuate abnormal activity of sodium channels without affecting normal synaptic transmission probably underlies the good tolerability of sodium channel blocking drugs. The prototypic example of first-generation sodium channel blockers is the broad-spectrum anticonvulsant lamotrigine (Lamic-tal™) which is now used widely to treat epilepsy. Lamotrigine may also have utility in the treatment of other disorders, e.g. bipolar disorder. Another prototypic sodium channel blocker, with a different efficacy profile, is sipatrigine (BW619C89), which is derived chemically from lamotrigine. Sipatrigine is a neuro-protective agent now in clinical trials for stroke. The development of the next generation of sodium channel blockers will be greatly facilitated by elaboration of the pharmacology of the various isoforms of sodium channel subunits, which itself is dependent upon the existence of reliable, rapid and high-throughput assays for sodium channel activity. The presentations developed three themes:

1. The first generation of sodium channel blockers: lamotrigine and sipatrigine.
2. Relating structure to function.
3. The prospects for the next generation of sodium channel blockers.

First-generation sodium channel blockers

The two prototypic sodium channel blockers are the phenyltriazine lamotrigine and the phenylpryimidine sipatrigine (see Figure 1). Both were synthesised and developed by Wellcome scientists at Beckenham. Lamotrigine was synthesised as part of a programme to discover new antifolates and shown to have anticonvulsant efficacy. Sipatrigine arose from a programme to develop analogues of lamotrigine and was subsequently shown to have neuroprotective efficacy. At the time it was considered that the efficacy of both compounds was mediated by inhibition of the release of the excitatory amino acids aspartate and glutamate. However, John Garthwaite (who joined Wellcome as head of neuroscience in 1992, and is now at the Wolfson Institute for Biomedical Research, University College London) reasoned that the mechanism of action was not precisely defined since both compounds blocked veratrine-evoked release of EAAs, but not potassium-evoked release. The fact that veratrine evokes release by opening sodium channels suggested that it is sodium channel blockade that was underlying the efficacy of both lamotrigine and sipatrigine. This was then demonstrated directly by electro-physiological studies of cells expressing recombinant $Na_v1.2$ sodium channels (Xie and Garthwaite, 1996).

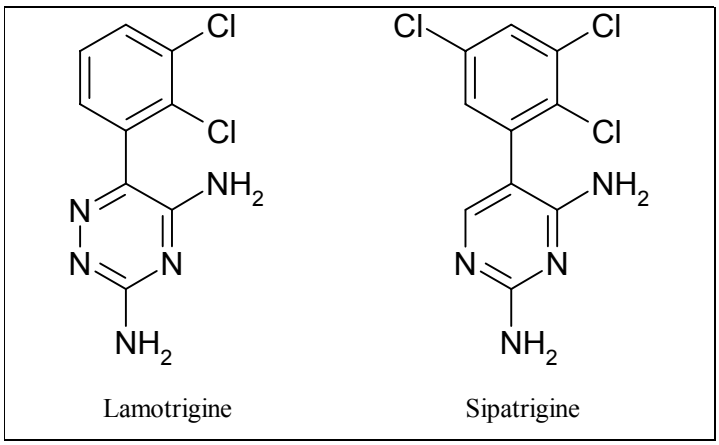

Figure 1 Prototypic first-generation sodium-channel blockers

Professor Garthwaite went on to describe how sodium channel blockers have great potential as therapies for disorders associated with neuro-degeneration since they protect both grey and white matter. He pointed out how the discovery of ways to protect the brain and spinal cord from degeneration in acute and chronic stress conditions represents one of major challenges facing neuroscience. Progress is clearly dependent upon understanding the underlying mechanisms, which are likely to be either specific to a particular disease state (for example, genetic susceptibility, viral infections) or more general (for example, those leading to cell death by necrosis or apoptosis). A step forward in understanding what might be one of the more general mechanisms was achieved over two decades ago with the realisation that glutamate is not only the main excitatory neurotransmitter in the brain, but also a powerful neurotoxin to many different CNS neurones. This work then led to the formulation of the 'excitotoxic' hypothesis wherein excessive glutamate receptor activation contributed to (or caused) neuronal cell death. Demonstrations that antagonists acting on glutamate receptors of both the NMDA and AMPA subclass were protective in animal models of stroke and trauma added weighty evidence in support of this hypothesis. The

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multiple failures of this approach in clinical trials in stroke victims, however, demands a rethink. It can be argued, with some justification, that the hypothesis was never subjected to proper experimental testing in humans (for example, inadequate dosing or too long a delay prior to drug administration; see Dawson et al., 2001). But another factor is that, to a greater or lesser extent, neuro-degenerative disorders affect both neurones in the grey matter and their axons running in the white matter. Moreover, the human brain has disproportionately more white matter than a rodent's. Hence, a better approach has to be one that is capable of protecting both grey and white matter.

Voltage-gated Na^+ channels are expressed at the surface of all neuronal elements (dendrites, somata and axons). Maintenance of ionic homeostasis in the face of continuous entry of Na^+ into the cytoplasm represents a major pathway for energy expenditure in the CNS. When energy is lacking (for example, because of poor blood perfusion) failure of Na^+ (and therefore K^+) homeostasis is expected to be one of the first consequences, with many secondary ones to follow should the situation persist. With excito-toxicity in full flurry, little thought was given to the possible importance of this pathway in neuro-degeneration, even though there were already clues in the literature that the classical Na^+ channel inhibitor, tetrodotoxin (TTX), had neuro-protective properties *in vitro* and *in vivo*. The identification of compounds that act in a voltage- and use-dependent manner on Na^+ channels (rather like some anticonvulsants) and protect grey matter at least as effectively as glutamate antagonists, provided additional evidence. Moreover, these compounds inhibited ischaemia-induced glutamate release, consistent with a primary action to preserve ionic homeostasis. Furthermore, investigation into the mechanism of ischaemic damage to white matter axons highlighted the central role played by Na^+ channels in triggering the axonopathy. In this case, irreversible damage appears to be the result of a secondary Ca^{2+} overload of the axoplasm. Hence, through targeting the same protein, it appears possible to provide dual protection of grey and white matter, at least in ischaemia. Whether any particular Na^+ channel subtype dominates in the pathogenesis of the damage remains unknown but channels that inactivate slowly on depolarisation may be especially significant.

Na^+ channels cycle between resting, activated and inactivated states. Inactivation proceeds many thousands of times faster when channels are open compared to their resting state. However, inactivation does proceed at a finite rate whenever membranes are depolarised from about -140 mV. Drugs that interact with Na^+ channels to block ion flux cause the channels to inactivate to a greater extent and with smaller depolarisations than they would normally exhibit. The relatively slow off-rate of drugs such as phenytoin means that there is an accumulated block with repeated

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Table 1 Mammalian sodium-channel α-subunits

Type	*Former name*	*Genbank number*[a]	*Gene symbol*	*Chromosomal location*	*Splice variants*	*Primary tissues*[c]
$Na_v1.1$	rat I HBSCI GPBI SCN1A	X03638 (r) X65362 (h) AF003372(gp)	SCN1A	Mouse 2 Human 2q24	$Na_v1.1a$	CNS PNS
$Na_v1.2$	rat II HBSCII HBA	X03639 (r) X61149 (r) X65361 (h) M94055 (h)	SCN2A	Mouse 2 Human 2q23-24	$Na_v1.2a$	CNS
$Na_v1.3$	rat III	Y00766 (r)	SCN3A	Mouse 2 Human 2q24	$Na_v1.3a$ $Na_v1.3b$	CNS
$Na_v1.4$	SkM1, μ-1 M81758 (h)	M26643 (r) Human 17q23-25	SCN4A	Mouse 11		Skeletal muscle
$Na_v1.5$	SkM2 H1	M27902 (r) M77235 (h)	SCN5A	Mouse 9 Human 3p21		Uninnervatec skeletal muscle, hear
$Na_v1.6$	NaCh6 PN4 Scn8a CerIII	L39018 (r) AF049239 (r) AF049240 (r) U26707 (m) AF049617 (m) AF050736 (h) AF225988 (h) AF003373 (gp)	SCN8A	Mouse 15 Human 12q13	$Na_v1.6a$	CNS, PNS
$Na_v1.7$	NaS hNE-Na	U35238 (rb) X82835 (h) PN1 U79568 (r) AF000368 (r)	SCN9A	Mouse 2 Human 2q24		PNS Schwann cel
$Na_v1.8$	SNS PN3 NaNG	X92184 (r) U53833 (r) Y09108 (m) U60590 (d)	SCN10A	Mouse 9 Human 3p22-24		DRG
$Na_v1.9$	NaN SNS2 PN5 NaT SCN12A	AF059030 (r) AJ237852 (r) AF118044 (m) AB031389 (m) AF126739 (h) AF188679 (h) AF109737 (h) AF150882 (h)	SCN11A	Mouse 9 Human 3p21-24	$Na_v1.9a$	PNS
Nax	$Na_v2.1$ Na-G SCL11 $Na_v2.3$	M91556 (h) M96578 (r) Y09164 (r) L36179 (m)	SCN7A SCN6A [b]	Mouse 2 Human 2q21-23		heart, uterus skeletal muscle, astrocytes, DRG

[a] The letter in parentheses after each accession number indicates the species of origin for the sequence, as follows: h, human; r, rat; rb, rabbit; m, mouse; gp, guinea pig; d, dog.
[b] This gene was originally assigned symbols SCN6A and SCN7A, which were mapped in human and mouse, respectively. The two most likely represent the same gene, and the SCN6A symbol will probably be deleted.
[c] DRG, dorsal root ganglion; PNS, peripheral nervous system; CNS, central nervous system (modified from Goldin et al., 2000).

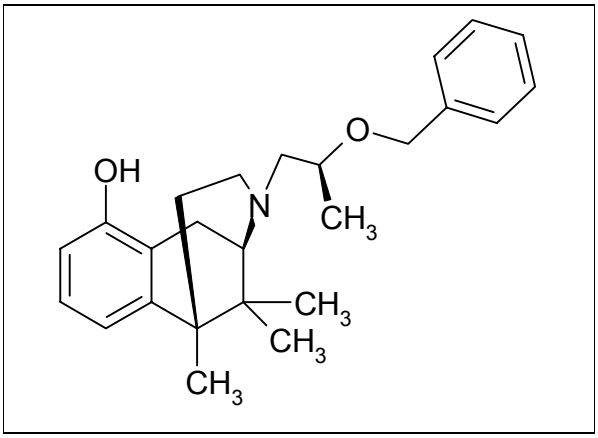

Figure 2 BIII890CL, which is in clinical trials for stroke

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depolarisations (use-dependent block). This means that, in the case of therapeutically relevant concentrations of phenytoin (8 μM), channel block is only significant if cells remain depolarised for at least five seconds. This may explain why phenytoin does not alter normal action potentials or excitatory synaptic potentials — these events last for less than 200ms. Sustained depolarisation, during ischaemia or seizures, greatly enhances the blocking action of phenytoin and similar drugs. Hodgkin and Huxley (1952) first described the three-state model for Na^+ channels, and a theory to explain use-dependent blockade of ion channels, termed the 'modulated receptor theory', has been developed based on their observations. This theory assumes that Na^+ channel blockers bind different channel states with different affinities, and that drug binding alters the transition rates between different states.

The study by Xie and Garthwaite (1996) showed that the inhibition of Na^+ currents by Sipatrigine BW619C89 is due to modulation of channel gating rather than an open channel block. A selective stabilisation of the inactivated state of the Na^+ channel appears directly to counter Na^+ entry into neurones and thus indirectly decrease depletion of ATP stores, calcium influx and excessive release of glutamate and aspartate. State-dependent modulation of Na^+ channels thus provides a mechanism for selective drug action, since only excessive activation is blocked, leaving normal synaptic transmission unimpaired. Sipatrigine, together with a number of other Na^+ channel blockers, has been shown to be effective in a number of models of acute brain injury (see Table 2). The spectrum of activity and the amount of efficacy achieved is impressive, particularly when compared with compounds that block the N-methyl-D-aspartate (NMDA) receptor. A number of Na^+ channel blockers have entered clinical trials for stroke, including sipatrigine, lifarizine, fosphenytoin (a phosphate ester prodrug of phenytoin) and lubeluzole.

Since Terry Smith (CeNeS Ltd) was not able to attend the meeting (or find a suitable replacement from his company) Alan M Palmer (Vernalis) presented Dr Smith's slides describing the clinical development of sipatrigine for the treatment of stroke. In addition to blocking Na^+ channels, sipatrigine has been shown to block a number of subtypes of Ca^{2+} channels (McNaughton et al., 2000), which may well contribute to the neuro-protective efficacy of this compound.

Several Phase II studies with this compound were completed by Wellcome and preliminary information on safety suggests that the development of visual hallucinations was the limiting factor in a dose-escalation study. Other side-effects included nausea, vomiting, agitation, confusion and drowsiness (Dorman et al., 1996). It is unlikely that these side-effects are due to blockade of Na^+ channels since they are not observed with lamotrigine, which is marketed for the treatment of epilepsy. The Phase II trial for BW619C89 (sipatrigine) was terminated when Glaxo merged with Wellcome and a decision was made to develop the NMDA (glycine site) receptor antagonist gavestinel (from Glaxo), which showed no efficacy in a randomised, double-blind, placebo-controlled trial (Lees et al., 2000).

Sipatrigine has undergone extensive preclinical studies leading to a series of clinical safety studies in both healthy volunteers and stroke patients. An efficacy study is planned in stroke patients using diffusion and perfusion weighted MRI to determine the effect of sipatrigine on infarct size as a surrogate marker. A dose-escalation study has commenced as a prelude to this study.

Sipatrigine has commenced development for clinical use. Preclinical safety and toxicology studies showed a profile of activity satisfactory for further development. Phase I intravenous studies in healthy volunteers reported no serious adverse events. In a series of safety and tolerance Phase II studies in stroke patients who received iv infusions of sipatrigine, the main adverse events observed were hallucinations and vomiting. Overall, therefore, sipatrigine has been shown to be clinically acceptable in healthy volunteers and stroke patients. From these data, there is good evidence that sipatrigine crosses the blood–brain barrier. There are insufficient data, however, to identify evidence of efficacy or the optimal dose of sipatrigine with which to establish such efficacy. To try to answer these questions, a clinical trial has commenced using MRI perfusion/ diffusion mismatches to investigate the effects of sipatrigine on a surrogate marker, namely the change in size of an ischaemic lesion in the cortex.

Lamotrigine for epilepsy

Dr Malcolm Nobbs (GlaxoSmithKline) gave the slides prepared by Marcus E Risner (GlaxoSmithKline, USA), who was unable to attend the meeting, that described lamotrigine as a treatment for epilepsy and other disorders. Lamotrigine (Lamictal), a chemically novel phenyltriazine, was synthesised and developed by Wellcome scientists in response to an unmet medical need for the treatment of epilepsy. They examined the possibility that antifolate compounds had anticonvulsant efficacy. Preclinical studies initiated in the 1970s demonstrated that one antifolate (lamotrigine) was, indeed, a potent anticonvulsant in several animal models. Subsequent studies revealed no teratogenic, carcinogenic or mutagenic liability, a wide therapeutic index and a favourable pharmacokinetic profile. Lamotrigine is thought to act primarily via a use-dependent blockade

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of voltage-sensitive sodium channels to stabilise the neuronal membrane. It diminishes the over-excitation of neurons displaying epileptiform activity and has no effect on normal neuronal activity. In the clinic, lamotrigine has proven to be a broad-spectrum anti-epileptic drug as an add-on therapy for adult and paediatric partial seizures and also as an add-on therapy for the generalised seizures of Lennox-Gastaut syndrome. It is also effective as a monotherapy, given either to patients with newly diagnosed partial or generalised seizures, or to patients converted from other anti-epileptic drugs. Lamotrigine's safety profile is generally unremarkable, and most adverse events reported by patients are mild or moderate in intensity, are seen in the first 6–8 weeks of therapy and resolve without the need to discontinue taking the drug. The most concerning adverse event is a skin rash, which is generally simple morbilliform in presentation, although more serious cutaneous reactions have also occurred; following the recommended dosing guidelines minimises this risk.

Lamotrigine is currently available for the treatment of epilepsy in over 90 countries, having first received approval in Ireland in 1990 and in the UK in 1991, and has been administered to well over three million patients worldwide. As a consequence of its widespread use, it has been observed that lamotrigine appears to improve mood, which has been substantiated and extended in a number of clinical trials where has been demonstrated in patients with bipolar disorder (Calabrese et al., 2000). This work is being taken forward by GlaxoSmithKline. Lamotrigine has also been shown to have efficacy in a number of different types of human neuropathic pain (Eisenberg et al., 2001).

Table 2 Na^+ channel blockers displaying neuroprotective efficacy in models of cerebral ischaemia and traumatic brain injury

	Evidence of efficacy in disease models		
Compound	*Focal ischaemia*	*Global ischaemia*	*Traumatic brain injury*
Sipatrigine	Yes	Yes	Yes
BW1003C87	Yes	Yes	Yes
Riluzole	Yes	Yes	Yes

Relating structure to function

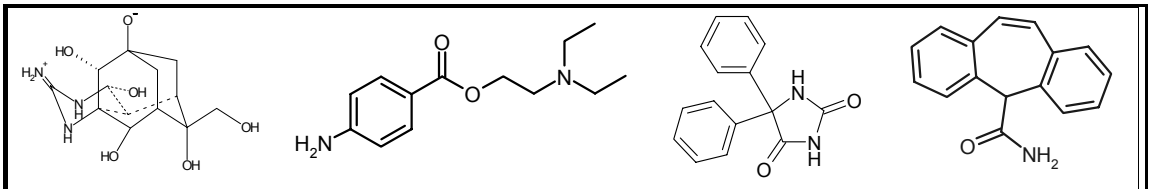
William A Catterall (University of Washington, USA) described elegant studies relating structure to function within sodium channels. The channels are composed of a large α-subunit together with one or two β-subunits. The α-subunit is the pore-forming subunit. β-subunits are single membrane-spanning glycoproteins containing immuno-globulin-like folds in their extracellular domains. They interact with the α-subunit through their extracellular domains and modulate channel expression and gating. The immunoglobulin-like folds have the structures of cell-adhesion molecules and interact with extracellular proteins like tenascin and cell-adhesion molecules like neurofascin. The α-subunits are organised into four homologous domains (I–IV), each of which contain six transmembrane α-helices (S1–S6).

The S4 segments contain positively charged residues, which serve as voltage sensors for channel activation and move outward under the influence of the electric field to initiate activation. The S5 and S6 segments and the short membrane-associated segments between them (SS1/SS2) form the pore. The fast inactivation of the open sodium channel is mediated by closure of a hinged-lid-like inactivation gate formed by the intracellular loop between domains III and IV. The hydrophobic motif IFM within this loop serves as the inactivation particle. This motif moves from a cytoplasmic location into the channel structure during inactivation and becomes inaccessible to chemical modification. The three-dimensional structure of the core of the inactivation gate, including the IFM motif, has been determined by NMR spectroscopy and forms the basis for a mechanistic interpretation of site-directed mutagenesis studies of the inactivation process. The inactivation gate folds into a receptor region formed by the IIIS4-S5 loop, the IVS4-S5 loop, and the intracellular end of the IVS6 segment.

Local anaesthetics and related drugs block the pore of sodium channels by binding to a receptor site formed by amino acid residues in transmembrane segment S6 in domains III and IV. Site-directed mutations of critical amino acids at similar positions in these segments greatly reduce the affinity for local anesthetic block and specifically disrupt high-affinity binding to the inactivated state. Many different structural classes of sodium channel blockers, including anticonvulsant, antiarrhythmic, and neuro-protective drugs, interact with this site in the pore.

In contrast, peptide scorpion toxins which alter gating of sodium channels bind to the extracellular ends of S4 segments and trap them in either an activated or non-activated state. The toxins from the α-scorpion trap the IVS4 segment in its inward position and slow or prevent inactivation; β-scorpion toxins trap the IIS4 segment in its outward position and greatly enhance activation. Voltage-sensor trapping may be a general mechanism of action of peptide toxins which affect ion-channel gating. These toxin receptors may provide novel sites for targeting new sodium channel modulating drugs.

Catterall presented his sliding helix model of voltage-dependent gating and showed how peptide scorpion toxins alter the gating of sodium channels. Toxins from the



Tetrodotoxin Procaine Phenytoin Carbemazepine

Figure 3 Miscellaneous sodium-channel blockers

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β-scorpion shift activation negatively by binding to the S3-S4 loop in domain II, whereas α-scorpion toxins (and sea-anemone toxins) slow coupling of activation to inactivation by binding to the S3-S4 loop in domain IV. In the former case, the channel must be activated for the toxin to have effect, and in the latter case, prolonged depolarisation drives the toxin off its receptor site. Other polypeptide toxins may alter voltage-dependent gating by binding tin to the S3-S4 loops of ion channels, for example hanatoxin binding to K^+ channels and the binding of both grammotoxin and Agatoxin IVA to Ca^{2+} channels. This suggests that voltage- sensor trapping may be a general mechanism of action of peptide toxins. The molecular determinants of lamotrigine binding to inactivated sodium channels have established that the amino acids IVS6 F1764A, IVS6 Y1771A and IIIS6 L1465A are critical. The molecular basis for similar drugs having different therapeutic actions (anticonvulsant, antiarrhythmic and neuro-protective) remains to be elucidated. By contrast, it was pointed out that BIII 890 CL, the Boehringer Ingelheim compound that is in clinical trials for stroke (see Figure 2; Carter et al., 2000), binds to the same site as lamotrigine, but with a 30-fold greater affinity. Compounds that are potent sodium channel blockers are likely to have a reduced probability of interacting with other receptors and channels and can therefore be expected to possess a better side-effect profile.

The role of sodium channels in pain

John N Wood (University College London) described the role of sodium channels in the mechanisms underlying pain. Electro-physiological studies of dorsal root ganglion (DRG) neurons, and the results of polymerase chain reaction (PCR), Northern blot and *in-situ* hybridisation analyses have demonstrated the molecular diversity of Na^+ channels that operate in sensory neurons. Several subtypes of α-subunit have been detected in DRG neurons and transcripts encoding all three β-subunits are also present. One α-subunit, $Na_v1.8$, is selectively expressed in C-fibre and A-fibre associated sensory neurons that are predominantly involved in damage sensing. The production of null mutant mice provides useful information on the specialised functions of particular sodium channels. $Na_v1.8$ null mutant mice are normal apart from deficits in inflammatory pain (induced by CFA or NGF) and noxious mechano-sensation. Neuropathic pain develops normally in the absence of $Na_v1.8$. These data support the idea that selective blockers of $Na_v1.8$ may be useful for treating acute or inflammatory pain. However, at the moment, there are no subtype selective blockers to explore this potentially attractive approach to pain treatment. An alternative approach to blocking channel function is to manipulate channel expression. Using yeast two-hybrid cloning a number of interacting proteins that bind $Na_v1.8$ have been identified. Disrupting essential or permissive interactions that facilitate high-level sodium-channel expression may be a route to targeting sodium channel subtypes and disruping nociceptive processing. The TTX's channel $Na_v1.3$ is present in sensory neurones during embryonic development, but is subsequently down-regulated. It is selectively up-regulated in DRG neurons in a variety of models of neuropathic pain. The expression of $Na_v1.3$ correlates well with the appearance of ectopic action potentials and allodynia in animal models of neuropathic damage, suggesting that $Na_v1.3$ selective blockers may be useful for the treatment of neuropathic pain. However, over-expression studies using $Na_v1.3$ in normal animals have yet to be carried out to confirm a causative role of $Na_v1.3$ in neuropathic pain syndromes.

Taken together, the evidence supports a selective and significant role for various sodium channel isoforms in different pain states. The development of isoform-specific channel blockers will prove invaluable in determining the role of sodium channel isoforms in pain pathways, and are likely to provide a fresh approach for the development of new analgesic drugs.

Sodium channels in hypertension and arrhythmia

Nick Carter (St George's Hospital, London) related sodium channel structure to function by describing how specific mutations in sodium channels cause distinct and deleterious symptoms. He specifically described sodium channelopathies relating to hypertension and arrhythmia. Essential hypertension is caused by a number of factors including genetics. Both single gene and polygenic contribution can alter the clinical phenotype and the majority of genes involved appear to affect renal physiology. Liddle syndrome is a rare monogenic hypertension

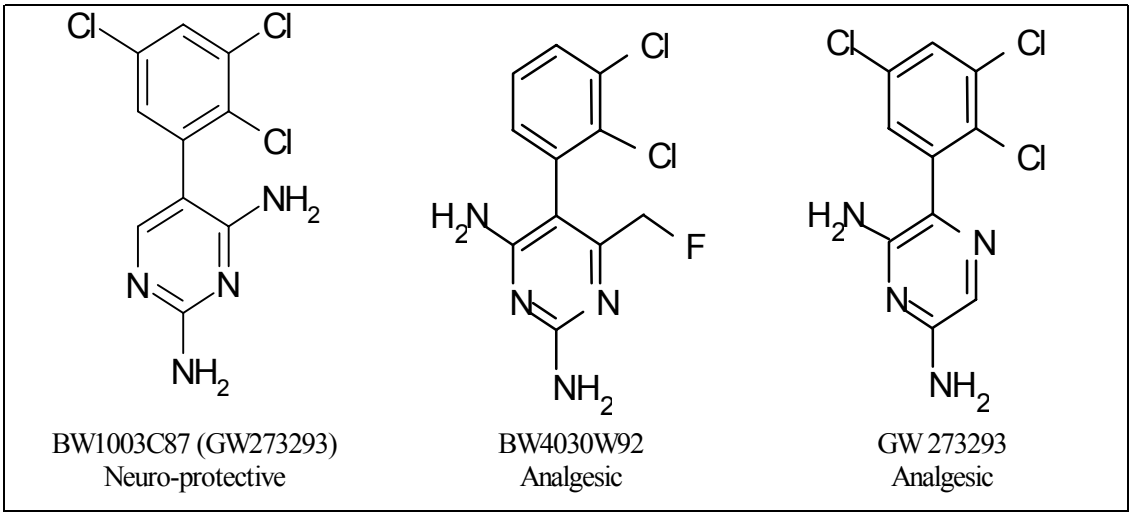

Figure 4 Phenylpyrmidines with different efficacies

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phenotype relating to mutations in the epithelial sodium channel gene ENaC.

Liddle syndrome is usually caused by truncation mutations in the β-subunit gene producing increased renal channel activity, sodium absorption, volume expansion and increased blood pressure. A mis-sense mutation in the C-terminus, the 'Liddle region', has been demonstrated to be a contributing factor in common polygenic multifactorial high blood pressure. The polymorphism involved (T594M) is frequent in African and Afro-Caribbean black people but is not found in Caucasians. Thus rare and frequent inherited channelopathies can contribute to hypertension. ENaC is inhibited by Amiloride and thus patients with Liddle syndrome may be more effectively treated with this compound, although routine diuretics have also proved effective. The molecular changes in ENaC, which cause increased channel activity, are dominant negative. Other ENaC mutations will be described which cause loss of channel function and hence sodium loss with concomitant low blood pressure.

Sudden cardiac death from arrhythmia can be caused by inherited channelopathies such as long QT syndrome. This is a dominantly inherited condition resulting from mutations in one of several ion-channel-coding genes important in mediating the cardiac action potential. One gene locus associated with this phenotype is $Na_v1.5$ coding for a sodium channel protein which, when altered by mutations in key regions of the channel, closes more slowly and causes the QT interval to be lengthened. This phenomenon predisposes to life-threatening arrhythmias. It is clear that any new sodium channel blocker should be devoid of arrhythmia-inducing activity, so knowledge of the extent of interaction at this channel subtype will be important in order to avoid unwanted side-effects.

The location of mutations that impair sodium channel activation and cause inherited diseases of hyperexcitablity were described by Professor Catterall. In addition to causing long QT syndrome, such mutations have also been found to cause periodic paralysis and febrile seizures. The latter disorder is caused by mutations on the β_1-subunit.

Prospects for next-generation sodium channel blockers

Dr Brian Cox (GlaxoSmithKline) described the structure–activity relationships of a series of sodium channel blockers. He pointed out that neuronal sodium channel blockers have been used in therapy for many years, long before a connection with the modulation of sodium channels was made or indeed the specific existence of sodium channels was known.

The origins of all the neuronal sodium channel blockers lie in two areas: the naturally occurring and complex toxins such as tetrodotoxin (TTX) and the synthetic molecules such as the local anaesthetic procaine, the anticonvulsant phenytoin and the antipsychotic and anticonvulsant drug carbamazapine (see Figure 3). TTX derives from the puffer fish (conveniently all its sodium channels are resistant to TTX) and binds to the outer pore of the majority of neuronal sodium channels. Both procaine and phenytoin are synthetic compounds and began therapeutic use in 1902 and 1937, respectively, but it was not until 1959 in the case of procaine and 1983 for phenytoin that their action on sodium channels was elucidated. Since the discovery of the first sodium channel blockers there has been enormous interest in the field. The search for better local anaesthetics and anticonvulsants has continued, as well as that of compounds finding new uses for entirely new indications, for example as antiarrhythmics, for stroke or bipolar disorder.

Lamotrigine was first synthesised and developed in response to an unmet medical need for the treatment of epilepsy, but has become an important lead for the discovery of further generations of compounds such as the stroke agent sipatrigine, the selective anticonvulsant GW273293 and the selective analgesic GW286103 (see Figure 4). There were good correlations between 1) TTX-resistant currents in DRG neurons (*in vitro)* and analgesia (*in vivo*); and 2) inhibition at cloned Type IIA sodium channels and *in vivo* anticonvulsant activity.

There was no relationship between anticonvulsant and analgesic activity (carrageenan paw), which supports the contention that different blockers have different efficacies. The foundation establishing structure–activity relationships for sodium channel blockers has now been laid (Clare et al., 2000; Anger et al., 2001). Further elaboration of structure–activity relationships will require the cloning and stable expression of the various subtypes of channel, together with the development of high-throughput assays.

New assays for sodium channel activity

The development of new and high-throughput assays to assess sodium channel activity was described by Dr Jesus E Gonzalez (Aurora Biosciences Corp, San Diego, USA). The assays use voltage-sensitive fluorescence resonance energy transfer (FRET) probes coupled with a Voltage/Ion Probe Reader (VIPR II™), a custom fluorescence plate reader. There are two probes. The first is oxonol, a highly fluorescent, negatively charged, hydrophobic ion that is sensitive to changes in membrane potential. In response to these changes, it can rapidly redistribute between two binding sites on opposite sides of the plasma membrane. The second fluorescent molecule is coumarin lipid, which binds specifically to one face of the plasma membrane and functions as a FRET donor to the voltage-sensing oxonol acceptor molecule. When the oxonol moves to the intracellular plasma membrane binding site upon depolarisation, FRET is decreased and results in an increase in the donor fluorescence and a decrease in oxonol emission. This approach enables sodium channel function to happen in a second or sub-second time-frame.

They have screened 125,000 compounds against both the type IIA-like Na^+ channel endogenously expressed in Chinese hamster ovary (CHO) cells and the human cardiac Na^+ channel (hH1a) heterologously expressed in HEK293 cells. A large group of compounds were active at both Na^+ channel types and a few compounds showed subtype selectivity. The functional FRET assays have significant advantages for medicinal

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From left to right, the SMR Award recipients, David Haigh, Richard Hindley, Michael Cawthorne, Stephen Smith and Barrie Cantello

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project team, each received a framed certificate in recognition of their achievement, presented by the chairman of the SMR, Dr David Cavalla. The monetary prize accompanying the award was donated to the charity, Diabetes UK, at the unanimous request of the award winners. **Dr Stephen Smith (now of GlaxoSmithKline)** delivered the award lecture. The prevalence and existing treatments for diabetes provide an important background to this research effort. Type 2 diabetes is a chronic disorder of glucose metabolism afflicting 5–10% of the adult population of Western societies and is predicted to rise from >150 million worldwide now to 220 million by 2010, particularly because of China. Diabetes management requires a combination of diet, exercise and drug programmes. The sulphonylureas (SUs) and metformin were introduced 20–40 years ago and do not directly target the fundamental problem of insulin resistance. They do not control glucose long term and many patients eventually require insulin. The research for a novel treatment to type 2 diabetes started in 1984 at Beecham Laboratories in Surrey and was based on the idea of targeting the insulin resistance, hopefully with small molecules. The goal was to identify compounds that would provide durable glucose control and also reduce the cardiovascular-associated disease problems known to accompany diabetes.

At the time virtually nothing was known about the molecular mechanisms of the insulin action and the project team had to rely on a catch-all mouse model of insulin-resistant type 2 diabetes. Thus, the target profile for any compound of interest was defined as follows: orally potent (1mg/kg), active in a mouse model (ob/ob mouse), active at three dose levels in eight-day repeat dose studies, active in dietary admixture, and have efficacy assessed by an oral glucose tolerance test with a reduction in the area under the curve of 25%. The lead compound was ciglitazone, a thiazolidinedione (TZD), which had been derived from the hypolipidaemic drug clofibrate, and which was only a very weak insulin sensitiser. A metabolite was found to be 30-fold more potent. SAR on the metabolite and the synthesis of over 300 compounds led to the discovery of three potential development compounds all of which fulfilled the target profile criteria: BRL 48482, BRL 48552 and BRL 49653.

In order to determine the final candidate choice, it was necessary to develop a selectivity screen that monitored haemodilutional effects. Any compound of interest would need to have no lowering of haematocrit in rodents at multiple doses of the anti-diabetic dose. BRL 49653 was shown to be 100-fold selective and was chosen for development in 1992. The company was now SmithKline Beecham. Clinical efficacy of rosiglitazone was established in 1995. During the early 1990s many groups had been looking for the identity of the molecular target of the TZDs. TZDs were known to promote the differentiation of fat precursor cells in tissue culture over several days, which suggested a mechanism involving changes in gene expression. The peroxisome proliferator-activated receptors (PPARs) and ligand-activated nuclear receptors were identified but the native ligands remained unknown at the time. PPAR-alpha was shown to be a target for fibrate hypolipidaemic agents and PPAR-gamma was the target for TZD insulin-sensitising anti-diabetic drugs. PPAR-gamma is highly expressed in fat, but less so in skeletal muscle and

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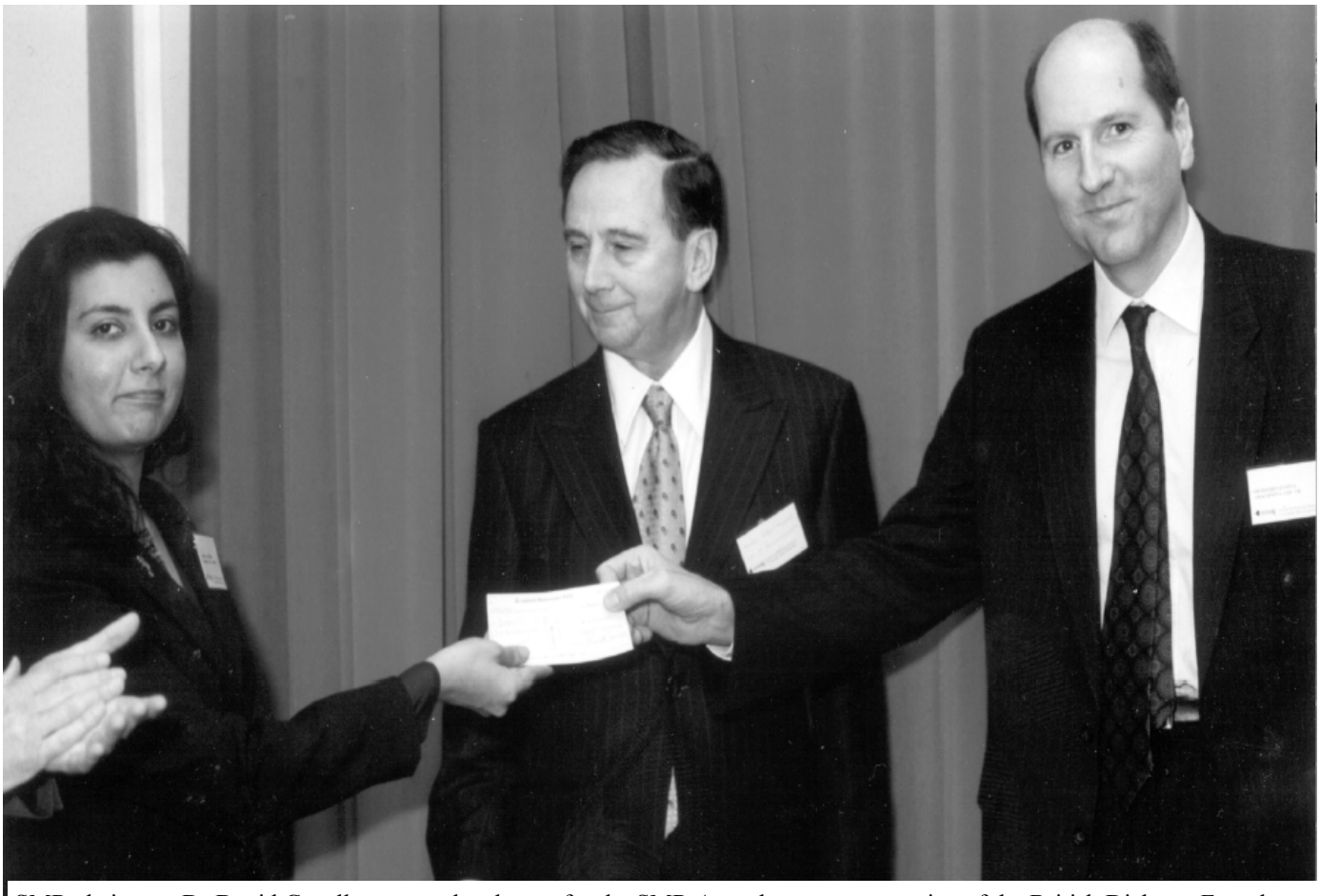
liver. PPAR-gamma activation leads recruitment of the retinoic acid nuclear receptor RXR which bind to genes containing peroxisome proliferator response elements (PPREs). Many of these are key gene-encoding proteins controlling lipid and glucose metabolism. Extensive clinical studies showed that Avandia maintains efficacy over the treatment periods. This is also maintained in the presence of sulphonyl ureas and metformin. Avandia was launched in the US in 1999 and the UK in 2000 and has been used in more than 2.5 million patients worldwide.

Successful drug discovery is a significant achievement for those involved and is really quite a rarity given the investment that is poured into R&D. Currently, there is a great demand for an increase in new and better medicines, which puts enormous pressure on the industry to deliver. **Dr Philip Brown (executive chairman, PJP Publications Ltd)**, who founded *SCRIP World Pharmaceutical News*, gave his perspective on the state of the pharmaceutical industry and provided an assessment of its future. For an industry that has thrived since the 1950s, he asked several fundamental questions. Was the industry running out of steam? What was driving the consolidation of so many companies (the merger and acquisitions, M&A)? Biotechnology sector companies have an important part to play in supplementing large pharmas' own research activities, but with the industry's need to reinvent product portfolios every 15 years or so in order to offset sale losses arising from patent expiry, will the biotech companies be able to deliver on time?

Overall, the rate of output of new chemical entities (NCEs) is no greater now than it was before the mergers. The generic industry is likely to be a beneficiary. With the need to charge more for medicines to recoup large investment costs and cover the shortfall in NCEs, this will encourage to an even greater extent the use of low-priced generics and be a safety valve on pricing. M&As offer the promise that bigger is better but appear no more than a financial survival strategy. It is clear that the large pharma are the drivers but it will be an issue of getting the R&D correct. The industry has become technology driven because of genomics. While it has provided more targets to choose from, there is a consequent need to increase the amount of data and information in order to make the correct choices of which to take forward. Transforming this into new products is taking considerable time and effort. Big pharma is good at the 'D' part: marketing, distribution, dealing with regulatory authorities, but the huge bureaucracies they have created may have stifled the creative 'R' environment preventing them innovating at the appropriate rate. There appears to be no doubt that smaller companies with less bureaucracy offer a creative opportunity, many of these are set up on the back of academic discovery. Something more flexible than M&A is needed. One solution may be for large pharma to create smaller cohorts from its research base to stimulate more creative environments.

Regrettably, due to illness and travel restrictions after 11 September, the meeting was deprived of two talks.



SMR chairman, Dr David Cavalla, passes the cheque for the SMR Award to a representative of the British Diabetes Foundation at the request of Professor Michael Cawthorne (centre) and the rest of the project team

Medicinal Chemistry at King's College London

by R.C. Hider

The Department of Pharmacy at King's College London has had a long history originating at Chelsea College in the late 1890s. Pharmacy gradually became an increasingly important subject at Chelsea College, and in the 1950s and 1960s the staff, under the leadership of Professor Arnold Beckett, made major contributions in the fields of drug stereochemistry, analytical science and medicinal chemistry. Pharmacy at Chelsea College merged with King's College in 1985, along with several other health sciences; for instance, Nutrition from Queen Elizabeth College, and Nursing from a number of London medical schools and Chelsea College.

Health science focus

Since that date, health sciences have been a strong component of the college. In 1998 we were fortunate to move to the completely refurbished Franklin-Wilkins building at the Waterloo site. This magnificent building accommodates the entire School of Health and Life Sciences. It is an enormous structure with six floors, each with a floor area of over 4,000 square metres. Pharmacy is located on the fifth floor, where we undertake the majority of teaching and research. Thus, for the first time in our long history, we are working in purpose-designed facilities, and in close association with a large part of the college. Waterloo is the centre of the major King's College sites. The Strand, where the physical sciences are taught, is only separated by Waterloo Bridge, and St Thomas' and Guy's, to the west and east of Waterloo, are both 10 to 15 minutes' walk away. Thus, not only does Pharmacy have close links with Life Sciences and Chemistry, but also with the Medical School, which is associated with three major teaching hospitals: St Thomas', Guy's and King's College.

Within the Franklin-Wilkins building there are several research centres: the Electron Microscopy Centre, the Mass-spectrometry Centre, and the Genomics Centre. These are all co-ordinated by the School of Health and Life Sciences and have recently received considerable income from successful SRIF bids. In addition, the Drug Control Centre, which grew out of the Pharmacy Department and is directed by Professor David Cowan, is located on the fourth floor of the Franklin-Wilkins building. The centre has in recent years played an increasingly important role both in the teaching and research activities of the school.

Pharmacy, in common with other UK departments, teaches a four-year MPharm degree, but unlike most other departments also runs three MSc courses, each of which has been taught for over 30 years: Biopharmacy, Pharmaceutical Analysis and Pharmaceutical Technology. These three degrees form a modular framework with the Forensic Science MSc degree. The school has a strong tradition of postgraduate teaching, not only in pharmacy but also in biological and analytical science.

The research activities in Pharmacy are distributed between five research groups: Natural Products and Medicinal Chemistry, Biochemical Toxicology and Drug Disposition, Drug Delivery and Absorption, Molecular Biophysics and Pharmacy Practice. The standard of research in the department has increased dramatically over the last decade. Thus, whereas our research rating in 1989 was 2, it increased to 4 in 1992, was maintained at 4 in 1996, and in the recent exercise of 2001 was rated 5. This gradual improvement has been achieved by the appointment of high-calibre staff who are interested in both research and teaching.

The medicinal chemists in the department make a major contribution to the activities of the four pharmaceutical science groups listed above. The chemists are involved with synthesising lead compounds which have emerged from natural product studies, with the Drug Delivery group in designing new formulations, with the analysts in designing new column matrices for separation purposes, and with the Molecular Biophysics group over matters relating to molecular design, particularly aspects which have a strong lead from molecular modelling. The Medicinal Chemistry group is well-funded by MRC, EPSRC, NIH, BBSRC, FSA, BTG, EU, charities and industry.

Synthetic chemistry is a major strength in the department, and includes three principal areas: peptides, chelation chemistry and natural products. Dr Sukhi Bansal works almost entirely with peptide chemistry and has produced an extremely useful fluorescent probe which has potential for labelling a wide range of biomolecules and has been used in the department for the investigation of peptide absorption across lung and intestinal tissue. Sukhi has also developed a new method for labelling peptides with ^{18}F ($T^{½}$=110 minutes) which is used for positron emission tomography. By using solid support synthesis, peptides can be produced within 20 minutes, and the method has found immediate clinical application here at King's College London. Dr Bansal's group concentrates on solid-phase peptide synthesis, and has developed a number of new synthetic procedures, including one for on-column synthesis of cyclic oligopeptides.

Hider's synthetic group

The synthetic group led by Bob Hider provides the international lead in the design of orally-active iron chelators. Deferiprone, which was designed by Hider in the mid-1980s, is now extensively used as a mainline treatment for thalassaemia in many parts of Europe, Iran and India.

Second-generation hydroxy-pyridones, also designed by Hider's group, are in preclinical development by Apotex (Canada) for use against iron overload associated with thalassaemia and sickle-cell anaemia. These compounds are the most powerful bidentate iron chelators known, and are currently under investigation for a range of additional clinical applications. One recent example is associated with the successful application of phototherapy to surface tumours, for instance, those located on the skin, bladder and oesophagus. The technique is based on the manipulation of local laser-generated oxygen radicals

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via protoporphyrin IX. Some chelators inhibit ferrochelatase, thereby enhancing the concentration of protoporphyrin IX and so sensitising the tumour. This concept is under development by several start-up companies at the present time.

The group has also developed a method for the measurement of non-transferrin-bound iron, a toxic species present in the plasma in many disease states, including haemochromatosis. This analytical procedure is now used throughout Europe, North America and South-east Asia. As a result of these advances related to iron chelation and iron pharmacokinetics, Hider was able to attract funding from the MRC to form the Iron Metabolism Group, which now has co-operative status with the MRC. This group includes biochemists, nutritionists, molecular biologists, clinicians and medicinal chemists, and fits well into the new interdisciplinary strategy of the School of Health and Life Sciences.

Interdisciplinary projects

There are many joint projects between the pharmacognisists and medicinal chemists at King's College. One which typifies this close interaction, is the development of a new treatment for vitiligo, a project led by Dr Amala Raman and currently funded by BTG. Dr Raman's research group has established that piperine is associated with pigment cell stimulation *in vitro*. The project involves the design, synthesis and *in vitro* and *in vivo* biological assessment of a range of synthetic analogues; a number of active analogues have been identified.

Underpinning many of the molecular design projects in the department, Dr David Barlow leads an active computational chemistry group, equipped with state-of the-art, high performance silicon graphics and Compaq alpha workstations. Dr Barlow's group is not only occupied in applying established molecular graphics and QSAR techniques to drug design problems, but is also highly innovative in the development of novel molecular-modelling software. The software tools most recently developed include programmes for modelling the structure of surfactant aggregates, for making sequence-based predictions of protein function, and for rapid quantification of molecular topographical similarity and complementarity. Specific success stories in terms of molecular structure prediction include the sequence-based prediction of the structure of the peptide hormone endothelin and the $Dcyt_b$ ferric reductase.

Molecular modelling also plays a critical role in an ongoing programme aimed at developing novel non-ionic and zwitterionic surfactants for use as drug-delivery systems. This work is a joint venture between Drs David Barlow and Jayne Lawrence and is one of only two such programmes in the UK. The combination of molecular modelling with sophisticated analytical tools such as neutron scattering has enabled a detailed picture of the molecular architecture of a range of surfactant systems (including vesicles and micelles), to be constructed both in the absence and presence of a drug. This knowledge has been essential both in the design of novel surfactants with built-in physico-chemical properties, as well as facilitating our understanding of the behaviour of existing surfactant drug delivery systems. The programme is well funded by a number of pharmaceutical companies including GSK and AstraZeneca.

Analytical science is a key activity in the department and overlaps with many of the medicinal chemistry interests. Drs Giuliano Siligardi and Alex Drake run a state-of-the-art spectroscopy lab with particular expertise in the application of circular dichroism to biological molecules and drug-macromolecule interactions. Drs Melissa Hanna-Brown and Andrew Hutt are involved in the development of new analytical techniques based on HPLC and CE for the rapid determination of drug partition characteristics and drug–lipid interactions. An additional interest is in the analysis and preparative resolution of chiral compounds for both chiroptical characterisation and pharmacological evaluation. The contributions of this group were recently recognised internationally by the awarding of the Desty Prize for Chromatographic Science to Melissa, and the Jan Weber Medal to Andrew — both in 2000.

The major task for medicinal chemists is to design new molecules with therapeutic potential. The chemists in the Department of Pharmacy at King's have an excellent opportunity to achieve this, being situated in a single building together with biochemists, immunologists and molecular biologists, and also in close contact with members of the Medical School — with whom we plan to increase our interaction and

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chemistry support, rapid prioritisation of candidate blockers and exploring drug/channel interactions. This comparative screening approach should be applicable to other members of the Na^+ channel family.

The discovery of the first generation of sodium channel blockers was made with little dependence on recombinant channels. It was established that such compounds block over-activated sodium channels, while permitting normal currents of sodium ions. This has provided a basis to develop such sodium channel blockers for the treatment of CNS disorders such as epilepsy, stroke, traumatic brain injury and pain.

Conclusion

Sodium channel blockers may also have utility for other types of illness, such as bipolar disorder. The ability of sodium channel blocking drugs to attenuate abnormal activity of sodium channels without affecting normal synaptic transmission probably underlies their good tolerability. With the discovery of nearly a dozen genes encoding different sodium channels, it is clear that the next generation of sodium channel blockers will have to be made with knowledge of subtype selectivity. Establishing how the different channels relate to different disease states is clearly an important challenge. Progress has begun with studies with null mutants for different sodium channels, together with evidence of maladaptive changes in sodium channel gene expression in neurons in certain pathological states.

These studies will be greatly complemented by blockers with clear subunit selectivity. Whether such compounds are feasible remains to be seen. It is possible that compounds with different efficacy profiles bind to the same site within transmembrane segments IIIS6 and IVS6 of inactivated sodium channels. The continued careful elucidation of structure–function relationships within the sodium channel will also facilitate future drug discovery.

The relationship between structure and function is also helped by the discovery that mutations in specific isoforms of sodium channel cause a variety of diseases, including paralysis, long QT syndrome and epilepsy. It is likely that more such channelopathies will be discovered in the future. The diversity and dynamic nature of sodium channel expression introduce a high degree of complexity into the nervous system. This not only presents a great challenge for neuroscience, but it also provides a golden opportunity for future work in drug discovery, particularly with the use of recombinant sodium channels and new high-throughput technologies to assess sodium channel function.

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Keating, MT and Sanguinetti, M.C.

Former SMR Award Winner, Professor Stenlake, Receives Further Accolade

We have been informed that one of the first recipients of the SMR Award for Drug Discovery, Professor John Stenlake, who was recognised in 1987 for his contribution to the discovery of atracurium, has been further acknowledged with the award of the Hanbury Medal for 2001 for original research in the natural history and chemistry of drugs.

The medal, jointly awarded by the Royal Pharmaceutical Society of Great Britain and the Linnean Society, acknowledged the invention and clinical merits of the novel skeletal muscle relaxant atracurium besylate for use in surgery and intensive care. The Department of Pharmaceutical Sciences at the University of Strathclyde and the Wellcome Foundation also shared a Queen's award for technological innovation in 1986 for atracurium.

We are very pleased for Professor Stenlake that his achievements, which we recognised early on, continue to receive recognition from the wider public.•

SMR Notes

Future SMR meetings (contact secretariat for more information, the e-mail address is secretariat@ socmr.org):

7 March 2002. Orphan Receptors (Novartis, Horsham).

27 June 2002. Drug Metabolism, Pharmacokinetics and Drug Discovery (National Heart and Lung Institute, London).

19 September 2002. Proteomics: joint meeting with BMCS section of RSC (Scientific Societies' Lecture Theatre, London).

NEW MEMBERS

Amersham Pharmacia Biotech: Dr AR Ali, Miss S Davies; *AstraZeneca:* Dr W McCoull, Dr C Reilly; *BioFocus:* Dr J Duffy Dr C Lauret; British Biotech: Dr SP East; *Cardiff University:* Dr KT Wann; *CeNeS:* Dr R Croxen, Dr AP Southan; *De Montfort University:* Dr AH Hainsworth; *University of Dundee:* Dr X Mwimbi; *GlaxoSmithKline:* Dr M Ahmed, Mr Y-KC Chung, Dr G Cooper, Dr DJ Davies, Dr M Davy, Mr AT Doran, Mr Neil Garton, Dr MD Hall, Dr RE Kelsell, Mr DJ Mitchell, Dr SF Moss, Mr TJ Smith, Dr S Westway; *Innovata Biomed:* Dr M Parry-Billings; *Medivir UK:* Dr C Clissold, Dr V Morisson; *Millennium Pharmaceuticals:* Dr LJ Payne; *Nature Publishing Group:* Dr AL Smith; *No affiliation:* Mr S Maccormick; *Odyssey Pharmaceuticals:* Dr MJ Powell; *Organon Laboratories:* Dr RE Armer, Ms KI Buchanan, Dr R Gilfillan, Dr AJR Mason; *OSI Pharmaceuticals:* Dr SC Hirst Dr M Fyfe; *Oxagen:* Dr N Lench; *Pfizer:* Dr GN Maw; *Pudue Pharma:* Dr P Gharagozloo; *St George's Hospital Medical School:* Miss KT Gormley; *Vernalis Research:* Ms NH Allen, Ms K Benwell, Dr N Carey, Mr J Horswill, Dr LJS Knutsen, Mr D Revell; *Xenova:* Dr F Wilson.

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