Ion Channel Modulator Pipelines:

Targets and Agents in Development

by Peter Norman, PhD, MBA

Published in August 2009 by Cambridge Healthtech Institute
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by Peter Norman, PhD, MBA

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Executive Summary

Ion channels form a large (400 plus members) and highly distinct class of proteins whose function is to transport ions (both anions and cations) across cell membranes to regulate various physiological processes. They play key roles in many physiological and pathophysiological processes, while mutations of single ion channel proteins have been shown to be the primary factor in a number of genetic diseases. Selective modulation of ion channel function by therapeutic agents is an approach to the treatment of disease that has traditionally been underexploited by the pharmaceutical industry.

The Human Genome Project has provided the foundation for a more systematic classification of ion channels than had hitherto been achieved. A systematic classification of families of channels, based upon structural homologies, has been developed to try to replace the various historical classifications. Ion channels may be activated by various stimuli and are commonly described as voltage-gated, i.e., those activated by changes in membrane potential, or ligand-gated, i.e., the action of certain ligands on their receptors regulates the channel opening. Other families of channels, the TRP families, are primarily activated by various noxious stimuli, but constitute major classes of drug targets for the development of novel analgesic agents. Most ion channels are specific, preferentially transporting a single ion (Na⁺, K⁺, Ca²⁺, or Cl⁻), but some channels are non-specific cation channels.

Historically, the development of ion channel modulators has proved to be a highly serendipitous process, albeit leading to some major commercial successes. And many factors have been responsible for the industry’s lack of interest in this class of drug targets. They have been seen as difficult to study, there has been a poor understanding of the biology, and reliable high-throughput screening methods have proved harder to develop. The past few years has seen the emergence of high-throughput, electrophysiology-based methods that permit a more direct
assessments of compounds for their ability to modulate the activity of ion channels. This development has led to increased interest in trying to identify ion channel modulators, with recent patent filings highlighting this.

Notwithstanding these problems, around 100 agents that modulate the function of certain ion channels have reached the market. Some of these have been major commercial successes and include many older drugs, while others still are. Despite the fact that generic forms of many of these agents are now available, sales of these branded drugs were around $20 billion in 2007. Despite the many potential targets for ion channel modulators, only a few channels are currently targeted. The two most successfully targeted channel types are the GABA\textsubscript{A} receptor ligand-gated channels and the L-type calcium channels, with a moderate number of drugs also available that target the K\textsubscript{v} potassium channel, the 5-HT\textsubscript{3} receptor, and the nicotinic receptor. Extensive generic competition has eroded the revenues of the L-type calcium channel blockers, although 2007 sales of amlodipine were still $3 billion, while zopiclone and eszopiclone were the only major revenue-generating GABA\textsubscript{A} receptor modulators, with respective sales of $1.6 billion and $600 million. The GABA analogs gabapentin and pregabalin, both marketed by Pfizer, which modulate T-type calcium channels, achieved respective revenues of $431 million and $1,829 million in 2007. Anticonvulsants that act on sodium channels also generated substantial revenues, with valproate ($1.6 billion), lamotrigine ($2.2 billion), and topiramate ($2.5 billion) the most notable amongst these. Of the more recently introduced ion channel modulators, only Pfizer's varenicline tartrate, for smoking cessation, has developed significant revenues ($883 million).

At the beginning of 2009, more than 100 novel ion channel modulators were reported to be in clinical development, but this figure remains substantially lower than the number of different channel proteins, and it also focuses on a small number of target classes. Major pharmaceutical companies currently account for just over one-third of all the ion channel modulators in development. The range of channel types targeted by the ion channel modulators in development is relatively limited and heavily skewed toward a few channel types, principally the GABA, glutamate, NMDA, and nicotinic ligand-gated channels. Potassium and sodium channel modulators are now the more popular targets amongst the voltage-gated channels. While there has been an explosion in interest in TRP channels, only TRPV1 channel modulators have so far reached clinical development. Around 80% of these agents are being developed for the treatment of CNS indications, with arrhythmia one of the more popular peripheral indications.
Seven ion channel modulators are currently awaiting regulatory approval, while the potassium blockers tedisamil and vernakalant have recently been approved as intravenous treatments for arrhythmia. The sodium channel modulator dronedarone has also recently been approved to treat heart rhythm disorder. Ten ion channel modulators are in Phase III studies for diverse indications, only four of which are being developed by major companies for highly commercially significant indications: dimebolin for Alzheimer's disease, safinamide for Parkinson's disease, and both perampanel and retigabine for epilepsy.

Of the 60 ion channel modulators in Phase II studies, 42 are being developed for CNS indications and mostly target ligand-gated channels. Nine of these are being developed for Alzheimer's disease, mostly focusing on nicotinic (4) and NMDA-glutamate (4) receptors. Two of the three agents in Phase II for depression target glutamate receptors, while three of the four being developed for treating neuropathic pain target NMDA-glutamate receptors. Four of the five being developed for (non-neuropathic) pain target TRPV1 channels, but the three agents being developed for the treatment of epilepsy all target different channel types. Two drugs each are in Phase II for the treatment of insomnia, Parkinson's disease, anxiety, bipolar disorder, smoking cessation, and stroke, with agents also in Phase II studies for the treatment of ADHD, fibromyalgia, CNS injury, schizophrenia, multiple sclerosis, and musculoskeletal pain.

Of the 18 drugs in Phase II studies for non-CNS indications, the majority act on voltage-gated channels. Three drugs, two of which target sodium channels, are in development for cystic fibrosis, while two each are in development for the treatment of asthma, atrial fibrillation, and tinnitus. Other conditions are cancer, cardiac arrest, genitourinary disease, glaucoma, incontinence, irritable bowel syndrome, steatohepatitis, and urinary tract inflammation.

A further 33 ion channel modulators are reported to be in Phase I development for diverse conditions. Six agents target glutamate receptors, three each targeting the AMPA and NMDA subtypes; five target GABA receptors; five target nicotinic receptors; and three target TRPV1 receptors. Two target potassium channels, three each sodium and calcium channels, while glycine receptors, P2X, receptors, CFTR, and the ASIC1a, HCN, and VDAC channels are all targeted by one development compound. Again, CNS disorders are predominant, with five agents being developed for treating Alzheimer's disease, three for schizophrenia, three for cognitive disorders, four for pain, and one more for neuropathic pain. The remainder are being developed for diverse indications.
Recent patenting activity from major pharmaceutical companies suggests that many have currently limited success in successfully identifying novel ion channel modulators. Only Pfizer, Merck, AstraZeneca, and GlaxoSmithKline have published more than 40 such applications in the period between January 2005 and March 2009, while only five have been published by Eli Lilly. Analysis of the targets pursued indicates the considerable interest in TRP channels and also shows considerable differences in the preferred target classes at each company. A number of smaller companies are significantly focused on the development of ion channel modulators, but only the more established Icagen and NeuroSearch currently have significant pipelines of ion channel modulators. More recently established companies, such as Parion and Lectus Therapeutics, are among those whose focus is almost exclusively on the development of ion channel modulators.

The commercial outlook for ion channel modulators in the near term is unpromising. Many older agents are seeing sales decline due to generic competition, and none of the more recently launched agents are showing signs of significant revenue growth. Only sales of pregabalin are growing steadily, helped by Pfizer’s success in gaining approval for additional indications. Of the late-stage pipeline compounds, the three antiarrhythmic agents—dronedarone, vernakalant, and tedisamil—appear to offer the best prospects of stimulating revenue growth. (Note: Dronedarone was approved by the US FDA on July 1, 2009.) In the slightly longer term, some of the ion channel modulators currently in Phase III studies appear likely to have a substantive commercial impact. The two new anticonvulsants, retigabine and perampanel, appear to have the potential to make significant inroads into the mature anticonvulsant market segment, while the development of dimebolin for both Huntington’s disease and Alzheimer’s disease also appears highly promising. While a number of the agents in early stage development have promise, the historical success rate of progressing ion channel modulators beyond Phase II to Phase III, and then to market, suggests that few will become commercially significant.

Few of the compounds currently in development are likely to have been identified by electrophysiology based screening methods. The recent development of high-throughput electrophysiology screening methods has at last provided a method of identifying agents that more directly affect ion channels at reasonable screening throughputs. The steady implementation and exploitation of these screening methods should produce better-quality leads and then, within a few years, precipitate the emergence of more ion channel modulators into clinical development.
Further interest in this class of targets is likely to be stimulated by the enabling power of these new technologies and the underexploitation of most of these drug targets. They thus represent a significant opportunity for a pharmaceutical industry facing the problems of too few innovative new drugs reaching the market, while seeing revenues decline due to increased generic competition. The outcome of this change in research strategy should become increasingly apparent with increasing numbers of patent filings claiming ion channel modulators.
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<table>
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<tr>
<th>Drug</th>
<th>Main Brand</th>
<th>Developer</th>
<th>Launched</th>
<th>2007 Sales ($ millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>vinpocetine</td>
<td>Cavinton, Intelectol</td>
<td>Gedeon Richter</td>
<td>1982</td>
<td>&lt; 50</td>
</tr>
<tr>
<td>valproate</td>
<td>Depakote</td>
<td>Abbott</td>
<td>1983</td>
<td>1575</td>
</tr>
<tr>
<td>zonisamide</td>
<td>Zonegran</td>
<td>Dainippon Sumitomo</td>
<td>1989</td>
<td>160</td>
</tr>
<tr>
<td>oxcarbazepine</td>
<td>Trileptal</td>
<td>Novartis</td>
<td>1990</td>
<td>692</td>
</tr>
<tr>
<td>felbamate</td>
<td>Felbatol</td>
<td>Carter-Wallace</td>
<td>1993</td>
<td>&lt; 50</td>
</tr>
<tr>
<td>lamotrigine</td>
<td>LAMICTAL</td>
<td>GlaxoSmithKline</td>
<td>1995</td>
<td>2194</td>
</tr>
<tr>
<td>topiramate</td>
<td>Topamax</td>
<td>Johnson &amp; Johnson</td>
<td>1995</td>
<td>2453</td>
</tr>
<tr>
<td>tiagabine</td>
<td>GABITRIL</td>
<td>Novo Nordisk</td>
<td>1996</td>
<td>&lt; 50</td>
</tr>
<tr>
<td>piracetam</td>
<td>Nootropil</td>
<td>UCB</td>
<td>1996</td>
<td>131</td>
</tr>
<tr>
<td>levetiracetam*</td>
<td>Keppra</td>
<td>UCB</td>
<td>2000</td>
<td>1330</td>
</tr>
<tr>
<td>rufinamide</td>
<td>BANZEL</td>
<td>Eisai</td>
<td>2007</td>
<td>&lt; 30</td>
</tr>
<tr>
<td>lacosamide</td>
<td>Vimpat</td>
<td>Schwarz (now UCB)</td>
<td>2008</td>
<td>N/A</td>
</tr>
</tbody>
</table>

* With the exception of levetiracetam, efficacy is attributed to the drug’s sodium channel activity.

**Source: Norman Consulting**

Although sodium channel activity is believed to contribute to the clinical profiles of the compounds shown in Table 4.6, most have multiple activities. It is unclear to what extent each activity contributes to the observed profile. Valproate has a number of actions that contribute to its activity; these include inhibition of GABA transaminase and calcium channel blockade as well as acting as a sodium channel blocker. It is also approved for the treatment of bipolar disorder, migraine, and schizophrenia. Zonisamide appears to act primarily through block of sodium and calcium channels. Oxcarbazepine is a derivative of carbamazepine with a superior side-effect profile; both agents appear to act primarily through sodium channel block.

Lamotrigine is widely used in the treatment of epilepsy and bipolar disorder and appears to be a relatively selective sodium channel blocker, although its site of action has not been confirmed. What is clear is that it has a better side-effect profile than most other anticonvulsant agents. Although topiramate is used in the treatment of epilepsy, its primary use is in the treatment of migraine with some usage for treating both epilepsy and
Late-Stage Development Compounds

A significant number of ion channel modulators are in the final stages of development. Three (tedisamil, vernakalant, and dronedarone) have recently been approved for use, while a further seven (Table 5.1) have been filed for approval.

Tedisamil

Solvay’s tedisamil (Pulzium) is a potassium channel blocker that has been developed for the treatment of arrhythmia and is described as a class III antiarrhythmic agent. An MAA was filed in March 2007 and approved in August 2008, with launches in the United Kingdom, Spain, and Sweden. However, the NDA, filed in December 2006, was rejected with a request for additional information. In October 2008, Solvay indicated its intentions to globally out-license tedisamil.
Cystic Fibrosis

VX-770

Vertex and the Cystic Fibrosis Foundation established a collaboration in March 2006 to develop regulators of CFTR. The adopted strategy was to identify novel compounds that enhance the translocation of the defective ΔF508-CFTR (the most frequent genetic defect) to the epithelial cell membrane. This should partially restore chloride channel function and thus alleviate the symptoms of the disease. VX-770 is an orally active potentiator of this translocation, and a Phase IIa study commenced in 2007. In 2008, it reported results of three Phase II studies with VX-770 that showed it to enhance lung function and sweat chloride levels in patients with both the ΔF508-CFTR and G551D-CFTR mutation.

Vertex has initiated the Phase III ENDEAVOR registration program designed to support registration of VX-770 in patients with the G551D mutation. Vertex initiated the STRIVE trial in May 2009 and expects the trial to be fully enrolled in the first quarter of 2010; the ENVISION trial was initiated in August 2009. Vertex expects to initiate a Phase II trial in patients homozygous for ΔF508-CFTR in the third quarter of 2009.

5.3. Phase II
CNS Conditions

Table 5.3. Ion Channel Modulators in Phase II Studies for CNS Disorders

<table>
<thead>
<tr>
<th>Drug</th>
<th>Developer</th>
<th>Target</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofinicline</td>
<td>Abbott</td>
<td>Nicotinic</td>
<td>ADHD</td>
</tr>
<tr>
<td>EHT-0202</td>
<td>ExonHit</td>
<td>GABA</td>
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Continued
Company Profiles

The previous chapter considered all the ion channel modulators currently in development and highlighted how few are being developed by most major companies. While a number of these companies have a substantial historical interest in this class of targets, many are currently showing little interest. A better indication of current efforts is provided by examining recent patenting activity from major companies. Table 6.1 shows the level of interest in such targets from seven of the top ten companies that have indicated greater interest in developing ion channel modulators. It does not take into account the impact of the pending mergers of Pfizer with Wyeth and Merck & Co. with Schering-Plough.

AstraZeneca

AstraZeneca’s focus is predominantly on ligand-gated channels with less evidence of interest in voltage-gated channels, but its recent patent portfolio in this area is larger than that of most companies. It established a collaboration with Targacept (see below) in December 2005 relating to the development of nicotinic receptor ligands for neuronal disorders. This has augmented its own efforts on this target and is in addition to its long-standing efforts on purinergic P2X receptor ligands. AstraZeneca’s interest in sodium, potassium, and TRP channels is more recent but suggests that it is seeking to broaden its portfolio of ion channel modulators.

Eli Lilly

Eli Lilly has had a major effort on glutamate receptor ligands for some time, targeting both the ligand-gated channels and metabotropic receptors. Although it established a partnership with Icagen in the 1990s, this has now expired. Lilly does not appear to have any ongoing collaborations in the ion channel field. As can be seen from Table 6.1, its recent efforts on these targets also appear to be sparse.

GlaxoSmithKline

GlaxoSmithKline has an established presence in marketing certain ion channel modulators and has a number of products in earlier-stage development. Recent patenting activity indicates that it has interest in most classes of ion channel targets, with least evidence of activity targeting potassium channels, GABA, and glutamate receptors. Although it has filed few patents relating to nicotinic receptors, this area is being addressed through its strategic alliance with Targacept to develop novel analgesics.
Chapter 8

EXPERT INTERVIEWS

Interviewees:

**John Kemp, PhD**, is Chief Research and Development Officer of Evotec (Hamburg, Germany), with extensive experience in neuroscience research.

**John Dunlop, PhD**, is Director of Neuropharmacology and Neurophysiology, Neuroscience Discovery Research, Wyeth Research (Princeton, NJ)

**William A. Catterall, PhD**, Chair of Pharmacology at the University of Washington (Seattle, WA)

*Insight Pharma Reports (IPR):* Ion channels offer one of the largest classes of potential drug targets yet remain relatively underexploited by the pharmaceutical industry. Do you feel that this is attributable to their complexity, the poor understanding of their pathophysiological roles, or the poor suitability of the screening methods that were available until recently?

**WC:** More meaningful high-throughput screening methods have only recently become available, but have yet to lead to any new drugs.

Toxicity concerns are a problem, with potentially catastrophic effects in the heart.

Ion channels are often implicated in episodic diseases, such as arrhythmia, epilepsy, and chronic pain, but effective animal models are an issue.
Question 10. In your opinion, has the lack of reliable screening assays been the major factor in decisions of large pharma to avoid the pursuit of many ion channel targets?

I disagree. I believe that major pharma companies have been actively pursuing ion channel targets.

n=47

Source: Insight Pharma Reports’ Ion Channels Survey—July 2009

Among respondents who answered “no,” reasons put forth for the hesitation to pursue ion channel targets included difficulty of target validation, the fact that ion channels need more laborious functional assays, target specificity, cost and payoff.
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• PepTalk: The Protein Information Week
• World Pharmaceutical Congress
• PEGS: The Essential Protein Engineering Summit
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Barnett, formerly a division of PAREXEL International, is a recognized leader in clinical education and training for all levels of staff involved in the drug development process. In addition, Barnett is the well-known publisher of the *Bio/Pharmaceutical R&D Statistical Sourcebook* and other reference manuals that help research facilities ensure compliance by providing updates about the latest federal regulations, while offering executives valuable information garnered from real-world studies, analyses, and widely respected industry opinion leaders. For more information on Barnett’s publications and educational programs, visit [www.barnettinternational.com](http://www.barnettinternational.com).

**Insight Pharma Reports** ([www.insightpharmareports.com](http://www.insightpharmareports.com))

Insight Pharma Reports is the premier life sciences information provider offering unparalleled coverage of key issues in drug discovery and development. The reports are used by leading pharmaceutical, biotech, diagnostic, and other life science companies to keep abreast of the latest developments in pharmaceutical R&D and their potential applications and business impacts. The reports are written by experts in consulting and industry, and are supported by hundreds of hours of primary and secondary research. Insight Pharma Reports provide comprehensive coverage of salient issues in a concise, well-organized format.

**CHI’s Marketing Services** ([http://proservices.healthtech.com](http://proservices.healthtech.com))

The Marketing Services group is an ideal solution for companies seeking assistance in all aspects of life sciences direct marketing. CHI’s Marketing Services continues to be chosen #1 over our competitors for one reason – We deliver results that impact the bottom-line with many services to choose from! Services include list rentals, direct marketing, product and service alerts, and mail piece designs.
**Cambridge Meeting Planners** (http://proservices.healthtech.com)

Cambridge Meeting Planners (CMP), a division of Cambridge Healthtech Institute, has a highly professional, experienced team dedicated to providing you with the finest services to match any budget. With five meeting planners who combined have over 50 years of experience in the field, CMP has extensive working relationships with hotels and vendors guaranteeing you superior service with all of your contract negotiation needs.

CMP is available to manage all of your preplanning and onsite meeting needs, including site selection, contracting, audio visual/food and beverage selection, hiring/managing security and temps, etc. CMP is there for you whether you need help planning a reception for 1000 or a working dinner meeting for 20 professionals. CMP can manage your entire event from soup to nuts and make your vision a reality. Types of events include:

- Conferences
- Tradeshows
- Usergroup meetings
- Product launches
- Focus groups
- Client appreciation events
- Team building excursions
- Recreational and hospitality programs
- And many more. Please visit our web site for a more detailed list.

**Cambridge Healthtech Associates** (www.chacorporate.com)

Cambridge Healthtech Associates (CHA) is the leading organizer and facilitator of biopharmaceutical collaboration. CHA reduces the costs of R&D by bringing together different companies to work cooperatively to evaluate novel technologies, assess vendors in emerging global markets and address other areas of shared concern. This is accomplished through short, six-month collaborative projects, market research surveys, roundtable summits, virtual meetings (via tele/web conference) and the Drug Safety Executive Council (an exclusive online community of industry leaders). For more information, visit www.chacorporate.com.

**Cambridge Healthtech Media Group** (www.chimediagroup.com)

Cambridge Healthtech Media Group, a division of Cambridge Healthtech Institute, delivers content to decisionmakers through its print, online, and electronic products designed to serve the life sciences community. The Media Group’s editors are at the pulse of the market and disseminate ground-breaking news, analysis, trends, and insights that shape the life science industry through a suite of published resources—*Bio-IT World* magazine—CHI’s flagship publication, three topic-specific eNewsletters, and web sites.

**Bio-IT World** (www.bio-itworld.com)

*Bio-IT World* magazine—CHI’s flagship publication—publishes critical insights, analysis, and opinion on the enabling technologies propelling the spread of information and the passage of drug candidates through the drug discovery process. *Bio-IT World*’s focus is increasingly one that explores the tools and results of predictive biology, drug discovery, informatics, and personalized medicine. The magazine also focuses on the strategic decisions made by companies in this area and the impact on the company’s performance.
A few key areas covered in-depth include: recent advances in whole genome analysis and next-generation sequencing, data handling technologies, the vast potential of adaptive clinical trials, in silico modeling, cheminformatics, electronic data capture, and much more. Please visit www.bio-itworld.com to view more feature articles on the life sciences industry and to subscribe.

**eNewsletters**

- **eCliniqua** (www.chimediagroup.com)
  
  Published 2x per month, eCliniqua provides authoritative news, views, and insights on management challenges related to innovative clinical research management and implementation processes and technology solutions. Specific topics covered include: innovations in development planning and protocol design; new approaches to sponsor-CRO and sponsor-site relationships; novel patient recruitment and retention strategies and practices; project management; emerging and established electronic clinical trial technologies and standards; regulatory and drug safety insights; and other critical topics focusing on the clinical research enterprise.

- **Predictive Biomedicine** (www.chimediagroup.com)
  
  Published 2x/month, Predictive Biomedicine covers the development and use of informatics and computational tools used to manage, present, and interpret experimental data as well as those used in modeling and bio-simulation. From data management challenges to systems biology initiatives, Predictive Biomedicine will report on industry’s efforts to reduce dependence on trial and error and adopt more data-driven predictive methods to drive drug discovery and developments.

- **Bio-IT World Weekly Update** (www.bio-itworld.com)
  
  Published weekly, Bio-IT World Weekly Update is a summary of the week’s latest news, industry highlights and trends, product reviews, upcoming events, and key stories from Bio-IT World magazine and its companion web site, www.bio-itworld.com.

**Lead Generation Programs** (chimediagroup.com)

The lead generation team at Cambridge Healthtech Media Group has access to a core audience from pharma, biotech, CROs, academia, technology, and niche service providers involved in the life sciences industry. The team can help you create a comprehensive media package—targeting specific demographics—and incorporating your message within the published resources that our audiences trust. Programs may include Microsites, white papers, webcasts, podcasts, custom surveys, special mailings, and other solution packages to meet your business needs.

To request information on the Lead Generation Programs, Custom Solution Packages, or to develop a comprehensive media package to reach a target audience, contact marketing_CHMG@healthtech.com.

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