

# Executive Summary

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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 ( $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Ca}^{2+}$ , or  $\text{Cl}^-$ ), 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 assessment 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<sub>A</sub> receptor ligand-gated channels and the L-type calcium channels, with a moderate number of drugs also available that target the K<sub>ir</sub> potassium channel, the 5-HT<sub>3</sub> 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<sub>A</sub> 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<sub>7</sub> 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.