Background

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What are Ion Channels?

Ion channels allow the movement of charged particles, known as ions, across cell membranes. Ion channels function in a variety of biological pathways including the firing of neurons and muscle cells and the activation of immune cells.

Overview

Ion channels are used to restore the balance of ions across a membrane. When open, ion channels allow charged molecules to move from an area of high concentration to low concentration without using energy. Ion channels serve as a counterbalance to active transport, a process whereby a cell uses energy to actively pump ions and other charged molecules across a membrane in order to establish ion gradients or alter the pH of an organelle to activate enzymes. There are two major types of ion channels:

- Voltage-gated ion channels
- Ligand-gated ion channels

When ions are present in a higher concentration on one side of a membrane than the other, a difference in voltage occurs across that membrane, creating a membrane potential. Voltage-gated ion channels open in response to a change in membrane potential, allowing the ions to move from the side of the membrane with the higher ion concentration to the side with the lower ion concentration.

Ligand-gated ion channels rely on the binding of a small molecule to the channel. The small molecule binding causes a change in the channel protein, opening the pore for the ions to travel through. As with voltage-gated ion channels, when ligand-gated ion channels open ions move from the side of the membrane with the higher ion concentration to the side with the lower ion concentration.

When targeted by therapeutics, ion channels are either inhibited, preventing the flow of ions, or held constitutively open by the action of agonists, preventing the accumulation of ions on one side of the membrane. The desired activity of the ion channel modulator depends on the disease being targeted.

Existing Products

There are several ion channel modulators currently in use. Examples are included in the table below.

Channel Type	Target Name	Development Status
	Ca^{2+} channel	Multiple FDA approved anti-hypertensives
	Na^{+} channel	Multiple FDA approved products including

Voltage-gated		local anaesthetics and anticonvulsants
	K^+ channel	Multiple sulfonylureas approved for diabetes
Ligand-gated	Glutamate-gated chloride channel	Ivermectin, FDA approved for onchocerciasis and in use for the treatment of lymphatic filariasis
	Acetylcholine-gated chloride channels	Levamisole, pyrantal, and tribendamadine (China only), for treatment of helminth infections Multiple FDA approved products for the treatment of tobacco dependence

Ion Channel Modulators as Non-Neglected Tropical Disease Therapeutics

Ion channel inhibitors are used to treat a wide range of conditions including:

- Hypertension
- Pain
- Convulsions
- Diabetes
- Tobacco dependence

The most well-known and widely-used ion channel inhibitors are the calcium channel inhibitors used to treat high blood pressure. The movement of calcium across cell membranes causes muscle contractions. While this is a normal biological process, contraction of the muscles of the circulatory system can exacerbate the condition of patients with high blood pressure or hypertension. Calcium channel blockers are used in patients with hypertension to reduce contraction of the smooth muscles of the arteries, allowing the arteries to dilate to reduce blood pressure.

Ion Channel Modulators as Neglected Tropical Disease Therapeutics

Ion channel inhibitors are used to treat parasitic worm infections including:

- Onchocerciasis
- Lymphatic filariasis
- Ascariasis
- Hookworm
- Schistosomiasis

Ivermectin is a glutamate-gated chloride channel inhibitor that is widely used in mass drug administration programs in the developing world to treat infections with parasitic worms that cause onchocerciasis and lymphatic filariasis.[1,2] Ivermectin is also used widely in veterinary medicine for the treatment of worm infections.[3] The drug is believed to work in these organism by inhibiting glutamate-gated chloride channels, which are only found in invertebrates, allowing these drugs to selectively target parasitic worms over their human hosts.[4] Disruption of the flow of chloride causes paralysis and starvation of the worm leading to death.

Levamisole and pyrantal pamoate can be used to treat the soil transmitted helminths ascariasis and hookworm, but are not widely used. Tribendamadine is used to treat ascariasis in China but has not been extensively evaluated or used outside of China. All three of these products are agonists of acetylcholine-gated chloride channels.[5] These drugs force the chloride channels to remain open rather inhibiting them; the resulting imbalance of chloride ions results in death of the worms.

Praziquantel is the only on market drug for the treatment of schistosomiasis. Although the mechanism of action of praziquantel is not entirely clear, it is believed that the drug inhibits calcium channels on the parasite.[6] More research is needed to understand if inhibition of calcium channels is the primary mechanism of action of praziquantel or part of a multi-target mechanism.

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2. Keiser J and Utzinger J (2010) “The drugs we have and the drugs we need against major helminth infections.” *Advances in Parasitology* **73**: 197-229.
3. Raymond V and Sattelle DB (2002) “Novel animal-health drug targets from ligand-gated chloride channels.” *Nature Reviews: Drug Discovery* **1**: 427-436.
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5. Hu Y et al. (2009) The New Anthelmintic Tribendimidine is an L-type (Levamisole and Pyrantel) Nicotinic Acetylcholine Receptor Agonist. *PLoS NTD* **3**: e499.
6. Doenhoff MJ et al. (2008) “Praziquantel: mechanisms of action, resistance and new derivatives for schistosomiasis.” *Curr Opin Infect Dis* **21**: 659-667.

Get Involved

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Pipeline & Analysis

Get Involved

PIPELINE

Product/Research Program	Developers	Discovery	Pre-clinical	Phase I	Phase II	Phase III
Crofelemer	Glenmark Pharmaceuticals Ltd. Luye Pharma Napo Pharmaceuticals, Inc. Salix Pharmaceuticals					
Moxidectin	Pfizer Inc. World Health Organization					
iOWH032	Galapagos NV Institute for OneWorld Health Roche					
Second-generation synthetic CFTR chloride channel inhibitors	Napo Pharmaceuticals, Inc.					
Virion Dengue	Biotron					
Discovery program for anti-diarrheal agents	Anacor Pharmaceuticals, Inc. Institute for OneWorld Health Novartis AG Roche					
ISPA-028	National Institute of Allergy and Infectious Diseases					

ANALYSIS

Modulators of ion channels have been validated as therapeutic targets for a variety of diseases included parasitic worms. Ion modulators are challenging to study as a target class, but advances in non-neglected disease applications of ion channel modulators have the potential to inform development of new neglected disease products. Additionally, modulators of ion channels have the potential to benefit from the recycling of chemical compound libraries developed through previous drug development programs or parallel development of compounds for non-neglected disease applications.

The relative strengths, weaknesses, opportunities and risk for ion channel modulators that are currently in development for neglected diseases are summarized here.

	Strengths	Weaknesses	Opportunities	Risks
Ligand-gated ion channels: Glutamate-gated chloride channels				
Relevant neglected tropical diseases: Onchocerciasis	In use for the treatment of heartworm in animals Based on proven	Because same mechanism of action as ivermectin, unlikely to overcome limitations	Potential for use in the treatment of other helminth infections such as lymphatic	May be susceptible to the same mechanisms of resistance as ivermectin

(Moxidectin, phase III)	mechanism of action for treatment of helminth infections	faced by ivermectin	filariasis	
Ligand-gated ion channels: ATP-gated anion channel				
Relevant neglected tropical diseases: Diarrheal diseases (crofelemer, phase II; iOWH032, phase I; Second-generation synthetic CFTR chloride channel inhibitors, pre-clinical)	Because target is in the intestine, can deliver drug orally with no need for systemic distribution Crofelemer already in phase III for irritable bowel syndrome		Potential to benefit from parallel research programs with cystic fibrosis, a genetic disorder caused by malfunctioning CFTR Potential for combination with oral rehydration therapy or organism specific treatments	Malfunctioning CFTR results in cystic fibrosis. Although poor bioavailability outside of the intestine limits risks with crofelemer, risks for toxicity are a concern. Crofelemer is already in phase II, not clear what the competitive advantages of backup/alternative programs are Current standard of care for diarrhea is oral rehydration therapy, not clear how difficult it will be to change this policy to allow use of a product such as crofelemer
Ligand-gated ion channels: Calcium-gated chloride channel				
Relevant neglected tropical diseases: Diarrheal diseases (crofelemer, phase II)	Because target is in the intestine, can deliver drug orally with no need for systemic distribution Crofelemer already in phase III for irritable bowel syndrome		Potential development of combination products with CFTR inhibitors Potential for combination with oral rehydration therapy or organism specific treatments	As CFTR is the primary target of crofelemer, it is unclear if CaCC also needs to be inhibited for effects Current standard of care for diarrhea is oral rehydration therapy, not clear how difficult it will be to change this policy to allow use of a product such as crofelemer
Other: Plasmodial surface anion channel (PSAC) inhibitor				
Relevant neglected tropical diseases: Malaria (ISPA-028)	Target unique to malaria Inhibitors can selectively target drug resistant parasites	Susceptibility to inhibitors appears to vary by parasite strain, may be susceptible to resistance or require more work to identify broadly effectively lead compound More understanding of the basic biology of this channel type is needed	Because channel is unique to the parasite, potential to develop highly selective drug. However, because the channel is unique the chances of repurposing existing ion channel inhibitors is lower.	Variability of channel susceptibility to inhibitors between parasite strains suggests risk of developing resistance is high

Chemical libraries of ion channel modulators developed for non-neglected diseases may be useful for new drug discovery for neglected diseases. Potential ion channel drug targets for neglected diseases are described below.

Neglected tropical disease	Voltage-gated ion channels	Ligand-gated ion channels

Soil transmitted helminths: ascariasis, trichuriasis, hookworm		Glutamate-gated chloride channel inhibitors and Acetylcholine-gated chloride channel agonists[1,2] Although ivermectin is less effective against these organisms, additional research may identify more potent analogs of ivermectin or moxidectin. Also there is potential for repurposing of compound libraries developed for nicotine addiction.
Other helminths: onchocerciasis, lymphatic filariasis		Glutamate-gated chloride channel inhibitors and acetylcholine-gated chloride channel agonists[1,2] Targets validated with on market products. May benefit from repurposing of compound libraries developed for nicotine addiction
Diarrheal diseases		Host CFTR and CaCC Potential for co-development of products with research programs for cystic fibrosis and/or non-infectious diarrhea (e.g. irritable bowel syndrome)
Malaria	Classical voltage-gated ion channels have not been identified.	Plasmodial surface anion channel (PSAC)[3]
Schistosomiasis	Ca^{2+} channels[4] Potential repurposing of calcium channel blockers developed for hypertension	

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References

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3. Nguitragool W et al. (2011) “Malaria Parasite clag3 Genes Determine Channel-Mediated Nutrient Uptake by Infected Red Blood Cells.” *Cell* **145**: 655-677
4. Doenhoff MJ et al. (2008) “Praziquantel: mechanisms of action, resistance and new derivatives for schistosomiasis.” *Curr Opin Infect Dis* **21**:659-667.

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Tools

Get Involved

Databases/Resources

Ion channels are more difficult to study than other enzymatic drug targets. Early research on the function of ion channels was made possible through the use of potent naturally occurring neurotoxins such as those found in spider and snake venom. The potential for therapeutics targeting ion channels has led to significant advances in the tools and techniques available for ion channel targeted therapeutics.

There are several databases with general information on ion channels, including:

- The Ion Channel Database
- Ligand-Gated Ion Channel Database
- Aureus Sciences Ion Channel Database

Assays

Tools available for ion channel drug development have been reviewed in the scientific literature.[1,2] Common assays include:

- Membrane binding assay
- Electrophysiology (including patch-clamp)
- Ion flux assays
- Fluorescent dyes
- Fret-based assays

The majority of these assays have been adapted to high throughput formats, however not every ion channel type generates enough signal for robust high throughput screening.

References

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2. Owen D and Silverthorne A. “CHANNELLING DRUG DISCOVERY: current trends in ion channel drug discovery research.” *Drug Discovery World*, Spring 2002.

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Product Details

Crofelemer

Synonyms:
Crofelemer
NP-303
SP-303

Disease:
Diarrheal diseases

Specific Indication:
Infectious diarrhea

Product Type:
Drug

PRV Elegible?
Yes

Target/Technology:
Ion channels

Mechanism of Action:
Cystic fibrosis transmembrane conductance regulator (CFTR) chloride channel and calcium activated chloride channel (CaCC) inhibitor

Molecule Class:
Natural product-derived oligomer

Administration Route:
Oral

Notes:

More information can also be found on this product at [Napo Pharmaceuticals]. Crofelemer is also in development for HIV/AIDS antiretroviral treatment-related diarrhea (Phase III) and irritable bowel syndrome (Phase II).

Clinical Trials:

Publications:

9886979

Discovery program for anti-diarrheal agents

Synonyms:
Discovery program for anti-diarrheal agents

Disease:
Diarrheal diseases

Specific Indication:
Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) chloride channel inhibitor; Calcium activ

Product Type:
Drug

PRV Elegible?
No

Target/Technology:
Ion channels

Mechanism of Action:

Molecule Class:

Administration Route:
Oral

Notes:

Clinical Trials:

Publications:

iOWH032

Synonyms:
3-(3,5-dibromo-4-hydroxyphenyl)-N-(4-phenoxybenzyl)-1,2,4-oxadiazole-5-carboxamide
iOWH032
Anti-secretory treatment for diarrheal disease

Disease:
Diarrheal diseases

Specific

Target/Technology:
Ion channels

Mechanism of Action:

Indication:
Secretory diarrheas (cholera and other watery diarrhea)

Product Type:
Drug

PRV Elegible?
No

Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) chloride channel inhibitor

Molecule Class:

Administration Route:
Oral

Notes:

More information on this product is available from iOWH].

Clinical Trials:

Publications:

ISPA-028

Synonyms:
ISPA-028
Plasmodial surface anion channel (PSAC) inhibitor discovery

Disease:
Malaria

Specific Indication:
Drug resistant P. falciparum

Product Type:
Drug

PRV Elegible?
No

Target/Technology:
Ion channels

Mechanism of Action:
Plasmodial surface anion channel (PSAC) inhibitor

Molecule Class:

Administration Route:

Notes:

Clinical Trials:

Publications:

21620134
20101003

Moxidectin

Synonyms:
Moxidectin

Disease:
Onchocerciasis (River Blindness)

Specific Indication:

Product Type:
Drug

PRV Elegible?
Yes

Target/Technology:
Ion channels

Mechanism of Action:
Glutamate-gated chloride ion channel inhibitor

Molecule Class:

Administration Route:

Notes:

In use for treatment of heartworm in animals.

Clinical Trials:

NCT00790998

Publications:

NCT01035619
NCT00300768

Second-generation synthetic CFTR chloride channel inhibitors

Synonyms:
Second-generation synthetic CFTR chloride channel inhibitors

Disease:
Diarrheal diseases

Specific Indication:
Infectious diarrhea

Product Type:
Drug

PRV Elegible?
Yes

Target/Technology:
Ion channels

Mechanism of Action:
Cystic fibrosis transmembrane conductance regulator (CFTR) inhibitor

Molecule Class:
Hydrazide derivatives

Administration Route:
Oral

Notes:

Clinical Trials:

Publications:

Virion Dengue

Synonyms:
Virion Dengue

Disease:
Dengue fever

Specific Indication:

Product Type:
Drug

PRV Elegible?
No

Target/Technology:
Ion channels

Mechanism of Action:
M protein inhibitor; blocks the ion channel activity of viroporins

Molecule Class:

Administration Route:

Notes:

Clinical Trials:

Publications: