

Fact Sheet – Xention’s Approach to Ion Channel Drug Discovery

The approach to ion channel drug discovery that we have adopted has several key components:

- Using electrophysiology early in the discovery process. The comprehensive use of electrophysiology in all stages of the medicinal chemistry process to support the identification and development of high-affinity ion channel ligands with appropriate selectivity and to optimise those ligands for the preferred mode of action.
- In silico ion channel screening. Computational approaches to in silico screening which have been validated by screening large virtual compound libraries against different ion channels.
- The XENBASE chemoinformatics database. This database is used to inform all activities within our research programmes.
- Xention’s ion channel-focused library. Our compound collection is supported by focused computational chemistry expertise to enable further enrichment.
- An extensive ion channel knowledge base relating to target expression profile, electrophysiological characteristics and pharmacological characteristics of ion channels to enable appropriate assay and protocol development, screening, and the development of clinically interesting modulators for selected targets.
- A large collection of ion channel related genes, recombinant cell lines and tissue culture expertise to enable ion channel counter-screening against non-target channels.

Using Electrophysiology Early in the Discovery Process

Electrophysiology is the gold standard for the study of ion channels and involves use of the patch-clamp technique in manual or automated format. This technique generates high-quality measurements of ion flow through the channel under investigation and an understanding of the nature and kinetics of blockade of the channel by putative drugs. In its traditional, manual form the technique is labour-intensive and requires highly skilled operators and its low throughput precludes its introduction early in the drug discovery process. Xention’s proprietary AutoPatch technology is an automated electrophysiology process that generates data identical to the conventional patch clamp technique, however, as an automated system it is sufficiently high throughput to be utilized early in the discovery process. By integrating electrophysiology early in discovery, our medicinal chemists are able to use genuinely high-content data to understand structure-activity relationships (SAR) i.e. the specific components of potential drug candidates that are responsible for the required activity on the target of interest, and we can thus develop compounds with preferred modes of action in a rational manner.

The XENBASE Chemoinformatics Database

Xention research activities are supported by an extensive and fully integrated chemoinformatics-bioinformatics software platform. Xention uses commercially available software to collect, analyse and store screening results in a standard Oracle database format, but our scientists are able to access the results and inform drug design decisions through a customised web interface. Furthermore, we have painstakingly assembled an ion channel-focused database (“XENBASE”) that is proprietary and second to none in its value to ion channel drug development.

These computational tools, in conjunction with our “wet” biology activities, has enabled the Company to develop:

- Enhanced and novel pharmacophore models;
- Privileged ion channel chemistry scaffolds; and
- Selectivity models for specific ion channels of interest.

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In Silico Ion Channel Screening

In silico screening describes the process of prioritizing large number of potential screening compounds through the judicious use of the information available for the specific target. This process allows us to ‘scan’ the vast quantity of commercially available chemistry to highlight those compounds that are worthy of inclusion in our discovery process for the generation of ‘real’ screening data. The principal sources of information directing this selection process are the two-dimensional and three-dimensional descriptors of preferred ion channel blockers that we generate using XENBASE. The recent availability of crystal structure information (Figure 1) has allowed us to generate good quality homology models of our targets (Figure 2) and to investigate possible binding modes of ligands to help with their further optimisation.

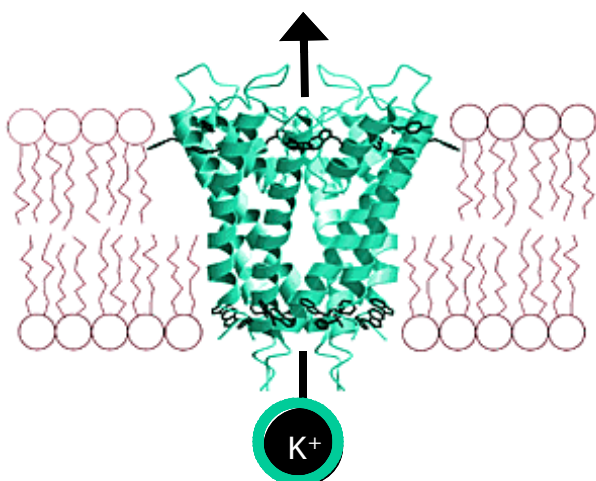


Figure 1.

A schematic picture of an ion channel showing the passage of (in this case) a potassium ion.

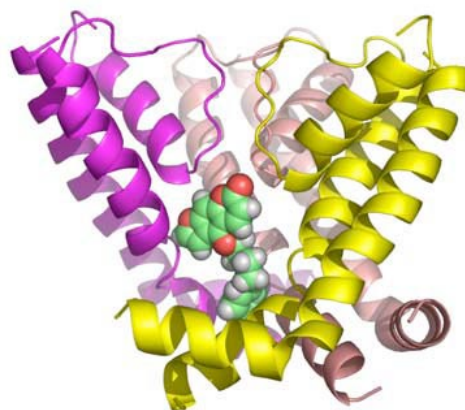


Figure 2.

An image of a small molecule docked into its hypothetical binding site in an homology model of one of our targets picture of an ion channel showing the passage of (in this case) a potassium ion.

Our Ion Channel Specific Compound Library

Compound libraries generally available in the industry have not been developed with ion channel targets in mind, and most scaffolds in pharma libraries are heavily biased towards targets such as GPCRs and enzymes. Thus, the starting material likely to be relevant for ion channel drug discovery is in low abundance from these libraries and hit rates are typically low.

To circumvent this problem, Xention has developed a compound library which is focused on ion channel targets. The library has been constructed from a number of components, each complementary and adding value, including the following:

- Pharmacophores developed from ion channel targets we have worked from which we generate compounds that correspond to these pharmacophore structures;
- Two-dimensional descriptors devised from our electrophysiology data which can use used to identify compounds to enrich our library;
- Compounds generated through our ongoing medicinal chemistry efforts most of which have novel scaffolds.