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Ion channel discovery – partnering to access specialized expertise

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It is well recognized that drug discovery is a highly complex process, with high rates of attrition and often unsustainable costs. This has led to a need for the major players in the field to change their entrenched working model. Over the last approximately 20 years there has been a number of high-profile mergers and site closures, which has in turn driven the need to establish and define a new working paradigm for research and development of new drugs, where outsourcing has become a key component. While removing requirements for in-house infrastructure and the associated staffing enables pharmaceutical companies to reduce costs and transfer the long-term risk to other organizations, outsourcing to collaborators also provides many enabling functions to the drug discovery process.

Although increasingly recognized as an important target class for development of new therapeutics, ion channel research remains a complex area of drug discovery. In this article we discuss the recent advances and how outsourcing to ion channel research specialists can add real value to a therapeutics program.

Outsourcing for expertise

Outsourcing – using an external organization to provide a service – is not a new concept and has been used to provide specific or bespoke needs for many years. Despite this, the size of its contribution to the drug discovery process is clearly growing. The contract research market is predicted to exceed $35 billion in sales in 2020 [1]. Contract research organizations (CROs) are continuously evolving, resulting in a wide variety of offerings and business models to support all stages of the research and development process, from initial target identification to Phase III clinical studies. These range from small, highly specialized CROs offering technical/scientific expertise within a sector, through to large multinational CROs offering a 'one-stop shop' to simplify legal requirements and reduce the burden of project management.

CROs are able to provide specialist or in-depth knowledge and expertise often not found in-house. The ability to access this support when needed gives organizations the flexibility to access a broader spectrum of skills than would have been previously possible. This in-depth knowledge is often associated with the availability of specialist equipment. Taking the example of electrophysiology within ion channel research, companies with a mixed portfolio of targets may deem the space and infrastructure required as not appropriate for their project needs.

The importance & complexity of ion channels as drug targets

Ion channels represent an important target class for development of new therapeutics for a range of indications. Established drugs that target ion channels include antiarrhythmics, antihypertensives, antidiabetic agents and anticonvulsants. Recently developed selective ion channel therapeutics such as the P2X3 inhibitor for chronic cough (Gefapixant; Merck & Co, NJ, USA), Nav1.8 inhibitors for treatment of pain (VX-150; Vertex, MA, USA) and CFTR modulators for cystic fibrosis (e.g., Trikafta; Vertex) demonstrate the potential of ion channel targets in therapeutic areas with high unmet need.

However, compared with other target classes, ion channels are a complex and challenging target family for early drug discovery. In contrast to kinases where there is high structural homology and a conserved small molecule binding site (facilitating structural-based drug design), the ion channel superfamily is structurally diverse, with a wide range of small molecule and toxin binding sites. For example, within the six transmembrane domain channel class, small molecule modulators predominantly bind within the pore region [2], but also at the voltage-sensor domain [3] and at both N- and C-terminal domains [4,5]. In addition, binding of small molecules can be dependent on a specific channel state or modality – for example, state-dependent block of Nav channels [6] and differential effects of TRPV1 blockers on proton, heat and capsaicin activation [7].

The complexity of gating alongside the diversity of binding sites means that a universal ion channel assay is an impossibility. This contrasts with other target classes, which are readily amenable to ultrahigh throughput screening using low cost and ultralow volume biochemical assays. However, the implementation of automated electrophysiology technology has had a profound impact on ion channel discovery, which has resulted in a significant number of clinical candidates. The importance of this technology within the ion channel CRO environment is highlighted by a recent CRO market report, where access to automated electrophysiology platforms is considered to be a key requirement for clients, where assay quality and expertise are rated above cost [8].

Innovations & progress in ion channel discovery

Ion channel high throughput screening campaigns have mainly used fluorescence-based assays of stable cell lines (e.g., Tl^+, Ca^{2+} or Na^+ dyes) to measure permeation of the channel. These have been adapted to electrical field-stimulation (e.g., FDSS/µCELL; Hamamatsu Photonics, Hamamatsu, Japan) and optogenetics [9] for phenotypic screening of excitable cells. Potencies of ion channel modulators from fluorescence assays do not always correlate with gold-standard manual patch clamp, therefore automated (giga-seal) electrophysiology platforms, such as QPatch HT (Sophion Bioscience, Ballerup, Denmark) and Patchliner (Nanion Technologies,

Munich, Germany) have become a key technology to support medicinal chemistry (reviewed in [10]). Automated electrophysiology provides high quality data-rich information for driving structure–activity relationship (SAR) and an ability to explore mechanism of action early in the screening cascade. Higher throughput systems, such as IonWorks Barracuda (Molecular Devices, CA, USA), Qube (Sophion) and Synchropatch (Nanion) also provide the throughput necessary for primary screening.

Historically, the dynamic nature of ion channels has made resolution of structures difficult and consequently relatively few ion channels have been resolved using crystallography-based techniques. However, recent advancements in the field of Cryo-EM have led to significant improvements in the observed resolution and a substantial increase in the number of published structures. For example, over 50 Cryo-EM structures for the transient receptor potential (TRP) channel family have been published in the last 6 years [11]. The recently disclosed human β3 GABAA homopentamer structure [12] is the highest resolution structure to date (at 1.7 Å), which is significantly below the accepted resolution of at least 2.5 Å required to model drug–protein interactions [11]. The recent development of direct electron detector cameras alongside improvements in computational processing has allowed greater resolution of structures, down to the atomic level [12,13]. This will undoubtedly lead to significant improvements in our ability to develop selective ion channel interacting small molecules and therefore an increase in ion channel targeting drugs.

Another area likely to see significant growth is that of utilizing ion channel biologics. While a number of peptide-based approaches have been developed for ion channels (e.g., ziconotide for treating severe chronic pain), monoclonal antibodies represent an area of key opportunity [14]. Antibodies have a number of advantages as therapeutics, including selectivity, distribution and half-life. Importantly they also have higher success rates in the clinic. However, to date ion channel antibody discovery has proved challenging. A prominent issue has been the challenge in expressing ion channel proteins recombinantly. New technologies have been developed to attempt to address this (such as the use of *Tetrahymena thermophila* by Tetragenetics, MA, USA). Improved structural data is also likely to aid future biologics discovery.

CROs play an important role in driving innovation and this is particularly evident within the ion channel field, as highlighted by the recent CiPA Initiative (sponsored by the FDA and other industry stakeholders) [15]. This initiative has brought together a consortium of commercial and academic laboratories, including several CROs, to extend and integrate the use of electrophysiology-based cardiac ion channel screening, *in silico* predictive modeling and human-induced pluripotent stem cell-derived cardiomyocytes for improving accuracy and reducing cost in predicting cardiac liability of new drug candidates [16,17].

The growth of outsourcing within the ion channel space (for both small molecules and biologics) has focused on technology and innovation. Automated electrophysiology in particular has proven itself to be an important and expanding mainstay of ion channel drug discovery, including providing accurate and relevant potency measures for driving SAR [8,10]. The continuing development of Cryo-EM techniques, allowing atomic resolution of 3D ion channel structures below 3Å [13], has markedly increased the potential of structure-based design of ion channel modulators to become a reality, which will initially provide outsourcing opportunities to academic groups. A focus on outsourcing of automated electrophysiology assays alongside structure-based design will provide a powerful combination for driving successful ion channel discovery.

Financial & competing interests disclosure

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