



Ion Channels: Targets Of High-Tech Screens

Featured Article

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Without ion channels, we would cease to move, think, or breathe—hence their involvement in many diseases and their attractiveness as drug targets. Indeed, says Sikander Gill, application scientist at [Aurora Biomed](#), “recent activities in the development of drugs that target ion channels have increased our understanding of channel modulators that offer significant therapeutic solutions to pathological conditions.”



While [patch-clamp](#) electrophysiology is still widely recognized as the gold standard for studying ion channels, because of its accuracy and the amount of information obtained, it is also low throughput for screening channel modulators, and requires skilled electrophysiologists. The lack of appropriate screening technologies is currently limiting the advancements within this field. Especially, there is a need for enhanced primary screening technologies and methods enabling efficient secondary screening on ligand-gated ion channels,” says Jonas Ohlsson, CEO at [Celletricon](#). Screening ion channels as drug targets requires higher throughput screens, such as with voltage-sensing dyes in imaging studies, and ion flux assays as primary screens. Unfortunately, this usually exacts a price of less informative data, at least compared to a good patch-clamp recording. “If high quality systems, such as automated patch-clamp, can be used earlier in drug discovery, there is less risk to miss potential blockbuster drugs,” says Cecilia Farre, senior scientist and marketing director at [Nanion Technologies](#). Automated patch-clamp systems have been advancing rapidly over the past few years to meet the demand for ion channel drug screening. “Scientists are actively looking for technologies that will allow them to utilize voltage-clamp assays as early in the process as possible, all the way to primary screening,” says Jeff Jensen, CEO of [Fluxion Biosciences](#).

Versatile systems for ion channel study

Nanion offers several systems to accommodate different patch-clamping studies. Their Port-a-Patch is “the world’s smallest patch-clamp rig,” according to Farre. Their Patchliner system offers moderate throughput with giga-seal recordings, as well as experimental features such as temperature control, which enabled scientists at Nanion to investigate the effects of heat and activation on the TRPV1 receptor. Transient receptor protein (TRP) channels are complex drug targets because they can be activated by ligands, temperature changes, and mechanical stimulation. “The TRPV1 channel is activated by capsaicin, the pungent compound from chili peppers, as well as temperatures above 42°C,” says Farre. “TRPV1 antagonists have shown analgesic effects, and therefore hold a promise to have effects on pain that is poorly handled by traditional pain killers. A serious side effect of several of the TRPV1 antagonists, though, was that they also affected the threshold for heat activation of TRPV1, which affected the core body temperature in the

test persons.”

Higher-throughput systems for ion channel screening

For higher-throughput work such as screening for ion channel drugs, Nanion will soon be introducing its SyncroPatch 96, which makes giga-seal recordings from 96 cells simultaneously. “Allowing a throughput of 5000 data points per day, it will be a very useful tool in drug discovery for ion channel screening efforts, for both ligand- and voltage gated ion channels,” says Farre. “It will further remove the bottleneck in drug screening for obtaining reliable data on ion channel active drugs. A general advantage with all Nanion’s platforms is that they show consistently high success rates for completed recordings, independent of what [cell line](#) is used as carrier of the ion channel. The success rates are the same for HEK, CHO, COS, RBL and other cells tested.”

An all-in-one approach is being taken by Celectricon with the launch of their new Dynaflow®HT early next year. The system is designed to perform all types of screens, from lead optimization to primary screening. “Most importantly, this system can be used for all types of ion channel screening assays, [including] those involving fast acting ligand-gated ion channels that are very difficult to run on other systems,” says Jonas Ohlsson, CEO of Celectricon. “The Dynaflow®HT patch-clamp chip technology is unique in that the technology is based on advanced microfluidics, enabling optimized patch clamping of cells, and fast and complex perfusion algorithms. Dynaflow®HT System solves the critical bottlenecks ion channel screening by offering increased throughput, enhanced data quality and assay flexibility, at a dramatically reduced running cost.”

Fluxion Biosciences also use microfluidics in their new IonFlux™ System, which uses a plate reader format for throughputs of up to 10,000 compounds per day. “The consumable looks and handles just like an SBS-standard 96- or 384-well plate, but the bottom of the plate is a microfluidic network,” says Jensen. IonFlux uses the microfluidic channels to patch the cells at junctions of small (~1 micron) and larger channels. “The use of this microfluidic network really facilitates automation and rapid fluid exchange, which are two needs we hear regularly from the drug discovery community,” says Jensen. “Fast solution exchange is especially important for screening of ligand-gated ion channels, which require fast compound application.”

Aurora Biomed offers high-throughput instruments and assays that are based not on the patch-clamp method, but rather on the intracellular and extracellular concentrations of tracer elements. Their Ion Channel Reader (ICR) systems are fully automated and use flame atomic absorption spectroscopy to detect tracer ions that move through ion channels of cells grown in 96- or 384-well formats during cell-based flux assays in response to a test compound. The tracer is chosen based on the channel being studied—for example, rubidium (Rb⁺) is used for potassium channels, and lithium (Li⁺) for sodium channels. “Drug potencies determined by flux screens are highly correlated with those of electrophysiology,” says Gill. “Calculated drug rank orders between the two methods are identical.” Aurora Biomed also has new screening assays for acid-sensing ion channels (ASICs) that mediate pain signals, stretch-activated channels (SACs) that are thought to be involved in arrhythmias and glaucoma, and for ion channels constituted in liposomes.

Getting more physiological

An emerging trend is finding ways to study or screen ion channels such that they are in a more physiologically relevant environment. “It’s quite a difference between investigating cell lines over-expressing a single ion channel compared to using more complex cells such as primary cells and stem cell-derived cardiomyocytes,” says Farre. “In such preparations, currents can be quite small, since they aren’t over-expressed, meaning that high-quality recordings are required to resolve the currents.” She also points out that current-clamp recordings from primary cells would yield

valuable information: “Looking at compound effects on action potentials rather than the individual ion channels will give a better indication of the compound effect in vivo, and thus save time in the drug discovery process. The Port-a-Patch and the Patchliner are currently the only platforms on the market supporting such recordings”

Another challenge is establishing a reliable method to use diseased tissue in automated patch-clamp systems, says Daniel Konrad, CEO of [bSys](#). The ability to screen compounds against ion channels in healthy and diseased primary cells would be invaluable. bSys offers high-throughput screening services that include automated patch-clamping with [Sophion](#)’s QPatch system, as well as five manual patch-clamping rigs with automated liquid handling. Their microfluidic chip-based drugbeam™ technology gives tight control of drug perfusion to a single patch-clamped cell. Different concentrations of compounds can be applied in such a focused fashion that the neighboring cells remain drug free. This allows you to use the same dish of cells—perhaps containing precious primary cells—for much longer. “Services include action potential studies on primary cells, and on stem cell-derived cardiac and neural cells,” says Konrad. “A further important point is that [fluorescence-activated cell sorting \(FACS\)](#) enables us to prepare cells from primary and disease-related tissue. This overcomes two important limitations: immunoprecipitation issues for transgenic cell lines, and the feasibility of diseased tissue screening.”

With the myriad of high-throughput tools available for ion channel work, look for scientists to begin checking off their drug targets. “Ion channels have been historically difficult targets to screen against,” says Jensen, “but this means ion channels represent a really great opportunity going forward.”

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