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Ion channel screening technologies: will they revolutionize drug discovery? ▼

Ion channels are becoming increasingly attractive to the drug discovery business as new targets for novel therapeutic agents. This is partly because of their extremely heterogeneous nature which gives rise to hundreds of different subtypes. It is estimated that even in *Caenorhabditis elegans* almost 100 unique potassium ion channel genes exist [1]. Furthermore, these different subtypes are involved in nearly all physiological processes and, of arguably more interest to the pharmaceutical industry, in many pathophysiological processes. Ion channels can be restricted to a defined subtype of tissue and they are easily accessible as targets for drugs because they face the extracellular matrix. In addition to their role as potential targets, the hazardous side effects of many drugs on the cardiac HERG ion channels will presumably prompt regulatory authorities to oblige the industry to screen for these side effects early in drug development; indeed the ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) is soon to publish a set of guidelines for cardiac safety assessment [2]. The increasing interest in ion channels is mirrored by the fact that new screening technologies have been developed and more companies have been founded during recent years that focus on the ion channel business.

So what has hampered an earlier breakthrough of ion channel screening in the field of drug discovery, especially in HTS? First, many of the ion channels have only recently been cloned and linking the ion channels to specific cellular functions is still under way in basic research. However, the delay might also have originated from the lack of established assays that enable reliable and fast screening for drugs that modulate the activity of ion channels. Unlike, for example, enzymes that can be studied in solution, the examination of the activity of, and the functional interaction of drugs with, ion channels has to be performed in a cellular context. However, this makes the development of cellular assays indispensable and one can easily imagine that the handling of cells in HTS requires highly sophisticated technology. In addition to these difficulties, the assay systems developed, to date, suffered from rather limited signal to noise ratios thus often disqualifying them from larger screening campaigns. Furthermore, the accuracy of the 'gold standard' in ion channel research – the patch clamp technique – can by no means be matched by these techniques.

In the past few years great efforts have been undertaken to meet the requirements of drug discovery. This includes the improvement of already existing technologies but also the development of new assay systems. Comprehensive overviews of state-of-the-art ion-channel technologies by Xu *et al.* and Netzer *et al.* were recently published in *Drug Discovery Today* [3,4]. Among these technologies the most promising are miniaturized and automated patch-clamp devices that combine the precision and information content of electrophysiological investigations with the throughput necessary for modern drug discovery programs. However, these systems are still under development and it has yet to be proved whether these technologies will match the demands of the market in future. It will be exciting to see if further developments will help the pharmaceutical industry to add new compounds modulating ion-channel activity to the list of best-selling drugs worldwide.

References

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