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Automated high-throughput patch-clamp techniques

Research using the conventional patch-clamp [1] has significantly advanced knowledge of the structure and function of ion channels over the past decade; however, the patch-clamp technique is labor-intensive and of low throughput and few novel ion channel modulators were identified using this technique. In the absence of functional electrophysiological assays for the high-throughput screening (HTS) of ion channel targets, alternative methods, such as ionic flux, ligand binding, the fluorometric imaging plate reader (FLIPR) and the voltage-ion probe reader (VIPR), have been used for ion channel screening. Although these assays offer higher throughput, their use is somewhat limited because they do not measure ion channel function directly, they lack sensitivity and/or they are not suitable for the evaluation of rapidly desensitizing ion channels.

In a recent issue of *Drug Discovery Today*, Wood *et al.* [2] reviewed novel automated approaches to ion channel screening, which provide increases in screening throughput and reductions in labor intensity. Three systems that are commercially available are IonWorks™ HT (Molecular Device Company; http://www.moleculardevices.com), PatchXpress™ 7000A (Axon Instruments; http://www.axon.com) and Flyscreen®8500 (Flyion GmbH; http://www.flyion.com).

IonWorks™ HT and PatchXpress™ 7000A represent planar-array-based screening platforms that offer 'patch-clamp on a chip' [3]. An electrode is fabricated at the bottom of each well of a 16–384-well plate, each electrode is connected to an amplifier and is able to make a whole-cell patch recording. Thus, robust parallel screenings of ion channels can be performed, which is in contrast to conventional patch-clamp systems where the recording is typically performed on one cell at a time. However, the rate of achieving whole-cell patch recording with current planar-array platforms is only ~60%–70% (for particular types of cell lines, the success rate is even lower). Thus, it remains a challenge to identify suitable substrates [e.g. silicon, glass, plastic, poly(dimethylsiloxane) or silicon nitride] for planar electrodes. Further enhancement of the precision and consistency of the microfabrication technology used to fabricate planar electrodes is also needed. It remains to be seen whether or not the planar-array screening platform can be applied to a wide range of cell lines, including primary-cultured cells. By contrast, Flyscreen®8500 represents an innovative system for pipette-based, automated patch-clamp recording. This approach simplifies the patch-clamp technique by pipetting cells inside the bottom of each electrode to enable a whole-cell patch recording, whereas conventional patch-clamp systems micromanipulate a single electrode to the surface of the cell to perform a whole-cell recording. Other commercial developers also offer innovative technologies that could produce competitive automated patch-clamp instruments in the near future [2,4].

Data acquisition and analysis software also play important roles in HTS. The programs designed for HTS analysis of ion channels might be different from those required for conventional electrophysiology. The software should be able to log in all events and recording traces, yet be intelligent enough to differentiate valid data from artifacts, and should also facilitate appropriate data handling and analysis to identify active compounds in an efficient fashion. An excellent example of data acquisition and analysis is illustrated by the successful use of an automated high-throughput electrophysiological-recording system for oocytes [5].

The past three to four years have witnessed innovations, refinements and improvements in patch-clamp technology that have enabled the transformation of a single-electrode patch-clamp to an automated, pipette-based or planar-array-based high-throughput patch-clamp recording. The Human Genome Project (http://www.ornl.gov/sci/techresources/Human_Genome/home.shtml) has identified more than 300 ion channel genes [6]. High-throughput electrophysiological recording holds the promise to accelerate the screening of novel ion-channel modulators that could potentially be used in the treatment of human diseases.

References

1 Hamill, O.P. *et al.* (1981) Improved patch-clamp techniques for high-resolution current recording from cells and cell-free membrane patches. *Pflügers Arch.* 391, 85–100

2 Wood, C. *et al.* (2004) Patch clamping by numbers. *Drug Discov. Today* 9, 434–441
3 Sigworth, F.J. and Klemic, K.G. (2002) Patch clamp on a chip. *Biophys. J.* 82, 2831–2832
4 Wang, X. and Li, M. (2003) Automated electrophysiology: high-throughput of art. *Assay Drug Dev. Technol.* 5, 695–708
5 Trumbull, J.D. *et al.* (2003) High-throughput electrophysiology using a fully automated, multiplexed recording system. *Receptors Channels* 9, 19–28
6 Venter, J.C. *et al.* (2001) The sequence of the human genome. *Science* 291, 1304–1351

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Real options are neither complicated nor unrealistic

In a recent issue of *Drug Discovery Today*, Pandey [1] gave a clear overview of the different valuation techniques that are available for pharmaceutical R&D projects. In the framework of strategic capital allocation, proper valuation enhances the quality of the decision-making process. As described by Pandey, companies today have the choice between three techniques – discounted cash flows (DCF), decision trees (also known as scenario analysis) and real options. In our opinion, the article written by Pandey does not adequately explain or use the notion of an option, and consequently falls short of describing the full potential of the real options approach. In this discussion, we would like to address some of the common misunderstandings relating to the real options that are applied to R&D valuations.

What is and is not an option?

Abandonment of a project following negative clinical trial results should not be seen as an option. A compound that yields negative results in a clinical trial phase (i.e. is ineffective or results in severe side-effects) cannot be launched. No company would continue the development of such a compound; such an abandonment is forced and in no way optional. Therefore, the consideration of project termination under these circumstances should not be confused with option valuation.

The largest risk associated with an R&D project is its technical uncertainty, that is to say, whether or not the compound under investigation works in the way that the researchers hope, without causing severe side effects. The clinical development of a compound serves to resolve this uncertainty. However, clinical trial results, which are the manifestation of the technical risk, not only influence the decision concerning whether or not a compound passes a clinical trial phase, they also impact on future sales expectations. The results acquired from the different stages of clinical trials about the efficacy and safety of the compound enable a more precise estimate of future sales than before clinical trials commenced. Thus, even compounds showing positive results in initial clinical trials might be abandoned. The choice of this particular option is driven by the future market potential of the compound. Although the market potential of a compound is determined by pharmacoeconomic parameters, including demographic developments, the regulatory and political framework and competition from other therapeutic agents targeting the same illness or disease, the quality of the drug itself also influences market potential.

The termination of a project because of negative results is not considered to be an option, as is often argued by defenders of the DCF method. However, the voluntary abandonment of a project because of changed conditions and further evidence of the sales potential of a drug is an option.

Decision trees – casting light on real options

Pandey [1] mentioned the incorporation of different scenarios into the valuation process. Unfortunately, the added value of the analysis of these scenarios was somewhat left in the dark. It helps to quantify precisely the real options that are available to a company.

Undoubtedly, the most important option concerning a compound is the option to launch (or the option to abandon despite approval) the product onto the market. The launch of a new product means an enormous marketing expenditure. The company only undertakes this endeavor if the estimated sales revenues exceed the launch costs.

The scenario analysis helps to identify situations where the company could exercise its option to abandon the project.

Advanced decision trees – real options

R&D investments occur over several stages and, thus, there are various points at which decisions must be made, not only immediately before the launch of a new product. Each phase of the process generates new information about the product. Perhaps the product did not meet the goals of the clinical trials – in this case the project must be abandoned. Perhaps the product only partially met the goals of the clinical trials, or a competitor launched a similar product. In these cases, an abandonment of the project should be considered because the revised estimate of the future sales must be lowered. To handle these options, the decision tree must be expanded slightly. In decision-tree construction, the sales potential of the product could assume several different states only at the time of launch (i.e. several scenarios are investigated at product launch). However, as the company acquires more information from clinical trials, it can be assumed that the sales potential of the product

  PII: S1359-6446(04)03110-1