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Location is key – recent progress in single-cell-based high-throughput assays ▲

Scientific discovery has been significantly impacted by technologies that have been created from the unique combination of biotechnology, material sciences and nanotechnology. This is clearly illustrated by the utilization of technologies that specifically position biological material in defined arrays or patterns and have proved invaluable in the high-throughput detection of specific DNA sequences as well as for compound screening against a variety of protein systems such as receptors, enzymes and transcription factors.

New challenges

As the human genome presents the challenge of discovering the unidentified role of novel and known genes, cell-based assays could take on an increasing importance in the race to discover gene function and novel drugs. These assays provide a significant advantage as they retain and permit an examination of the impact of novel chemical entities or new genes on complex cellular events, such as intracellular signaling pathways, that represent part of physiological processes. However, current cell-based assay formats examine a population of cells by measuring integrated signals and do not easily permit single-cell analysis. Recent advancements in the positioning of cells have provided the opportunity to monitor individual cellular events such as electrical, morphological and chemical signals in high-throughput formats.

It is becoming increasingly evident that precise positioning of cells is a crucial component to permit detection and analysis of signals from individual cells, especially for the screening of targets such as ion channels. Although the most direct measure of ion channels has come from electrophysiological recordings of single cells under voltage clamp control, these techniques have not been previously adaptable to the rigors of high throughput.

Recent work by Straub *et al.*[1] suggests a promising combination of silicon chip design and appropriate cell lines to achieve an 'iono-electronic' coupling by growing individual cells expressing recombinant ion channels on a surface that is covered with an array of field effect transistors. The cells' location was crucial to permit these measurements. Several companies, such as Aviva Biosciences, Axon Instruments, Cytion, CeNeS, Cellectricon, Essen Instruments and Sophion Bioscience, have embarked on designing other novel devices to measure ion channel currents in response to voltage clamping in an array-like format also by the precise positioning of cells. These efforts could soon permit direct electrical readouts of ion channel activity of individual cells in a high-throughput format.

New opportunities

Although these technologies are not yet fully developed, it is not difficult to imagine the utility and immense opportunities such devices could offer. From the drug discovery perspective, imagine being able to screen compounds and natural products on ion channels to find novel drugs at more than 10,000 data points per day. From the biology perspective, it is well known that ion channel proteins form complex heteromultimeric proteins that arise from several genes. Imagine the ability to address these different combinations in a matter of a few days or weeks instead of months and years. Moreover, one could begin to address the complexities of intracellular signaling events on ion channel function in a systematic fashion, i.e. proteomics of ion channels at the single-cell level in a high-throughput format. From the genomics perspective, imagine the potential of these devices to permit the examination of novel ion channel genes and modulators discovered from the deep corners of the genome sequence at a rate never before applied to the scientific and drug discovery community.

Single-cell variability, although marveled in the co-ordination of complex tissue functions, have hampered single-cell studies as variability has complicated scientific conclusions. Cellular individuality has also been suggested to underpin a variety of disease states such as cancer, arrhythmias and nervous system disorders, but remains difficult to quantify. These devices could permit the electrophysiological evaluation of native cells isolated from normal as well as disease tissues. Cellular variation would be examined in a more meaningful

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statistical manner as hundreds and thousands of cells could be profiled individually for their physiological and pharmacological responses. Furthermore, individual cells of interest could be pre-selected, such as specific density of receptor markers, appropriate combination of receptor/ion channel systems, and particular pathogenic or phenotypic states. One could also envision the potential to place specific types of cells that detect complex environmental factors to these devices like, for example, those that sense taste, smell and sound.

Importance of location

Other areas of study that could be enhanced by cellular positioning are subcellular organization and microdomain measurements. Furthermore, subcellular positioning of receptors could be examined as cells are positioned in specific locations. Nature has already shown us the impact of specialized subcellular structures such as the neuromuscular junction and cell contacts and communication. Although the positioning of cells on substrates and microfluidic recording systems could impact the utility of these positioning and recording technologies, by combining recent progress in ion channel clustering and trafficking systems, it might be possible to engineer cells expressing recombinant ion channels or receptors with appropriate scaffolding proteins to achieve both positioned and timed surface expression.

Another potential application of cellular positioning is to measure events in microdomains in the intact cell. There are significant advantages of applying imaging and other detection technologies when the cell subject is positioned in a precise location. This type of device could permit examining, for example, enzymatic activity, pH and calcium levels in a given subcellular microdomain on thousands of cells.

Location might hold the key! Continual improvement and integration of a variety of scientific disciplines, including material sciences, silicon device fabrication techniques, microelectronics, medical technology and cell biology, physiology and pharmacology will continue to significantly impact on this area of scientific discovery.

Reference

1 Straub, B. *et al.* (2001) Recombinant maxi-K channels on transistor, a prototype of iono-electronic interfacing. *Nat. Biotechnol.* 19, 121–124

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Drug discoverers – you need us! – Reply ▲

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Response from Frank King

Professor Federsel raises two interesting points: the status of Process R&D as a state-of-the-art technology and a greater involvement of Process R&D in the drug candidate selection process. From my own perspective as a medicinal chemist who has worked in the industry for nearly 24 years, I wholeheartedly support Prof. Federsel's assertions. Process R&D has come a long way from simply producing kilogram quantities of known compounds (if it was ever as simple as that!). As Prof. Federsel points out, speed-to-market is vital for the commercial viability of drugs, especially in areas where there is high competitiveness for first-to-market. In addition, efficient synthesis to reduce cost of goods, product lifetime extensions and environmentally friendly synthetic procedures are all-important factors in the modern pharmaceutical industry.

The second point Prof. Federsel makes about greater involvement of Process R&D in the candidate drug selection process is an extension of what we term the 'developability' concept. Driven by a need to reduce failure rates and thus improve the probability of success, the more enlightened pharmaceutical companies have removed the research/development interface. This has enabled ADME and toxicology to be increasingly applied early in the research phase so that the candidate with the highest probability of success is identified. Thus, the candidate selected might not be the most potent compound, nor the one with the best *in vivo* activity, but the one with the best overall profile for rapid and successful development. The inclusion of Process R&D early in candidate selection can only improve decision-making.

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One-third of Swedish food plants has anti-inflammatory records ▼

One-third of Swedish food plants has anti-inflammatory records. It is commonly known among patients with rheumatoid arthritis that meat products will worsen their clinical symptoms. These patients therefore try a lacto-vegetarian diet, often with positive results[1,2]. Several clinical studies on the relieving effect of a vegetarian diet on rheumatic pains have been published,

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