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Research Highlights

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Dose-response profiling for drug combination therapies

In the fight against severe diseases such as cancer the use of drug combinations instead of single drugs is most promising to aid the patient's healing. However, the optimum drug combination is commonly found by experience of clinicians rather than by systematic studies. With the goal to establish a more methodical approach, a Dutch/German researcher team has recently developed a screening device to test the effect of all possible mixtures of two different substances on living cells.[1] The base platform of the device is a standard 12-well plate, filled with agarose. A diffusion device (see figure 1) is then placed on top of the plate using an alignment tool. Afterwards, cells and compounds are filled into the device, so that the cells are exposed to a concentration gradient of the compounds. The authors first validated the diffusion profiles of the compounds inside the matrix. Then, cell viability of different leukemia cell lines and primary patient cells were tested when the cells are exposed to a combination of chemotherapeutics. The response of the cells were analysed by adopting the so-called MTT viability assay, in which a purple salt is formed that is unsoluble in the hydrogel matrix and hence, provides local information on cell viability. Dose-response profiles of six different cell lines for three different drugs were recorded in parallel. Compared to standard microtiter plate-based assays the novel diffusion device has significant advantages since it reduces the number of required cells, the number of required pipetting steps and enables the formation of stable drug gradients, and could be a step towards personalized medicine.

Supercooled water drops

The investigation of formation of ice is not only of academic interest to understand the fundamental properties of water; it is important in different fields such as storage of biological compounds at low temperatures, snowmaking in ski resorts, atmospheric chemistry or ice formation at the wings of aircrafts. The initial process of ice formation is the nucleation, which is energetically unfavourable due to the high free-energy interfaces between the liquid water and nucleates. For this reason, a metastable, supercooled liquid water phase can exist. Without external perturbations such as impurity particles or mechanical vibrations, the metastable phase – far away from equilibrium – can be transferred to the stable, ice phase by localised density fluctuations. This so-called homogeneous phase transfer has been investigated by G. M. Whitesides and co-workers at Harvard University in a microfluidic drop generating device.[2] In a flow-focussing channel design, water droplets (diameter: 80–100 μm) were generated in a hydrophobic carrier (liquid fluorocarbon) at high frequency of tens of thousands of droplets within a few minutes. The droplets were cooled down to low temperature in seven cooled zones. Very low temperatures of −40 °C were stabilised using a combination of heat exchanging and thermoelectric cooling by Peltier elements. Freezing of water inside the droplets were detected by a high-speed camera that takes up to 16,000 frames/sec. The researchers could observe that freezing of deeply supercooled water has two stages: first, a rapid growth of dendritic ice crystals occurs (within 1 ms in 150 μm sized drops at −35 °C), and second, the remaining water freezes slowly. Generation, cooling, detection and analysis of more than 37,000 droplets were performed. Homogeneous phase transfer occurred at temperatures between −36 and −37,8 °C. Moreover, influences of impurities causing heterogeneous phase transfer, here by addition of silver iodide, were investigated. The microdevice is unique for studies on nucleation and ice formation concerning speed of droplet formation and data acquisition rate, temperature stabilisation and the high total number of analysed droplets. Besides ice nucleation, it can be used for investigation of other metastable liquids as well as other processes with fast kinetics.

Large-scale bipolar electrode microarray

In a recent publication, Richard M. Crooks and co-workers from The University of Texas at Austin describe a micro-electromechanical array composed of 1000 individual bipolar electrodes.[3] It is controlled with just two driving electrodes and a simple power supply. Due to the special configuration of the bipolar

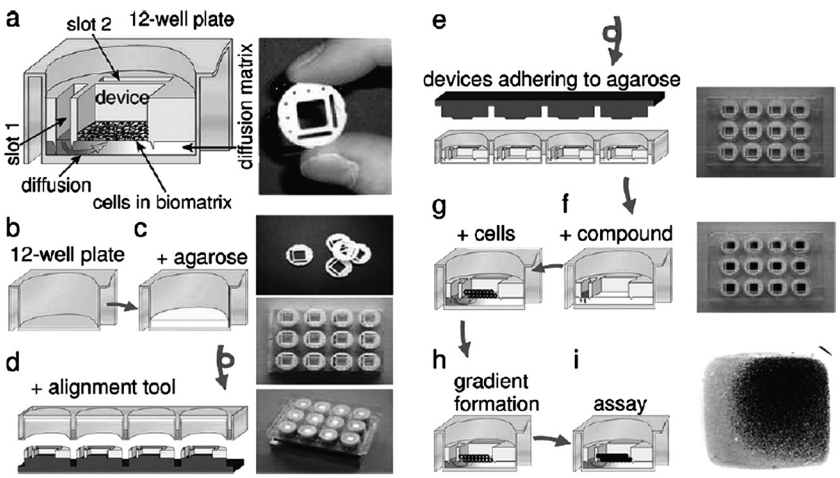

Fig. 1 Dose-response profiling of chemotherapy on cells. The figures show sketches and photographs (right panels) of the device. (a) A 12-well plate is used to establish a diffusion matrix of therapeutic compounds on leukemia cells. (b–i) Process steps required to assemble the device and initiate the cell study. (Reprinted with permission from ref. 1. Copyright 2009 American Chemical Society).

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electrochemistry system, both anodic and cathodic overpotential exists in the same electrode. In the here presented electrode array, processes occurring at the cathode end of each electrode are correlated to light emission at the anode end *via* electrogenerated chemiluminescence, *i.e.* oxygen is reduced at the cathode, and $Ru(bpy)_3^{2+}$ and tri-n-propylamine are oxidised at the anode, where the chemiluminescence can be quantified. The researchers demonstrate the uniformity of the chemiluminescence for each electrode. Importantly, the electrode array is fabricated on a glass slide and embedded in a simple electrochemical cell so that the number of electrodes in the array can be easily increased, and the device can be adapted to robotic fluid dispensers, which makes it possible to use the electrode array for quantitative sensing applications.

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