Neo3DPlate™: A Novel High Throughput Screening Enabled Microfluidic 3D Cell Culture Plate

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Purpose

During primary high throughput screening (HTS), drug candidates are typically evaluated using biochemical and/or 2-dimensional (2D) cultured cell-based assays. With the pharmaceutical industry constantly looking for more predictive in vivo like screening models, 3-dimensional (3D) cell culture has become a more valuable tool compared to its 2D counterpart. In the past few years, considerable progress has been made to refine the quality and reproducibility of growing cancer cell aggregates or tumors using either specially designed scaffolds or hanging-drop well plates. However, currently no tools exist in the market that support HTS based drug screening of 3D cultured cells. In the current study, we have demonstrated the feasibility of a microfluidic well plate, Neo3DPlate™, for the culture and subsequent drug screening of cells at nano-liter scale grown in a 3D fashion.

Methods

A polydimethylsiloxane siloxane (pdms) based microfluidic chamber system in a 96-well arrangement was designed using soft lithography techniques. 3D culture chambers were first optimized for reproducible cell trapping in order to obtain uniform aggregates/tumors. Fluorescent lung carcinoma (GFP-A549) cells in media were mixed with matrigel and were pipetted into the chambers using a commercially available electronic pipette (e.g. Matrix Impact II). Microscopic images of the trapped cells were acquired before placing the devices in an incubator. Media was replenished in continuous interval every 24 hrs. Both bright-field and fluorescent microscopy was used to monitor the cellular growth and aggregate formation inside the 3D culture chambers over a period of 5 days. Preliminary drug response experiments were performed using doxorubicin and paclitaxel, two commonly used anti-cancer drugs for a period of 24-96 hrs.

Results

3D cell culture and drug screening potential was investigated in the Neo3DPlate™. Results show that a uniform population of cells (592±34) can be trapped in the microfluidic chambers using an off-the-shelf electronic pipette (Fig. 1B). Microscopic images confirm the healthy growth and aggregation of cells with no visual contamination, as monitored over a period of 5 days. No degradation or changes in matrix properties of matrigel was observed during the incubation period. A549 cells was shown to aggregate at day 3 and formed distinct tumors at the end of day 5, which was confirmed by both bright-field and fluorescence microscopy (Fig. 1A). Quantification of fluorescence intensities revealed increase in number of aggregates/tumors (almost an 100% increase from day 1 to 5) (Fig. 1C). Drugs, both doxorubicin and paclitaxel, showed degradation of tumors and decrease in fluorescence intensities as an indication toward anticancer drug effects.

Conclusion

The present study demonstrates the potential of an HTS ready miniaturized 3D cell culture platform. The Neo3DPlate™ provides a cost-efficient, ultra-low volume, error-free, simple to use, 3D cell culture HTS well plate that is compatible with currently used robotic liquid handling workstations. Further qualitative and quantitative studies are underway to validate the Neo3DPlate for high throughput screening.

Figure 1: (A) Fluorescent and bright-field images of lung carcinoma (A549) cells in matrigel trapped inside the Neo3DPlate™ chambers. (B) Number of cells suspended in matrigel trapped into the chambers using an electronic pipette. (C) Mean fluorescence intensities of the cells grown over a 5-day period. Increase in fluorescence intensity demonstrates increased proliferation/aggregation of cells.