Digital Microfluidic Platform for Creating, Maintaining, and Analyzing Cell Spheroids

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SUMMARY

UCLA researchers from the Departments of Bioengineering and Chemistry & Biochemistry have developed an automated droplet (digital) microfluidic platform for creating, maintaining, assaying and analyzing three-dimensional (3D) cell spheroids.

BACKGROUND

Cell spheroids are three-dimensional (3D) aggregates of cells, grown in vitro that mimic the morphology and cellular heterogeneity of physiological tissues. These characteristics make spheroids especially good models of avascular tumors. While cell spheroids offer numerous advantages over two-dimensional (monolayer) cell cultures, their use in life science and pharmaceutical research has been constrained by tedious manual preparation protocols or the requirement for expensive robotic liquid handlers to automate the process. This user-friendly, automated, and inexpensive system for making and assaying multicellular spheroids represents a significant advance in spheroid culture and analysis, enabling broader adoption of 3D cell-based assays in pharmaceutical and life science research.

INNOVATION

UCLA researchers from the Departments of Bioengineering and Chemistry & Biochemistry have developed an automated droplet (digital) microfluidic platform to create, maintain, assay and analyze three-dimensional (3D) cell spheroids. The platform can be used to form individual 3D cell spheroids or an array, and supports their long-term viability by controlling the ambient growth conditions and enabling medium exchange on-demand. Spheroid growth can be monitored in real time by optical microscopy. Cell secretions can be analyzed by assaying the surrounding culture medium in situ or ex situ. Exogenous agents such as growth factors, drugs, imaging reagents, differentiation cocktails, or other reagents of interest can be delivered to any spheroid at any time. Consequently, the platform offers significantly greater temporal and spatial control of reagent delivery than is achievable with current manual hanging-drop spheroid protocols. Because droplet movement on the device is controlled solely by the application of electric fields, all liquid handling is automated, can easily be programmed, and requires no moving parts. These are significant advantages over existing methods.

APPLICATIONS

This invention can be used to support a broad range of basic and applied research in which a 3D cell spheroid model is relevant. Examples include:

▶ Research on the formation of solid tumors and their response biological and chemical agents (e.g. drug candidates)
▶ Spheroid invasion assays
▶ Analysis of gene and protein expression profiles of 3D microtissues
▶ Stem cell culture and differentiation
▶ High throughput drug screening
▶ Formation of homogeneous or heterogeneous microtissues for tissue engineering

This platform can also be used to automate any assay or protocol that utilizes hanging drops. Examples of such applications include:

▶ Protein crystallization
▶ Embryo culture for in-vitro fertilization
▶ Bacterial motility assays

ADVANTAGES

This platform provides significant advantages over current state-of-the-art methods for cell spheroid creation and manipulation, including capabilities for manipulating and analyzing individual spheroids in an array. The platform:

▶ Automates cell spheroid formation and maintenance
▶ Makes it possible to manipulate and assay spheroids individually or in parallel
▶ Makes it possible to reconfigure assay protocols in real-time
▶ Supports in-situ, real-time analysis of cell spheroids
▶ Has low capital costs
▶ Requires small sample and reagent volumes

STATE OF DEVELOPMENT

Digital microfluidic devices have been developed that demonstrate the ability to deliver cells, media, and protein solutions to a well, establish a stable
hanging drop, successfully maintain a viable 3D cell spheroid over multiple days, and induce stem cell differentiation in situ. Further work will focus on developing drug screening assays and overall system optimization.

PATENT STATUS

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ADDITIONAL TECHNOLOGIES BY THESE INVENTORS

- Spontaneous Droplet-Into-Droplet Insertion for Formation of Polymer Particles
- Synthesis of Thioether Containing Trialkoxysilanes