Microfluidic Platform for Screening Chemically Defined Conditions that Facilitate Clonal Expansion of Human Pluripotent Stem Cells

Grant Award Details

Microfluidic Platform for Screening Chemically Defined Conditions that Facilitate Clonal Expansion of Human Pluripotent Stem Cells

Grant Type: Tools and Technologies I

Grant Number: RT1-01022

Investigator:

Name:	Hsian-Rong Tseng
Institution:	University of California, Los Angeles
Type:	PI

Human Stem Cell Use: Embryonic Stem Cell

Cell Line Generation: iPS Cell

Award Value: $914,096

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

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Grant Application Details

Application Title: Microfluidic Platform for Screening Chemically Defined Conditions that Facilitate Clonal Expansion of Human Pluripotent Stem Cells

Public Abstract: Human pluripotent stem cells (hPSCs) hold a great potential to treat many devastating injuries and diseases. However, current hPSC cloning still faces challenges in creating animal product-free culture conditions for performing genetic manipulation and induced differentiation of hPSCs for cell-based therapy. In order to obtain the ideal culture conditions for hPSC cloning, microfluidic technology can be applied as a powerful tool. Microfluidic systems handle and manipulate tiny amounts of fluids at volumes a thousand times smaller than a tear drop. The goals of our proposal are to develop and validate a robotic microfluidic platform, composed of a robotic liquid dispensing system, a fluorescence microscope, cell culture chips and an operation interface. We will apply such a robotic platform to (i) perform chemical screening in search of culture conditions and small molecules that facilitate single-cell expansion of hPSCs and (ii) achieve a better understanding on how chip-based culture environments and the molecules identified in the screens affect the hPSC fate. Compared to the macroscopic setting employed for the conventional hPSC research, the advantages of the robotic microfluidic technology are sample/reagent economy, precise fluidic delivery, scalability and automated operation.

As the proposed project unfolds, we anticipate making contributions in the following four areas.

First, the successful demonstration of the microfluidic platform will provide a powerful technology for contemporary hPSC research. Since the size of each cell culture chamber is very small, the consumption of hPSC samples and the associated reagents will be significantly reduced (2 to 3-orders lower than the conventional setting).

Second, two quantitative assays will be developed: (i) a phenotype assay for parallel detection of pluripotency, apoptosis, proliferation and differentiation, and (ii) a cell signaling assay for parallel monitoring of four signaling nodes, which are potential targets of the molecules identified in the screens. Since the regulation of hPSC survival is not well understood, the resulting phenotypic/signaling signatures can help to identify which cell signaling events and surrounding environments are responsible for hPSC fate. Most importantly, the improved understanding of the mechanisms regulating hPSC survival can help to guide the optimization of hPSC culture conditions.

Third, this microfluidic platform promises to improve the screening process in search of culture conditions for hPSC self renewal and differentiation, as well as identify small molecules that facilitate single-hPSC expansion.

Fourth, we will test this microfluidic technology for everyday use in other hPSC laboratories. A user friendly operation interface will be developed and then tested in the other hPSC groups. The final versions of the chip design and control programs will be freely available for download from the PI's research group web site.

Statement of Benefit to California:	As the proposed project unfolds, we hope to benefit the state of California and its citizens on seven fronts: Human pluripotent stem cells (hPSCs) hold a great potential for regenerative medicine to treat many devastating injuries and diseases, such as Alzheimer's disease, Parkinson's disease, diabetes, Lou Gehrig's disease, cancer, cardiovascular disease, rheumatoid arthritis and spinal cord injuries. The proposed robotic microfluidic platform allows us to create animal product-free culture conditions for performing genetic manipulation and induced differentiation of clonal hPSCs. In addition, animal product-free culture conditions will eliminate immuno-rejection challenges for regenerative medicine. The successful demonstration of the proposed new-generation microfluidic platform, composed of a robotic liquid dispensing system and a fluorescence microscope, will present a new technology for far-reaching application to all types of stem cell research with significantly improved operation efficiency. In contrast, conventional stem cell research is plagued by the use of macroscopic setting, resulting in several constraints: high sample/reagent consumption, poor precision to control the environments of hPSC experiments and the lack of integrated platforms for accurate measurements. Using the proposed microfluidic platform, the costs for hPSC research will be significantly reduced. We estimate that each hPSC experiment in the microfluidic cell array chip consumes 0.9 microliters of cell culture reagents/media, which are 2 to 3 orders of magnitude lower than commonly used 384-well plates (requiring 100 microliters of reagents/media for a single study). Therefore, many hPSC studies that require large-scale hPSC experiments can utilize the proposed microfluidic platform in a cost-efficient manner. The proposed robotic microfluidic platform allows greater precision of measurements. By using a robotic pipette for dispensing hPSC samples and screening solutions, critical parameters for hPSC experiments can be monitored and controlled with superior precision, which is unattainable in conventional macroscopic conditions. The robotic microfluidic platform promises to understand the mechanisms behind hPSC survival and to speed up the drug screening process in search of chemically defined conditions for hPSC clonal expansion. In our design, the microfluidic cell array chip will contain a 4 x 10 cell array. The average throughput is 1600 to 8000 screens/day. User-friendly interfaces of the proposed technology will be created for everyday use in other hPSC laboratories. The final versions of the chip design and control programs will be freely available for download from the PI's research group web site.
