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# Stem Cell Culture System Simulating Continuous Fluctuating Pressure *in vivo*

**Muhang Li[1,2], Junning Cui[1,2]*, Ran Tang[1,2,3] and Kai Li[3]**

[1]Center of Ultra-precision Optoelectronic Instrument Engineering, China

[2]Key Lab of Ultra/precision Intelligent Instrumentation (Harbin Institute of Technology), China

[3]School of Life Science and Technology, China

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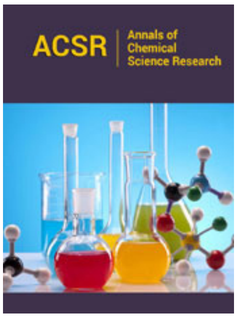


***Corresponding author:** Junning Cui, Center of Ultra-precision Optoelectronic Instrument Engineering, Key Lab of Ultra/precision Intelligent Instrumentation (Harbin Institute of Technology), Ministry of Industry and Information Technology, China

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## Abstract

In order to improve the survival rate of stem cells in therapy after large-scale culture and transplantation into patients, a stem cell culture system simulating continuous fluctuating pressure *in vivo* was proposed in this paper. The system analogs the human pulse signals by regularly regulating the internal pressure. It provides blood pressure training for the large-scale culture of stem cells in vitro, which can improve the survival rate after stem cell transplantation, so as to elevate the success rate of cell therapy, and finally provide direction for the development of new culture instrument.

**Keywords:** Continuous fluctuating pressure; Pulse signals simulation; Stem cell culture technology

## Introduction

Currently, China has leapt into the front ranks of the world in the field of stem cell research. With the theoretical and technical accumulation in the early stage of stem cell clinical research, China's stem cell therapy industry has entered a period of rapid development. Studies have shown that intravenous or arterial transplantation is helpful to facilitate the homing ability of stem cells and improve the therapeutic effect [1,2]. Meanwhile, the survival rate of stem cells after transplantation can also affect the cell therapy effectiveness [3]. However, stem cells are prone to mass death due to sudden blood pressure when injected into the blood vessels. Therefore, we hypothesized that in the stage of stem cell culture in vitro, training stem cells in simulated human blood pressure environment, screening and expanding the culture of stem cells resistant to blood pressure stress can enhance the survival rate after transplantation.

Most human cells are exposed to various biomechanical forces depending on their microenvironment [4-6]. To investigate the cellular response to mechanical forces, scientists use a variety of methods to simulate the mechanical forces environment in vivo. In 1975, Rodan et al. [7] used pulses generated by solenoid valves to control the pneumatic piston device to exert continuous pressure on the cells. In 2002, Blackman et al. [8] simulated the blood flow pulsation shear force waveform using stepper motor drive and designed a medium circulation pathway. In 2009, Haudenschild et al. [9] connected the bioreactor and load sensor in series in a cell culture chamber to generate fixed pressure by controlling the position of the motion actuator and used the sensor to collect and analyze relevant data as well. There were many approaches widely used, including fluid-generated shear stress, periodic tensile stress, continuous pressure generated by confined air, and periodic hydrostatic pressure [10-14].

It has been established that mechanical forces stimulation can enhance the survival, apoptosis, differentiation, and proliferation of stem cells [10,15,16]. In 2020, Jin et al. [17], from Peking University School of Stomatology, demonstrated that mechanical force both *in vivo* and *in vitro* can activate TRPV4 expression in periodontal ligament stem cells (PDLSCs), increase cell proliferation and reduce the differentiation ability of PDLSCs, and thus promote the regeneration of periodontal tissue.

## Stem Cell Culture System Simulating Continuous Fluctuating Pressure *in Vivo*

According to the principle of blood pressure, pulse 60 times/min, stem cells are subjected to systolic and diastolic pressure coercion every second after being injected into the blood. Therefore, the survival rate of transplanted stem cells resistant to vascular stress will be significantly higher than that of ordinary stem cells. In order to screen stress-tolerant stem cells for proliferation culture, we proposed an *in vitro* stem cell culture system simulating the continuous periodic(cyclic) changes of systolic and diastolic blood pressure in human body. The system is simple to operate, stable in performance and precise in control. It is suitable for most stirred 3D stem cell culture instrument (Figure 1).

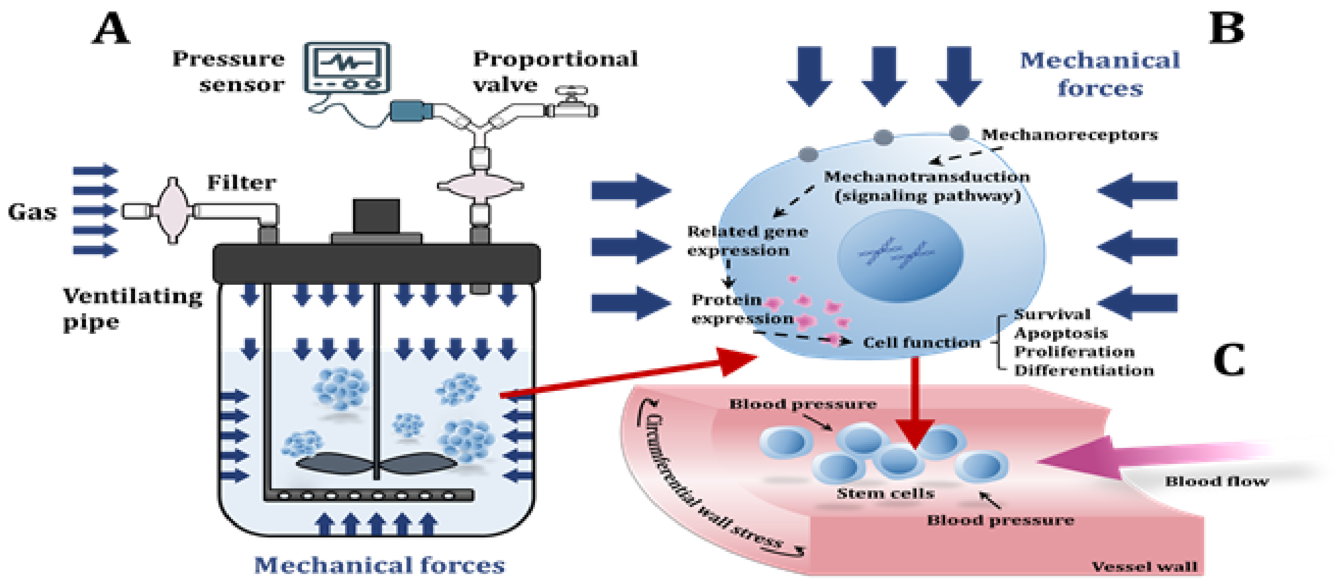


**Figure 1:** Stem cell culture system mimicking continuous fluctuating pressure in vivo. A: Design concept of system. B: Stem cells under mechanical forces. C: Stem cells in blood vessels.

The principle of simulating continuous fluctuating pressure culture system in human body is as follows. Put the well-grown stem cells into the culture instrument and turn on the gas cylinder switch. The gas enters the buffer vessel from the cylinder through the compression pump, solenoid valve and filter, and then enters the cell culture instrument through the ventilating pipe. The gas in the culture instrument can be discharged through the proportional valve in conformity with the set procedure. According to the preset systolic and diastolic blood pressure values, actuation duration and frequency, the control motherboard drives and controls the compression pump and proportional valve to provide continuous and stable fluctuating pressure for the cell culture system. At the same time, the system can be equipped with a variety of optional sensors to monitor the culture process in real time and collect culture data, which is convenient for scientists' subsequent analysis and optimization.

In summary, the system provides a feasible optimization method for the development of 3D stem cell culture instrument *in vitro* by regulating parameters such as pressure magnitude, frequency, and actuation duration in the culture process. The system has the following advantages.

A. The structure is simple, the load is easy to transfer, and does not depend on the cell culture state.

B. The system can adjust the internal pressure and pulse frequency simulated by the culture environment within a reasonable range, enabling precision medicine for the type of disease and patient's physiological condition.

## Conclusion

The majority of the optimization of existing stem cell culture technology *in vitro* is to improve the similarity with the human homeostasis from the perspective of medium formulation, but this ignores the impact of physical environment on stem cell homing. We proposed a system to simulate blood pressure and pulse in vitro, which is more in line with systemic homeostasis than existing techniques, so as to realize precision medicine. Our study aims to promote technological innovation and industrial development in the stem cell therapy area in China.

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