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It's all About Stem Cells

From modern medicine to novel foods

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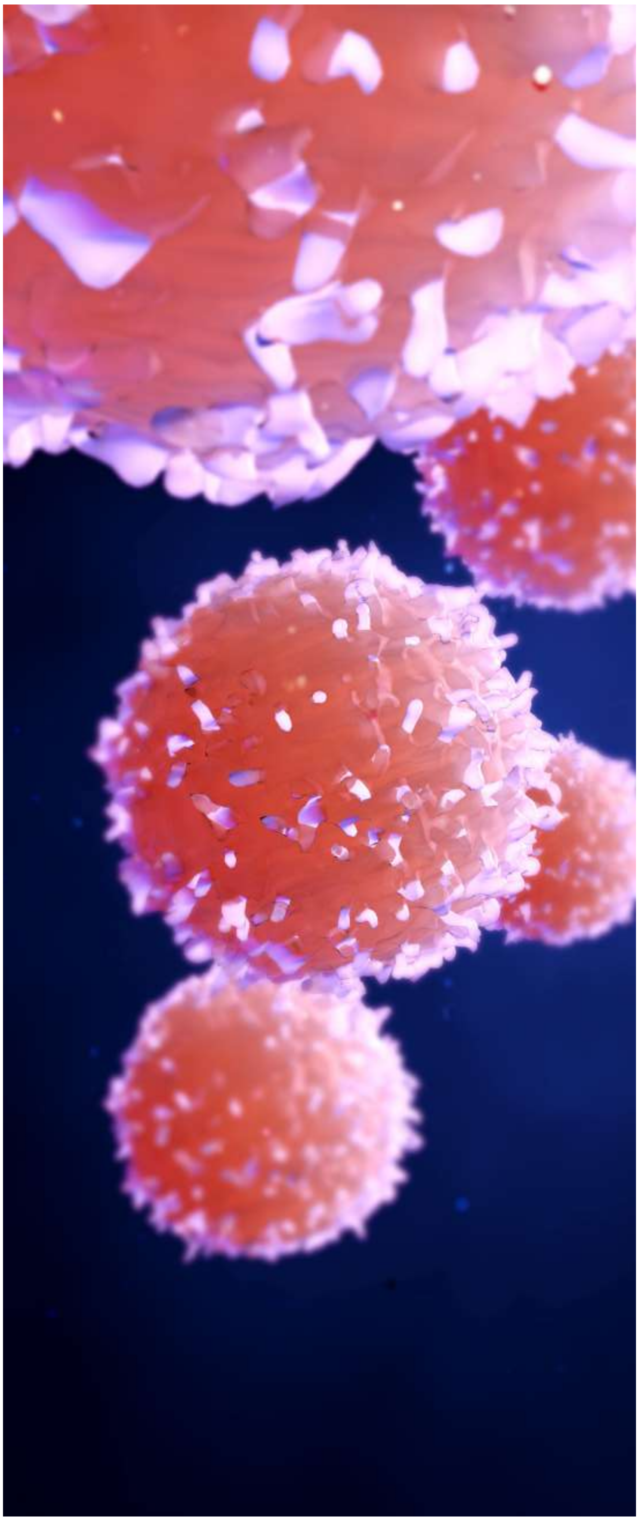

Do You Want to Learn More About Design of Experi-ments?
Today's bioprocess professionals need to stay on top of many things: Scale-up parameters and equipment capabilities, control strategies and automation, validation requirements and documentation to name a few. New fields of applications like stem cell technology are evolving into powerful tools of the future.
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WE CAN CHANGE THE WORLD

How Stem Cell Technology is revolutionizing 21st century industries from personalized medicine to meat production

ADDITIONAL CONTENT

- eBook: Bioprocessing Basics

Introduction

The term "stem cell" is a broadly encompassing designation, referring to an undifferentiated cell of a multicellular organism which possesses the capacity to generate more cells of the same type. Furthermore, stem cells, when appropriately activated, can produce a wide variety of differentiated cell types.

Today, three broad categories of mammalian stem cells are recognized. (a) Totipotent cells are found only in early embryos and possess the programing to produce a complete organism. (b) Pluripotent stem cells are more restricted in their potential abilities. They occur in the inner cell mass of the blastocyst and can form upwards of 200 different cell types present in the adult individual. (c) Multipotent stem cells are derived from fetal tissue, cord blood and adult stem cells. They have been employed for many years for the treatment of a wide range of blood disorders.

Our modern concept of stem cell biology is credited to the observations of Till and McCulloch in the early 60s, who provided the first evidence of the existence of blood stem cells. In the decades that followed an army of researchers and clinicians carried out volumes of work on the properties and possible applications of stem cells. So moving into the 21st century, they have become a vital tool in the treatment of disease. And this demand has accelerated the development of a wide choice of stem cell lines.

In this report we will consider bioreactors and their challenges, including the demand for stem cells in current medical science which calls for robust systems for their cultivation and handling. Stem cells can be obtained from donors but the actual numbers are quite low. A solution for the generation of adequate numbers is to scale of the culture of these cells *in vitro*.

Although it was commonly thought that stem cells could not be cultivated in stirred tank bioreactors dues to high shear stress, this was found to be incorrect. Thus today bioreactor technology, including critical culture parameters, bioreactor configurations, and pursuit of pioneering technologies in the bioprocess development stage is now hotly pursued.

Stirred-tank bioreactors of all sizes have been adopted for production of stem cells on a large scale. This report will compare them to uncontrolled systems such as shaker flasks and detail how they provide dramatic improvements for monitoring and control of key cultivation parameters. In this regard, facilitating scale-up and ensuring consistency throughout the project's development phases are of primary concern. Controlling agitation and gassing conditions will provide smooth performance while minimizing shear forces, essential for maximum yields of product.

The most dynamic sector of drug development is in the realm of biologics. Antibodies are perhaps the most important product, but many other protein-based therapies are recognized today for their contribution to successful new pharmaceuticals.

Personalized medicine today includes a range of agents that may be configured to fit individual histories. Much research is directed toward compartmentalizing patients to optimize their treatment with innovative protein therapeutics. In this regard, one of the most important current applications of stem cell technology is in the area of cardiovascular disease modeling. In particular, induced pluripotent stem cells (iPSCs) are under study as a platform to better understand cardiomyopathies, rhythm disorders, valvular and vascular disorders at the cellular level. They lend themselves especially as tools in the study of precision medicine and therapeutic screening. Because they can be expanded without limit in bioreactors, they provide a convenient source of experimental material to evaluate pharmaceutical agents on a cellular level, although this requires sub cloning and monitoring of their properties to ensure the absence of wanted variation in the lines over time.

Another technology under consideration are stem cell-derived neurospheres, of great interest to neuroscientists. Bioreactors may allow tight regulation of process parameters, thereby improving homogeneity of neural spheroid cultures for novel pharmacological devices such as Multi-Organ Chip systems.

In this time of rapid change there are dramatic application on the horizon for stem cell technology. One of the most important in terms of its impact on society is focused on cultured meat, which could have extraordinary economic, health, animal welfare and environmental benefits over traditional meat. Appropriate stem cell lines, grown in bioreactors, could in principle produce unlimited quantities of excellent quality meat products. When widely adopted, the commercial production of this new source of protein will upend whole industries, with dramatic effects on our entire society.

REFERENCES

1. Ramalho-Santos, M. and Willenbring, H. 2007. On the Origin of the Term "Stem Cell". Cell Stem Cell 1 (1) 35-38.

ADDITIONAL CONTENT

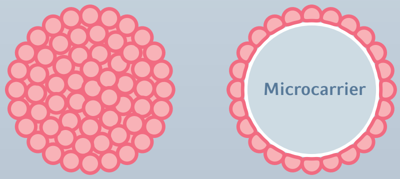
Our Top 5 List of Stem Cell Bioprocessing Papers:

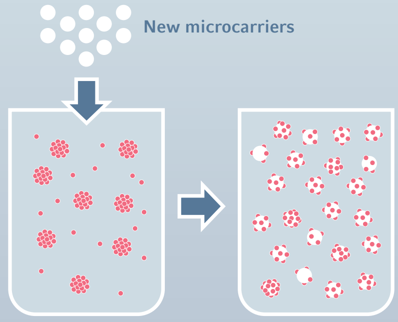
1. Abecasis *et al.*, 2017.
2. Panchalingham *et al.*, 2015.
3. Kropp *et al.*, 2017.
4. Sart *et al.*, 2014.
5. Kempf *et al.*, 2015.

Stay Informed

Stem Cell Expansion in Bioreactors

Stem cell culture in stirred-tank bioreactors makes scale-up easier and allows comprehensive monitoring and control of parameters like temperature, pH, and dissolved oxygen. Here are some tips to help you transfer your stem cell culture from dishes and flasks to bioreactors.





1 Culture surfaces

In bioreactors, adherent stem cells can be expanded in suspension as cell-only aggregates or on micro-carriers. The size of cell-only aggregates can be influenced by seeding density, stirring speed, and the bioreactor impeller design. Culture on micro-carriers under restrictive cell culture conditions (e.g. a serum-free medium) requires coating them with peptides or proteins like fibronectin or collagen.

3 Cell expansion

Bead-to-bead transfer: The progressive addition of fresh microcarriers increases the surface area for growth while avoiding dissociating cells from the beads (passage step).

> Visually monitor the carrier occupation percentage closely to determine the optimal timing for addition of fresh carriers.

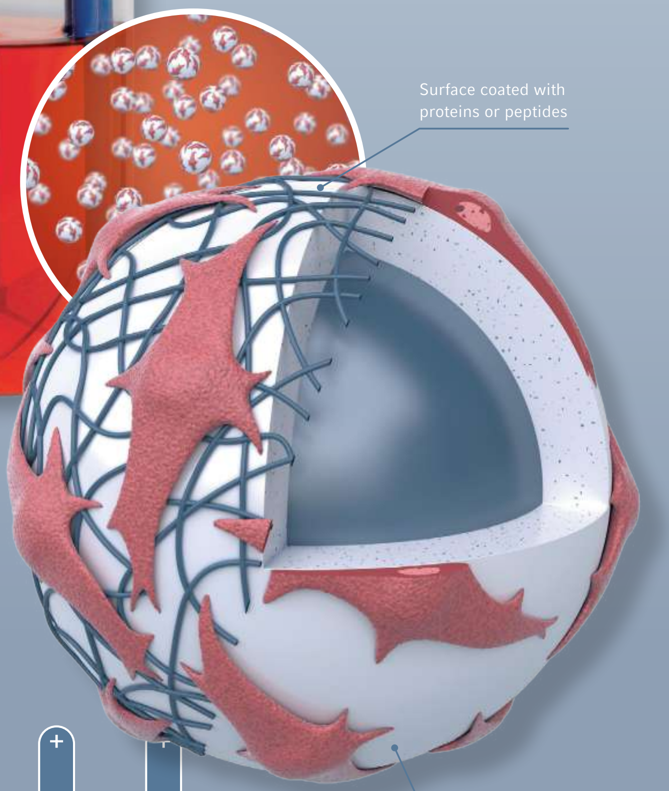
2 Inoculation

Some guiding values for culture on microcarriers:*

Description	Value
Cell seeding density	2,000–10,000 hMSCs/cm²
Microcarrier loading density	1–4 g dry beads/L
Cell-to-bead ratio	min. 3–5 cells/bead

* Case-by-case optimization required

To improve cell attachment:
> Reduce initial culture volume
> Do not agitate during the first few hours



4 Case-by-case optimization needed

Due to cell heterogeneity (tissue sources, storage conditions, preexpansion conditions, culture medium, and others) and the large number of interactive process parameters (dissolved oxygen, pH, stirring speed, cell substrate, bioreactor type, and the like), each process will require individual optimization.

> Software-aided monitoring and control of critical process parameters helps to improve process stability and reproducibility.