Sophisticated Stem Cell Solutions

with DASGIP Parallel Bioreactor Systems

Application Stem Cells

Stem Cells on Focus

Stem cell technology is now on the verge of achieving product status in regenerative medicine. The accompanying governmental regulations and demands for clinical studies demand validated approaches and as such reproducible experimental results. Therefore, cultivation procedures need to be closely observed and precisely controlled – in researcher's smaller volumes as well as in larger production scales.

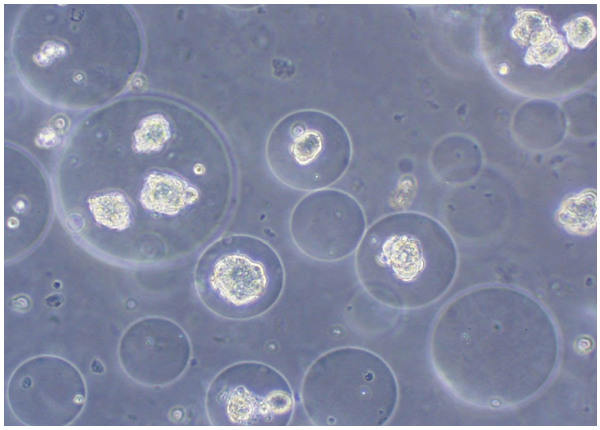
To satisfy stem cell's unique expansion and differentiation conditions of e.g. embryonic (ES), adult and induced pluripotent stem (iPS) cells, DASGIP has refined its cell cultivation products for dynamic cultivation. Individual solutions meet the specific demands for the cultivation of various stem cells, such as embryoid bodies, neurospheres or adherent cells (on microcarriers) in suspension.

Expansion and Proliferation

Many different cultivation parameters influence the growth and behavior of stem cells. Conventionally, particular attention is paid on the media composition. The influence of cytokines and growth factors on the cell expansion and proliferation has been extensively studied. The upcoming production stage, though, adds on new, important physical parameters whose influence on the cell behavior is less investigated:

■ Oxygen Tension

The impact of the amount of oxygen in solution seems to give a hint of the importance of this parameter for stem cell research: hypoxic conditions e.g. support the proliferation of colony forming cells, enhance the number and size of hematopoietic colonies and reduce apoptosis within embryoid



bodies. The need to measure and regulate the oxygen tension in the culture is currently not fulfilled. Usually the cultures are placed in an incubator under atmospheric conditions with fixed O_2 and CO_2 which does not lead to constant condition within the culture. To ensure a predefined oxygen tension the DASGIP DO sensor measures the O_2 content in suspension and DASGIP's Gas Mixing Station adjusts automatically the atmosphere's blending.

Dr. Jochen Ringe at Berlin-Brandenburg Center for Regenerative Medicine and Tissue Engineering Laboratory (Charité-University Medicine in Berlin, Germany) e.g. established bioreactor cultures of adherent mesenchymal stem cells (MSC) in the DASGIP Parallel Bioreactor System. His carrier-based studies were run with strict control of agitation and oxygen tension; revealing a carrier-to-carrier cell transfer enabling a simplified cell expansion without cell passaging.

■ Control of pH

The activity of cell metabolism controlling enzymes is strongly pH dependant, and thus the resulting growth and differentiation of stem cells is affected as well. Suboptimal pH conditions will lead to inhibition or changing routes of differentiation; e.g. hematopoietic progenitors towards granolycyte-macrophage or towards erythroid lineages. In

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contrast to the simple addition of buffers and predefined CO_2 resulting in pH shifts and inhomogeneities during cultivation, the DASGIP Bioreactor System allows the precise control of pH levels. The cultures' pH values are measured using a pH sensor and then precisely regulated by adjusted CO_2 gassing or by the addition of acid and base.

This feature is used e.g. by the German stem cell pioneer Professor Oliver Brüstle (University Bonn and Life & Brain GmbH, Germany) working on microcarrier-coupled hES cells as well as Professor Peter Zandstra (Stem Cell Bioengineering Lab at University of Toronto, Canada) who is successfully using the DASGIP System with mES cells since 2004.

■ Shear Importance

Mixing is essential for dynamic cultivation conditions. Apart from the impact on the differentiation, the resulting shear stress might damage the cells. Thus, agitation should be high enough to keep cell agglomerates in homogeneous suspension or to dislodge single cells out of agglomerates, but has to be lower than the critical level damaging the agglomerates itself. To meet these special demands DASGIP provides customized impellers as well as agitation patterns.

Cooperating with the Fraunhofer Institute for Cell Therapy and Immunology (Leipzig, Germany) DASGIP has enhanced its impeller design for homogeneous suspensions of non-human ES and human progenitor cells in regard to size and shape.

DASGIP Parallel Systems

DASGIP provides stirred bioreactor solutions for dynamic stem cell cultivation guaranteeing homogenous conditions throughout the complete culture. DASGIP System benefits include:

DASGIP Mini Spinner for Stem Cell Cultivation

- High experimental throughput by parallel operation of up to 16 precisely controlled bioreactors
- Working volumes range between 30 mL (Mini Spinner) and 6 L (Cell Culture Vessels)
- Suitable for embryonic, adult and induced pluripotent stem cells
- Online monitoring and individual control of pH, DO, agitation and temperature along user-defined protocols
- Automated feeding and cyclic perfusion

Benefits

As shown above the DASGIP Technology offers the full flexibility to adjust cultivation parameters to the needs of numerous different stem cell lines. Moreover, the cultivation in a closed system like the DASGIP Parallel Bioreactor System helps to overcome the risks of man-made mistakes and contaminations which appear during the frequent cell passaging or when working with hanging drop methods. Optimal control of the cultivation parameters, growth conditions and the cell behavior is thereby ensured.

Quality System certified by DQS ■ DIN EN ISO 9001 ■ Reg.-No. 63431