Challenge based learning (CBL)

Continuous bioreactor to address graft-versus-host disease

Note for teachers: A CBL user guide can be found at www.jandeboerlab.com/TissueEngineering with instructions and tips to run an effective CBL teaching session.

Background and vision

Human mesenchymal stem cells (hMSC) have been a promising therapeutic cell source in tissue engineering over the past 15 years. However, hMSC engineering has proven to be more technically complicated than just extracting them, expanding them *in vitro*, and implanting them back into the patient. This is the reason why many therapeutic strategies with hMSC fail in clinical trials. Extensive research and pre-clinical/clinical validation is still necessary to make hMSCs a versatile, safe, and effective therapeutical tool. Human *allogenic* mesenchymal stem cells (haMSCs) have been engineered and cultured in bioreactors under highly-controlled conditions to study their inherent immunosuppressive capacity. Results have shown that they can be promising therapeutic candidates in graft versus host disease (GvHD). This challenge's vision is to develop a stable culturing platform to generate readily available and effective immortalized MSCs for GVhD disease treatment.

Motivation and stakeholders

Human stem cells have the potential to become a tissue-engineered therapeutic tool in the future, but precise culture settings need to be established for each medical condition. To generate large numbers of cells, prototype bioreactor systems have been engineered in which cells are seeded onto polymeric particles, which are the free-floating scaffolds on which cells can proliferate. When new particles are added to the bioreactor, cells should move from a full particle to an empty one. This system can ensure continuous cell growth as long as the system is continuously fed with empty particles and the culture conditions are closely monitored. In standard 2D cell culture, confluency is manually monitored by direct viewing of a flask under a light microscope. At the moment, there is no automatic way to monitor the cell-occupancy of particles in bioreactors to ensure non-stop growth of haMSCs. The design of bioreactors to grow hMSCs should consider the needs, requirements and regulatory, financial and technical boundary conditions defined by stakeholders such as patients suffering from GvHD, medical doctors delivering cell-based therapies, stem cell biologists, and bioengineers who manufacture cell culture platforms.

Problem definition

In order to culture human allogenic MSC, nutrient level needs to be monitored in bioreactors. A proper model and design of a bioreactor to control haMSC's growth and metabolism would need to control the following variables: a) proliferation rate, b) nutrient availability and consumption rate, and c) the rate at which new polymeric particles must be added to the bioreactor.

Challenge

To design a bioreactor system to produce a continuous source of immortalized human allogeneic mesenchymal stem cells as a therapeutic option to mitigate graft-versus-host disease. Pay close attention in the design of an automatic method to determine the particle-occupancy percentage to ensure continuous cell growth.

Learning framework

Reading the Bioreactor chapter and related literature will help you to understand:

1. GvHD and the therapeutic potential of haMSCs to treat this medical condition.
2. The different types of bioreactors.
3. Methods to analyze bioreactor variables using sensors and probes.

For a more focused examination of the challenge, read scientific literature and create a mind map to include information about the following:

4. The parameters that need to be controlled in the bioreactor.
5. Existing biosensors to detect the cell's metabolic shift inside a bioreactor.

End product

A three-minute video explaining the solution of your challenge. Please include your motivation and the steps to execute your solution.