Cell-based therapy – building the bridge from bench to bedside

Regenerative medicine is now beginning to make the jump from niche experiments to standardized clinical therapies. A pharmaceutical industry study documents that, 69% of the surveyed companies have already invested in cellular-based regenerative medicine products, 64% in drug discovery and 56% in combination products that include tissue engineered scaffolds and device components [1]. As a result of their ease of accessibility and expansion, many mesenchymal stem cell (MSC) based treatments are now approaching the commercial marketing. In the year 2014 there were 3,479 clinical trials worldwide for cell-based therapies with mesenchymal stem cells in all phases of clinical trials [2, 7]. Nearly 20% of the phase 1 clinical trials are just starting their research programs while 20% of all clinical trials are already in phase 3. As trials begin to emerge from phase 3, cell-based products will soon be entering the pharmaceutical market [8].

Mesenchymal stem cells – first choice for stem cell based therapies
According to Eytan Abraham and Lena Pinzur, mesenchymal stromal cells are an auspicious cell type for cell therapy, because they have a limited differentiation capacity [3]. These cells can be isolated from various tissues like bone marrow, placenta, adipose tissue etc. and used to secrete cytokines, chemokines, growth factors, etc. Today, the cells are removed from the patient, proliferated in vitro for cell expansion (glucose, pH, dissolved oxygen, etc.), harvested, and injected to the patient. As to whether autologous or allogeneic cell therapies are the optimal approach is still undecided. An interview of 16 pharma companies made by the Regenerative Medicine Annual Report from 2014 showed that 50% of the interviewed companies are already investing in patient-specific autologous cellular therapies. Investment in allogeneic cell therapies was nearly the same with 58% [1].

State of the art
Over the past 20 years, many cell therapies have been proven at lab scale, preclinical and phase 1 and 2 clinical trials. If cell therapy works, the cell source, composition, production and investment capital will be the primary differentiation factors. Especially important is the production of large numbers of high quality cells for clinical trials. Companies have started to develop special cell culture technologies to enable high-density cell cultivation to support this process. As these technologies scale up to produce large quantities of cells, one critical factor is the use of automated controlled bioreactor systems, which can be used under GMP (Good Manufacturing Practice). The following describes the requirements for upscaling the process of allogeneic cell-based therapies.

![Map of clinical trials](image1.png)
Manufacturing process
Between 150 up to 600 million cells per clinical treatment are typically needed for allogeneic cell-based therapies [4, 5]. Depending on the number of patients to be treated and doses, the cell quantities can reach dimensions of trillion of cells as a minimal batch size. It is obvious that traditional cell culture systems like T-flasks, roller bottles or even multi-layer culturing systems will not work for this mass production of cells. The biggest concern of those technologies is the quality of the cells. On the other hand, larger stainless steel reactors are often not cost effective for the required volumes. In order to achieve the volumes needed at the quality and standardization required the use of automated and controlled bioreactor systems like hollow-fiber culture surfaces (e.g. Cellab® Bioreactor Systems) and micro-carrier based systems [5, 6]. These cell culture technologies allow the production of cells in high densities under optimal culture conditions at cost effective price points.

Future prospects
Given the emerging importance of cell-based therapies it is essential that researchers consider their bioreactor choices on an end-to-end basis when they start a research or trial program. This means considering not only the best tool for R&D by also for the eventual scale up to an appropriate production model under GMP standards while also cost effective even for individual doses. With Cellab® Hollow Fiber Bioreactor System, both the research needs and scale-up requirements are met in a seamless matter. In addition, with the high density system, expensive media, serum, and downstream filtration are also reduced making the system more cost effective than alternatives.

References