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REVIEW

Technological developments for small-scale downstream processing of cell therapies

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Abstract

Despite considerable regulatory and clinical hurdles, the development and use of cell-based therapies are gaining momentum. As more of these therapies move toward commercial approval and larger-scale distribution, associated manufacturing and processing technologies are being advanced. Modern technologies directed at downstream processing seek to distribute such therapies from the manufacturing site to the patient more efficiently and reliably. Novel small-scale downstream solutions boost the transformation of cell therapies from abstraction to reality.

Introduction

Cell-based therapies are promising to revolutionize the way we approach our fight against disease and chronic conditions. Such therapies are based on the simple idea that introducing healthy cells into a patient helps the affected person to battle otherwise detrimental conditions. In the past decade, cell therapy has garnered a lot of focus and attention, and recent estimates suggest that approximately 1900 clinical trials of cell-based therapies are being conducted around the world. More than 300 of these are sponsored by about 250 companies with the goal of developing commercial therapies against a wide variety of conditions or diseases [1].

The scope of the cell therapy industry is steadily expanding. The worldwide stem cell therapy market is estimated to grow at a rate of 39.5% from 2015 to 2020, to reach $330 million by 2020 [2]. The entire stem cell transplantation and cell therapy market in the United States was estimated to generate $2 billion in revenue in 2015 [3]. Potential faster growth is restrained by strict regulatory guidelines [4], high entry costs for companies stepping into this novel field, and the type of scientific, clinical and technical challenges so often associated with development of an emerging technology.

Based on the way cell therapies are used, they can be divided into two subtypes, allogeneic and autologous. Allogeneic cell therapy introduces cells from human donors into other human recipients. In contrast, autologous cell therapy uses cells that have been harvested from the very patient to which the therapy is subsequently applied. The distinction has significant consequences for manufacturing processes: allogeneic therapies require extensive tests for suitability, compatibility and purity and have a linear distribution pattern. Autologous therapies are characterized by a circular distribution pattern and lower production scale, which means that there are pressures to manufacture them proximate to the patient, either on-site at the clinic where the therapy is eventually administered or in nearby micro-facilities. Although many companies currently conduct centralized manufacturing of autologous cell therapies while in development, this circular distribution pattern significantly increases the logistics costs associated with the handling of these patient-specific products. For both therapies, other important quality parameters of the therapeutic, such as purity, viability and potency, have to be evaluated before application to the patient.

Allogeneic therapies enjoy a scalability advantage, with potentially lower production cost [5], but genetically unmodified autologous therapies have the benefit that immunoreactivity is not as big a concern after injection of the cell therapy into the patient. Because the therapeutic stems from the patient, rejection is more unlikely than in allogeneic therapy

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Table I. Select technological developments for downstream processing of cell therapies, with particular focus on engineering solutions that have been devised for lower-volume sample handling.

Process	Device	Company	Website
Cell washing, separation and volume reduction	COBE 2991 Cell Processor	Terumo BCT	www.terumobct.com
	CliniMACS Cell Separation System	Miltenyi Biotec	www.miltenyibiotec.com
	CliniMACS Prodigy	Miltenyi Biotec	www.miltenyibiotec.com
	Lovo Cell Processing System	Fresenius Kabi	http://www.fresenius-kabi.com
	Sepax 2	Biosafe	www.biosafe.ch
	kSep Centrifuge Systems	kSep Systems	www.ksepsystems.com
Cryopreservation—freezing	CryoMed Controlled Rate Freezers	Thermo Fisher Scientific	www.thermoscientific.com
	Bio-Cool Controlled Rate Freezers	SP Scientific	www.spscientific.com
	CoolCell cell freezing containers	BioCision	www.biocision.com
	CryoStor® Media	BioLife Solutions	www.biolifesolutions.com
Cryopreservation—cGMP-compliant media			
	Synth-a-Freeze Cryopreservation Medium	Thermo Fisher Scientific	www.thermofisher.com
	CryoSolutions Cryopreservation Media	Akron Biotech	www.akronbiotech.com
Cryopreservation—storage containers	CellSeal Cryogenic Vials	Cook Regentec	www.cookregentec.com
	Crystal® Closed Vials	Aseptic Technologies	www.asepticteh.com
	West Ready Pack System	West Pharmaceutical	www.westpharma.com
	KryoSure Cryopreservation Bags	Saint Gobain	www.americanfluoroseal.com
Transport/shipment	BioT ULT Transporter	BioCision	www.biocision.com
	CX and CXR vapor shippers	Taylor-Wharton	www.taylorwharton.com
	Cryoport Express Dry Vapor Shipper	Cryoport	www.cryoport.com
	MVE CryoShipper QWick & Vapor	Chart MVE	www.chartindustries.com
Thawing	ThawSTAR™ Automated Cell Thawing System	BioCision	www.biocision.com
	Point-of-Care Thawing Device for PLX	Pluristem Therapeutics	www.pluristem.com

Note: Special emphasis was given to technological improvements for freezing and thawing of cell therapy products.

approaches. Three autologous therapies have been sanctioned in the United Stated thus far. The first was approved in 1997 and consists of chondrocytes for cartilage repair (Carticel, Genzyme/Sanofi; now VeriCel). An autologous prostate cancer treatment was approved in 2010 (Provenge, Dendreon; now Valeant), followed by a fibroblast product for filling wrinkles (LaViv, Fibrocell) [6].

Because of the enormous potential of cell-based therapies, manufacturing technologies are currently undergoing rapid developments that address the predicted need for increased utility. This review focuses on the technological advancements made in the downstream part of cell therapy processing and introduces novel ideas and products in cell washing and volume reduction, fill and finish procedures (such as cryopreservation) and the post-thaw cell revival process. Table I summarizes select technological developments for each of these processes. We focus here on engineering solutions that have been developed for lower-volume sample handling and are therefore small and flexible enough to be installed in micro-facilities or clinics. We pay particular attention to technological improvements for the freezing and thawing of cell therapy products.

Cell washing and volume reduction

Where cell therapy manufacturing includes cell expansion in bioreactors, the cell suspensions have to be subsequently concentrated and filtered to reach the required cell density and purity for the final fill volumes needed for the specific therapeutic application. Culture lots greater than 20 L in volume benefit from scalable technologies such as tangential-flow filtration (TFF, Pall Corporation) or continuous-flow centrifugation [7]. Although simple bench-top centrifugation equipment may work for some small sample volumes and cell types, there is a unique need for certain cell types and/or medium quantities requiring more advanced systems.

The first such system to achieve reliable cell solution concentration and filtration was the trailblazing COBE 2991 Cell Processor (Terumo BCT), which was introduced about 30 years ago. Miltenyi Biotec's CliniMACS Cell Separation System has been used in cell processing since 1997. Its latest incarnation, the CliniMACS Prodigy system, is an integrated cell culture platform that can grow, concentrate and separate the cells in preparation for final formulation and packaging. The Lovo Cell Processing System (Fresenius Kabi) is a newly developed automatic cell separator and concentrator that removes supernatant from cells and stores the cells in viable media. Biosafe's Sepax 2 provides similar cell separation and concentration in a benchtop system that weighs less than 40 pounds. Finally, a variety of kSep Centrifuge Systems provides scalable clarification, concentration, wash, and separation of cells in a low-shear environment (kSep Systems).