Journal of Controlled Release 381 (2025) 113561

Contents lists available at ScienceDirect

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

Automated manufacturing of cell therapies

Alice Melocchi [a,b,*], Brigitte Schmittlein [b,1], Sudeshna Sadhu [b,1], Sunaina Nayak [b], Angela Lares [b], Marco Uboldi [a], Lucia Zema [a], Benedetta Nicolis di Robilant [c], Steven A. Feldman [d], Jonathan H. Esensten [e]

[a] Sezione di Tecnologia e Legislazione Farmaceutiche "M. E. Sangalli", Dipartimento di Scienze Farmaceutiche, Università degli Studi di Milano, Milano, Italy
[b] Multiply Labs, San Francisco, CA, USA
[c] Dorian Therapeutics, San Francisco, CA, USA
[d] Center for Cancer Cell Therapy, Stanford Cancer Institute, Stanford University School of Medicine, Stanford, CA, USA
[e] Advanced Biotherapy Center (ABC), Sheba Medical Center, Tel Hashomer, Israel

ARTICLE INFO

Keywords:
Robotics
Cell manufacturing
Automation
High-throughput production
Autologous cell therapies

ABSTRACT

Advanced therapy medicinal products (ATMPs), particularly genetically engineered cell-based therapies, are a major class of drugs with several high-profile Food and Drug Administration (FDA) approvals in the past decade. However, the high cost and limited production capacity of these drugs remain a barrier to access. These costs are primarily due to the complex manufacturing processes (often a single batch for a single patient), which increases personnel and facility expenses, and the challenges associated with tech-transfer from research and development stages to clinical-stage production. In order to scale up and scale out in a cost-effective way, automated solutions capable of multi-step manufacturing have been developed in academia and industry. The aim of the present article is to summarize the design approaches and key features of current multi-step automated systems for cell therapy manufacturing. For each system described in the literature, we will discuss different aspects in detail such as cell specificity, modularity, processing models, manufacturing locations, and integrated quality control. Our analysis highlights that developers need to balance competing needs in an environment where the biological, business, and technological factors are constantly evolving. Thus, designing engineering solutions that align with the pharmaceutical end-user is essential. Adopting a risk-based approach grounded in published data is the most effective strategy to evaluate existing and emerging automated systems.

1. Introduction

Interest in Advanced Therapy Medicinal Products (ATMPs), also called Human cells, tissues, and cellular and tissue-based products (HCT/Ps) in the United States, has grown both in academia and the pharmaceutical industry [1–3]. These products leverage their biological, physiological, or structural properties to treat or prevent the development of diseases and regenerate, repair, or replace a cell or tissue.

Abbreviations: ATMPs, Advanced Therapy Medicinal Products; CAR-NKs, Chimeric Antigen Receptor-Natural Killer cells; CAR-Ts, Chimeric Antigen Receptor T-cells; CBER, Center for Biologics Evaluation and Research; CDER, Center for Drug Evaluation and Research; CHOs, Chinese Hamster Ovary Cells; CNCs, Controlled Non-Classified Area; COGs, Cost of Goods; CSCs, Human Cardiac Stem Cells; DCs, Dendritic Cells; ESCs, Embryonic Stem Cells; EMA, European Medicines Agency; FDA, Food and Drug Administration; GMP, Good Manufacturing Practice; FMEA, Failure mode effects analysis; HCT/Ps, Human cells, tissues, and cellular and tissue-based products; HDFs, Primary Human Dermal Fibroblasts; HEPA, High Efficiency Particulate Air; hiPSCs, Human-Induced Pluripotent Stem Cells; hMSCs, Human Mesenchymal Stromal Cells; HSCs, Hematopoietic Stem Cells; HOSs, Human Caucasian Osteosarcoma Cells; ICAMM, International Consortium for Advanced Medicine Manufacturing; iPSCs, Induced Pluripotent Stem Cells; ISO, International Organization for Standardization; Mo-DCs, Monocyte-Derived Dendritic Cells; MSCs, Mesenchymal Stromal Cells; NK, Natural Killer Cells; PATs, Process Analytical Technologies; PSCs, Pluripotent Stem Cells; PBMCs, Peripheral Blood Mononuclear Cells; QbD, Quality by Design; RNA, Ribonucleic Acid; TCR-Ts, T Cell Receptor-Engineered T Cells; TILs, Tumor Infiltrating-Lymphocytes; Tregs, Regulatory T Cells.

* Corresponding author at: Sezione di Tecnologia e Legislazione Farmaceutiche "M. E. Sangalli", Dipartimento di Scienze Farmaceutiche, Università degli Studi di Milano, Milano, Italy.
E-mail address: alice.melocchi@unimi.it (A. Melocchi).
[1] Co-second authors (these authors equally contributed to this work).

https://doi.org/10.1016/j.jconrel.2025.02.057
Received 26 December 2024; Received in revised form 18 February 2025; Accepted 19 February 2025
Available online 22 February 2025

ATMPs consist of blood-derived cells for some therapies (*e.g.* T-lymphocytes, B-lymphocytes, Dendritic Cells (DCs) and Natural Killer Cells (NKs)) and non-blood cells for some tissue engineering applications (*e.g.* stem cells, induced pluripotent stem cells) [4–6]. Particularly impressive results in terms of efficacy and patient compliance have been obtained with effector T cell products, as they are characterized by high selectivity and expansion potential. Treatment of cancer and autoimmune diseases stand out as major areas of clinical success among the diverse applications of effector T cells [7,8]. Due to many clinical successes over the past decade novel gene- and cell-therapies are under intense development [9–12]. After infusion, such living therapeutics can travel to the site of disease, demonstrate specificity against a selected target, and provide long-lived benefits by proliferating and persisting in the patient's body. Examples of approved therapies include Tumor infiltrating-lymphocytes (TILs), chimeric antigen receptor T-cells (CAR-T), and T cell receptor-engineered T cells (TCR-T) [13–15]. Allogeneic and autologous strategies are under investigation [16–19]. Allogeneic therapies use cells derived from a qualified 3rd-party donor, whereas autologous therapies use the patient's own cells. Allogeneic treatments have shown promise in some settings, but require a qualified donor for obtaining starting material and are associated with higher risk of rejection and graft-*versus*-host disease. In contrast, autologous therapies pose lower rejection risks and do not cause graft-*versus*-host disease. Since most currently approved therapies are autologous, they are the focus of current research efforts [20,21].

Since 2017, when the first commercially successful cell-based therapy was approved by the Food and Drug Administration (FDA), more than 2,000 new clinical trials have been initiated to demonstrate potential of these living therapeutics [21–27]. The success of these trials have generated a high demand for cell therapies. More than 100,000 batches of CAR-T cell products are required for the European market alone over the next decade [28]. However, cell therapy costs still represent a challenge for widespread implementation into clinical practice. Novartis priced one infusion of tisagenlecleucel (Kymriah), the first approved B-cell precursor acute lymphoblastic leukemia CAR-T cell therapy, at $475,000 [28–31]. Today, each CAR-T infusion ranges from $373,000 to approximately $500,000 [32–36]. On top of that, additional costs for the patient include hospitalization, hospitalization post-cell infusion, and follow-up care. These numbers are also driven by the high average cost of developing cell therapies for the pharmaceutical company, including research and development, manufacturing as well as regulatory approval.

ATMPs are in general challenging to manufacture, formulate, characterize, and test for quality [37]. This complexity affects the manufacturing process, resulting in high expenses [38,39]. Current cell therapy manufacturing relies on a number of ordered steps that are generally performed by highly qualified operators (Fig. 1) [40,41]. The complexity of the multi-step process, coupled with inherent biological variability, leads to variable manufacturing outcomes, including poor efficacy or non-sterility of the final products. Manufacturing failures are still common for some commercial products. Approximately 4–7 % of patients are unable to receive their CAR-T treatment due to manufacturing issues [42].

In addition to process complexity, many pharmaceutical companies are unprepared for the increase in scale when transitioning from clinical trials to a commercial production process, especially if they rely heavily on manual manufacturing methods [41]. Indeed, a large number of personnel is needed to produce each therapy. Assuming a hypothetical 10-day manufacturing process, and up to 300 processes running in parallel each day, the full-time employees including manufacturing and support staff, technicians, quality assurance, quality control and logistics would number approximately 1,700 for a single facility [43]. This workforce would not only be hard to find, but also economically challenging to sustain. Labor-intensive and stressful bench-top manual manufacturing also leads to operators' high turnover rates up to 70 % in 18 months. This turnover slows production and contributes to high cost because extensive training is required before new operators are ready to work on the production floor [44,45]. At the same time, the instruments used in smaller-scale experiments do not directly translate to larger clinical-scale production, which further increases the costs related to tech-transfer [46]. Finally, the expenses are very high for maintaining complex equipment and highly classified facilities for aseptic processing [47–54].

Initial attempts to contain cell therapy costs and to increase

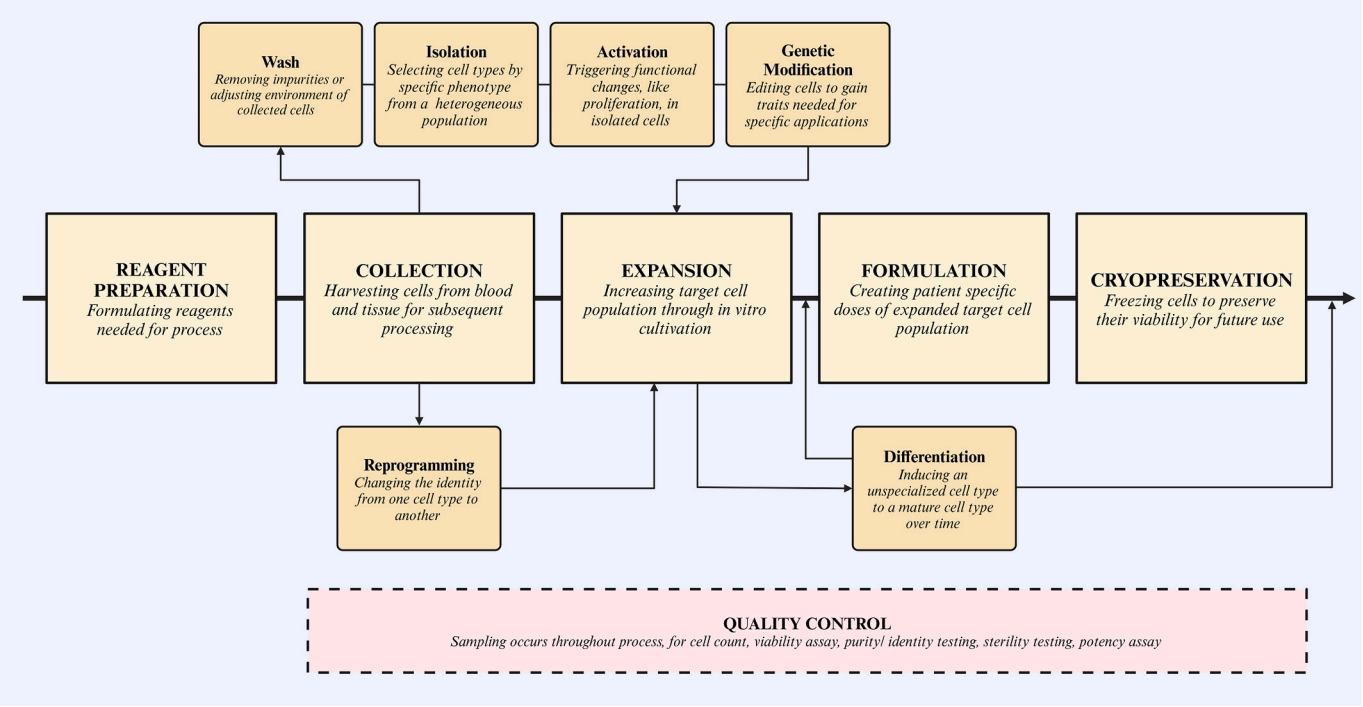

Fig. 1. Outline of the most common manufacturing steps for cell therapies.

throughput include novel *in vivo* gene transfer methods, engineering alternative cell sources, development of allogeneic therapies, and automation [55,56]. Automation offers key advantages in the manufacturing process due to repeatability and accuracy of tasks, traceability of completed operations, integration of sensing and controls, and general reduction of human involvement [57–62]. These qualities of automated systems provide reductions in product variability, manufacturing errors, risk of contamination, operator exposure to hazardous materials, and facility cleanroom requirements. Additionally, the smaller footprint of automated systems compared with manual systems increases productivity per unit area. A single employee can operate many automated systems simultaneously, increasing the number of tasks completed per unit time, supporting rapid process scalability without the need to train staff in manual processing.

Technology developers have developed a variety of research- and clinical-grade solutions to simplify and automate cell expansion. The G-Rex® vessels were introduced to improve upon the use of flasks and of static bags [28,63–69]. Taking advantage of a gas-permeable membrane, the G-Rex® bioreactor enables continuous delivery of oxygen and nutrients to cells, thus eliminating the need for manually changing the media multiple times during the culturing days. As a step forward, automated bioreactors were also developed, including hollow-fiber, stirred-tank, and rocking motion bioreactors (*e.g.* Ambr15®, Ambr250® bioreactors, Terumo Quantum Cell Expansion System, Xuri Cell Expansion System®) [70–73]. Limula is working on a novel closed bioreactor that serves as both a centrifuge and a culture vessel for T cells [74]. Through cell monitoring, automated perfusion protocols, and rocking motions to transfer oxygen and nutrients to cells, these devices reduce operator involvement. Systems automating cell washing, isolation/enrichment, genetic editing, and formulation have been developed. For example, automated cell washing steps can be performed by Sepax (BioSafe), PureCell Select™ (Pall Corporation) and RoboSep (Stem Cell Technologies) [75–80]. MaxCyte's GTx platform performs automated gene editing steps using a clinically validated electroporator. Peer systems include the Thermofisher CTS Xenon™ Electroporation System, Lonza's Nucleofector®, and the Miltenyi CliniMACS® Electroporator [81]. Miltenyi's CliniMACS Plus® automates the isolation/enrichment process, using a closed system and established MACS technology for clinical grade cell separation [82]. Terumo's FINIA Fill and Finish equipment is used for automatically formulating cell suspensions with cryo-media and aliquoting the product into cryovials [83,84]. In a further development step, pharmaceutical companies, startups, and academic laboratories have started to test more complex engineering approaches to automate multiple steps at a time [58,60,85,86]. The literature describing the various automation approaches has dramatically increased over the last few years, highlighting the urgent need to improve the current manufacturing of cell therapies. The increasing numbers of presentations and abstracts on manufacturing automation at international conferences indicates that more articles on the topic are expected to be published in the near future [87–103].

The aim of the present work is to summarize key quality attributes and to compare characteristics and performance of manufacturing systems intended to automate multiple steps of the cell therapy production process. We detail advantages and challenges of systems that are currently commercially available, under development, or are expected to reach the market in the next few years.

2. Multi-step cell manufacturing systems

2.1. Overview

The multi-step automation solutions described so far in the peer-reviewed scientific literature are summarized in Tables 1 and 2 as well as in Fig. 2. Of note, among the devices that can automate multiple steps of the cell manufacturing process, only those that could perform the expansion steps were included, as this is the most time- and labor-intensive task. Systems described in Tables 1, 2 and shown in Fig. 2 are only those with published results, either already in use for clinical manufacturing of therapies (Chapter 2.1.1 and Table 1) or currently under development (Chapter 2.1.2 and Table 2). In the former case, many research articles describe commercially available solutions for different cell types, focusing on evaluating the final cell output. For automated solutions still in the research phase, the core focus was describing the proof-of-concept automation features and their potential.

2.1.1. Clinical production

The AutoCulture® by Kawasaki Heavy Industries, CliniMACS Prodigy® by Miltenyi Biotec, Lonza Cocoon® and Cell X Precision Robotic Cell Culture Platform are used for automating either commercial or clinical trial production of cell therapies.

Kawasaki Heavy Industries completed development of AutoCulture® in 2012 and published results in 2013 for automated culture of human cardiac stem cells (CSCs) [104,154–156]. In 2016, the system was used in clinical trials to culture MSCs for knee cartilage cell therapy. The system consists of tube and flask de-cappers, media pumps, a pipette, a centrifuge, a rotating plate, and a CO_2 incubator. Flasks and other consumables are robotically operated within an ISO 5 environment with downward airflow through a high efficiency particulate air (HEPA) filter system. It is designed for large-scale stem cell cultivation: notably, it includes a consumable throughput analysis feature that predicts when they will become short and provides alerts.

Miltenyi Biotec published initial findings comparing manual *versus* CliniMACS Prodigy® automated CAR-T therapy production in 2016 [28,105–123,157]. Two years later, the system was approved by the European Medicines Agency (EMA) for manufacturing MolMed's allogeneic T cell therapy intended for patients suffering from high risk leukemia (Zalmoxis) [158]. It has since demonstrated efficacy for treating patients with chemotherapy refractory tumors [111,114]. Current research on the CliniMACs Prodigy® highlights its applications for: *i)* clinical manufacturing, such as GSK's pipeline of CAR- and TCR-T products, *ii)* the culture of various cell types, including mesenchymal stromal cells (MSCs), induced pluripotent stem cells (iPSCs), NKs and DCs, as well as *iii)* the scalable production of large cell quantities, from 5×10^9 cells in the standard version to 1.5×10^{10} cells in the large scale one [108,109,115,116,120]. The system consists of a closed, single-use consumable set for aseptic processing, a temperature controlled centrifugation unit for cell culture and separation, a magnetic unit for target cell enrichment, a peristaltic pump for fluid transfer, and pinch valves to direct flow.

In 2020, Lonza entered into a partnership with Sheba Medical Center in Israel to manufacture CD19 CAR-T cell immunotherapy using the Cocoon® platform [28,124,125,159]. One year later, Leucid Bio agreed to use the Cocoon® platform to manufacture CAR T cells for a forthcoming Phase I clinical trial [160,161]. Lonza subsequently published its first paper comparing viral *versus* non-viral gene editing of peripheral blood mononuclear cells (PBMCs) using the Cocoon® in 2021, and a study on manual *versus* automated Cocoon® production of CAR-T cells in 2023. The Cocoon instrument contains a peristaltic pump and control valves for fluid delivery, a heated chamber for culturing, and a cooled chamber for preloading process reagents. It is compatible with customizable cassettes, tailored to the specific needs of each product. The recommended capacity for the system is approximately 2×10^9 viable cells.

Cell X Technologies' precision robotic cell culture platform published results in 2023 for iPSC generation and expansion [126,127]. It was selected in 2024 to automate Aspen Neuroscience, Inc.'s iPSC manufacturing [162]. The Cell X system couples an off-the-shelf robotic liquid handling unit with an in-house designed syringe pump and aspiration pump, along with micropipettes, culture plates, peristaltic pumps, and an automated microscope. The workstation was designed to be placed within a laminar flow hood. The flow hood plus adjacent incubators are then placed within the Cell X Biospherix Xvivo system to

Table 1
Key features of systems, in the clinical production stage, that automate multiple-steps of the cell manufacturing process.

	Cell Types Tested	System Design						Operator involvement			Suitability for centralized and decentralized manufacturing	References
		All-in-one *versus* modular	Use of industry-standard equipment	Use of custom-developed equipment	Serial *versus* parallel manufacturing approach	Aseptic processing	Controlled parameters	Automated steps	Manual steps	Automated decision making		
AutoCulture®	- Human Cardiac Cells (CSCs)	Modular system with integrated equipment	- Tube and flask de-cappers - Flask holders - Flask tappers - Media pumps - Pipette head - Centrifugal separator - Rotating plate - CO_2 incubator	Not available	Serial	- Equipped with a connecting hatch to multiple CO_2 incubators to minimize cross contamination risk - Designed for use in cleanroom environment (machine cabinet maintains class 100 environment)	- Culture parameters (humidity, temperature) - Robot arm motion - Quality control photos for morphological assessment - Cell density - Culture volume - Centrifugation parameters (speed, time) - Process timing - Material tracking	- Expansion - Wash - Formulation	- Reagent preparation - Quality control (*e.g.* cell count, viability assay, purity/ identity testing, sterility testing, potency assays, recording of cell morphology) - Cryopreservation	Not available	Decentralized	[104]
Miltenyi CliniMACS Prodigy®	- CAR-T - CAR-NK - DCs - NK - Hematopoietic Stem Cells Autologous (HSCs) - Macrophages - Mesenchymal Stromal Cells (MSCs) - Pluripotent Stem Cells (PSCs) - Regulatory T Cells (Tregs) - TILs	All-in-one system, completely custom developed	Not available	Completely custom developed, compatible with CliniMACS® Electroporator (Miltenyi)	Serial	- Closed system with sterile welding - Can be used in an International Organization for Standardization (ISO) 7 or 8 classified cleanroom	- Cell density - Culture volume - Process timing - Peristaltic pump flow rates - Centrifugation parameters (speed, time) - Cell separation protocols - Culture parameters (growth factors, medium, gas conditions, temperature) - Custom protocols (modify individual steps for specialized workflows) - Alerts and performance monitoring (threshold for performance alarms)	- Isolation (Magnetic) - Activation (soluble reagent) - Genetic modification - Reprogramming - Differentiation - Expansion - Wash - Formulation	- Reagent preparation - Quality control (*e.g.* cell count, viability assay, purity/ identity testing, sterility testing, potency assays) - Cryopreservation	- Artificial Intelligence (AI) was used to interpret data collected from the Miltenyi Prodigy® platform during the CAR-T manufacturing process - Provided valuable insights into the manufacturing process - Helped drive decisions to optimize manufacturing parameters	Centralized and decentralized	[105–123]
Lonza Cocoon®	- CAR-T - TILs - HSCs - T Cell Receptor-Engineered T Cells (TCR-Ts) - Tregs	All-in-one system, completely custom developed	Not available	Completely custom developed, compatible with D-Nucleofector™ LV Unit (Lonza)	Serial	- Needle free connectors or sterile welding - Can be used in a Controlled Non-Classified Area (CNC), ISO 8 and 7	- Temperature control - Culture parameters (growth factors, medium, gas conditions)	- Activation (Dynabeads or soluble reagent) - Genetic modification - Isolation / enrichment	- Reagent preparation - Quality control (*e.g.* cell count, viability assay, purity/ identity testing, sterility testing, potency assays)	- The pH is controlled automatically by monitoring and modulating the CO_2 level in the	Centralized and decentralized	[124,125]

(*continued on next page*)

Table 1 (*continued*)

	Cell Types Tested	System Design						Operator involvement			Suitability for centralized and decentralized manufacturing	References
		All-in-one *versus* modular	Use of industry-standard equipment	Use of custom-developed equipment	Serial *versus* parallel manufacturing approach	Aseptic processing	Controlled parameters	Automated steps	Manual steps	Automated decision making		
							- Protocol development and execution - Alarm notifications - Electronic record generation - Safeguards for process issues - Syringe pump aspiration and dispensing heights can be adjusted based on cell type / adhesion level - Peristaltic pump flow rates - Picking strategy (whole or partial colony) - wash and refill steps - Non-enzymatic passaging solution - Culture parameters (temperature, CO_2, O_2, humidity) - Automated imaging - Collaborative robotic arm movement - Process steps and sequencing	- Expansion - Wash - Formulation - Genetic modification - Reprogramming - Differentiation - Expansion	- Cryopreservation - Reagent preparation - Collection - Activation - Quality control (*e.g.* cell count, viability assay, purity/ identity testing, sterility testing, potency assays) - Cryopreservation	equipment environment - The operator needs to start the process, but once the commands have been provided, minimal human involvement is necessary		
Cell X Precision robotic cell culture platform	- Induced Pluripotent Stem Cells (iPSCs)	Modular system with integrated and custom developed equipment	- Robotic liquid handling system - Inverted fluorescent microscope	- Syringe pump - Aspiration pump - Disposable micropipette tips for both the syringe and aspiration pumps - Two multi-well cell culture plates - Peristaltic pumps - Microscope	Parallel	- Closed system (ISO 5 closed aseptic isolator)					Decentralized	[126,127]

ensure an aseptic environment.

2.1.2. Research and development

Pre-commercial stage devices are either developed for cell therapy process development, or currently undergoing testing to manufacture commercial products.

Sartorius launched the CompacT SelecT CellBase in 2005 and published data in 2008 for its implementation in support of cell-based assays for Alzheimer's drug discovery, comparing manual *versus* automated Chinese hamster ovary cell (CHOs) cultures [128–140]. Since then, published data demonstrates the feasibility of culturing a variety of cells, including dermal fibroblasts, MSCs, and iPSCs, and automated large-scale transient transfection of human cell lines. A laminar flow chamber houses a robotic culturing system, where flasks are transferred between fluid pumping and incubation stations.

Researchers from Zurich University of Applied Sciences developed an automated cell-culture platform, with results published in 2011, designed for the isolation, expansion, and quality control of human primary cells, particularly intervertebral disc cells, for regenerative medicine [141]. The platform integrates novel features such as automated biopsy handling, tissue homogenization, confluence measurement, and immunostaining for phenotype analysis, ensuring reproducibility, safety, and high-quality cell production. The system demonstrated comparable results to manual methods in terms of cell yield, viability, and phenotype.

Fraunhofer built the AUTOSTEM platform in 2016 and published research in 2017 for automated manufacturing of bone marrow derived MSCs [142–145,163]. In 2022, scientists demonstrated its capability to manufacture MSCs with similar yield and phenotype to those manually produced. The device uses two chambers of different classification levels, grade A and grade D. Each chamber contains a six-axis robot with custom designed grippers. The grade A environment is used for formulation, fill, and cell collection. It contains a centrifuge, cell counter, decapper, and pipetting device. The grade D area enables cell expansion and media exchange, containing two 3 L single-use bioreactors and −80 °C reagent storage.

In 2018, researchers from Osaka university in Japan developed and tested the Tissue Factory for cultivating three ATMPs: multi-layered skeletal myoblast sheets, human chondrocytes, and human iPSCs [146]. The goal was to develop an open platform to connect multiple single function apparatuses together and mediate exchange of materials across them. The system consists of 9 hexagonal modules that can move around *via* a robotic unit attached to the base. They can be connected and detached using standardized connection interfaces to enable material transport. Modules contain a mixture of custom-made and industry standard cell culturing consumables and equipment to complete each cell culture step. To ensure sterility, materials are aseptically introduced to any of the cell processing modules through a material preparation isolator.

Following a slightly different modular approach, several research institutions in Germany built and tested the StemCellFactory, publishing data in 2020 for automated generation and expansion of iPSCs [147,148]. The system focuses only on the culture of iPSCs, demonstrating reprogramming and clone derivation steps. Four modules are equipped with laminar airflow and arranged according to process steps: reprogramming, isolation, expansion, and quality control. Materials are transported between modules *via* a robotic arm arranged on a horizontal axis. Industry standard equipment incorporated includes a Hamilton liquid handling system, a Sigma centrifuge, the CellCelector (for isolation), and two automated LiCONIC incubators. Each of them worked independently, with no central software in charge for overall control.

Microfluidic technologies have recently emerged as a novel approach for the production of autologous cell therapies [149–152]. These chips reduce the chances of contamination and allow for parallel processing. In 2023, a small-volume microfluidic bioreactor, *i.e.* the Mobius Breez microbioreactor was commercialized (Erbi Biosystems, MilliporeSigma) for cell culture-on-a-chip. Initially, it was tested for both microbial and mammalian cell cultures and more recently for CAR-T manufacturing. It integrates mixers, injectors, and sensors for real-time monitoring and closed-loop control of perfusion flow rate, optical density, temperature, CO_2, dissolved O_2 and pH levels. It encompasses a base station controller and a CO_2 controller supporting up to four pods, each with a microfluidic chip linked to a bottle rack assembly, supplied as a sterile, single-use consumable. The consumable can be aseptically connected *via* sterile welding, producing cells for different patients in four separate chambers. This chip harvests more than 60×10^6 viable T cells from patient donors and more than 200×10^6 from healthy donors. In this way, the Mobius Breez microbioreactor addresses a common drawback of microfluidic devices by meeting the minimum cell dose of Tisa-cel (Kymriah) and exceeding the maximum cell dose of Axi-cel (Yescarta). Interestingly, CAR-T cells produced at high densities in the microbioreactor were highly functional despite higher proportions of T cells expressing differentiation and senescence markers.

Proof-of-concept results for automated T cell expansion performed by the Multiply Labs robotic cluster were published in early 2024 [153]. This self-contained system employs industry-standard cell therapy manufacturing equipment and has the potential to automate small- and large-scale expansion for multiple products in parallel. A robotic arm on a rail moves consumables between robotic modules. Purpose-built robotic cartridges interact with cell processing equipment. The system works with single-use consumables outfitted with functionally closed connectors to facilitate aseptic cell transfer. Reagent addition is performed using an integrated bag, pump, and weighing apparatus. Sampling from bioreactors is performed *via* syringe. After demonstrating that the robotic cluster could produce cells with similar proliferation, viability, genetic expression to a manual culture, the company is currently undergoing pilot studies for end-to-end automated production of cell therapies.

2.2. Feature analysis

Here we analyze the core features representing the focus of each column of Tables 1 and 2. The critical discussion will be focused on *i)* cell agnostic *versus* cell specific, *ii)* all-in-one *versus* modular, *iii)* serial *versus* parallel, *iv)* centralized *versus* decentralized manufacturing compatibility. In addition, insights on operator involvement, controls (*i.e.* closed *versus* open loop control, real-time *versus* off-line, sterility) and quality assessment will be provided.

2.2.1. Cell specificity

A range of cell types, both adherent and suspension, can be cultured on automated systems for therapeutic applications: immune cells (*e.g.* NK cells, tumor infiltrating leukocytes, blood and monocyte-derived dendritic cells (Mo-DCs), and regulatory T cells), gene modified cells (*e.g.* CAR-T, CAR-NK), and stem cells (*e.g.* pluripotent stem cells (PSCs) including induced hematopoietic stem cells (HSCs), MSCs and cancer stem cells). There are two common approaches to ensure cell type compatibility: developing cell-agnostic equipment designed to automate the production of different cell types (*e.g.* CliniMACS Prodigy®), or developing equipment tailored for a specific cell type (*e.g.* Autostem, AutoCulture). For the latter, the configuration of the equipment is dependent on the target products and the unique steps needed for their production (Fig. 1). Non-adherent or suspension cell types (*e.g.* T cells, NK cells) often undergo expansion with genetic modification. On the other hand, adherent cell types (*e.g.* iPSCs, MSCs) are less likely to have genetic modification. While equipment designed for a specific cell type is clearly optimized for the intended manufacturing process, they often lack versatility, a key quality of cell-agnostic solutions. In any case, both cell-agnostic and cell-specific equipment need to accommodate the inherent variability of living systems. For example, in autologous cell therapy products, there is considerable variability in starting material quality and quantity [164]. This variability can have critical effects on

Table 2
Key features of systems, in the research and development stage, automating multiple-steps of the cell manufacturing process.

	Cell Types Tested	System Design						Operator involvement			Suitability for centralized and decentralized manufacturing	References
		All-in-one *versus* modular	Use of industry-standard equipment	Use of custom-developed equipment	Serial *versus* parallel manufacturing approach	Aseptic processing	Controlled parameters	Automated steps	Manual steps	Automated decision making		
CompacT SelecT CellBase	- Chinese Hamster Ovary Cells (CHOs) - Embryonic Stem Cells (ESCs) - Human Caucasian Osteosarcoma Cells (HOS) - iPSCs and their derivatives - MSCs - Transfected cell lines	Modular system with integrated equipment	- Vi-CELL XR Cell Viability Analyzer in semi-autonomous mode (Beckman Coulter) - Incubator - Flasks - Peristaltic pump - Serological pipettes - Incucyte (Sartorius)	Not available	Parallel (for a single product)	- Robotic system is encased in a laminar flow chamber	- Cell density - Culture volumes - Reagents and additives - Temperature control - Compounds for assay Screening concentration - Viability assay parameters - Plate setup - Data normalization - Custom protocols (modify individual steps for specialized workflows) - Plating and scaling parameters	- Genetic modification - Reprogramming - Differentiation - Expansion - Quality control (*e.g.* cell count)	- Reagent preparation - Collection - Isolation of Primary Human Dermal Fibroblasts (HDFs) lines from skin samples - Tissue enzymatic dissociation to obtain primary HDFs cultures - Quality control (*e.g.* cell count, viability assay, purity/identity testing, sterility testing, potency assays) - Cryopreservation	Not available	Decentralized	[28–140]
Zurich University System	- Human intervertebral disc cells	Modular system with integrated equipment	- EVO 150 liquid-handling robot (Tecan Freedom) - Centrifuge (Hettich Rotanta 46 RSC Robotic) - Cellavista automated microscopic cell analyzer for non-invasive monitoring (Roche) - Incubator - Dispomix cell homogenizer	Not available	Parallel (for a single product)	- Robotic system is encased in a laminar flow chamber (Class 1000, VDI 2083 purity) - Regular sterilization cycles	- Temperature: - CO_2 - Cell density - Cell phenotype	- Isolation - Expansion - Washing - Quality control (*e.g.* cell count, viability assay, purity/identity testing, sterility testing, potency assays)	- Reagent preparation - Cryopreservation	- Tracking and adjustment of cell density based on confluence data - Flagging of issues due to image analysis	Decentralized	[141]
AUTOSTEM	- Human Mesenchymal Stromal Cells (hMSCs),	Modular system with integrated and custom	- Two 3 L single-use bioreactors	- Bone marrow	Serial	- Combination of cleanroom environments (A,	- Culture volume - Cell density	- Collection - Isolation - Expansion - Formulation	- Reagent preparation - Isolation of MSCs from tissues	- Feedback control employed for reagent	Decentralized	[142–145]

(*continued on next page*)

Table 2 (*continued*)

	Cell Types Tested	System Design						Operator involvement			Suitability for centralized and decentralized manufacturing	References
		All-in-one *versus* modular	Use of industry-standard equipment	Use of custom-developed equipment	Serial *versus* parallel manufacturing approach	Aseptic processing	Controlled parameters	Automated steps	Manual steps	Automated decision making		
	derived from bone marrow	developed equipment		collection device, consisting of a pump, vacuum, collection needle		D) depending on the use case: - Grade A environment is operated as an isolator and sterilized between production runs by vaporized hydrogen peroxide - Grade D environment is used for upstream processing	- Culture parameters (Bioreactor pH, O_2, CO_2, temperature) - Agitation speed for microcarrier mixing - Microcarrier concentration - Flow rates - Centrifugation parameters (speed, time) - Cryovial fill volume - Freezing temperature - Vacuum pressure (for bone marrow collection) - Process timing	- Quality control (*e.g.* cell count, viability assay, purity/identity testing, sterility testing, potency assays) - Cryopreservation		delivery by opening and closing tube line squeeze valves that respond to weight data from the bioreactor scales, facilitating feedback control of feed volume and rate - Decision trees automate adaptive processes based on measurement data - The user can incorporate decision trees that execute different process branches based on measurement data or user input to automate adaptive processes		
			- NC3000 cell counter (Chemometec) - Centrifuge - Decapper - Pipetting device - −80 °C freezer									
Tissue Factory	- Multi-layered myoblast sheets - Human articular chondrocytes - Human-Induced Pluripotent Stem Cells (hiPSCs)	Modular system with integrated and custom developed equipment	Not available	- Cell culture dish - The Large Scale Culture vessel - Medium/ cell suspension containers - Enzyme treatment container - Gelatin gel mold	Parallel (in a cluster-type production method, the other apparatuses are separate and can be used during the cell culture period)	- Each module has a biologically sealed chamber that can be decontaminated by hydrogen peroxide - An isolator is used to introduce materials into the system	- Culture parameters (humidity, temperature, CO_2) - Culture volume - Cell density - Robot control - Airflow/ pressure - Hydrogen peroxide vapor concentration and duration	- Collection - Isolation - Expansion - Production of multi-layered skeletal myoblast sheets - Gelatin gel Preparation - Cell sheet stacking	- Reagent preparation - Differentiation - Reprogramming - Quality control (*e.g.* cell count, viability assay, purity/identity testing, sterility testing, potency assays) - Cryopreservation	Not available	Decentralized	[146]

(*continued on next page*)

Table 2 (*continued*)

	Cell Types Tested	System Design						Operator involvement			Suitability for centralized and decentralized manufacturing	References
		All-in-one *versus* modular	Use of industry-standard equipment	Use of custom-developed equipment	Serial *versus* parallel manufacturing approach	Aseptic processing	Controlled parameters	Automated steps	Manual steps	Automated decision making		
StemCellFactory	- hiPSCs	Modular system with integrated and custom developed equipment	- MicroLAB STAR (Star line, Hamilton Robotics) liquid handling unit (LHU) - Plate reader (BMG FLUOstar OPTIMA, BMG Labtech) - Centrifuge (Sigma 4-16 K, Sigma) - Clone picker (AVISO CellCelector, ALS GmbH) - Decapper station (proprietary technology of Fraunhofer IPT) - Material gate (proprietary technology of Fraunhofer IPT)	- High-speed automated microscope	Parallel (for a single product)	- Entire unit is encased in a clean room cabinet, operating at an airflow of 1440 m^3/h (Goller Reinraumtechnik GmbH)	- Enzyme treatment (digestion and cutting) - Centrifuge settings - Process steps and sequencing - Custom protocols (modify individual steps for specialized workflows) - Visualization of data - Culture parameters (Bioreactor pH, O_2, CO_2, temperature) - Airflow - Liquid handling unit parameters, including heating/cooling station - Passaging frequency - Culture volume - Cell density - Confluence threshold for passaging	- Collection - Isolation - Reprogramming - Differentiation - Expansion	- Reagent preparation - Quality control (*e.g.* cell count, viability assay, purity/identity testing, sterility testing, potency assays. Semi-automated using Cedex analyzer (Roche) - Cryopreservation	- Automated cell passaging using image-based confluence measurements	Decentralized	[147,148]
Mobius Breez microbioreactor	- T cells - Microbial and mammalian cultures	All-in-one system, completely custom developed	Not available	Completely custom developed	Parallel (4 pods enable up to 4 separate cultures per instrument)	- Closed system compatible with sterile welding	- Perfusion flow rate - Optical density - Culture parameters (temperature, CO_2, O_2, pH) - Cell retention - Fluid inputs - Fluid outputs - Viral vector inoculation	- Activation (semi-automated) - Genetic Modification (semi-automated) - Expansion	- Reagent preparation - Collection - Activation - Quality control (*e.g.* cell count, viability assay, purity/identity testing, sterility testing, potency assays) - Cryopreservation	- Embedded optical density, dissolved O_2 and pH sensors, which enable real-time monitoring - Closed-loop control of these process parameters *via* a pneumatic controller that	Centralized and decentralized	[149–152]

(*continued on next page*)

Table 2 (*continued*)

	Cell Types Tested	System Design						Operator involvement			Suitability for centralized and decentralized manufacturing	References
		All-in-one *versus* modular	Use of industry-standard equipment	Use of custom-developed equipment	Serial *versus* parallel manufacturing approach	Aseptic processing	Controlled parameters	Automated steps	Manual steps	Automated decision making		
										adjusts the O_2 and CO_2 concentrations of the gas in the headspace of the growth chamber		
Multiply Labs robotic cluster	- T cells	Modular System with integrated and custom developed equipment	- G-Rex 100 M bioreactor (Wilson Wolf) - Heracell incubator (Thermofisher) - Xuri cell expansion system (Cytiva)	- Peristaltic pump - Reagent warming/ cooling	Parallel	- Functionally closed system - Designed for modular ISO 5-7 environment	- Culture volume - Reagent storage and addition temperature - Cell density - Reagents and additives - Peristaltic pump flow rates - Culture parameters (temperature, humidity, O_2, CO_2) - Process steps and sequencing - Robotic movements - Xuri parameters: rocking speed, angle - Process timing - Air pressure (for air transfer between bioreactors)	- Activation - Expansion	- Reagent preparation - Isolation - Genetic modification - Quality control (*e.g.* cell count, viability assay, purity/identity testing, sterility testing, potency assays) - Cryopreservation	Not available	Decentralized	[153]

Fig. 2. Images of systems automating multiple steps of the cell manufacturing process described in the literature (included with permission: AutoCulture® from [104]; Lonza Cocoon® from [124]; Cell X precision robotic cell culture platform from [126]; CompacT SelecT CellBase from [140]; Zurich University System from [141]; AUTOSTEM from [144]; Tissue Factory from [146]; StemCellFactory from [148]; Mobius Breez microbioreactor from [150]; Multiply Labs robotic cluster from [153]).

manufacturing outcomes. Therefore, automated systems must be able to dynamically adapt to a wide range of cell behaviors. An automated system will need to be able to adjust the number of cells and culture conditions to prevent either overgrowth of cells or addition of a small number of cells to an overly large culture vessel. Some of these decisions may require human or AI-based judgement and intervention.

2.2.2. *All-in-one versus modular systems*

Two automation strategies, all-in-one *versus* modular, are evident from our literature review [28,43,59,165]. The former is based on all-in-one instruments, in which multiple steps are performed by a single device in-house developed by a specific company (*e.g.* CliniMACS Prodigy®, Lonza Cocoon®). On the other hand, the latter relies on integrating equipment already in use for clinical manufacturing of cell therapies from multiple vendors, each performing a specific set of sub-processes (*e.g.* AUTOSTEM, StemCellFactory).

All-in-one systems benefit from standardization of set-up, ease of use, and convenient data acquisition [43,60]. However, it may happen that these solutions do not appropriately fit the peculiarities of a given manufacturing process, and other devices are required for specific unit operations. This can necessitate additional manual steps. For example, the Lonza Cocoon® has an integrated magnet for cell enrichment that is compatible with the use of Dynabeads (a Thermofisher enrichment reagent commonly used in industry). Since all-in-one instruments may lack standardized interfaces for connectivity and data exchange, their use in combination with instruments from other providers could be limited. Recognizing the versatility issue, companies started developing additional proprietary systems to be coupled with their all-in-one devices for specific process steps (*e.g.* Miltenyi CliniMACS Prodigy® direct compatibility with the CliniMACS® Electroporator for closed system electroporation). Although the all-in-one approach could be considered less flexible, and advantage is that the complexity of hardware and software is hidden from the operator.

The 2023 International Consortium for Advanced Medicine Manufacturing (ICAMM) meeting, involving experts from academia, industry, regulatory authorities and policy makers, explored new ways to accelerate adoption of manufacturing approaches for advanced medicines and specifically for cell therapies. This meeting highlighted the importance of pursuing modularity in view of its adaptability and versatility [166]. The modular approach is similar to modern assembly lines that can be found in different industries [55]. Modularity represents an evolution of manual production-line based manufacturing used in cell therapy (*e.g.* BioSpherix Xvivo modular laminar). In modular systems, the item being processed moves from one station to the next, with each station dedicated to a specific step.

The modular approach involves additional complexity because hardware and software integration between different devices is needed [42,59,167]. To simplify this task, a mind-set change is required among equipment suppliers, who need incentives to improve the compatibility of their device with automated processes. An overall modular architecture offers major customization possibilities: for instance, keeping the system continuously updated by adding newly-developed equipment or including instruments used in specific cell processes. In addition, by allowing the integration of different equipment for the same cell manufacturing step, dependence on a single supplier could be reduced. Indeed, in the early development stage, it is important to assess equipment interchangeability within the same process by demonstrating that analogous products can be produced without significantly altering relevant characteristics (Dutch Innovation program NXTGEN-HIGHTECH) [37,168].

For the physical integration of various equipment necessary for the modular approach, one of the solutions described is the use of robotic arms equipped with custom-made interfaces (*e.g.* AUTOSTEM, Multiply Labs robotic cluster) [144,153]. Collaborative robots, designed to work alongside humans, are generally preferred, because they are less expensive, easy to deploy and program, safer, and more consistent than their industrial counterparts when dealing with relatively light items. Since the robot generally mimics human hand motions for transferring cells between processing units, this type of automation has considerably low comparability risk [60]. However, recreating human motion may not always be the most effective way of performing an action. Robotic arm operations could also be optimized further, for instance in terms of speed, precision, reliability. To this end, major efforts are also required

from the software perspective, not only to program the robotic arm but also to save and import data and facilitate communication between devices [85]. Indeed, many equipment manufacturers have not yet recognized the need for open interfaces and currently offer either no or only limited connectivity to software or devices from other suppliers.

Finally, custom-made software could be used to ensure cross-compatibility between modular system devices by extracting data *via* generic and self-contained interfaces. Software with service-oriented architecture is often advantageous to meet the demand for flexibility, while giving maximum control over data and devices. This approach is particularly promising because it lays the basis for a generic system that can also manage additional devices. Moreover, the development of novel software creates an opportunity to automatically generate electronic batch records to avoid laborious manual documentation and to ensure an automated flow of information for traceability purposes. However, building custom software could be challenging, as it requires extracting encrypted data from different devices and major capital investment.

2.2.3. Serial versus parallel manufacturing approach

Serial *versus* parallel production is another key aspect of automated equipment design [43]. For serial manufacturing, different steps are performed sequentially, whereas parallel involves completing several batches at a time. Equipment for stem cell therapy production is usually designed for parallel cell expansion (*e.g.* StemCellFactory, CompacT SelecT CellBase), while those for T cells (*e.g.* CliniMACS Prodigy®, Lonza Cocoon®) usually utilize serial expansion. While serial systems are more traceable and present less cross-contamination risk, they rely on the one-device-per-patient approach, making them potentially less scalable than parallel systems [59]. Indeed, multiple batches can be manufactured only with several all-in-one devices working at the same time, which would require major upfront investment, not only for purchasing the equipment but also for ensuring enough facility space to run the various processes. Also, a single all-in-one system may be tied up for weeks just for cell expansion, whereby the majority of the instrument is not used, and cannot be utilized for another batch. This provides an inefficient manufacturing workload.

On the other hand, parallel systems have the potential to scale up and to make autologous cell therapy manufacturing economically more attractive by culturing multiple patients' cells within the same framework. For this reason, parallel processing is proposed as a key strategy to achieve scalability in automation while still allowing for flexibility, to meet individual patient or therapy needs. For example, the Mobius Breez device incorporates four separate temperature-controlled chambers, each with a unique cell product [149–152]. To achieve parallel production of multiple therapies and considering that cell expansion is probably the longest step, some authorities also propose increasing the number of bioreactor cartridges within a centralized incubator [133,143,145]. This would be done using closed tubing kits that are replaced before the respective process step, so cells from several patients may be processed in parallel without the risk of cross-contamination. However, further data needs to become available to ultimately demonstrate the suitability of this approach that is still at the research and development stage (*e.g.* AIDPATH project funded by the European union, Multiply Labs robotic cluster) [153,164,167–170].

Another aspect is scalability *versus* customization, particularly for cell agnostic, modular automated manufacturing platforms. While all-in-one systems have limited customization options post-commercialization, modular systems could favor process customization even after marketing, for instance allowing modifications on specific subtasks without the need to stop the process completely. To manufacture products in parallel on a single modular system, advanced process planning software can be used to optimize daily or weekly production schedules and manage multiple custom processes at once. This software would minimize system downtime and maximize throughput. Furthermore, reinforcement learning and adaptive scheduling algorithms can be utilized to address resource allocation problems, process uncertainties, and prevent the need for frequent re-planning. Ultimately, these planning tools aim to enable scalable production of patient- or therapy- specific products, independent of predetermined process parameters.

Both all-in-one and modular automated systems can enhance scalability over current manual manufacturing of cell therapy by monitoring the process in real-time and collecting extensive data for multiple patient batches running concurrently. Many systems discussed in this review capture such data: batch/identification number, possible contamination, and equipment parameters (*e.g.* calibration, alerts). Logging this data improves scalability by limiting the labor force involved and by avoiding errors or mix-ups that could cause process failures. This would reduce costs and support more efficient operations.

2.2.4. System design towards aseptic processing

To ensure sterility of the final product, different approaches are pursued, including: *i)* enclosing the entire unit or having the high-risk area encased in a classified cleanroom or biosafety cabinet (*e.g.* AUTOSTEM, StemCellFactory, CompacT SelecT CellBases), often coupled with sterilization of the items to be introduced (*e.g.* hydrogen peroxide for Tissue Factory), *ii)* utilizing single-use consumables compatible with sterile welding to achieve a closed system (*e.g.* CliniMACS Prodigy®, Lonza Cocoon®), and *iii)* employing functionally closed aseptic connections made on demand (*e.g.* Multiply Labs robotic cluster) [167,171,172]. Functionally closed systems keep the product isolated from the environment, but can connect and disconnect different output and input materials as required by the processing operation. Besides reducing the chance of contamination, closed systems are generally preferred because they allow the manufacturing to be performed in a non-classified environment, without compromising safety of the final cell products. However, classified cleanrooms are often used even for closed systems [173]. In general, the use of closed systems likely reduces the costs associated with the construction/maintenance of highly classified facilities. However, single-use consumables are expensive and sterile welding is error-prone. Functionally closed connections enable a system to maintain its closed state after connection. This allows for lowering of cleanroom classification requirements and ability to connect different consumables in a convenient/standardized way. One of the issues that has to be addressed, is that key reagents for cell therapy (*e.g.* viral vectors, media, growth factors) are typically supplied in non-closed-system compatible containers such as screw top tubes. Therefore, a feasible strategy would be to partner with raw materials suppliers to develop interfaces compliant with closed/functionally closed technologies. The same challenges need to be addressed for sampling, which in many cases requires system opening [153].

2.2.5. Quality control

In-process and final product testing play a fundamental role in cell therapy manufacturing [6,174]. For releasing a batch, regulatory agencies require characterizing the final product with validated analytic assays to confirm it meets relevant release criteria including identity, purity, and potency. Limited sample volumes are required to avoid wasting product [6,44].

To reduce testing delays and accelerate product release, there are efforts to improve in-process quality control [43,60,165]. Indeed, there is a clear trend towards the use of process analytical technologies (PATs), to avoid open manipulation of samples for quality control purposes [175,176]. Current manufacturing processes mainly rely on predefined schedules and open off-line measurements, which are associated with high operator involvement, increased chances of errors, and contamination. To ensure proper cell evaluation, additional characterization equipment is necessary, requiring larger space in the manufacturing facility, and highly skilled employees to operate them and to analyze results. Development of smart manufacturing platforms taking advantage of PATs could lead to important efficiency gains.

Indeed, PAT integration may enable more robust processes that would also be more flexible and faster to adapt towards cells' biological variability [165–167]. First attempts towards this type of integration have been described, mainly for culture condition optimization. The monitored parameters often include gas levels (*e.g.* CO_2, O_2, N_2), pH, dissolved oxygen, metabolites (*e.g.* glucose, lactate), perfusion flow rate, and temperature. For example, the Mobius Breez bioreactor continuously monitors dissolved oxygen and pH, using a pneumatic optical digital controller to quickly regulate the O_2 and CO_2, thereby improving conditions for cell growth [149–151]. Non-invasive online sensors are preferred because they provide real-time data without disturbing the cell culture [139]. However, most integrated sensors can only perform bulk indirect measurements of the cells' environment and thus rely on comparison to an earlier time point [171]. Therefore, they require proper calibration, especially in the case of cell culture changes.

Depending on the cell type, access to image-based measurements is advantageous for biologists. Thus, a few systems have started to implement these sensors for both evaluation of morphological features of growing cells and as a quality check. For example, the StemCellFactory takes advantage of microscopic image-based confluence data to determine the dilution ratio, whereas Autoculture® and Cell X precision robotic cell culture platform uses imaging technology for cell morphology and characterization [104,149]. Furthermore, certain modular systems implement industry standard cell analysis technologies. The CompacT SelecT CellBase integrates with the Incucyte and the Vi-CELL XR Cell Viability Analyzer, while the AUTOSTEM uses an incorporated NC3000 cell counter for sampling and analysis [128–140,142–145]. Therefore, there is an opportunity for modular systems to also integrate analytic instruments in the manufacturing platform. To this end, the most efficient option is to select equipment already designed to be automation friendly, such as the Accelix flow cytometer, which can give real-time immunophenotyping results using pre-loaded cartridges [177].

Automated, easy-to-use and integrated PATs would provide data monitoring capabilities required for supporting the Quality by Design (QbD) approach, which could help improve final cell product quality and handle manufacturing complexity, as highlighted by A-CELL STUDY [6,174,177–181]. QbD initially requires the description of the desired product quality characteristics (*i.e.* quality target product profile) and the identification of attributes that directly affect safety and efficacy of the product (*i.e.* critical quality attributes). Parameters impacting these attributes (*i.e.* critical process parameters) are selected to develop a design space that quantifies how parameter variability affects the critical quality attributes. Then, a control strategy must be validated to maintain processing conditions within an acceptable range and to ensure continuous improvement.

The use of PATs will also lay the basis for the development of a feedback-driven manufacturing platform with automated decision making, *i.e.* able to modify the process in real-time based on the results [43,60,165,169]. By collecting a large amount of data, PATs could be combined with artificial intelligence and machine learning. In the long term, this approach could allow better design of the manufacturing process and correlation of cell characteristics with patient clinical responses. In preliminary findings, artificial intelligence was used to interpret findings collected from the CliniMACS Prodigy® to drive decisions that optimized manufacturing parameters and to provide valuable process insights [44]. Moreover, the digital twin approach, consisting of a virtual representation of a cell culture process using data and complex models, has been employed at the research level [169,180]. Scientists can simulate and predict cell behavior, enabling optimization of the manufacturing process by identifying potential issues and adjusting parameters before anything occurs in the real-world. This way, it would be possible to improve consistency of the final product quality and to ultimately ensure its efficacy (*e.g.* T2EVOLVE and ImSavar projects) [165]. Characterization of cellular products (*e.g.* viability, apoptosis profile, single-cell ribonucleic acid (RNA) transcriptomics, metabolomics, single-cell mass cytometry, performance in cell-based immunosuppression assays) has been tested for facilitating product and process design through data-driven modeling [44]. Moreover, various data analysis approaches (*e.g.* linear/nonlinear regression, canonical correlation analysis, machine learning algorithms) have been proposed for developing predictive models linking multi-omics characterization findings (resulting from mass cytometry, transcriptomics, metabolomics, lipidomics, and secretomics) and clinical outcomes.

Although online measurements and PATs implementation have the potential to reduce and to speed up testing for final product release, some tests are more challenging to automate. Assessment of sterility, endotoxin levels, and mycoplasma contamination still represent a major challenge [28]. The introduction of colorimetric and fluorescence-based CO_2 measurements of metabolic activity (*e.g.* BacT/Alert 3D and BD BACTEC systems) or adenosine triphosphate detection by bioluminescence (Rapid Milliflex Detection System) has allowed for faster evaluation of microbiological contamination. However, current guidelines for ensuring product sterility require a 14 day test for bacteria, and in some cases 28 day test for fungus. As the time-to-vein is a major constraint for cell therapies, various companies are working on rapid testing methods (*e.g.* Microsart ATMP Sterile Release kit by Sartorius) [28]. To further improve production, modular systems tried to implement such controls. For instance, the StemCellFactory benefits from a plate reader using an absorption-based method to detect contamination *via* regular turbidity measurements [147,148].

2.2.6. Operator involvement

All the various automated systems here still require a certain degree of human involvement. Depending on the equipment considered, the operators might need to perform either initial cell collection and thawing; or the last process steps, such as formulation and cryopreservation (Fig. 1).

For adherent cell culture, particularly of induced pluripotent stem cells, the expansion process is more complex than for suspension cultures, often requiring media exchanges, splitting cells, analyzing cell morphology, picking healthy clones and discarding unhealthy ones. For this reason, the AUTOSTEM, StemCellFactory, CompacT SelecT CellBase, Autoculture, Tissue Factory, and Cell X Precision systems all automate primarily the expansion step, as it is the most complex, long, and labor-intensive of the adherent cell culture process. A few of these technologies additionally automate collection, isolation, washing, reprogramming, differentiation, and genetic modification. Preliminary efforts were also directed towards automating quality control (*e.g.* cell counting and imaging) as this is essential for assessing stem cell morphology and confluence level.

For the systems that primarily are used for culturing suspension cells, like the CliniMACS Prodigy®, Lonza Cocoon® and Mobius Breez bioreactor, the manufacturing steps are relatively standard across cell products. These systems primarily perform isolation of cell apheresis, washing and buffer exchange, genetic engineering (using vector or electroporation), expansion (including reagent addition), and formulation. For cell agnostic systems (*e.g. C*liniMACS Prodigy®), culturing adherent cells as well as suspension cells may require manual coating of the culture chamber as well as microbeads and enzymatic dissociation methods for cell removal. Quality control testing is often done manually in an adjacent facility or cleanroom; and currently, there is minimal automated cell counting or imaging.

Overall, reagent and vector preparation are manual steps, together with sampling for quality control testing. This is mainly due to design constraints requiring open manipulation in a highly controlled environment. However, there are a few automated systems in which these issues started to be addressed by developing closed, pre-made consumables and pre-formulated reagents.

2.2.7. Suitability for centralized and decentralized manufacturing

Automation would have a major impact on the balance of centralized

versus decentralized point-of-care manufacturing of cell therapies. For centralized manufacturing, all production steps occur at a single location separate from the patient's place of care. In the decentralized approach, also known as the point-of-care strategy, products are manufactured by local facilities, allowing for proximity to the patient. The dominant model is centralized plants operating a rigid and structured manual process, with almost no room for modifications [180–183]. Such a process can take anywhere from 3 to 6 weeks for product delivery. In the centralized approach, transporting patients' starting material to and from manufacturing facilities may challenge product sterility, stability and cell viability. The duration of transportation, temperature fluctuations, and potential for mechanical stress further exacerbate concerns about cell quality. Applying proper cryopreservation techniques to prevent microbial contamination and maximize cell yield while allowing for long-term storage is crucial to the overall manufacturing process [184]. Developing robust technologies for the safe and efficient processing, transportation, and cryopreservation of these living therapies is essential. Point-of-care decentralized manufacturing can be performed within hospital settings. Decentralized manufacturing would likely have initial start-up costs, as hospitals or health systems will need to invest in building and maintaining a compliant manufacturing facility. However, besides favoring patients' access to cell therapies, onsite facilities would facilitate transport, limiting the time between production and administration. Currently, most point of care manufacturing uses all-in-one systems. However, modular manufacturing systems might be suitable, as long as their footprint is reasonable. Overall, use of automated systems can help standardize manufacturing and minimize product variation, improving intra- and inter-batch comparability, across different distributed locations. Examples of equipment that claim suitability for this approach include the CliniMACS Prodigy® and other systems in development, such as the Cell Shuttle by Cellares [121].

3. Challenges and prospects of automation

Despite the many advantages provided by implementation of automated systems in cell therapy, as discussed above, there are also a few challenges and open questions [60].

First, automation can reduce process visibility, which is often considered essential from the operator's perspective. This is often referred to as the black-box-issue and novel ways to address it should be pursued, such as software with better monitoring capabilities. This provides the operators with more details on what is happening in the process.

Moreover, although automation reduces risk of error, completely eliminating failures is impossible. While automation decreases operational complexity, it often increases system complexity and risk potential. Failure mode effects analysis (FMEA) can identify potential problems and address them by design improvements. Thus, a key mitigation strategy is performing de-risking comparability studies prior to manufacturing patient/donor-derived material. In addition, during process validation, intentional simulation of failure modes can verify the capability of the automated device to detect the failure, put the process into a stable state until intervention, and recover.

There are also regulatory challenges to the implementation of automation [185,186]. Compliance with Good Manufacturing Practice (GMP) is mandatory for all medicinal products, including cell therapies. GMP standards require trained personnel, proper equipment, written protocols, and traceability of starting materials and finished products. The current regulatory guidelines for ATMP manufacturing, including those released by EMA and FDA, provide only limited discussion on the application of GMP principles to automated systems [187,188]. For instance, the EMA guidance states briefly that automated equipment must be suitable for its intended purpose, adequately qualified, and should not be used outside of the recommendations of its manufacturer. FDA has recently released a guidance on the Advanced Manufacturing Technologies Designation Program (December 2024) [189,190]. Once a technology developer is accepted to this program, the FDA provides early regulatory advice. The criteria for advanced manufacturing technology designation are broad: reducing development time or increasing supply of a drug. There is no detailed discussion of unique regulatory considerations for such technologies. Thus, it is critical that developers take advantage of early, nonbinding regulatory meetings with the FDA to discuss non-clinical studies, manufacturing, and clinical development plans. These meetings provide valuable feedback and allow the FDA to assess new technologies. Importantly, current regulations and guidances were developed with the assumption that human hands are touching most if not all parts of the manufacturing process of cell and gene therapy. As advanced automation technologies become available, these assumptions and relevant guidances will need to be revised. For example, the elaborate classification systems for cleanrooms are based upon the assumption that humans will be present in those spaces, and those humans will generate both viable and non-viable particles that could contaminate a drug product. However, automated and robotic systems present totally different risks when in operation compared to humans. Finally, other regulators outside of Europe and the United States may have their own approach to implementation of automation. Regulators widely considered to be more conservative, such as in Switzerland and Japan, may wield outsized influence on the pace and extent of the adoption of automated manufacturing technologies [191,192]. Given such differences, a globally harmonized approach to regulation of automation technology would be highly beneficial to support rapid development.

Another critical question is the timing of automation implementation during drug development, especially because current commercial systems are not designed for early process development. In early development, manual processing is advantageous to delay costs associated with automation and to maintain a high degree of flexibility in monitoring, controlling, and modifying a process that is not optimized. For example, the CliniMACS Prodigy® is equipped with pre-programed and validated application-specific processes and is only compatible with Miltenyi reagents, so it can be relatively inflexible if extensive process development is required.

During process development, all-in-one systems are more challenging and expensive, due to limited modularity. Therefore, one approach is to defer automation until the process is fully understood and locked. A different strategy is to implement automation only for a few key process steps that significantly impact product quality attributes, where the manual process would present unacceptable variability and/or error rate. Finally, companies could employ step-wise implementation, where unit operations are automated when the corresponding bioprocess step is sufficiently developed. This approach, more easily adapted to a modular automation approach, is associated with lower time-dependent costs and risks, but could result in low end-stage cost efficiency.

To identify the proper automation solution to be implemented, and the best time, a comprehensive approach to determine cost of goods (COGs) is essential. The analysis should consider direct costs including labor, materials, transport of patient/donor starting material, and in-process as well as final product testing. Then, indirect costs should be considered such as quality systems and facility maintenance costs. Additionally, there is amortization of non-recurring investment, including development costs, capital expenditures for facilities, and equipment.

Taking into account the significant time, cost, and validation effort associated with developing a new manufacturing system, it is difficult to justify bringing novel, custom-made automated solutions to the market [58]. Various cell therapy companies are thus using off-the-shelf automation. Indeed, already-available equipment provides ready-to-use solutions and has the benefit of a much broader experience base, often resulting in more refined equipment that has been extensively tested in numerous research and clinical settings. Because what is already available on the market does not fit all the needs of cell therapy

manufacturing, many pharmaceutical companies are partnering with startups and manufacturing companies to design novel systems. For instance, Argos and Invetech have entered into an agreement under which Invetech will develop manufacturing systems to support production needs for fully personalized immunotherapies based on Argos' Arcelis® technology platform, in order to fully automate RNA isolation and amplification from tumor homogenate in a single use format [193]. In addition, Charles River Laboratories partnered with Ori Biotech, Bristol Myers Squibb with Cellares, and Legend with Multiply Labs to collaborate on the development of novel automated platforms, either focusing on all-in-one or modular systems [193–197]. Partnerships can also involve companies developing analytical tools. For instance, Lonza has recently partnered with Agilent Technologies to define critical quality attributes and implement analytical packages into the current Cocoon® system [198]. The above examples demonstrate that collaboration between automation companies and pharmaceutical companies is necessary for progress.

4. Evaluation frameworks

Various evaluation frameworks have been developed to compare novel manufacturing solutions to those already on the market. These evaluation frameworks de-risk implementation of new systems and increase standardization [59,199–203].

In one of these frameworks, researchers attributed specific scores to hardware, consumables, and software features, and pre-clinical or clinical trial data [203]. Hardware should be designed for sterile manipulation and cleanroom compatibility, using materials like stainless steel for cleanability and avoiding difficult-to-reach crevices and sharp corners. It should minimize particle generation by motors, pumps and other repetitive actions. It should also have uninterrupted power supply, backup generators, and validated filtered lines to process gasses (*e.g.* 0.2 μm, nonfiber-releasing filters). Single-use consumables, besides meeting regulatory expectations for particulates/extractables/leachable components, should have a consistent supply chain with additional vendor alternatives to avoid potential shortages. Supply chains should be carefully evaluated in case of proprietary consumables. Software represents another scoring feature for the framework. It must be compliant with 21 Code of Federal Regulations Part 11 for data integrity and security of electronic records and signatures. For visibility and convenience, software should enable user-level access to record process interactions and, if possible, remote monitoring. Finally, for data transfer and back-up, ethernet ports and connectivity to a validated server are a priority, limiting the use of any transfer devices. This feature could represent a challenge for modular systems, as they need to communicate with equipment from a variety of vendors. Finally, ready-to-implement systems should be provided with appropriate supporting documentation for both software and hardware: protocols for installation, operational and performance qualification, cleaning, and preventative maintenance. Availability of pre-clinical and clinical data is a plus. New equipment may score lower due to a limited product history.

Another evaluation framework proposes specific improvements for a few key areas of regenerative cell therapy manufacturing [200]. In order to enable fully end-to-end manufacturing, the authors suggest the use of existing technologies in a modular fashion to accomplish specific steps, utilizing modern robotics to combine them. For non-destructive quality control, they recommend in-line biosensors that are either therapy agnostic but universally used, or sensors that are most useful for a specific product. To enable sterile, patient-specific processes, closed, semi-universal disposable consumables are preferred, coupled with in-line or single-use sensors for microbial contamination detection. A decentralized manufacturing approach is proposed to reduce time from tissue collection to reinfusion, which could be aided by advancements in non-cryogenic storage methods, for example by developing novel stabilization media.

Complementing the above frameworks, the present analysis benefits from a broader perspective that compares the critical features of multi-step systems described in the literature.

5. Conclusions

Systems automating multiple steps of cell therapy manufacturing processes were critically reviewed in this work, comparing their unique features and challenges. Overall, automation should be considered a long-term asset that would provide major savings over years as demand for products increases [42,204]. The rapid pace of new scientific discoveries and treatment modalities requires developers of automated systems to balance between current and future needs [55,205]. There is no guarantee that the robust manual manufacturing strategies developed for the cell therapy industry today will be sufficient for future products.

Currently, detailed evaluation of equipment is difficult, mostly due to limited available data for systems in the pre-commercial stage. To make it feasible and to justify replacement of existing automated devices with others under development, a mindset change is required [58]. Following the open science approach, companies should publish findings regarding the performance of systems under development without compromising intellectual property. Indeed, generating data justifies the value of new technologies to all stake holders: scientists with concerns surrounding the applicability of automation in cell therapy manufacturing, regulators responsible for protecting public health, and investors looking for cost-effective strategies to ensure compliance while maximizing financial returns. For the various automated systems that will come to market in the next few years, it is important to highlight that there is not a unique answer, or solution, that is suitable for all cell therapies. A risk-based approach must be taken, in order to identify which would be most beneficial for the intended use.

CRediT authorship contribution statement

Alice Melocchi: Writing – review & editing, Writing – original draft, Visualization, Supervision, Project administration, Formal analysis, Conceptualization. **Brigitte Schmittlein:** Writing – review & editing, Writing – original draft, Visualization, Investigation, Formal analysis, Conceptualization. **Sudeshna Sadhu:** Writing – review & editing, Writing – original draft, Visualization, Formal analysis, Conceptualization. **Sunaina Nayak:** Visualization, Formal analysis. **Angela Lares:** Writing – review & editing, Conceptualization. **Marco Uboldi:** Writing – original draft. **Lucia Zema:** Writing – review & editing. **Benedetta Nicolis di Robilant:** Writing – review & editing, Conceptualization. **Steven A. Feldman:** Writing – review & editing, Conceptualization. **Jonathan H. Esensten:** Writing – review & editing, Conceptualization.

Declaration of competing interest

- Brigitte Schmittlein, Sudeshna Sadhu, Sunaina Nayak and Angela Lares wish to disclose that they are current employees of Multiply Labs, Inc. or were employed with the company at the time of this review drafting. They hold equity in the company;
- Alice Melocchi wish to disclose that she is one of the co-founders of Multiply Labs, Inc. and hold the position of Chief Scientific Officer;
- Benedetta Nicolis di Ribilant is a paid advisor to Multiply Labs, Inc. and holds equity in the company;
- Steven Feldman leads the Laboratory for Cell and Gene Therapy Manufacturing (LCGM) at Stanford University. The LCGM entered a collaboration agreement with Multiply Labs, Inc. for studying the performance of cell therapy manufacturing robots produced by the company, by comparing them with manual processes. In this collaboration, Multiply Labs provides access to the robotic systems and covers the cost of materials to run the experiments;
- Jonathan H. Esensten is a paid advisor to and receives sponsored research funding from Multiply Labs, Inc. He serves on its scientific

advisory board and holds equity in the company. He is paid advisor to Limula, serves on the scientific advisory board, and holds equity in the company. He also receives sponsored research funding from Lonza, Inc. for the development of cellular therapy manufacturing devices.

Data availability

No data was used for the research described in the article.

References

[1] G.C. Wilkins, K. Lanyi, A. Inskip, O.J. Ogunbayo, P. Brhlikova, D. Craig, A pipeline analysis of advanced therapy medicinal products, Drug Discov. Today 28 (2023) 103549, https://doi.org/10.1016/j.drudis.2023.103549.

[2] A. Goula, V. Gkioka, E. Michalopoulos, M. Katsimpoulas, M. Noutsias, E.F. Sarri, C. Stavropoulos, A. Kostakis, Advanced therapy medicinal products challenges and perspectives in regenerative medicine, J. Clin. Med. Res. 12 (2020) 780–786, https://doi.org/10.14740/jocmr3964.

[3] E. Hanna, C. Rémuzat, P. Auquier, M. Toumi, Advanced therapy medicinal products: current and future perspectives, J. Mark. Access Health Policy 4 (2016) 31036, https://doi.org/10.3402/jmahp.v4.31036.

[4] A. Horan, S. Warreth, T. Hervig, A. Waters, The expanding role of blood and tissue establishments in the development of advanced therapy medicinal products, Cytotherapy 26 (2024) 524–530, https://doi.org/10.1016/j.jcyt.2024.02.012.

[5] D.B. Mello, F.C.P. Mesquita, D. Silva dos Santos, K.D. Asensi, M.L. Dias, A. C. Campos de Carvalho, R.C.S. dos Goldenberg, T.H. Kasai-Brunswick, Mesenchymal stromal cell-based products: challenges and clinical therapeutic options, Int. J. Mol. Sci. 25 (2024) 6063, https://doi.org/10.3390/ijms25116063.

[6] S. Zia, V. Pizzuti, F. Paris, F. Alviano, L. Bonsi, A. Zattoni, P. Reschiglian, B. Roda, V. Marassi, Emerging technologies for quality control of cell-based, advanced therapy medicinal products, J. Pharm. Biomed. Anal. 246 (2024) 116182, https://doi.org/10.1016/j.jpba.2024.116182.

[7] J. Sakowska, L. Arcimowicz, M. Jankowiak, I. Papak, A. Markiewicz, K. Dziubek, M. Kurkowiak, S. Kote, K. Kaźmierczak-Siedlecka, K. Połom, N. Marek-Trzonkowska, P. Trzonkowski, Autoimmunity and cancer - two sides of the same coin, Front. Immunol. 13 (2022) 793234, https://doi.org/10.3389/fimmu.

[8] Y. Zhang, Z. Zhang, The history and advances in cancer immunotherapy: understanding the characteristics of tumor-infiltrating immune cells and their therapeutic implications, Cell. Mol. Immunol. 17 (2020) 807–821, https://doi.org/10.1038/s41423-020-0488-6.

[9] Y.-R. Li, Z. Lyu, Y. Chen, Y. Fang, L. Yang, Frontiers in CAR-T cell therapy for autoimmune diseases, Trends Pharmacol. Sci. 45 (2024) 839–857, https://doi.org/10.1016/j.tips.2024.07.005.

[10] J. Vukovic, D. Abazovic, D. Vucetic, S. Medenica, CAR-engineered T cell therapy as an emerging strategy for treating autoimmune diseases, Front. Med. 11 (2024) 1447147, https://doi.org/10.3389/fmed.2024.1447147.

[11] S. Guedan, M. Ruella, C.H. June, Emerging cellular therapies for cancer, Annu. Rev. Immunol. 37 (2019) 145–171, https://doi.org/10.1146/annurev-immunol-042718-041407.

[12] F. Dazzi, J.M. van Laar, A. Cope, A. Tundall, Cell therapy for autoimmune diseases, Arthritis Res. Ther. 9 (2007) 206, https://doi.org/10.1186/ar2128.

[13] A. Golchin, T.Z. Farahany, Biological products: cellular therapy and FDA approved products, Stem Cell Rev. Rep. 15 (2019) 166–175, https://doi.org/10.1007/s12015-018-9866-1.

[14] https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products last access on December 15, 2024.

[15] S. Bellino, A. La Salvia, M.F. Cometa, R. Botta, Cell-based medicinal products approved in the European Union: current evidence and perspectives, Front. Pharmacol. 14 (2023) 1200808, https://doi.org/10.3389/fphar.2023.1200808.

[16] J. Freed, J. Talano, T. Small, A. Ricci, M.S. Cairo, Allogeneic cellular and autologous stem cell therapy for sickle cell disease: whom, when and how, Bone Marrow Transplant. 47 (2012) 1489–1498, https://doi.org/10.1038/bmt.2011.245.

[17] V. Karantalis, I.H. Schulman, W. Balkan, J.M. Hare, Allogeneic cell therapy: a new paradigm in therapeutics, Circ. Res. 116 (2015) 12–15, https://doi.org/10.1161/CIRCRESAHA.114.305495.

[18] H. Kawamoto, K. Masuda, Trends in cell medicine: from autologous cells to allogeneic universal-use cells for adoptive T-cell therapies, Int. Immunol. 36 (2024) 65–73, https://doi.org/10.1093/intimm/dxad051.

[19] N.N. Malik, M.B. Durdy, Chapter 7 - Cell therapy landscape: autologous and allogeneic approaches, in: A. Atala, J.G. Allickson (Eds.), Translational Regenerative Medicine, Academic Press, 2015, pp. 87–106.

[20] M. Abou-El-Enein, G. Bauer, N. Medcalf, H.-D. Volk, P. Reinke, Putting a price tag on novel autologous cellular therapies, Cytotherapy 18 (2024) 1056–1061, https://doi.org/10.1016/j.jcyt.2016.05.005.

[21] B. Kazmi, C.J. Inglefield, M.P. Lewis, Autologous cell therapy: current treatments and future prospects, Wounds 21 (2009) 234–242.

[22] I. Bisson, E. Green, M. Sharpe, C. Herbert, J. Hyllner, N. Mount, Landscape of current and emerging cell therapy clinical trials in the UK: current status, comparison to global trends and future perspectives, Regen. Med. 10 (2015) 169–179, https://doi.org/10.2217/rme.14.71.

[23] M.D. Li, H. Atkins, T. Bubela, The global landscape of stem cell clinical trials, Regen. Med. 9 (2014) 27–39, https://doi.org/10.2217/rme.13.80.

[24] L. Wang, G. Liu, L. Zheng, H. Long, Y. Liu, A new era of gene and cell therapy for cancer: a narrative review, Ann. Transl. Med. 11 (2023) 321, https://doi.org/10.21037/atm-22-3882.

[25] V. Wang, M. Gauthier, V. Decot, L. Reppel, D. Bensoussan, Systematic review on CAR-T cell clinical trials up to 2022: academic center input, Cancers 15 (2023) 1003, https://doi.org/10.3390/cancers15041003.

[26] A.R. Saez-Ibañez, S. Upadhaya, T. Partridge, D. Winkelman, D. Correa, J. Campbell, The changing landscape of cancer cell therapies: clinical trials and real-world data, Nat. Rev. Drug Discov. 4 23 (2024) 736–737, https://doi.org/10.1038/d41573-024-00094-4.

[27] S. Sengsayadeth, B.N. Savani, O. Oluwole, B. Dholaria, Overview of approved CAR-T therapies, ongoing clinical trials, and its impact on clinical practice, Br. Soc. Haematol. 3 (2022) 6–10, https://doi.org/10.1002/jha2.338.

[28] J. Dias, J. Garcia, G. Agliardi, C. Roddie, CAR-T cell manufacturing landscape - lessons from the past decade and considerations for early clinical development, Mol. Therapy Methods Clin. Developm. 32 (2024) 101250, https://doi.org/10.1016/j.omtm.2024.101250.

[29] S. Fiorenza, D.S. Ritchie, S.D. Ramsey, C.J. Turtle, J.A. Roth, Value and affordability of CAR T-cell therapy in the United States, Bone Marrow Transplant. 55 (2020) 1706–1715, https://doi.org/10.1038/s41409-020-0956-8.

[30] A.E. Hay, M.C. Cheung, CAR T-cells: costs, comparisons, and commentary, J. Med. Econ. 22 (2019) 613–615, https://doi.org/10.1080/13696998.2019.1582059.

[31] F. Xie, Highly priced gene therapies: a wake-up call for early price regulation, PharmacoEconomics 36 (2018) 883–888, https://doi.org/10.1007/s40273-018-0664-z.

[32] G. Choi, G. Shin, S. Bae, Price and prejudice? The value of chimeric antigen receptor (CAR) T-cell therapy, Int. J. Environ. Res. Public Health 19 (2022) 12366, https://doi.org/10.3390/ijerph191912366.

[33] M. Abou-el-Enein, J. Gauthier, The value of CAR-T-cell immunotherapy in cancer, in: N. Kröger, J. Gribben, C. Chabannon, I. Yakoub-Agha, H. Einsele (Eds.), The EBMT/EHA CAR-T Cell Handbook, Springer, Cham, 2022, https://doi.org/10.1007/978-3-030-94353-0_46.

[34] R. Borgert, Improving outcomes and mitigating costs associated with car t-cell therapy, Am. J. Manag. Care 27 (2021) S253–S261, https://doi.org/10.37765/ajmc.2021.88737.

[35] A.E. Hay, M.C. Cheung, CAR T-cells: costs, comparisons, and commentary, J. Med. Econ. 22 (2019) 613–615, https://doi.org/10.1080/13696998.2019.1582059.

[36] J.K. Lin, L.S. Muffly, M.A. Spinner, J.I. Barnes, D.K. Owens, J.D. Goldhaber-Fiebert, Cost effectiveness of chimeric antigen receptor T-cell therapy in multiply relapsed or refractory adult large B-cell lymphoma, J. Clin. Oncol. 37 (2019) 2105–2119, https://doi.org/10.1200/JCO.

[37] I. Johanna, A. Daudeij, F. Devina, C. Nijenhuis, B. Nuijen, B. Romberg, C. de Haar, J. Haanen, H. Dolstra, E. Bremer, Z. Sebestyen, T. Straetemans, I. Jedema, J. Kuball, Basics of advanced therapy medicinal product development in academic pharma and the role of a GMP simulation unit, Immuno Oncol. Technol. 20 (2023) 100411, https://doi.org/10.1016/j.iotech.2023.100411.

[38] Ten Ham, R.M.T., Hövels, A.M., Hoekman, J., Frederix, G.W.J., Leufkens, H.G.M., Klungel, O.H., Jedema, I., Veld, S.A.J., Nikolic T., Van Pel, M., Zwaginga, J.J., Lin, F., de Goede, A.L., Schreibelt, G., Budde, S., de Vries, I.J.M., Wilkie, G.M., Dolstra, H., Ovelgönne, H., Mei, J P., Mountford, J.C., Turner, M.L., Hoefnagel, M.H.N. What does cell therapy manufacturing cost? A framework and methodology to facilitate academic and other small-scale cell therapy manufacturing costings. Cytotherapy, 22, 388–397. doi:https://doi.org/10.1016/j.jcyt.2020.03.432.

[39] E.R. Scheffer Cliff, A.H. Kelkar, D.A. Russler-Germain, F.A. Tessema, A.J. N. Raymakers, W.B. Feldman, A.S. Kesselheim, High cost of chimeric antigen receptor t-cells: challenges and solutions, Am. Soc. Clin. Oncol. Educ. Book 43 (2023) e397912, https://doi.org/10.1200/EDBK_397912.

[40] A. Campbell, T. Brieva, L. Raviv, J. Rowley, K. Niss, H. Brandwein, S. Oh, O. Karnieli, Concise review: process development considerations for cell therapy, Stem Cells Transl. Med. 4 (2015) 1155–1163, https://doi.org/10.5966/sctm.2014-0294.

[41] N.K. Lee, J.W. Chang, Manufacturing cell and gene therapies: challenges in clinical translation, Ann. Lab. Med. 44 (2024) 314–323, https://doi.org/10.3343/alm.2023.0382.

[42] M. Ayala Ceja, M. Khericha, C.M. Harris, C. Puig-Saus, Y.Y. Chen, CAR-T cell manufacturing: major process parameters and next-generation strategies, J. Exp. Med. 221 (2024) e20230903, https://doi.org/10.1084/jem.20230903.

[43] E. Abraham, N. Trainor, N. Ostrout, M.M. Hewitt, Cell therapy products are revolutionizing multiple therapeutic areas; to maintain this pace of innovation, manufacturing solutions must adapt, Curr. Opin. Biomed. Eng. 20 (2021) 100340, https://doi.org/10.1016/j.cobme.2021.100340.

[44] J. Tomtishen, The role of automation in meeting the growing demand for CAR T-cell therapies, Am. J. Manag. Care 29 (2023) SP427–SP428, https://doi.org/10.37765/ajmc.2023.89391.

[45] M. Mizuno, Y. Sugahara, D. Iwayama, N. Miyashita, H. Katano, I. Sekiya, Stress and motivation of cell processing operators: A pilot study of an online

questionnaire survey, Regenerat. Therapy 21 (2022) 547–552, https://doi.org/10.1016/j.reth.2022.10.004.
[46] A. Aijaz, M. Li, D. Smith, D. Khong, C. LeBlon, O.S. Fenton, R.M. Olabisi, S. Libutti, J. Tischfield, M.V. Maus, R. Deans, R.N. Barcia, D.G. Anderson, J. Ritz, R. Preti, B. Parekkadan, Biomanufacturing for clinically advanced cell therapies, Nat. Biomed. Eng. (2018) 362–376, https://doi.org/10.1038/s41551-018-0246-6.
[47] S. Abbasalizadeh, H. Baharvand, Technological progress and challenges towards cGMP manufacturing of human pluripotent stem cells based therapeutic products for allogeneic and autologous cell therapies, Biotechnol. Adv. 31 (2013) 1600–1623, https://doi.org/10.1016/j.biotechadv.2013.08.009.
[48] https://bioprocessintl.com/manufacturing/facility-design-engineering/facilities-for-novel-therapies-demystifying-design-and-engineering-requirements-for-gene-therapy-and-car-t-processing-facilities/ last access on December 15, 2024.
[49] S. Eaker, M. Armant, H. Brandwein, S. Burger, A. Campbell, C. Carpenito, D. Clarke, T. Fong, O. Karnieli, K. Niss, W. Van't Hof, R. Wagey, Concise review: guidance in developing commercializable autologous/patient-specific cell therapy manufacturing, Stem Cells Transl. Med. 2 (2013) 871–883, https://doi.org/10.5966/sctm.2013-0050.
[50] D.C. Kirouac, P.W. Zandstra, The systematic production of cells for cell therapies, Cell Stem Cell 3 (2008) 369–381, https://doi.org/10.1016/j.stem.2008.09.001.
[51] E.M. Iancu, L.E. Kandalaft, Challenges and advantages of cell therapy manufacturing under good manufacturing practices within the hospital setting, Curr. Opin. Biotechnol. 65 (2020) 233–241, https://doi.org/10.1016/j.copbio.2020.05.005.
[52] Y.Y. Lipsitz, N.E. Timmins, P.W. Zandstra, Quality cell therapy manufacturing by design, Nat. Biotechnol. 34 (2016) 393–400, https://doi.org/10.1038/nbt.3525.
[53] F. Lopez, C. Di Bartolo, T. Piazza, A. Passannanti, J.C. Gerlach, B. Gridelli, F. Triolo, A quality risk management model approach for cell therapy manufacturing, Risk Anal. 30 (2010) 1857–1871, https://doi.org/10.1111/j.1539-6924.2010.01465.x.
[54] N.M. Mount, S.J. Ward, P. Kefalas, J. Hyllner, Cell-based therapy technology classifications and translational challenges, Philos. Trans. R. Soc. Lond. 370 (2015) 20150017, https://doi.org/10.1098/rstb.2015.0017.
[55] M.E. Kempner, R.A. Felder, A review of cell culture automation, JALA J. Assoc. Lab. Autom. 7 (2002), https://doi.org/10.1016/S1535-5535(04)00183-2.
[56] A. Ramamurthy, A. Tommasi, K. Saha, Advances in manufacturing chimeric antigen receptor immune cell therapies, Semin. Immunopathol. 46 (2024), https://doi.org/10.1007/s00281-024-01019-4.
[57] D.A. Brindley, I.B. Wall, K.E. Bure, Automation of cell therapy biomanufacturing minimizing regulatory risks and maximizing return on investments, BioProcess Internat. 11 (2013) S42–S49.
[58] M.N. Doulgkeroglou, A. Di Nubila, B. Niessing, N. König, R.H. Schmitt, J. Damen, S.J. Szilvassy, W. Chang, L. Csontos, S. Louis, P. Kugelmeier, V. Ronfard, Y. Bayon, D.I. Zeugolis, Automation, monitoring, and standardization of cell product manufacturing, Front. Bioeng. Biotechnol. 8 (2020) 811, https://doi.org/10.3389/fbioe.2020.00811.
[59] P. Moutsatsou, J. Ochs, R.H. Schmitt, C.J. Hewitt, M.P. Hanga, Automation in cell and gene therapy manufacturing: from past to future, Biotechnol. Lett. 41 (2019) 1245–1253, https://doi.org/10.1007/s10529-019-02732-z.
[60] D. Smith, T.R.J. Heathman, A. Klarer, C. LeBlon, Y. Tada, B. Hampson, Towards automated manufacturing for cell therapies, Curr. Hematol. Malig. Rep. 14 (2019) 278–285, https://doi.org/10.1007/s11899-019-00522-y.
[61] S.C. Nath, L. Menendez, I. Friedrich Ben-Nun, Overcoming the variability of iPSCs in the manufacturing of cell-based therapies, Int. J. Mol. Sci. 24 (2023) 16929, https://doi.org/10.3390/ijms242316929.
[62] A.D. Kaiser, M. Assenmacher, B. Schröder, M. Meyer, R. Orentas, U. Bethke, B. Dropulic, Towards a commercial process for the manufacture of genetically modified T cells for therapy, Cancer Gene Ther. 22 (2015) 72–78, https://doi.org/10.1038/cgt.2014.78.
[63] S. Eaker, E. Abraham, J. Allickson, T.A. Brieva, D. Baksh, T.R.J. Heathman, B. Mistry, N. Zhang, Bioreactors for cell therapies: current status and future advances, Cytotherapy 19 (2017) 9–18, https://doi.org/10.1016/j.jcyt.2016.09.011.
[64] I. Ganeeva, E. Zmievskaya, A. Valiullina, A. Kudriaeva, R. Miftakhova, A. Rybalov, E. Bulatov, Recent advances in the development of bioreactors for manufacturing of adoptive cell immunotherapies, Bioengineering 9 (2022) 808, https://doi.org/10.3390/bioengineering9120808.
[65] M. Stephenson, W. Grayson, Recent advances in bioreactors for cell-based therapies, F1000Research 7 (2018) 517, https://doi.org/10.12688/f1000research.12533.1.
[66] Y.Y. Wu, D. Yong, M.W. Naing, Automated cell expansion: trends & outlook of critical technologies, Cell Gene Therapy Insights 4 (2018) 851–871, https://doi.org/10.18609/cgti.2018.086.
[67] N. Frank, M. Miller, D. Sethi, An optimized HEK293T cell expansion protocol using a hollow-fiber bioreactor system, Cytotherapy 8 (2023) bpad018, https://doi.org/10.1093/biomethods/bpad018.
[68] E. GiGotti, S. Tettamanti, S. Zaninelli, C. Cuofano, I. Cattaneo, M.C. Rotiroti, S. Cribioli, R. Alzani, A. Rambaldi, M. Introna, J. Golay, Optimization of therapeutic T cell expansion in G-rex device and applicability to large-scale production for clinical use: GMP-compliant polyclonal T cell expansion in G-rex, Cytotherapy 24 (2022) 334–343, https://doi.org/10.1016/j.jcyt.2021.11.004.
[69] K.T. Lim, D.K. Patel, H. Seonwoo, J. Kim, J.H. Chung, A fully automated bioreactor system for precise control of stem cell proliferation and differentiation, Biochem. Eng. J. 150 (2019) 107258, https://doi.org/10.1016/j.bej.2019.107258.
[70] U. Uslu, M. Erdmann, M. Wiesinger, G. Schuler, B. Schuler-Thurner, Automated good manufacturing practice–compliant generation of human monocyte-derived dendritic cells from a complete apheresis product using a hollow-fiber bioreactor system overcomes a major hurdle in the manufacture of dendritic cells for cancer vaccines, Cytotherapy 21 (2019) 1166–1178, https://doi.org/10.1016/j.jcyt.2019.09.001.
[71] M. Rotondi, N. Grace, J. Betts, N. Bargh, E. Costariol, B. Zoro, C.J. Hewitt, A. W. Nienow, Q.A. Rafiq, Design and development of a new ambr250® bioreactor vessel for improved cell and gene therapy applications, Biotechnol. Lett. 43 (2021) 1103–1106, https://doi.org/10.1007/s10529-021-03076-3.
[72] N. Frank, M. Miller, D. Sethi, An optimized HEK293T cell expansion protocol using a hollow-fiber bioreactor system, Cytotherapy 8 (2023) bpad018, https://doi.org/10.1093/biomethods/bpad018.
[73] S.E. Tannenbaum, B.E. Reubinoff, Advances in hPSC expansion towards therapeutic entities: a review, Cell Prolif. 55 (2022) e13247, https://doi.org/10.1111/cpr.13247.
[74] C. Jimenez Boudousquié, C. Navarro, Y. Pierson, L. Henry, "One pot'" production of chimeric antigen receptor t cells in a novel bioreactor design, Cytotherapy 26 (2024) S130.
[75] A. Li, G.D. Kusuma, D. Driscoll, N. Smith, D.M. Wall, B.L. Levine, D. James, R. Lim, Advances in automated cell washing and concentration, Cytotherapy 23 (2021) 774–786, https://doi.org/10.1016/j.jcyt.2021.04.003.
[76] F.C. Bombaldi De Souza, E.D. Mariano, D. Navarro Da Rocha, K. Menezes, T. C. Lopes De Castro, R.V. Capelletti, Y. Magalh Aes Berto, F.G. Duarte, W. Jeveaux, R.D. Fanganiello, J.M. Ferreira, "One pot" production of chimeric antigen receptor t cells in a novel bioreactor design, Cytotherapy 26 (2024) S130, https://doi.org/10.1016/j.jcyt.2024.03.247.
[77] A.G. Lopes, R. Noel, A. Sinclair, Cost analysis of vein-to-vein CAR T-cell therapy: automated manufacturing and supply chain, Cell Gene Therapy Insights 6 (2020) 487–510, https://doi.org/10.18609/cgti.2020.058.
[78] A. Li, D. James, R. Lim, The Gibco™ CTS™ Rotea™ system story - A case study of industry-academia collaboration, Gene Ther. 30 (3–4) (2023) 192–196, https://doi.org/10.1038/s41434-021-00266-6.
[79] A. Li, G.D. Kusuma, D. Driscoll, N. Smith, D.M. Wall, B.L. Levine, D. James, R. Lim, Advances in automated cell washing and concentration, Cytotherapy 23 (2021) 774–778, https://doi.org/10.1016/j.jcyt.2021.04.003.
[80] F. Zinno, F. Landi, M.C. Scerpa, V. Aureli, A. Lanti, S. Ceccarelli, M. Caniglia, M. J. Miele, N. Daniele, A. Landolfo, A.M. Cometa, F. Locatelli, G. Isacchi, Processing of hematopoietic stem cells from peripheral blood before cryopreservation: use of a closed automated system, Transfusion 51 (2011) 2656–2663, https://doi.org/10.1111/j.1537-2995.2011.03180.x.
[81] H.W. Song, R.P. Somerville, D.F. Stroncek, S.L. Highfill, Scaling up and scaling out: advances and challenges in manufacturing engineered T cell therapies, Int. Rev. Immunol. 41 (6) (2022) 638–648, https://doi.org/10.1080/08830185.2022.2067154.
[82] A. Bosio, V. Huppert, S. Donath, P. Hennemann, M. Malchow, U.A.O. Heinlein, Isolation and enrichment of stem cells, in: U. Martin (Ed.), Engineering of Stem Cells. Advances in Biochemical Engineering / Biotechnology 114, Springer, Berlin, Heidelberg, 2009, https://doi.org/10.1007/10_2008_38.
[83] D. Sethi, A. Cunningham, De-risking the final formulation, fill and finish step in cell therapy manufacturing: considerations for an automated solution, Cell Gene Therapy Insights 6 (2020) 1513–1519, https://doi.org/10.18609/cgti.2020.165.
[84] M. Park, M. Safford, J. Scheers, L. Hammill, D. Pleitez, T. Jerbi, E.M. Koudji, S. Yelity, S. Campion, M.M. Miller, S.L. Gibb, A. Sargent, Automation preserves product consistency and quality for the formulation, fill, and finish of T cell-based therapies, Cytotherapy (2024) 1566–1570, https://doi.org/10.1016/j.jcyt.2024.07.006.
[85] O. Ball, S. Robinson, K. Bure, D.A. Brindley, D. Mccall, Bioprocessing automation in cell therapy manufacturing: outcomes of special interest group automation workshop, Cytotherapy 20 (2018) 592–599, https://doi.org/10.1016/j.jcyt.2018.01.005.
[86] S. Chang, B. Greenwald, K. Roy, The digital revolution: technological innovations to enable automation in cell therapy manufacturing, Cell Gene Therapy Insights 8 (2022) 355–369, https://doi.org/10.18609/cgti.2022.053.
[87] N.D. Frank, K. Villa, M. Jones, S. Mendoza, M. Miller, T. Acker, T. Smith, N. Schwab, D. Lee, D. Sethi, Comparative analysis of t cell expansion by bioreactor type: impacts on process metrics and cell quality, Cytotherapy 26 (2024) S167, https://doi.org/10.1016/j.jcyt.2024.03.326.
[88] C. Hutchins, A. Henderson, A. Heden, E. Barnes, M. Abaca-Cleopas, M. Acworth, B. McEnroe, K. Mudie, B. Dropulic, D. Schneider, G. Kennedy, S. Tey, Place-of-care manufacturing of car19-t cells using an automated closed-system device, Cytotherapy 23 (2024) S195, https://doi.org/10.1016/S1465324921006125.
[89] B. Coisman, K. Goldner, B. McCuaig, M. Zhang, T. Bai, J. Jamieson, C. Lucini, L. Ye, N. Goff, J. Kim, K. Qiao, J. Olins, J. Decker, A. Shay, G. Kaur, A. Talukdar, P. Kopesky, Advancements in closed and automated CD34+ hematopoietic stem and progenitor cell manufacturing utilizing the miltenyi clinimacs prodigy system: enabling cost-effective next-generation therapies, Cytotherapy 26 (2024) S132, https://doi.org/10.1016/j.jcyt.2024.03.251.
[90] V. Sadetckaia, S. Davoudi, K. Po, A. Balgi, N. Orr, P. Harvie, P. Marcus, N. Patel, High throughput screening of lipid nanoparticles for enhanced drug delivery to immune cells, Cytotherapy 26 (2024) S144, https://doi.org/10.1016/j.jcyt.2024.03.281.
[91] X. de Mollerat du Jeu, M. Ahmadi, D. Hayoun, M. Dotson, Y. Ji, J. Padilla, N. Putnam, An automated 24-hour car T manufacturing process, Cytotherapy 26 (2024) S163, https://doi.org/10.1016/j.jcyt.2024.03.318.

[92] K. Drechsel, D. Mauer, N. Mockel-Tenbrinck, C. Lehmann, H. Bohnenkamp, V. Huppert, M. Assenmacher, I. Johnston, A. Kaiser, Towards automated manufacturing of clinical scale gene-modified T cells, J. Immunother. Cancer 2 (2014) P21, https://doi.org/10.1186/2051-1426-2-s3-p21.

[93] R.C. Farino, R. Jamal, M. Ryan, N. McKenzie, C. Mizzoni, S. Deshpande, Y. Liu, A. Maystrenko, D. Arab, M. Maggioni, P. Zotos, F. Zanoni, F. Parvizi, M. de Lageneste, F. Franchi, End-to-end automated manufacturing of autologous CAR T cell therapies with the new SEFIA™ cell therapy manufacturing platform, Cytotherapy 26 (2024) S166–S167, https://doi.org/10.1016/j.jcyt.2024.03.325.

[94] S. Gibb, M. Miller, Manufacturing of low-seed CAR-T cells on a GMP-grade hollow-fiber bioreactor platform, Cytotherapy 26 (6) (2024) E24, https://doi.org/10.1016/j.jcyt.2024.04.049.

[95] K. Godthardt, T. Kuchler, S. Knobel, Standardized GMP compliant expansion of human pluripotent stem cells using a closed cultivation system, Cytotherapy 26 (2024) S225, https://doi.org/10.1016/j.jcyt.2024.03.458.

[96] L. Herbst, Q.A. Rafiq, S. Goldrick, I. Papantoniou, R. Schmitt, F. Erkens, S. Hort, B. NeiBing, G. Popp, P. Franz, N. Koenig, M. Hudecek, Fully automated CAR-T cell manufacturing system enables process insight and control, Cytotherapy 25 (2023) S8–S9, https://doi.org/10.1016/S1465-3249(23)00138-X.

[97] L. Herbst, A. Felser, F. Groten, G. Shaw, M. Murphy, B. NieBing, R. Schmitt, Fully-automated cultivation of iPSCs and differentiation to iMSCs using the autocrat system, Cytotherapy 26 (2024) S48, https://doi.org/10.1016/j.jcyt.2024.03.082.

[98] R. Jamal, D. Prieto Uzcategui, N. McKenzie, S. Carmichael, M. Parvizi, Functionally closed and semi-automated natural killer cell workflow for GMP-compliant manufacturing, Cytotherapy 25 (2023) S172–S173.

[99] J. Ling, N. McMahon, K. Zimmern, J. Jung, M.C. Herzig, R. Zamilpa, T. D'souza, B. Christy, A 3D printed bioreactor enables automated and scalable manufacturing of mesenchymal stem cells (MSCs) and MSC-derived exosomes, Cytotherapy 26 (2024) e3–e4, https://doi.org/10.1016/j.jcyt.2024.04.015.

[100] B. Mccuaig, K. Goldner, B. Coisman, J. Jamieson, M. Zhang, T. Bai, N. Goff, C. Lucini, J. Kim, K. Qiao, L. Ye, J. Decker, J. Olins, A. Shay, G. Kaur, A. Talukdar, P. Kopesky, Scaling manufacturing of cd34+ hematopoietic stem and progenitor cells (hspcs) with an automated and integrated cell isolation system, Cytotherapy 26 (2024) S138, https://doi.org/10.1016/j.jcyt.2024.03.265.

[101] N. Menasria, S. Quenneville, N. Delalleau, A. Quenon, P. Petit, G. Pasquetti, M. Chetboun, T. Hubert, V. Gmyr, M.C. Vantyghem, F.N. Pattou, J. Kerr-Conte, SEPAX-SEFIA a repurposed closed system for human islet purification and processing in cGMP environment, Transplantation 65 (2023), https://doi.org/10.1097/01.tp.0000994100.40609.d5.

[102] E. Rodriguez-Mesa, A. Sherborne, R. Barhouma, L. Prevedello, J. Lam, K. Patel, Isolation, enrichment, and expansion of naïve Tregs in a closed system, using the Clinimacs Prodigy and Macsquant Tyto cell sorter, Cytotherapy 26 (2024) e26, https://doi.org/10.1016/j.jcyt.2024.04.054.

[103] L. Yu, Automation of rapid CAR-T cell manufacturing on a single platform, Cytotherapy 26 (2024) S147–S149, https://doi.org/10.1016/j.jcyt.2024.03.290.

[104] D. Kami, K. Watakabe, M. Yamazaki-Inoue, K. Minami, T. Kitani, Y. Itakura, M. Toyoda, T. Sakurai, A. Umezawa, S. Gojo, Large-scale cell production of stem cells for clinical application using the automated cell processing machine, BMC Biotechnol. 13 (2013) 102, https://doi.org/10.1186/1472-6750-13-102.

[105] J.E. Adair, T. Waters, K.G. Haworth, S.P. Kubek, G.D. Trobridge, J.D. Hocum, S. Heimfeld, H.P. Kiem, Semi-automated closed system manufacturing of lentivirus gene-modified haematopoietic stem cells for gene therapy, Nat. Commun. 7 (2016) 13173, https://doi.org/10.1038/ncomms13173.

[106] U. Mock, L. Nickolay, B. Philip, G.W.K. Cheung, H. Zhan, I.C.D. Johnston, A. D. Kaiser, K. Peggs, M. Pule, A.J. Thrasher, W. Qasim, Automated manufacturing of chimeric antigen receptor T cells for adoptive immunotherapy using CliniMACS prodigy, Cytotherapy 18 (2016) 1002–1011, https://doi.org/10.1016/j.jcyt.2016.05.009.

[107] C. Priesner, K. Aleksandrova, R. Esser, N. Mockel-Tenbrinck, J. Leise, K. Drechsel, M. Marburger, A. Quaiser, L. Goudeva, L. Arseniev, A.D. Kaiser, W. Glienke, U. Koehl, Automated enrichment, transduction, and expansion of clinical-scale CD62L+ T cells for manufacturing of gene therapy medicinal products, Hum. Gene Ther. 27 (2016) 860–869, https://doi.org/10.1089/hum.2016.091.

[108] D. Lock, N. Mockel-Tenbrinck, K. Drechsel, C. Barth, D. Mauer, T. Schaser, C. Kolbe, W. Al Rawashdeh, J. Brauner, O. Hardt, N. Pflug, U. Holtick, P. Borchmann, M. Assenmacher, A. Kaiser, Automated manufacturing of potent CD20-directed chimeric antigen receptor T cells for clinical use, Hum. Gene Ther. 28 (2017) 914–925, https://doi.org/10.1089/hum.2017.111.

[109] L. Fernández, A. Fernández, I. Mirones, A. Escudero, L. Cardoso, M. Vela, D. Lanzarot, R. de Paz, A. Leivas, M. Gallardo, A. Marcos, A.B. Romero, J. Martínez-López, A. Pérez-Martínez, GMP-compliant manufacturing of NKG2D CAR memory T cells using CliniMACS prodigy, Front. Immunol. 10 (2019) 2361, https://doi.org/10.3389/fimmu.2019.02361.

[110] J.M. Marín Morales, N. Münch, K. Peter, D. Freund, U. Oelschlägel, K. Hölig, T. Böhm, A.C. Flach, J. Keßler, E. Bonifacio, M. Bornhäuser, A. Fuchs, Automated clinical grade expansion of regulatory T cells in a fully closed system, Front. Immunol. 10 (2019) 38, https://doi.org/10.3389/fimmu.2019.00038.

[111] O. Molostova, L. Shelikhova, D. Schneider, R. Khismatullina, Y. Muzalevsky, A. Kazachenok, L. Preussner, G. Rauser, J. Abugova, E. Kurnikova, D. Pershin, V. Zubachenko, A. Popov, O. Illarionova, N. Miakova, D. Litvinov, G. Novichkova, A.A. Maschan, R. Orentas, B. Dropulic, M. Maschan, Local manufacture of CD19 CAR-T cells using an automated closed-system: robust manufacturing and high clinical efficacy with low toxicities, Blood 134 (2019) 2625, https://doi.org/10.1182/blood-2019-130370.

[112] O. Oberschmidt, M. Morgan, V. Huppert, J. Kessler, T. Gardlowski, N. Matthies, K. Aleksandrova, L. Arseniev, A. Schambach, U. Koehl, S. Kloess, Development of automated separation, expansion, and quality control protocols cells and alpharetroviral chimeric antigen receptor engineering, Human Gene Therapy Methods 30 (2019) 102–120, https://doi.org/10.1089/hgtb.2019.039.

[113] M. Castella, M. Caballero-Baños, V. Ortiz-Maldonado, E.A. González-Navarro, G. Suñé, A. Antoñana-Vidósola, A. Boronat, B. Marzal, L. Millán, B. Martín-Antonio, J. Cid, M. Lozano, E. García, J. Tabera, E. Trias, U. Perpiña, J.M. Canals, T. Baumann, D. Benítez-Ribas, E. Campo, J. Yagüe, A. Urbano-Ispizua, S. Rives, J. Delgado, M. Juan, Point-of-care CAR T-cell production (ARI-0001) using a closed semi-automatic bioreactor: experience from an academic phase I clinical trial, Front. Immunol. 11 (2020) 482, https://doi.org/10.3389/fimmu.2020.00482.

[114] M. Wang, F. You, X. Wang, B. Li, H. Xu, Y. Wang, G. Pan, S. Sun, H. Meng, Y. Zhao, Y.-S. Chen, B. Zhang, L. Yang, Automation platform for CAR-T manufacturing: the benefits and the clinical outcomes, Blood 134 (Supplement_1) (2019) 1960, https://doi.org/10.1182/blood-2019-123656.

[115] C.P. Vieira, T.M. McCarrel, M.B. Grant, Novel methods to mobilize, isolate, and expand mesenchymal stem cells, Int. J. Mol. Sci. 22 (2021) 5728, https://doi.org/10.3390/ijms22115728.

[116] K. Kolostova, E. Pospisilova, R. Matkowski, J. Szelachowska, V. Bobek, Immune activation of the monocyte-derived dendritic cells using patients own circulating tumor cells, Cancer Immunol. Immunother. 71 (2022) 2901–2911, https://doi.org/10.1007/s00262-022-03189-2.

[117] G.A. Fenton, D.A. Mitchell, Cellular cancer immunotherapy development and manufacturing in the clinic, Clin. Cancer Res. 29 (2023) 843–857, https://doi.org/10.1158/1078-0432.CCR-22-2257.

[118] N. Francis, M. Braun, S. Neagle, S. Peiffer, A. Bohn, A. Rosenthal, T. Olbrich, S. Lollies, K. Ilsmann, C. Hauck, B. Gerstmayer, S. Weber, A. Kirkpatrick, Development of an automated manufacturing process for large-scale production of autologous T cell therapies, Mol. Therapy Methods Clin. Developm. 31 (2023) 101114, https://doi.org/10.1016/j.omtm.2023.101114.

[119] H.K. Palani, A.K. Arunachalam, M. Yasar, A. Venkatraman, U. Kulkarni, S. A. Lionel, S. Selvarajan, A. Korula, A. Abraham, B. George, J.E. Adair, R. Orentas, B. Dropulic, V. Mathews, Decentralized manufacturing of anti CD19 CAR-T cells using CliniMACS prodigy®: real-world experience and cost analysis in India, Bone Marrow Transplant. 58 (2023) 160–167, https://doi.org/10.1038/s41409-022-01866-5.

[120] N. Albinger, S. Müller, J. Kostyra, J. Kuska, S. Mertlitz, O. Penack, C. Zhang, N. Möker, E. Ullrich, Manufacturing of primary CAR-NK cells in an automated system for the treatment of acute myeloid leukemia, Bone Marrow Transplant. 59 (2024) 489–495, https://doi.org/10.1038/s41409-023-02180-4.

[121] F. Jahan, L. Penna, A. Luostarinen, L. Veltman, H. Hongisto, K. Lähteenmäki, S. Müller, S. Ylä-Herttuala, M. Korhonen, K. Vettenranta, A. Laitinen, U. Salmenniemi, E. Kerkelä, Automated and closed clinical-grade manufacturing protocol produces potent NK cells against neuroblastoma cells and AML blasts, Sci. Rep. 14 (2024) 26678, https://doi.org/10.1038/s41598-024-76791-2.

[122] I.E. Yonezawa Ogusuku, V. Herbel, S. Lennartz, C. Brandes, E. Argiro, C. Fabian, C. Hauck, C. Hoogstraten, S. Veld, L. Hageman, K. Teppert, G. Koutsoumpli, M. Griffioen, N. Mockel-Tenbrinck, T. Schaser, R. de Groot, I.C.D. Johnston, D. Lock, Automated manufacture of ΔNPM1 TCR-engineered T cells for AML therapy, Mol. Therapy Methods Clin. Developm. 32 (2024) 101224, https://doi.org/10.1016/j.omtm.2024.101224.

[123] A.R. Fraser, C. Pass, P. Burgoyne, A. Atkinson, L. Bailey, A. Laurie, N.W. A. McGowan, A. Hamid, J.K. Moore, B.J. Dwyer, M.L. Turner, S.J. Forbes, J.D. M. Campbell, Development, functional characterization and validation of methodology for GMP-compliant manufacture of phagocytic macrophages: A novel cellular therapeutic for liver cirrhosis, Cytotherapy 19 (2017) 1113–1124, https://doi.org/10.1016/j.jcyt.2017.05.009.

[124] N. Trainor, K.A. Purpura, K. Middleton, K. Fargo, L. Hails, M. Vicentini-Hogan, C. McRobie, R. Daniels, P. Densham, P. Gardin, M. Fouks, H. Brayer, R.G. Malka, A. Rodin, T. Ogen, M.J. Besser, T. Smith, D. Leonard, A. Bryan, Automated production of gene-modified chimeric antigen receptor T cells using the cocoon platform, Cytotherapy 25 (2023) 1349–1360, https://doi.org/10.1016/j.jcyt.2023.07.012.

[125] B.H. Neo, S. Bandapalle, J. O'Connor, K. Lin, K. Daita, J. Sei, M. Zander, T. Gleissner, J. Schroeder, E. Abraham, Y. Shi, The Cocoon® Platform Integrated with the 4D-Nucleofector™ LV Unit: A Nonviral Workflow for Modifying Primary T-Cells, 2021.

[126] L.R. Bohrer, N.E. Stone, N.K. Mullin, A.P. Voigt, K.R. Anfinson, J.L. Fick, V. Luangphakdy, B. Hittle, K. Powell, G.F. Muschler, R.F. Mullins, E.M. Stone, B. A. Tucker, Automating iPSC generation to enable autologous photoreceptor cell replacement therapy, J. Transl. Med. 21 (2023) 161, https://doi.org/10.1186/s12967-023-03966-2.

[127] V.P. Mantripragada, V. Luangphakdy, B. Hittle, K. Powell, G.F. Muschler, Automated in-process characterization and selection of cell-clones for quality and efficient cell manufacturing, Cytotechnology 72 (2020) 615–627, https://doi.org/10.1007/s10616-020-00403-w.

[128] R.J. Thomas, A. Chandra, Y. Liu, P.C. Hourd, P.P. Conway, D.J. Williams, Manufacture of a human mesenchymal stem cell population using an automated cell culture platform, Cytotechnology 55 (2007) 31–39, https://doi.org/10.1007/s10616-007-9091-2.

[129] Z. Lou, Y. Wang, S. Nawoschik, D. Riddell, R. Martone, J. Dunlop, Implementing CompacT SelecT automated cell culture in support of alzheimer's disease-targeted drug discovery, SLAS Technol. 13 (2008) 131–135, https://doi.org/10.1016/j.jala.2007.12.001.

[130] R.J. Thomas, A. Chandra, P.C. Hourd, D.J. Williams, Cell culture automation and quality engineering: a necessary partnership to develop optimized manufacturing

processes for cell-based therapies, J. Lab. Autom. 13 (2008) 152–158, https://doi.org/10.1016/j.jala.2007.12.003.
[131] R.J. Thomas, D. Anderson, A. Chandra, N.M. Smith, L.E. Young, D. Williams, C. Denning, Automated, scalable culture of human embryonic stem cells in feeder-free conditions, Biotechnol. Bioeng. 102 (2009) 1636–1644, https://doi.org/10.1002/bit.22187.
[132] Y. Liu, P. Hourd, A. Chandra, D.J. Williams, Human cell culture process capability: a comparison of manual and automated production, J. Tissue Eng. Regen. Med. 4 (2010) 45–54, https://doi.org/10.1002/term.217.
[133] Y. Zhao, B. Bishop, J.E. Clay, W. Lu, M. Jones, S. Daenke, C. Siebold, D.I. Stuart, E. Yvonne Jones, A. Radu Aricescu, Automation of large scale transient protein expression in mammalian cells, J. Struct. Biol. 175 (2011) 209–215, https://doi.org/10.1016/j.jsb.2011.04.017.
[134] D. McLaren, T. Gorba, A. Marguerie De Rotrou, G. Pillai, C. Chappell, A. Stacey, S. Lingard, A. Falk, A. Smith, P. Koch, O. Brüstle, R. Vickers, J. Tinsley, D. Flanders, P. Bello, S. Craig, Automated large-scale culture and medium-throughput chemical screen for modulators of proliferation and viability of human induced pluripotent stem cell-derived neuroepithelial-like stem cells, J. Biomol. Screen. 18 (2012) 258–268, https://doi.org/10.1177/1087057112461446.
[135] F.A.C. Soares, A. Chandra, R.J. Thomas, R.A. Pedersen, L. Vallier, D.J. Williams, Investigating the feasibility of scale up and automation of human induced pluripotent stem cells cultured in aggregates in feeder free conditions, J. Biotechnol. 173 (2014) 53–58, https://doi.org/10.1016/j.jbiotec.2013.12.009.
[136] P.R.T. Archibald, A. Chandra, D. Thomas, G. Morley, T. Lekishvili, A. Devonshire, D.J. Williams, Comparability of scalable, automated hMSC culture using manual and automated process steps, Biochem. Eng. J. 108 (2016), https://doi.org/10.1016/j.bej.2015.07.001.
[137] P.R.T. Archibald, A. Chandra, D. Thomas, O. Chose, E. Massouridès, Y. Laâbi, D. J. Williams, Comparability of automated human induced pluripotent stem cell culture: a pilot study, Bioprocess Biosyst. Eng. 39 (2016) 1847–1858, https://doi.org/10.1007/s00449-016-1659-9.
[138] S.A. Aleksandrova, Y.A. Nashchekina, S.V. Nadezhdin, S.A. Vasiliev, R. R. Savchenko, L.A. Pokrovskaya, M.I. Blinova, N.A. Mikhailova, M.G. Khotin, Osteoinductive properties of secretome of human mesenchymal stem cells, obtained with automatic cell culture system, Cell Tissue Biol. 14 (2020) 492–500, https://doi.org/10.1134/S1990519X20060024.
[139] C.A. Tristan, P. Ormanoglu, J. Slamecka, C. Malley, P.H. Chu, V.M. Jovanovic, Y. Gedik, Y. Jethmalani, C. Bonney, E. Barnaeva, J. Braisted, S.K. Mallanna, D. Dorjsuren, M.J. Iannotti, T.C. Voss, S. Michael, A. Simeonov, I. Singeç, Robotic high-throughput biomanufacturing and functional differentiation of human pluripotent stem cells, Stem Cell Rep. 16 (2021) 3076–3092, https://doi.org/10.1016/j.stemcr.2021.11.004.
[140] F.A. Fadeyev, D.V. Sedneva-Lugovets, O.V. Madyarova, Scale-out cultivation of human dermal fibroblasts using robotic cell culture system: comparison of manual and automated processing, Cell. Ther. Transpl. 11 (2022) 63–71, https://doi.org/10.18620/ctt-1866-8836-2022-11-2-63-71.
[141] N. Franscini, K. Wuertz, I. Patocchi-Tenzer, R. Durner, N. Boos, U. Graf-Hausner Ursula, Development of a novel automated cell isolation, expansion, and characterization platform, J. Lab. Autom. 16 (2011) 204–213, https://doi.org/10.1016/j.jala.2011.01.002.
[142] M. Murphy, F. Barry, C. Leschke, B. Vaughan, C. Gentili, J. O'Dea, V. Ogourtsov, Q.A. Rafiq, J. Ochs, M. Kulik, N. Koenig, The autostem platform for closed manufacture of bone marrow-derived mesenchymal stromal cells using a closed, scalable and automated robotic system, Cytotherapy 19 (2017) s122, https://doi.org/10.1016/j.jcyt.2017.02.199.
[143] M. Murphy, J. Ochs, R. Schmitt, F. Barry, Adaptation of the autostem robotic platform for GMP-compliant manufacture of bone marrow-derived mesenchymal stromal cells, Cytotherapy 20 (2018) s47–s48, https://doi.org/10.1016/j.jcyt.2018.02.125.
[144] J. Ochs, M.P. Hanga, G. Shaw, N. Duffy, M. Kulik, N. Tissin, D. Reibert, F. Biermann, P. Moutsatsou, S. Ratnayake, A. Nienow, N. Koenig, R. Schmitt, Q. Rafiq, C.J. Hewitt, F. Barry, J.M. Murphy, Needle to needle robot-assisted manufacture of cell therapy products, Bioeng. Transl. Med. 7 (2022) e10387, https://doi.org/10.1002/btm2.10387.
[145] L. Herbst, F. Groten, M. Murphy, G. Shaw, B. Nießing, R.H. Schmitt, Automated production at scale of induced pluripotent stem cell-derived mesenchymal stromal cells, chondrocytes and extracellular vehicles: towards real-time release, Processes 11 (2023) 2938, https://doi.org/10.3390/pr11102938.
[146] T. Kikuchi, M. Kino-oka, M. Wada, T. Kobayashi, M. Kato, S. Takeda, H. Kubo, T. Ogawa, H. Sunayama, K. Tanimoto, M. Mizutani, T. Shimizu, T. Okano, A novel, flexible and automated manufacturing facility for cell-based health care products: tissue factory, Regenerat. Therapy 9 (2018) 89–99, https://doi.org/10.1016/j.reth.2018.08.004.
[147] Q.A. Rafiq, K. Twomey, M. Kulik, C. Leschke, J. O'Dea, S. Callens, C. Gentili, F. P. Barry, M. Murphy, Developing an automated robotic factory for novel stem cell therapy production, Regen. Med. 11 (4) (2016) 351–354, https://doi.org/10.2217/rme-2016-0040.
[148] A. Elanzew, B. Nießing, D. Langendoerfer, O. Rippel, T. Piotrowski, F. Schenk, M. Kulik, M. Peitz, Y. Breitkreuz, S. Jung, P. Wanek, L. Stappert, R.H. Schmitt, S. Haupt, M. Zenke, N. König, O. Brüstle, The StemCellFactory: a modular system integration for automated generation and expansion of human induced pluripotent stem cells, Front. Bioeng. Biotechnol. 8 (2020) 580352, https://doi.org/10.3389/fbioe.2020.580352.
[149] H.L.T. Lee, P. Boccazzi, R.J. Ram, A.J. Sinskey, Microbioreactor arrays with integrated mixers and fluid injectors for high-throughput experimentation with pH and dissolved oxygen control, Lab Chip 6 (2006) 1229–1235, https://doi.org/10.1039/b608014f.
[150] K.S. Lee, P. Boccazzi, A.J. Sinskey, R.J. Ram, Microfluidic chemostat and turbidostat with flow rate, oxygen, and temperature control for dynamic continuous culture, Lab Chip 11 (2011) 1730–1739, https://doi.org/10.1039/c1lc20019d.
[151] H. Schwarz, K. Lee, A. Castan, V. Chotteau, Optimization of medium with perfusion microbioreactors for high density CHO cell cultures at very low renewal rate aided by design of experiments, Biotechnol. Bioeng. 120 (2023) 334–343, https://doi.org/10.1002/bit.28397.
[152] W.X. Sin, N.S. Jagannathan, D.B.L. Teo, F. Kairi, S.Y. Fong, J.H.L. Tan, D. Sandikin, K.W. Cheung, Y.H. Luah, X. Wu, J.J. Raymond, F.L.W.I. Lim, Y. H. Lee, M.S.F. Seng, S.Y. Soh, Q. Chen, R.J. Ram, L. Tucker-Kellogg, M. E. Birnbaum, A high-density microfluidic bioreactor for the automated manufacturing of CAR T cells, Nat. Biomed. Eng. (2024), https://doi.org/10.1038/s41551-024-01219-1.
[153] A. Melocchi, B. Schmittlein, A.L. Jones, Y. Ainane, A. Rizvi, D. Chan, E. Dickey, K. Pool, K. Harsono, D. Szymkiewicz, U. Scarfogliero, V. Bhatia, A. Sivanantham, N. Kreciglowa, A. Hunter, M. Gomez, A. Tanner, M. Uboldi, A. Batish, J. Balcerek, M. Kutova-Stoilova, S. Paruthiyil, L.A. Acevedo, R. Stadnitskiy, S. Carmichael, H. Aulbach, M. Hewitt, X. De Mollerat Du Jeu, B. di Robilant, F. Parietti, J. H. Esensten, Development of a robotic cluster for automated and scalable cell therapy manufacturing, Cytotherapy 26 (2024) 1095–1104, https://doi.org/10.1016/j.jcyt.2024.03.010.
[154] https://global.kawasaki.com/en/corp/newsroom/news/detail/?f=20180320_9882 last access on December 15, 2024.
[155] https://global.kawasaki.com/en/corp/newsroom/news/detail/?f=20161227_5800 last access on December 15, 2024.
[156] https://global.kawasaki.com/en/corp/newsroom/news/detail/?f=20161227_5800 last access on December 15, 2024.
[157] https://www.miltenyibiotec.com/IT-en/about-us/newsroom/press-releases/molmed-and-miltenyi-biotec-ema-approves-the-utilization-of-the-clinimacs-prodigy-r-equipment.html last access on December 15, 2024.
[158] https://www.miltenyibiotec.com/US-en/about-us/newsroom/press-releases/molmed-and-miltenyi-biotec-ema-approves-the-utilization-of-the-clinimacs-prodigy-r-equipment.html last access on December 15, 2024.
[159] https://www.lonza.com/news/2020-09-08-05-00 last access on December 15, 2024.
[160] https://www.pharmtech.com/view/leucid-bio-to-use-lonza-s-cocoon-platform-for-automated-manufacturing-of-car-t-cells last access on December 15, 2024.
[161] https://www.leucid.com/news last access on December 15, 2024.
[162] https://aspenneuroscience.com/aspen-neuroscience-announces-collaboration-and-license-agreement-with-cell-x-technologies/ last access on December 15, 2024.
[163] https://www.ipt.fraunhofer.de/en/projeherbstcts/autostem.html last access on December 15, 2024.
[164] C. Baguet, J. Larghero, M. Mebarki, Early predictive factors of failure in autologous CAR T-cell manufacturing and/or efficacy in hematologic malignancies, Blood Adv. 8 (2024) 337–342, https://doi.org/10.1182/bloodadvances.2023011992.
[165] S. Hort, C. Sanges, J.J.L. Jacobs, M. Hudecek, R.H. Schmitt, Digital transformation of CAR-T cell therapy - challenges and potential for industry 4.0, Procedia CIRP 120 (2023) 1034–1040, https://doi.org/10.1016/j.procir.2023.09.121.
[166] J.S. Srai, P. Bauer, C. Badman, M. Bresciani, C.L. Cooney, A. Florence, D. Hausner, K. Konstantinov, S.L. Lee, S. Mascia, M. Nasr, B.L. Trout, Emerging applications and regulatory strategies for advanced medicines manufacturing - towards the development of a platform approach, J. Pharm. Sci. 113 (2024) 1701–1710, https://doi.org/10.1016/j.xphs.2024.04.016.
[167] P. Jayaraman, R. Lim, J. Ng, M.C. Vemuri, Acceleration of translational mesenchymal stromal cell therapy through consistent quality GMP manufacturing, Front. Cell Developm. Biol. 9 (2021) 648472, https://doi.org/10.3389/fcell.2021.648472.
[168] https://www.nwo.nl/en/researchprogrammes/knowledge-and-innovation-covenant/mission-driven-calls-kic-2020-2023 last access on December 15, 2024.
[169] S. Hort, L. Herbst, N. Bäckel, F. Erkens, B. Niessing, M. Frye, N. König, I. Papantoniou, M. Hudecek, J.J.L. Jacobs, R.H. Schmitt, Toward rapid, widely available autologous car-t cell therapy – artificial intelligence and automation enabling the smart manufacturing hospital, Front. Med. 9 (2022) 913287, https://doi.org/10.3389/fmed.2022.913287.
[170] https://www.sciencrew.com/c/6499?title=AIDPATH last access on December 15, 2024.
[171] Y.Y. Wu, D. Yong, M.W. Naing, Automated cell expansion: trends & outlook of critical technologies, Cell Gene Therapy Insights 4 (2018) 851–871, https://doi.org/10.18609/cgti.2018.086.
[172] M. Abou-El-Enein, M. Elsallab, S.A. Feldman, A.D. Fesnak, H.E. Heslop, P. Marks, B.G. Till, G. Bauer, B. Savoldo, Scalable manufacturing of car t cells for cancer immunotherapy, Blood Cancer Discov. 2 (2021) 408–422, https://doi.org/10.1158/2643-3230.BCD-21-0084.
[173] X. Dai, Y. Mei, J. Nie, Z. Bai, Scaling up the manufacturing process of adoptive T cell immunotherapy, Biotechnol. J. 14 (2019) 1800239, https://doi.org/10.1002/biot.201800239.
[174] T.F. O'Connor, S. Chatterjee, J. Lam, D.H.P. de la Ossa, L. Martinez-Peyrat, M.H. N. Hoefnagel, A.C. Fisher, An examination of process models and model risk frameworks for pharmaceutical manufacturing, Int. J. Pharm. X 8 (2024) 100274, https://doi.org/10.1016/j.ijpx.2024.100274.

[175] B. Wang, A.C. Bowles-Welch, C. Yeago, K. Roy, Process analytical technologies in cell therapy manufacturing: state-of-the-art and future directions, J. Adv. Manufact. Proc. 4 (2022) e10106, https://doi.org/10.1002/amp2.10106.
[176] M.M. Hewitt, N. Trainor, N. Ostrout, E. Abraham, Cell therapy manufacturing: process analytic technologies needed to achieve flexible, feedback-driven automation, Curr. Opin. Biomed. Eng. 20 (2021) 100358, https://doi.org/10.1016/j.cobme.2021.100358.
[177] C. van den Bos, R. Keefe, M. Keville, M. McCaman, Manufacturing and quality of advanced therapeutics: Cellular therapies, CAR-T and gene therapies, in: R. Pörtner (Ed.), Biopharmaceutical Manufacturing. Cell Engineering vol. 11, Springer, Cham, 2023, https://doi.org/10.1007/978-3-031-45669-5_15.
[178] D.M. Hoang, Q.T. Nguyen, T.T.K. Phan, A.T.L. Ngo, P.T. Pham, T.Q. Bach, P.T. T. Le, H.T.P. Bui, L.N. Thanh, Advanced cell-based products generated via automated and manual manufacturing platforms under the quality by design principle: are they equivalent or different? Heliyon 9 (2023) e15946 https://doi.org/10.1016/j.heliyon.2023.e15946.
[179] https://alliancerm.org/manufacturing/a-cell-2022 last access on December 15, 2024.
[180] A. Shoshi, Y. Xia, A. Fieschi, T. Ackermann, P. Reimann, M. Weyrich, B. Mitschang, T. Bauernhansl, R. Miehe, A flexible digital twin framework for ATMP production – towards an efficient CAR T cell manufacturing, Procedia CIRP 125 (2024), https://doi.org/10.1016/j.procir.2024.08.022.
[181] N.K. Lee, J.W. Chang, Manufacturing cell and gene therapies: challenges in clinical translation, Ann. Lab. Med. 44 (2024) 314–323, https://doi.org/10.3343/alm.2023.0382.
[182] S. Kadauke, M.H. Bonamino, B.L. Levine, R. Harrison, O. Karnieli, In-hospital manufacturing of cellular therapies using automated systems, Clin. Chem. 69 (2023) 954–960, https://doi.org/10.1093/clinchem/hvad102.
[183] L. Weng, Cell therapy drug product development: technical considerations and challenges, J. Pharm. Sci. 112 (2023) 2615–2620, https://doi.org/10.1016/j.xphs.2023.08.001.
[184] R.P. Harrison, S. Ruck, N. Medcalf, Q.A. Rafiq, Decentralized manufacturing of cell and gene therapies: overcoming challenges and identifying opportunities, Cytotherapy 19 (2018) 1140–1151, https://doi.org/10.1016/j.jcyt.2017.07.005.
[185] R. Giancola, T. Bonfini, A. Iacone, Cell therapy: cGMP facilities and manufacturing, Muscles Ligam. Tendons J. 2 (2012) 243–247.
[186] P. Bedford, J. Jy, L. Collins, S. Keizer, Considering cell therapy product "good manufacturing practice" status, Front. Med. 5 (2018) 118, https://doi.org/10.3389/fmed.2018.00118.
[187] https://www.ema.europa.eu/en/news/new-guidelines-good-manufacturing-practices-advanced-therapies.
[188] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/advanced-manufacturing-technologies-designation-program.
[189] National Academies of Sciences, Engineering, and Medicine, Health and Medicine Division; Board on Health Sciences Policy, Forum on Regenerative Medicine, in: S.H. Beachy, J. Alper, M. Drewry (Eds.), Emerging Technologies and Innovation in Manufacturing Regenerative Medicine Therapies: Proceedings of a Workshop—In Brief, National Academies Press (US), Washington (DC), 2024 Feb 16, https://doi.org/10.17226/27483.
[190] https://www.fda.gov/emergency-preparedness-and-response/mcm-issues/advanced-manufacturing.
[191] D.G.M. Coppens, S. de Wilde, H.J. Guchelaar, M.L. De Bruin, H.G.M. Leufkens, P. Meij, J. Hoekman, A decade of marketing approval of gene and cell-based therapies in the United States, European Union and Japan: an evaluation of regulatory decision-making, Cytotherapy 20 (2018) 769–778, https://doi.org/10.1016/j.jcyt.2018.03.038.
[192] https://www.swissmedic.ch/swissmedic/en/home/humanarzneimittel/authorisations/information/benchmarking-studie-2023.html.
[193] J. Meneghel, P. Kilbride, G.J. Morris, Cryopreservation as a key element in the successful delivery of cell-based therapies - a review, Front. Med. 7 (2020) 592242, https://doi.org/10.3389/fmed.2020.592242.
[194] https://www.europeanpharmaceuticalreview.com/news/27981/invetech-argos-therapeutics-partner-automated-production-personalized-immunotherapies-cancer-infectious-diseases/ last access on December 15, 2024.
[195] https://www.fiercepharma.com/pharma/ori-doubles-down-charles-river-collaboration-promising-new-data-its-automated-cell-therapy last access on December 15, 2024.
[196] https://news.bms.com/news/details/2024/Bristol-Myers-Squibb-and-Cellares-Announce-a-380M-Worldwide-Capacity-Reservation-and-Supply-Agreement-for-the-Manufacture-of-CAR-T-Cell-Therapies-to-Bring-the-Promise-of-Cell-Therapy-to-More-Patients-Faster/default.aspx last access on December 15, 2024.
[197] https://www.fiercepharma.com/pharma/robotics-expert-multiply-labs-strikes-cell-therapy-automation-partnership-legend last access on December 15, 2024.
[198] https://www.agilent.com/about/newsroom/presrel/2021/15dec-ca21034.html last access on December 15, 2024.
[199] M.N. Doulgkeroglou, A. Di Nubila, B. Niessing, N. König, R.H. Schmitt, J. Damen, S.J. Szilvassy, W. Chang, L. Csontos, S. Louis, P. Kugelmeier, V. Ronfard, Y. Bayon, D.I. Zeugoli, Automation, monitoring, and standardization of cell product manufacturing, Front. Bioeng. Biotechnol. 8 (2020) 811, https://doi.org/10.3389/fbioe.2020.00811.
[200] J.G. Hunsberger, T. Shupe, A. Atala, An industry-driven roadmap for manufacturing in regenerative medicine, Stem Cells Transl. Med. 7 (2018) 564–568, https://doi.org/10.1002/sctm.18-0060.
[201] D. Stroncek, A. Dinh, H. Rai, N. Zhang, R. Somerville, S. Panch, The need for uniform and coordinated practices involving centrally manufactured cell therapies, J. Transl. Med. 20 (2022) 184, https://doi.org/10.1186/s12967-022-03385-9.
[202] D. Stroncek, A. Dinh, H. Rai, The need for uniform and coordinated practices involving centrally manufactured cell therapies, J. Transl. Med. 20 (2022) 184, https://doi.org/10.1186/s12967-022-03385-9.
[203] M. Verbarendse, R. Snyder, U. Lakshmipathy, Mini-review: equipment evaluation for process scalability and readiness for current good manufacturing practices in cell therapy workflows, Cytotherapy 25 (2023) 1107–1112, https://doi.org/10.1016/j.jcyt.2023.05.005.
[204] R. McCoy, S. Ward, N. Gaddum, J. Hasan, The necessity of automated manufacture for cell-based immunotherapies: a cost-based analysis, Cell Gene Therapy Insights 6 (2020) 673–690, https://doi.org/10.18609/cgti.2020.071.
[205] C.H. Hulme, C. Mennan, H.S. McCarthy, R. Davies, T. Lan, L. Rix, J. Perry, K. Wright, A comprehensive review of quantum bioreactor cell manufacture: research and clinical applications, Cytotherapy 25 (2023) 1017–1026, https://doi.org/10.1016/j.jcyt.2023.04.004.