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Cells as advanced therapeutics: State-of-the-art, challenges, and opportunities in large scale biomanufacturing of high-quality cells for adoptive immunotherapies☆

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ABSTRACT

Therapeutic cells hold tremendous promise in treating currently incurable, chronic diseases since they perform multiple, integrated, complex functions *in vivo* compared to traditional small-molecule drugs or biologics. However, they also pose significant challenges as therapeutic products because (a) their complex mechanisms of actions are difficult to understand and (b) low-cost bioprocesses for large-scale, reproducible manufacturing of cells have yet to be developed. Immunotherapies using T cells and dendritic cells (DCs) have already shown great promise in treating several types of cancers, and human mesenchymal stromal cells (hMSCs) are now extensively being evaluated in clinical trials as immune-modulatory cells. Despite these exciting developments, the full potential of cell-based therapeutics cannot be realized unless new engineering technologies enable cost-effective, consistent manufacturing of high-quality therapeutic cells at large-scale. Here we review cell-based immunotherapy concepts focused on the state-of-the-art in manufacturing processes including cell sourcing, isolation, expansion, modification, quality control (QC), and culture media requirements. We also offer insights into how current technologies could be significantly improved and augmented by new technologies, and how disciplines must converge to meet the long-term needs for large-scale production of cell-based immunotherapies.

Contents

Abbreviations: aAPC, artificial APC; ACT, adoptive cell therapy; CDM, chemically defined media; cGMP, current Good Manufacturing Practices; DC, dendritic cell; CPP, critical process parameter; CQA, critical quality attribute; FACS, fluorescence activated cell sorting; HAS, human serum albumin; HLA, human leukocyte antigen; hMSC, human mesenchymal stromal cell; HPL, human platelet lysate; HS, human serum; IPC, in-process control; LN, lymph node; mAbs, monoclonal antibodies; MACS, magnetic activated cell sorting; MHC, major histocompatibility complex; PBMC, peripheral blood mononuclear cell; PFM, protein free media; PL, platelet lysate; QbD, Quality-by-Design; QC, quality control; SBT, sleeping beauty transposon; SCM, serum-containing media; SFM, serum-free media; TC, tissue culture; TCR, T cell receptor; TFF, tangential flow filtration; TIL, tumor infiltrating lymphocyte.

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1. Introduction

Adoptive cell therapies (ACT) using T cells and DCs have gained impressive momentum in the past few years, and have shown promise in treating cancer, infectious diseases, autoimmune disorders, and transplant related complications. In particular, two T cell immunotherapies have demonstrated powerful anti-cancer activity. First, Tumor Infiltrating Lymphocytes (TILs) derived from resected tumors and expanded *ex vivo* to clinically relevant doses have shown to effectively treat metastatic melanoma, [1] cholangiocarcinoma [2], and cervical cancer [3]. Second, T cells isolated from a patient's peripheral blood mononuclear cells (PBMCs) and genetically engineered to express a tumor-specific T cell receptor (transduced-TCR) or chimeric antigen receptor (CAR) [4–10] have demonstrated great success in clinical trials, especially against blood cancers. In addition, DC-based immunotherapies have been used to treat diseases such as cancer and HIV since the 1990s with varying success. A DC-based vaccine (Provenge) for prostate cancer received FDA approval a few years ago, and several clinical trials are ongoing or have been completed for the treatment of various cancer types [11,12]. Human mesenchymal stromal cells (hMSCs) have also been recognized for their ability to counter inflammation-related conditions, reduce graft-*versus*-host disease (GVHD) reactions, and modulate immune responses [13].

The potential for these therapies to alleviate and, in some cases, provide functional cures for chronic and often untreatable conditions is now well recognized; however, their clinical potential cannot be realized without technologies to reproducibly manufacture high-quality cells, at large-scale and with low cost. Unlike traditional pharmaceutical manufacturing, the products in question are living entities that can change with every process manipulation. In particular, the associated costs are a matter of ongoing discussion that will continue to evolve as products become more defined [14–17]. To briefly describe the essence and magnitude of these challenges, cell manufacturing currently has no industry-wide standards, and regulations for cell therapies are limited. In most cases the mechanism of action for therapeutic cells is poorly understood and thus critical quality attributes (CQAs), such as properties of cells that can be measured to assure functional quality and ensure reproducibility, are largely unknown. Similarly, critical process parameters (CPPs) that are necessary to maintain and ensure cell quality and consistency across batches and facilities have not been identified; this includes (but is not limited to) process variables like culture conditions, durations, media compositions, and 2D *versus* 3D cultures. Thus, cell manufacturing currently does not involve Quality-by-Design (QbD) principles that allow for well-optimized processes to enable high-quality, large-scale production of therapeutic cells. These add to an

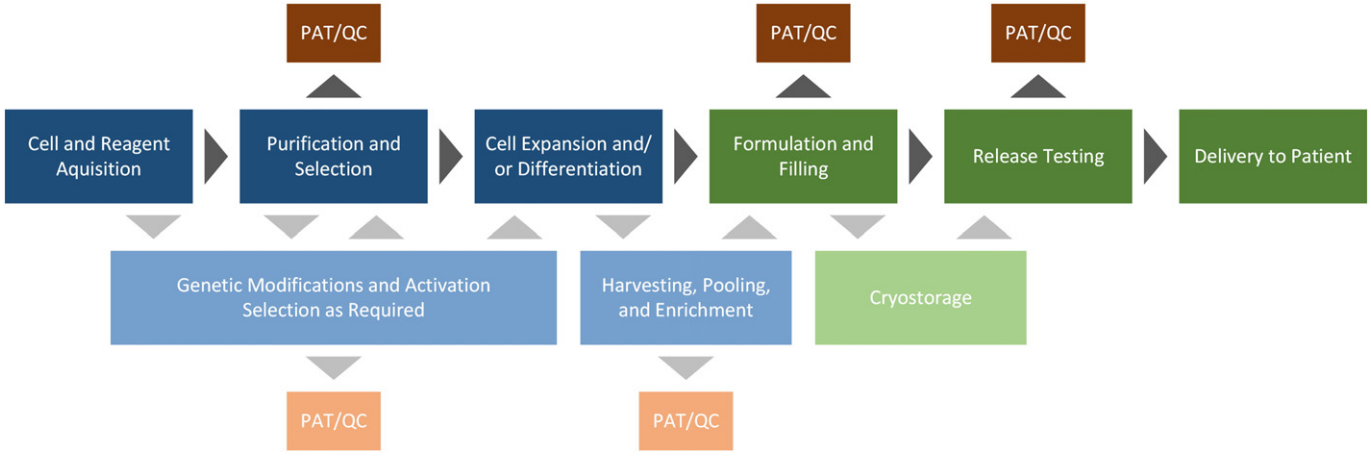

Fig. 1. General overview of current state-of-the-art cell manufacturing processes. Bold colors on the top half indicate processing steps common to most cell types; watershed colors on the bottom half indicate process steps that may be added depending on application. Upstream and downstream processing are indicated by blue and green, respectively. Orange boxes indicate desired QC and PAT for key process steps. Abbreviations: QC, quality control; PAT, process analytical technologies.