BIOIVT

ELEVATING SCIENCE®

WHITE PAPER

Disease State Primary Cells Bring Verification and Validation Studies

Introduction

The field of cell and gene therapy has seen unprecedented growth in the last decade. Autologous and allogeneic therapies have cast a wide net of indications, including oncology, regenerative medicine and genetic disorders. The development of manufacturing processes for therapies, as well as the testing of ancillary equipment, consumables, media and reagents, are traditionally done using starting material from healthy donors. But are these "normal" cells truly representative of the real world, where starting materials are sourced from patients with diseases? As a mitigation strategy, researchers should consider verification and validation (V&V) testing using disease state leukopaks and disease state immune cell subsets to ensure they're fit for purpose in autologous applications.

Defining "Disease State"

Simply put, a disease state donor is an individual who has been clinically diagnosed with a specific disease indication. However, disease progression, prior treatments and co-morbidities may drastically affect the resultant severity of disease at time of collection. It is therefore critical that any supplier of disease state material documents the patient's full clinical history. BioIVT's clinical collection sites offer a comprehensive clinical data set for our products, complete with more than 300 relevant data points. This allows customers to develop their own cohort of disease state patients for their unique V&V strategies.

Standard Patient History

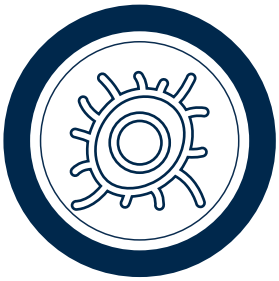
- Age
- Gender
- Race
- Smoking Status
- Alcohol use
- Medical treatments
- Medication

Oncology-Specific

- Diagnosis timeline
- Tumor stage
- Co-morbidities

Autoimmune-Specific

- Disease severity
- Score/status of donors



Infectious Disease-Specific

- Acute vs chronic disease state
- Confirmation of infection or exposure

Tantamount to the quality of patient material and clinical data is the ethical collection of products from donors. Patients debilitated by disease should not be burdened with additional procedures that may negatively impact their outcome. At BioIVT, we take pride in our IRB-approved, donor-consented collection methods that prioritize patient safety. Accordingly, most leukopak collections are limited to a half-pak size for disease state donors. Other cohorts, such as oncology disease states, are restricted to even smaller volumes to decrease impact on donor health and safety. Immune cell subsets derived from disease state donors are isolated with qualified standard operating procedures (SOPs) to ensure no product goes to waste. For more information on how BioIVT ethically collects biospecimens, please visit our Regulatory Resources.

Differences Between Normal Donors and Disease State Donors

While the successes of autologous cell therapies in the hematology/oncology space have been significant, they are not yet considered a first-line treatment. According to the MD Anderson Cancer Center, only if patients have "been through two lines of unsuccessful treatment, they can get the FDA-approved commercial product."[1] In fact, each FDA-approved therapy carries a lengthy set of prior authorization criteria before patients can receive the drug. [2,3,4,5]

Therapy Name	Indications	Manufacturer	Prior Authorization Criteria
KYMRIAH® (tisagenlecleucel)	• ALL • DLBCL	Novartis	• 3-25 years of age • Refractory or relapsed disease • Failed 2+ cycles of chemotherapy • Documentation of CD19 tumor expression • No active infections
YESCARTA® (Axicabtagen Ciloleucel)	• DLBCL • Non-Hodgkin lymphoma	Kite Pharma	• 18 years of age or older • Refractory or relapsed disease • Failed anthracycline-containing chemotherapy regimen • CD20 expression (for CD20+ disease) • No active infections
TECARTUS™ (Brexucabtagene autoleucel)	• Mantle cell lymphoma	Kite Pharma	• 18 years of age or older • No active infections • No prior allogeneic hematopoietic stem cell transplantation • No central nervous system lymphoma • Relapsed or refractory disease • At least one previous systemic therapy failure
ABECMA™ (idecabtagene vicleucel)	• Multiple myeloma	Brisol Myers-Squibb	• 18 years of age or older • At least 4 prior treatment regimens including 1 IMiD® agent, proteasome inhibitor, or anti-CD38 antibody • Relapsed or refractory disease

Due to these prior treatments, typically radiotherapy and chemotherapy, the quality of patients' cells decreases. The diminshed proliferation of cells, reduced production of cytokines and changes to the populations of immune cell subsets have been reported in the presence of common anticancer agents.[6,7,8] Even traditional CD3/CD28 activation methods performed on chemotherapy-exposed T cells result in impaired levels of proliferation relative to untreated cells.[9] This effect on cellular activation may also lead to low transduction efficiency, i.e., the number of T cells that are transformed to chimeric antigen receptor (CAR) T cells by viral vector.[10] These subtle changes represent a set of variabilities that are not captured in traditional V&V testing using healthy-patient material alone.

While oncology remains the primary focus for much of the cell and gene therapy industry, ex vivo cell therapies exist for other indications, such as autoimmune disorders. Repairing defects and deficiencies of immunosuppressive regulatory T cells in so-called "tolerizing cellular therapies" provides a novel solution to systemic lupus erythematosus (SLE), Crohn's disease and graft versus host disease (GVHD).[11] Regenerative medicine therapies derived from autologous mesenchymal stem cells (MSCs) or induced pluripotent stem cells (iPSCs), such as those for Type 1 diabetes,[12] can also benefit from starting materials derived from relevant disease indications. As these spaces evolve, researchers may want to compare their manufacturing methods on true disease state patient material to confirm applicability of their test results to the real world.

Disease State Products for Verification & Validation of Devices and Reagents

Therapeutic researchers are not the only ones who can benefit from the accuracy offered by disease state products. Manufacturers of bioreactors, cell culture vessels and other cell processing kits or devices typically validate their products with healthy donor cells to prove reliability and reproducibility. While these steps are essential to the launch of any cell and gene therapy product, representative data sets of appropriate disease state patient material would help manage expectations for the end user and offer insights into process optimization. Similarly, cell culture media and reagent suppliers could fine tune formulations to better suit real-world use, saving their customers time and improving patient outcomes.

BioIVT's portfolio of disease state leukopaks and immune cell subsets is well positioned to provide researchers with enhanced data accuracy not found with healthy starting material alone. Visit our leukopak product pages for the disease state indications we offer and download our Clinical Specimen Inventory for updated lists of disease state PBMCs and BMMCs. For MSCs, please see our bone marrow product page to schedule a collection.

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21-0030.01