

Opening the Gates to Autologous Cellular Therapies

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Cell-based therapies may hold the promise of providing new opportunities for managing immune-mediated chronic diseases and some forms of cancer and for repairing or replacing degenerated tissues with regenerated healthy tissues. The cellular raw material used for these therapies may be from an allogeneic source (e.g., an established cell line) or autologous in origin. Products manufactured from allogeneic sourced materials could allow “off-the-shelf” patient treatment if immunogenicity can be controlled. Although they have

more complex manufacturing requirements, especially related to logistics management, autologous cell-based therapies could allow truly personalized and potentially more effective treatment of a patient’s condition.

Numerous autologous cell-based therapies currently are being developed in public and private biotech companies across the United States and, to a lesser degree, around the world, as shown in Table 1. For treatment of cancer, autologous therapies are being developed that promote “up regulation” or “re-education”

of the patient’s immune system to re-establish effective recognition and control of malignant cells. For immune-mediated disorders, the goal of therapy is to “dampen down” the immune response by “retraining” key elements of the patient’s immune system. Autologous regenerative therapies are based on the general premise that inserting normal cells into damaged tissue will promote in situ repair.

The Production Process

The spectrum of raw materials required for production of autologous

TABLE 1: Autologous Peripheral Blood Cell Based Therapies in Clinical Studies

Company	Therapeutic	Targeted Disease	Clinical Phase
Dendreon	Sipuleucel-T	Prostate Cancer	III
IDM	UVIDEM®	Melanoma	II
	COLLIDEM®	Colorectal Cancer	I/II
	BEXIDEM®	Bladder Cancer	II/III
Northwest Biotherapeutics	DCVAX® - prostate	Prostate Cancer	III
	DCVAX® - brain	Glioblastoma	II
Argos Therapeutics	AGS-003	Renal Cell Carcinoma	I/II
	AGS-004	HIV	II
	AGS-005	CLL	I/II (single site)
VIRxSYS	VRX496	HIV	II
Opexa Therapeutics	Tovaxin®	Multiple Sclerosis	Ib

Sources: Corporate Web sites and www.clinicaltrials.gov

TABLE 2: Relative Characteristics of Autologous Cellular Therapy Clinical Trials

	CLINICAL TRIAL PHASE			
	I	Ila	Ilb	III
Subjects enrolled	10-30	20-50	100-200	1000-2500
Enrollment sites	1-3	3-10	10-30	30-100
Collections sites	1-3	3-10	10-30	30-100
Manufacturing sites	Local	Local/Central	Central	Central

TABLE 3

Licensed Autologous Cellular Therapeutic Scenario

Medical specialists in private practice clinics across the U.S. will be allowed to prescribe the therapy.

Therapy will be prescribed for 5,000 to 50,000 patients in the U.S. annually.

Each patient must undergo one or more collections of autologous raw material.

Patients will expect that convenient (close to home) collection options exist.

At a minimum, collection sites will be needed in all major and second-tier metropolitan areas.

therapeutic agents includes normal tissue (e.g., chondrocytes and adipocytes) and abnormal tissue (e.g., malignant tumor cells), peripheral blood cells and bone marrow-derived cellular components. The production process generally includes collecting the autologous raw material from the patient in a prescribed manner, processing the material at the collection site or transporting it to a central site for manufacturing, and returning the finished product to the patient's physician for administration. Each manufacturer's proprietary process includes some degree of ex vivo manipulation of the raw material before sending the product back to the patient. Manipulations include, but are not limited to, "simple" expansion of a targeted cell population, exposure of selected and expanded antigen-presenting cells to a target antigen or gene insertion, to name a few.

The requirements (number of products collected, quality of the collected product, packaging and shipping requirements for delivery to the manufacturing site, etc.) for autologous raw materials increase or are enhanced through the clinical research stages (Table 2). Early-stage clinical trials (phase I and IIa) usually are performed at one or a small number of academic medical centers. Collection of autologous raw materials for these studies is commonly performed

within the medical center(s). The optimal parameters for product collection and handling are usually evaluated and/or confirmed in these early-stage studies.

If a therapeutic agent progresses to later-stage trials, the number of subjects required for enrollment in each phase increases. Medical specialists in private medical clinics often are engaged as co-investigators in phase IIb and phase III trials of an investigational agent to facilitate accrual of subjects into the studies. These clinics often have limited or no capacity to perform the collection of the needed raw material from subjects enrolled at that site, and cell therapy manufacturers typically do not foster the expertise or infrastructure to collect the raw materials. For efficiency, raw material collection is outsourced to third-party service providers; however, in the later-stage studies requiring a large number of collections sites, the inability to find a willing service provider to perform the collections can become a limiting factor in the development of the product.

Getting into the Sourcing Business

Manufacturers seek to develop collection agreements with entities that can meet their specifications, including close proximity to a patient enrollment site, capacity and experience to perform the collection of the product, willingness

of the entity's leadership to support the collection activities, and a fair cost for the services. For therapies developed from cellular elements of peripheral blood, institutions that routinely collect whole blood or blood components, such as community blood centers, are a logical first choice for sourcing raw materials. However, real or perceived barriers have, to date, prompted the leaders of many blood centers to refrain from providing these services. A few of the identified barriers include the following:

- **Potential competition with core business activities for resources.**

The core business of the blood center is the collection, processing and distribution of transfusable blood components. Fitting specialized collections for noncore customers into core activities often is seen as an inconvenience instead of as an opportunity. For example, an apheresis procedure performed for collection of mononuclear cells may need to occur on a designated date and time to meet manufacturing requirements for the therapeutic product. This procedure could last up to five hours, making staff and equipment unavailable for standard blood component collection during that time and potentially resulting in lost opportunities to collect saleable blood components. As a "best

case" example, in the same five hours, a blood center could perform two plateletpheresis collections, potentially yielding four (or more) components and generating more than \$2,000 in revenue upon sale of the products to its core customers. From the perspective of generating revenue, the blood center in this scenario would choose to collect the plateletpheresis products unless the MNC collection would generate the same revenue or, preferably, more.

Financial and resource allocation assessments such as these often are prejudiced toward the blood center's core activities and values, and diminish the perceived value of providing the specialized services. This increases the likelihood that the blood center would elect not to participate as a collection site or, if it participated, would refuse to provide a collection if an opportunity arose to use staff and equipment to produce a core product. This obviously makes the blood center a less reliable provider for collection services and forces the manufacturer to seek an alternative.

A more balanced view of the opportunity presented would be to position the collection of the specialized product as adding value to the blood center instead of competing with the core business activities. In the scenario, options are likely to exist or could be readily created to allow the platelet products to be collected on another date or at another time when resources exist to do so. In that way, additional revenue is generated by performing the MNC collection, and an additional customer's needs are served.

The blood center collection staff may view the cell therapy manufacturer as the customer for the collection and per-

ceive it to be a large, impersonal private company in a distant city to which they feel they have no obligation. However, the patient requiring the MNC collection and seeking the blood center's direct assistance in dealing with his or her medical condition is the blood center's local customer. This view may provide some balance to the discussion of which customer should be served if resources need to be prioritized.

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- **Potentially unrecoverable upfront costs.**

A moderate degree of preparation is required before an initial specialized collection can occur. For example, procedures must be written first or existing procedures must be modified and approved by internal compliance authorities. Staff must be trained on these procedures, which may introduce minor or major variances from standard procedures (e.g., donor selection criteria, product labeling requirements, and prod-

uct storage and shipping requirements). Costs associated with these activities are not included in the cost of the product collection and should be recovered. Without some assurance that an adequate volume of collections will be requested by the manufacturer, the blood center may be unable to amortize its upfront costs over enough collections to allow their recovery. In those circumstances, an upfront payment of "initiation" costs may be required, but the manufacturer may be unwilling or unable to provide this type of compensation. Centers located in major metropolitan areas that hold the potential of a large number of recruited subjects may be more likely to receive this type of funding compared to centers in areas with limited recruitment opportunities. However, even if the costs of the preparatory efforts are not fully recovered, the blood center staff gains experience that can be applied in full or in part to reduce the preparatory effort with any follow-on opportunities in this new and growing area of activity.

- **Lack of experience with management of atypical donors.**

Individuals who incidentally or expressly do not meet standard acceptance criteria for autologous whole blood donation may be enrolled as study subjects, e.g., HIV-infected individuals in cell-based vaccine trials or individuals with active cardiac disease enrolled in adult stem cell trials. Staff is unlikely to have experience collecting blood components from these types of patients and, therefore, lack confidence in managing the collection. This lack of confidence could potentially lead to distraction and errors,

placing the donor and/or the staff member at increased risk. The blood center may be unwilling to accept this risk.

Training provided to staff prior to starting collections should help improve their confidence, especially if an opportunity is available to learn from peers who have more experience with collections. The manufacturer should be able to arrange for such training with the assistance of staff from sites involved in earlier stages of the study. Additionally, in most cases, the staff will quickly become more confident as they perform the procedures and gain experience with atypical donors.

- **Lack of experience with management of nonstandard products.**

Cell therapy manufacturers often are unaware of the degree to which their product's subject selection and collection criteria differ from those for routine blood donors. In preclinical and early-stage clinical research, the companies often rely on academic medical centers experienced in performing nonstandard blood product collections for source materials. Such collections often are the rule rather than the exception in these sites, while the reverse would be true in a community blood center performing collections for later-stage studies. The collected materials often must be managed in a manner that differs from that used by the blood center for its standard products. This requires the staff to learn and adopt the manufacturer's required processes for collection, labeling, packaging and shipping, but only for these particular products. The collected products are unlikely to have standard blood banking

codes assigned, reducing the ability of the blood center's computer system to trace and track all aspects of the product handling. This may require workarounds or manual record keeping, creating the opportunity for errors, increasing costs and imposing an element of risk the blood center may be unwilling to accept. Training is, again, a key element that will allow staff to gain confidence in dealing with the product management issues.


Currently, few options are available to manufacturers for product collection if a community blood center elects not to participate.

Barriers, whether perceived or real, should be considered valid; however, all can be overcome. It falls to each blood center's leaders to make the determination about whether the effort is worth the opportunity. In fact, a number of blood centers already have done so and are active participants in autologous cell-based product development efforts. Many more will be needed before the first autologous cellular therapy achieves licensure (Table 3).

Currently, few options are available to manufacturers for product collection if a community blood center elects not to participate. Blood centers are the gatekeepers related to access to the raw materials for production of autologous cellular therapeutics. No other distrib-

uted "system" of blood product collection providers exists. The success or failure of autologous cellular therapies, therefore, may hinge on the willingness of blood center leaders to "lift the gate," thus eliminating an additional barrier by providing collection services that allow access to these essential raw materials.

The leaders of community blood centers often have downplayed the risk of maintaining the status quo and have taken a passive approach to opportunities that lie outside the boundaries of their core business. It would be shortsighted to ignore the growth opportunities that exist for blood centers in support of cell therapeutics production or to minimize the risk to the cell therapy industry if access to raw materials is impaired. Any barrier to participation can be overcome with the commitment of the blood center's senior leader. This individual must see the value of seizing these opportunities and assure that measures are in place to accomplish the core business while laying the framework for the future of transfusion medicine, which will certainly include autologous cell-based therapies.

Blood centers are the current gatekeepers; however, if their gates remain closed, alternatives will be pursued by cell therapy manufacturers and other partners. Stakeholders need to work together to travel this road successfully. The promise of autologous cell therapies depends on it. 

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