“Trials” and Tribulations

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BACKGROUND
The UF & Shands Stem Cell Laboratory in Gainesville, Florida is an active, FACT accredited cell processing and storage facility. The Stem Cell Laboratory functions within our Bone Marrow Transplant (BMT) program in an 852 bed, tertiary care hospital, and is not affiliated with the hospital’s clinical laboratory. Our program performs approximately 150 transplants per year, both pediatric and adult, and both allogeneic and autologous. The Stem Cell Laboratory is an unclassified facility equipped with Class 100 biological safety cabinets. Approximately 300 products pass through the laboratory each year. The laboratory is staffed with five licensed medical technologists under the supervision of a laboratory coordinator, with a research coordinator overseeing cellular therapy clinical trials.

HISTORY
Our involvement in cellular therapy for patients with cardiovascular diseases began in 2007 with two Baxter, Inc.-sponsored trials. The first was ACT34-CMI, involving the intramyocardial injection of autologous, G-CSF mobilized peripheral blood cells, enriched for CD34+ cells using immunomagnetic beads for patients with chronic myocardial ischemia to determine the tolerability, efficacy, safety, and dose range for reduction of angina episodes. The second, ACT34-CLI, employed autologous CD34+ cells for patients with critical limb ischemia to assess symptomatic relief and wound healing. For these trials, we provided cell collection, isolation and preparation services for the UF Cardiovascular Medicine Division and a local private hospital. In both cases, the autologous product was collected at our facility, with CD34+ selection performed in-house. Beginning in 2008, our site was named as one of five clinical research centers for the National Heart, Lung and Blood Institute (NHLBI) Cardiovascular Cell Therapy Research Network (CCTRN) for the purpose of conducting trials to test the efficacy of cellular therapies on cardiovascular function for acute and chronic cardiac conditions. To date, this network, www.cctrn.org, has completed enrollment to three clinical trials (TIME, Late-TIME, and FOCUS). All three clinical trials involved collection of autologous bone marrow, followed by in-house enrichment of MNCs using the Sepax device (Biosafe, SA, Geneva, Switzerland), and then preparation of the product for intracardiac injection. Patients were given either the manipulated product or a placebo, both of which were prepared by our laboratory staff, and cardiac function was subsequently evaluated for 24 months (TIME and Late-TIME) and 60 months (FOCUS). In addition, our site served as one of the biorepositories for the CCTRN studies, storing post-processed surplus cells for colony and functional assays. Moreover, we
functioned as the processing laboratory for a satellite site, the Florida Hospital Pepin Heart Institute, Tampa, Florida.

We are currently recruiting subjects into two additional cardiology clinical trials, with a third on the horizon. The NIH NHLBI’s Cardiothoracic Surgical Trials Network (CTSN) Left Ventricular Assist Device (LVAD) Therapy Trial requires intramyocardial injection of allogeneic mesenchymal precursor cells (Mesoblast, Limited) during implantation of an LVAD, and involves receipt, storage, and cell preparation of the allogeneic mesenchymal cells. The second trial, Amorcyte, Inc., AMR-001, entails the intracoronary infusion of autologous bone marrow derived CD34+ selected cells in patients with acute myocardial infarction. Cells are harvested from the bone marrow and selected for CD34+ cells at an Amorcyte, Inc contracted facility, Progenitor Cell Therapy, LLC, using proprietary methods. The goals of both of these trials are to evaluate safety and the effect on cardiac function. In addition, there is an imminent Baxter, Inc.-sponsored study involving intramyocardial delivery of G-CSF mobilized autologous CD34+ cells in patients with refractory angina pectoris and chronic myocardial ischemia, requiring subject apheresis with subsequent offsite centralized CD34+ selection and dose preparation.

APPROACH

Conducting cellular therapies for patients with cardiovascular diseases in our Stem Cell Laboratory provides exposure of the technologists to cutting edge therapies, but also requires enormous preparatory efforts and exquisite coordination among multiple disciplines. Generally, new clinical trials involve preliminary review of the established protocols to determine if our laboratory can provide the required services. We must determine our capability to perform these services within our existing workflow, staffing, budgetary and regulatory constraints. We must also evaluate our facility to determine if we have the capacity to accommodate the clinical trial requirements or if new technologies are needed, such as instrumentation, equipment, supplies and reagents. In situations when our Stem Cell Laboratory Directors are not involved in designing the clinical trial (especially in the case of industry-initiated studies), there is very little, if any, opportunity for protocol modifications. Therefore, each trial becomes a stand-alone effort requiring special attention outside the routine protocols of the laboratory.

Assessing the skillset needed by our staff required for each of these studies is essential. Often, protocols require processes that depart from routine stem cell laboratory protocols, which may necessitate additional validation and training (i.e. new instrument acquisition and surgical protocols). The need for specialized training must be considered and incorporated into the existing workload. Demanding, time-consuming cellular therapy manipulations may take an entire day, which are sometimes cumbersome for our single shift staffing. We attempt to manage this by training multiple staff members in all clinical trials. This enables greater flexibility within the laboratory. However, cross-training laboratory technologists require greater time commitment upfront. In many cases established protocol timelines require creative scheduling, not only for the Stem Cell Laboratory staff, but also for physicians, support staff, and internal/external testing laboratories. Throughout, we must remain vigilant to avoid compromising services for our day-to-day BMT patient population.
Essential for any Stem Cell Laboratory is to ensure that required quality standards and regulations are met. In many cases, we are presented with already approved FDA IND clinical protocols, which were prepared without the benefit of cellular therapy personnel design, or familiarity with FACT (Foundation for the Accreditation of Cellular Therapy) accreditation standards. We must work to reconcile our internal regulatory and accreditation requirements with the (sometimes exacting) requirements of the clinical protocol. This experience has prompted our laboratory directors to make every attempt possible to participate in shaping new cell therapy protocol designs before IND application.

KNOWLEDGE GAINED

Our experiences have taught us that critical, strategic planning plays a key role. An established framework, with continuing process development, and key team member input, contributes to a more streamlined, positive outcome. Early on, we learned the importance of our cardiology colleagues involving us before agreement to participate in a specific trial. Our laboratory must quickly review the project protocol for participation. This translates into collaboration not only between the cardiologists and the Stem Cell Laboratory, but also within the hospital's BMT program, whose staff provides key functions such as collection and infusion, as well as other hospital departments and ancillary testing laboratories. As we participate in more and more trials, we are better equipped to anticipate and assess any bottlenecks, pitfalls, or protocol concerns. In addition, our laboratory directors are actively involved in multidisciplinary meetings with cardiologists, cardiothoracic surgeons and vascular surgeons so that we have opportunities to help shape the science and study protocol.

BENEFITS

Absorbing cardiac cellular therapy clinical trials into our laboratory workflow has been demanding, but has provided us with tremendous benefits, far exceeding the challenges. This experience has allowed us to establish our laboratory at the center of cell-based therapy at UF & Shands and parlay these new skills for other disciplines, such as neurology, endocrinology and ophthalmology. We have found that our newly acquired skillset is marketable within our own academic institution as well as with collaborations with outside institutions. Additionally, we now serve an important role in translational studies and as a reference for future clinical studies. We look forward to providing important contributions to the ever-evolving world of cellular therapy.
IMAGES
REFERENCES


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