In This Issue:

- PI Highlight
- Cell Therapy Technology Transfer in a Global Market Place
- Want to apply to PACT?
- PACT Cell Processing Facilities
- General Facility SOPs

Contact PACT

Please contact the PACT Coordinating Center if you have any questions regarding the PACT program.

Visit our website at: www.pactgroup.net

Contact:
Debbie Wood or Lani Ibenana

Address:
The Emes Corporation
401 North Washington Street
Suite 700
Rockville, MD 20850
Telephone: (301) 251-1161
Email: pactinfo@pactgroup.net

Q: Please describe your clinical and research interests.

A: I have been interested in the use of stem cells to treat neurological diseases for over 25 years. Rather than focusing on neuronal replacement, most of my efforts have been to replace dying or damaged support cells in the brain or spinal cord called astrocytes. As in many cases, astrocyte replacement alone was not sufficient for functional effects in animal models of disease, I began to develop ways to modify astrocytes to release powerful growth factors such as GDNF. This resulted in a reliable protective effect when these cells were transplanted into a number of different disease models including ALS, Parkinson’s disease, Huntington’s disease and Stroke.

Q: How has PACT been a resource for you in pursuing a clinical trial in cell therapy?

A: We were fortunate to be funded by CIRM to do all of the CMC and preclinical work to take a human neural stem cell line engineered to secrete GDNF to the clinic for treating ALS. However, upon scale up at the City of Hope (COH) GMP manufacturing facility we had an unforeseen effect of containing over a billion cells in 1 liter of media prior to vialing. Although viable prior to freezing, upon thaw we only had 40% survival – too low for our clinical trial. With PACT funding, we were able to establish a new production process that batched the cells and allowed for smaller groups prior to freezing. This resulted in successful manufacturing of the final batch of product (1,200 vials) that are currently being used in a Phase I/IIa clinical trial for ALS.

Q: How has your partnership with PACT and the COH Center for Biomedicine and Genetics (CBG) impacted your clinical research?

A: Without the PACT funding we would not have been able to perform the crucial scale up test runs that resulted in a process flow that allowed for optimal survival of the cells following thaw. The NIH funding came at a crucial time in the development of the project and allowed us to complete all other aspects of a very complex CIRM grant and complete our IND submission which was ultimately approved. We hope the final impact of the PACT funding will be to have an effect on ALS – one of the most devastating neurological disorders.

For this I am truly thankful!
Today’s cell therapy market is global with 55 products receiving regulatory approval worldwide as of 2016 (1) and an additional nine products in 2017 (Alexey Bersenev, personal communication). Between stem and progenitor cell therapies for regenerative medicine, correction of genetic defects and restoration of hematopoiesis, there are currently more than 800 clinical trials underway worldwide (2). The majority of clinical trials are sponsored by academic institutions; however, the number of industry-sponsored trials continues to rise (1). The price tag for cell therapy trials is high compared to conventional drugs. While many factors contribute to high pricing associated with cell therapies, a critical factor is the cost of manufacturing the product.

Partnerships are becoming increasingly important to leverage the high cost of bringing cell therapy products to patients. These partnerships result in a concerted effort to share skills, knowledge, technologies, manufacturing methods, manufacturing samples and facilities among governments, universities and industry to ensure that scientific and technological developments are accessible to a wider range of users who can then further develop and exploit the technology into new products, processes, applications, materials or services. Technology transfer may occur among universities, from universities to businesses, from large businesses to smaller ones, from governments to businesses and across borders. Regulatory agencies worldwide are increasingly cognizant of the need to align requirements, to the extent possible, to facilitate universal accessibility to new cell therapy products.

The Center for Biologics Evaluation and Research (CBER) regulates cellular therapy products in the US and uses existing statutes for oversight and to provide scientific and regulatory advice to manufacturers in the area of novel product development (3). Current guidance on manufacturing for cell and gene therapy products provide a graded approach to implementation of good manufacturing practices (GMP) that is consistent with the clinical trial phase; however, the FDA has recently implemented new programs for approval for some cell therapy products that are deemed to fall outside the existing FDA’s pre-market requirements (4). The new policies result, in part, in an effort to implement provisions of the 21st Century Cures Act (5) and include Regenerative Medicine Advanced Therapy (RMAT) (6), Breakthrough Therapy, Fast Track, Priority Review and Accelerated Approval. Approval of cell therapy products via some of these pathways deviate from traditional clinical trial phase progression and bring into question when and how GMP manufacturing is to be implemented. This is to become increasingly
important as the priorities of sponsors are weighed between the time required to develop a robust manufacturing protocol versus the need to accrue patients in clinical trials in a timely manner to meet timelines and milestones aligned with financial goals and limitations. In any case, rapid transition to GMP at the receiving site may seem like an obvious goal, but in practice reckless speed may lead to an unstable process resulting in unnecessary expense and delay. A comprehensive, step-wise approach to technology transfer is in the interest of all parties to provide the framework for future product improvement regardless of the stage of development at the time of transferal.

Figure 2 provides a generalized roadmap with key points to consider when engaged in a technology transfer process. The initial inquiry between potential partners will take account of the scope of work to be accomplished. A well-defined scope of work is the most important aspect of the technology transfer process and will include a review of scientific literature, data and SOPs from the transferring site. An assessment of the access to and suitability of starting materials, supplies, equipment, facilities, skilled labor and technology available at the receiving site will need to be performed in the way of a gap analysis. The scope of work must take into account the time and resources required for assay set-up, comparability studies and validation, as well as the manufacturing process comparability, engineering and validation runs. Time and resources to establish and execute a training program, develop batch records, SOPs, lot-release testing requirements, stability studies and IND documents should all be considered in the scope of work. Once it has been determined that the receiving site has the capability to deliver on expectations, an all-inclusive budget must be established up front to ensure that financial goals are met.

Contract negotiations should proceed coincidentally while the scope of work and budget are undergoing development. Collaboration with the organization’s Office of Technology Transfer and Contracting is essential to establish documents that meet the expectations and protect the interests of all parties. In addition to a confidentiality disclosure agreement (CDA), service and quality agreements must be established. Together these agreements clearly define the responsibilities of all parties as they relate to milestones and time lines to be met, compliance with regulatory agencies, reporting responsibilities, sample storage, retention, testing and transportation. The interval for contract development and to reach consensus will take time but is well worth thorough effort to anticipate obstacles that are surely to arise and thus avoid
misunderstandings that may compromise the relationship and project. Once the manufacturing expectations have been clearly outlined in the various contracts, it is well worth the time and expense to conduct an independent audit to verify that the manufacturing site can meet the requirements agreed upon.

The training plan should begin by allowing receiving site personnel to undergo process development document review. Once all relevant information has been reviewed, the transferring site personnel should plan to participate in observation of and hands-on training at the receiving site. Receiving site personnel perform the process under the observation of transferring site subject matter experts. Receiving site personnel then execute engineering runs of the process in the appropriate environment (i.e., cleanroom). Before the training plan is initiated a draft master batch record is created and all necessary supplies, reagents and equipment are acquired and qualified.

Assays to be developed and/or utilized for in-process and lot-release testing for product safety, purity, identity, potency and stability should be validated prior to initiation of training for the manufacturing protocol itself. Assay validation protocols should meet pre-defined acceptance and rejection criteria, include appropriate reference materials, standards and/or controls and establish accuracy, sensitivity, specificity and reproducibility of the test methods. Comparability testing of relevant assays for the manufacturing protocol under development should constitute the first step of training between transferring and receiving site personnel. Once consensus is reached that the assay testing methods are thoroughly validated, training may begin on the manufacturing protocol itself. This usually commences with an engineering run in which it is agreed upon that steps may be recognized where changes will be recommended or required. This is particularly the case for completion of the master batch record. Having finalized all manufacturing and documentation steps, multiple (usually 3) full-scale validation runs that include all manufacturing, testing and documentation steps are required to ensure that the process will yield reproducible results when employed for clinical use.

Retention samples obtained from the validation runs should be tested to determine the stability of the final product. Stability studies are intended to assign an expiration date and time to the product at the time of release for infusion as well as to determine the stability of a stored product throughout the expected length of the clinical trial. Product characterization and/or potency assays are generally utilized to assess product stability. SOPs may be finalized at this phase and provided to the client and/or regulatory agencies as part of the chemistry, manufacturing and controls (CMC) portion of the investigational new drug (IND) application.
Regardless of the timing of technology transfer (pre-clinical versus clinical trial phase) or the identity of the transferring and receiving sites (industry → academia, academia → industry, academia → academia or industry → industry) following a well-developed technology transfer process will ensure that the project is completed on-time and on-budget. This will greatly facilitate the ultimate goal to ensure that the potential of novel cell therapies can continue to advance to benefit patients who need alternatives for medical problems for which there are limited or unsatisfactory options.

References

Want to apply to PACT?

PACT began accepting applications on February 1, 2017!

If you are interested in applying for PACT services, please review the materials available on the PACT website under the Apply to PACT (http://www.pactgroup.net) tab including information regarding the PACT scope and evaluation criteria used for evaluating PACT applications. If you think your application meets the PACT scope criteria, you may register and apply through the online Application System at any time. You can also contact the Coordinating Center at pactgroup@emmes.com if you need assistance with your application or have any additional questions.

PACT can provide general facility SOPs upon request to assist you in developing your own cell processing facility SOPs.

PLEASE NOTE that these SOPs are for INFORMATIONAL PURPOSES ONLY and therefore require validation by your own facility. To see a full list of SOPs available for request go to the PACT website and look under the Resource Center tab.

SOP Categories available for request:
- Cleaning Procedures
- Deviation Management
- Environmental Monitoring
- Personnel Training
- Quality Assurance / Quality Control
- Quality Management
- SOP: Development and Management
- Validation Process
Below are just a few of the various products and services that PACT offers:

**Progenitor Cells**
C-kit+ cells, endothelial cells, hematopoietic stem cells, MSCs, iPSCs

**Lymphocytes**
Virus-specific T-cells, Tumor-infiltrating lymphocytes (TILs), EBV-transformed B cell lines

**Genetically Modified Cells**
CAR-T-cells, Cytotoxic T lymphocytes, fibroblasts

**Services**
Cell culture isolation, expansion, and cryopreservation, cell depletion/cell enrichment, cell manufacturing for large animal models

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**PACT Cell Processing Facilities**

The following 5 Cell Processing Facilities were awarded for this PACT contract:

**Center for Cell and Gene Therapy**
Baylor College of Medicine
PI: Adrian Gee, MI Biol, PhD
Contract Number: HHSN268201600015I

**University of Minnesota, Molecular and Cellular Therapeutics Facility**
PI: David McKenna, MD
Contract Number: HHSN268201600014I

**Moffitt Cancer Center**
PI: Linda Kelley, PhD
Contract Number: HHSN268201600013I

**Interdisciplinary Stem Cell Institute**
Cellular Manufacturing Program, University of Miami, Miller School of Medicine
PI: Joshua Hare, MD
Contract Number: HHSN268201600012I

**City of Hope, Center for Biomedicine and Genetics**
PI: Joseph Gold, PhD
Contract Number: HHSN268201600011I

**PACT Coordinating Center:**
The EMMES Corporation
Contract Number: HHSN268201600020C

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This project has been funded in whole or in part with Federal funds from the National Heart, Lung, and Blood Institute, National Institutes of Health, Department of Health and Human Services.