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REVIEW

The National Heart, Lung, and Blood Institute-funded Production Assistance for Cellular Therapies (PACT) program: Eighteen years of cell therapy

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Abstract

The Production Assistance for Cellular Therapies (PACT) Program, is funded and supported by the US Department of Health and Human Services' National Institutes of Health (NIH) National Heart Lung and Blood Institute (NHLBI) to advance development of somatic cell and genetically modified cell therapeutics in the areas of heart, lung, and blood diseases. The program began in 2003, continued under two competitive renewals, and ended June 2021. PACT has supported cell therapy product manufacturing, investigational new drug enabling preclinical studies, and translational services, and has provided regulatory assistance for candidate cell therapy products that may aid in the repair and regeneration of damaged/diseased cells, tissues, and organs. PACT currently supports the development of novel cell therapies through five cell processing facilities. These facilities offer manufacturing processes, analytical development, technology transfer, process scale-up, and preclinical development expertise necessary to produce cell therapy products that are compliant with Good Laboratory Practices, current Good Manufacturing Practices, and current Good Tissue Practices regulations. The Emmes Company, LLC, serves as the Coordinating Center and assists with the management and coordination of PACT and its application submission and review process. This paper discusses the impact and accomplishments of the PACT program on the cell therapy field and its evolution over the duration of the program. It highlights the work that has been accomplished and provides a foundation to build future programs with similar goals to advance cellular therapeutics in a coordinated and centralized programmatic manner to support unmet medical needs within NHLBI purview.

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INTRODUCTION

The objective of the National Heart Lung and Blood Institute (NHLBI) Production Assistance for Cellular Therapies (PACT) program is to promote the advancement of clinical research using cellular therapies for replacement or regeneration of damaged/diseased cells, tissues, and organs. PACT also supports targeted cell-based treatments for serious diseases, including orphan indications lacking effective therapies, in addition to translational and early phase clinical research of novel therapies targeting heart, lung, and blood diseases. The development of a successful clinical cell therapy requires technology transfer of research from laboratory-based manufacturing processes and analytical methods to cell manufacturing facilities that are compliant with current Good Manufacturing Practices (cGMP) to fulfill regulatory, safety, and quality standards. PACT reviews requests for investigational new drug (IND)-enabling translational services, as well as clinical cellular therapy manufacturing services in support of an existing IND.

Throughout the 18-year history of the program, PACT invited applications for scientifically meritorious translational development to support progress along IND-enabling pathways to fulfill its primary objective. The PACT program activities included optimizing manufacturing processes, development of analytical methods, and standard operating procedures (SOPs), in support of proof of concept and safety studies using relevant animal models of disease, as well as product manufacture in support of early phase clinical trials within NHLBI's program scope. PACT also provided regulatory assistance to investigators, including gap analysis, review of meeting package materials and questions, and guidance regarding the conduct of the US Food and Drug Administration (FDA) meetings.

PARTICIPATING INSTITUTIONS

The program began in 2003 (PACT 1) with three participating Cell Processing Facilities (CPFs) and then expanded to five CPFs with the program's first competitive renewal in 2010 (PACT 2). In the current and final iteration of the program, July 2016 through June 2021 (PACT 3), five CPFs are contracted to provide cell therapy production and translational services. The Emmes Company, LLC, Rockville, MD, has functioned as the Coordinating Center (CC) continuously throughout. Table 1 lists the participating institutions in each contract. A Steering Committee composed of principal investigators from each CPF and the CC, the NHLBI program officer(s), and an independent, NHLBI-appointed Chair, provides overall governance for the program and oversees the conduct and maintenance of PACT projects.

PROCESSING PACT APPLICATIONS

Investigators from academia as well as small businesses were able to receive PACT support. Investigators with scientifically meritorious and innovative ideas lacking the resources to manufacture cell products for Good Manufacturing Practices/Good Laboratory Practices (GMP/GLP) studies, or other IND-enabling studies at their own facilities, were encouraged to apply. The investigator provided supporting information, including proof of the proposed concept, product characterization

TABLE 1 PACT CPF

Institution	Location	PACT 1	PACT 2	PACT 3
PACT Coordinating Center				
The Emmes Company, LLC	Rockville, MD	•	•	•
Current PACT CPF				
Baylor College of Medicine Center for Cell and Gene Therapy	Houston, TX	•	•	•
University of Minnesota Molecular and Cellular Therapeutics Facility	St. Paul, MN	•	•	•
City of Hope Center for Biomedicine and Genetics	Duarte, CA		•	•
Interdisciplinary Stem Cell Institute, Cellular Manufacturing Program (ISCI-CMP) University of Miami Miller School of Medicine	Miami, FL			•
Moffitt Cancer Center	Tampa, FL			•
Previous PACT CPF				
University of Pittsburgh, Center for Human Cell Therapy	Pittsburgh, PA	•		
Center for Human Cell Therapy – Boston Children's Hospital	Boston, MA		•	
University of Wisconsin-Madison Waisman Biomanufacturing	Madison, WI		•	

Abbreviations: CPF, Cell Processing Facility; PACT, Production Assistance for Cellular Therapies.

data, and a description of product development along regulatory pathways. Request for Service Applications (RSAs) were reviewed by NHLBI to assess if the project met the PACT scope and mandatory criteria, including:

(i) clinical cell products that aid in the repair and regeneration of damaged and diseased cells and tissues;
(ii) cell product manufacturing for preclinical studies, or cell product translational support, including scale up or validation, etc.;
(iii) proposals that further foster and standardize cell therapies; and
(iv) interpreting regulatory requirements for the study of cellular therapies under an FDA-approved IND.

An external Scientific Review Board, convened by the PACT CC, independently reviewed the RSA and provided scientific recommendations for NHLBI's consideration. Clinical and translational applications were reviewed in a two-tiered process (scope and full review). Schematics for the review and approval process for Clinical/Translational and Regulatory RSAs are provided in Figure 1.

Confidentiality and intellectual property considerations were addressed prior to the start of any work, and the CPF staff worked collaboratively with the investigator to develop the project timeline and milestones. Clinical and translational application requests were accepted through May 1, 2020. Requests for regulatory-only assistance were accepted through December 4, 2020.

Clinical product manufacturing support

Support for cell therapy products for early phase clinical trials began under the PACT 1 and 2 awards (2003–2015) and resumed in late 2018, 1 year after the renewal of the program under PACT 3. Clinical product manufacturing support included development of product-specific manufacturing SOPs and batch production records, validation of manufacturing processes, and preparation of the Chemistry, Manufacturing, and Control (CMC) section of the IND application. Additional assistance has included establishment of prospectively defined process and manufacturing controls, equipment validation, product release testing and specifications, and preparation of the analytical development plan, including methods qualification/validation, and development of certificates of analysis. When the program began in 2003 only clinical product manufacturing services were offered, based on the stated needs of the research community. However, once the program was initiated, it became apparent that a large proportion of projects required substantial non-, or preclinical translational development to successfully complete their IND applications and initiate phase I clinical trials. Therefore, PACT added the category of translational development services to the program. In the first iteration of PACT (2003–2010) requests for clinical product manufacturing services predominated, but in the second iteration of PACT (2010–2015) requests for clinical product manufacturing made up a smaller proportion of the requests for services due to an expanding number of requests for translational development services.

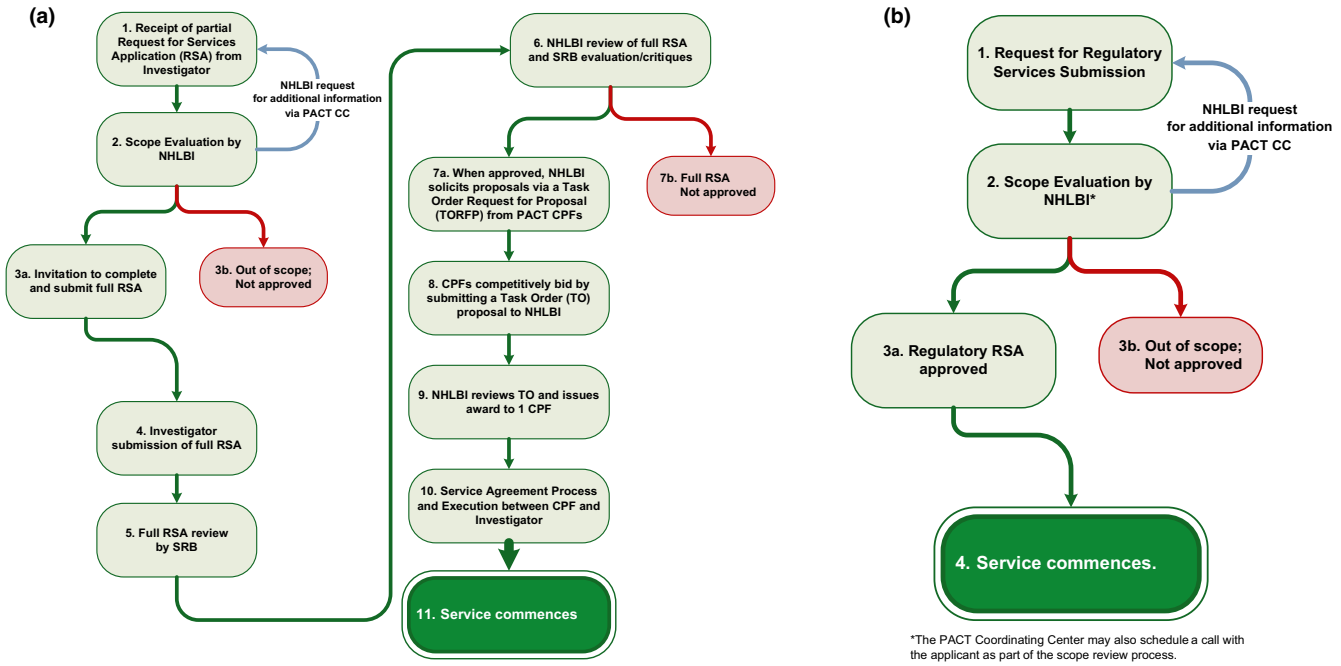

FIGURE 1 RSA review and approval process. (a) Clinical or translational RSA review and approval process. (b) Regulatory RSA review and approval process. CPF, Cell Processing Facilities; NHLBI, National Heart Lung and Blood Institute; PACT, Production Assistance for Cellular Therapies; RSA, Request for Service Applications; SRB, Scientific Review Board

Translational development services

PACT has supported cell therapy manufacturing for pivotal preclinical studies requiring adherence to GLP, Good Clinical Practices (GCP) and cGMP products, including safety and toxicology (specifically genotoxicity and tumorigenicity). Translational services supported product development, including technology transfer, equipment suitability, process scale-up, qualification of clinical grade production components, development of aseptic manufacturing processes, and development and qualification of bioanalytical methods for the conduct of nonclinical studies.

Regulatory support

Regulatory support available under PACT 1 and 2 focused on assistance from the CPFs with preparation of the CMC section for IND submissions. Beginning under the PACT 3 award and based on feedback from PACT-supported investigators, broader regulatory support was made available to investigators through the PACT CC. Regulatory support was provided alone or in combination with other services. The PACT CC performed gap analyses, assisted with regulatory strategy, preclinical study requirements, and provided guidance for meeting requests and briefing packages for Initial Targeted Engagement for Regulatory Advice on Center for Biologics Evaluation and Research (CBER) Products (INTERACT) and pre-IND discussions with the FDA. Upon approval, the PACT CC conducted a kick-off call with the client to further discuss and assess client provided deliverables prior to conducting a gap analysis. Services were provided based on the client's objectives, stage of product development, and upon reviewing materials, data and reports prepared by the client. In 2019, the NHLBI began providing regulatory support in the Cure Sickle Cell Initiative (CSCi) program via PACT, including products following the investigational device exemption (IDE) pathway, support for electronic common technical document (eCTD) submissions, and quality assurance of manufacturing control processes. Regulatory support is provided by the CC to approved investigators through the end of the program.

PACT PROGRAM HIGHLIGHTS AND ACCOMPLISHMENTS

Product manufacturing support

Since inception and through May 1, 2020, PACT has supported a total of 133 full (clinical or translational) applications (Figure 2). Specifically, in the PACT 3 period of performance, a total of 73 scope applications were submitted, with the majority being for translational support (Table 2). There were 47 applications approved for a full application. Of the 39 full applications submitted, 23 were approved. Additional application metrics are provided in Table 3. Regulatory requests could be submitted as a combination request with clinical or translational applications.

Of the 21 translational projects that were approved under the PACT 3 award, 10 have been completed (as of December 14, 2020). With requests for clinical support resuming in 2018, 12 complete clinical RSAs were submitted before the RSA cutoff date of May 1, 2020, with two clinical RSAs approved. Of the remaining 10 clinical applications, five were deemed not to be within scope of the NHLBI PACT program, four were considered to be of modest importance that it would only incrementally contribute to the field, and one was rejected because the requested manufacturing services could not be completely conducted within the program period of funding.

Regulatory support

One of the highlights in PACT 3 has been the regulatory support offered through the CC. Drug, biologic, and device investigators have access to a regulatory team that can provide detailed review and feedback in preparation for the FDA meetings or submissions, which is invaluable to investigators even where institutions also have internal regulatory affairs programs. Through PACT, the NHLBI has been able to offer regulatory support for other NHLBI/National Institutes of Health (NIH) programs, including the NHLBI CSCi and the NIH Regenerative Medicines Innovation Project (RMIP).

In PACT 3, regulatory support has been an expanded service with 27 applications approved. No regulatory applications were rejected (one application remained incomplete/not submitted). Regulatory activity on four applications has been completed as of December 4, 2020, and support for current projects will begin close out/closure before the program end date. The PACT 3 program has completed regulatory gap analysis requests for these applications, followed by tailored support for the applicant based on their product development pathway. The program supported three INTERACT meetings and five pre-IND meetings as of December 4, 2020. Support has been provided for an initial IND submission (Quarter 3 2020), which followed support for INTERACT and pre-IND meetings with CBER. A list of the approved regulatory projects and services provided by the PACT CC in PACT 3 through December 4, 2020, is shown in Table 4.

In some instances, investigators who had submitted requests for translational manufacturing services that were rejected after scientific review due to an inadequate product development plan were recommended by the program to submit a regulatory request for a gap analysis. In these situations, the gap analysis either assisted the applicant to strengthen and subsequently write a clear and complete development plan that resulted in a new, successful translational service application, or provided a

	Translational			Clinical			*Regulatory
System Organ Class	PACT 1	PACT 2	PACT 3	PACT 1	PACT 2	PACT 3	PACT 3
Cardiac disorders	4	11	9	11	0	0	9
Immune system disorders	5	8	4	5	8	0	4
Neoplasms, benign and malignant	6	1	0	10	3	0	0
Congenital, familial and blood genetic disorders	1	3	3	2	0	0	9
Infections	1	4	1	6	3	1	1
Respiratory, thoracic and mediastinal disorders	1	5	1	2	1	1	1
Injury, poisoning and procedural complications	0	0	1	1	1	0	1
Congenital, familial and genetic disorders	0	1	0	0	0	0	1
Eye disorders	0	2	0	0	0	0	0
Metabolism and nutrition disorders	1	0	0	1	0	0	0
Musculoskeletal and connective tissue disorders	1	1	0	0	0	0	0
Nervous system disorders	0	1	0	0	0	0	1
Skin and subcutaneous tissue disorders	0	1	0	0	0	0	0

*Regulatory requests were only available in PACT 3
Total number of requests supported by PACT = 160

FIGURE 2 List of projects supported by PACT program since inception by SOC and by application type (translational, clinical, and regulatory) as of December 4, 2020. PACT, Production Assistance for Cellular Therapies; SOC, standard of care

TABLE 2 PACT 3 scope RSAs submitted by application type

RSA application type	Total
Translational development only	34
Regulatory assistance and translational development	7
Regulatory assistance only	16
Clinical manufacturing only	11
Regulatory assistance and clinical manufacturing	5
Total	73

Abbreviations: PACT, Production Assistance for Cellular Therapies; RSA, Request for Service Applications.

TABLE 3 PACT 3 application metrics

Event	Total[a]
RSA Scope Approved – Full RSA	47
RSA Scope Approved – Regulatory RSA	27
Scope RSAs Rejected – Full RSA	10
Scope RSAs Rejected – Regulatory RSA	0
Full RSAs Approved	23
Full RSAs Rejected	16
Task Order RFPs Issued	23
Task Orders Awarded[b]	31

Abbreviations: PACT, Production Assistance for Cellular Therapies; RSA, Request for Service Applications.

[a]Seventy-three Scope RSAs were submitted during PACT 3; 12 were combination regulatory/full RSAs.

[b]Includes eight Task Orders awarded for two technical projects.

framework for product development for projects that were found to not yet be ready for PACT manufacturing services. Early regulatory discussion focused on the suitability of nonclinical and manufacturing information to support proposed investigational studies and inform ongoing product development efforts.

Advancing the science

The broad array of disease classifications that have been covered by PACT-supported services is highlighted in Figure 2 (grouped per MedDRA, System Organ Class level). Over 80 publications cite PACT support of new investigational studies. Many of these are for projects completed with PACT 1 and PACT 2, as work from PACT 3 is ongoing and results are pending publication. Papers continue to be published by recipients in industry and academia citing support from PACT. The following three disease areas (related to general categories from Figure 2) and area of PACT support in cell therapy manufacturing and testing are some of the most significant advancements in which PACT has played a role during its 18 years.

Hematopoietic cell transplantation: Infections and immune system disorders

A significant example of the achievements of PACT has been its support of the clinical development of virus-specific

TABLE 4 List of regulatory projects and services provided

Product/Project	Sponsor	Gap analysis	INTERACT and pre-IND meeting package	IND submission
CD83 CAR T cell	Academic	✓		
iPSC-derived cardiomyocytes	Commercial	✓	✓	
Exosome-educated macrophage	Academic	✓		
MSCs	Academic	✓		
MSCs	Academic	✓		
FVIII TCR-engineered Treg cells - regulatory support	Commercial	✓	✓	
CRISPR/Cas9 modified autologous human hematopoietic stem cells	Academic	✓	✓	✓[a]
PIM1 – CSCs - regulatory support	Academic	✓		
Analytical validation of the SCD Biochip assays	Academic	✓		
Modified CRISPR/Cas Gene Editing	Commercial	✓		
Gene-edited CD34+ hematopoietic stem and progenitor cells	Commercial	✓		
CD34+ HSPC product	Academic	✓		
hiPSC-derived cardiac progenitor cells	Academic	✓	✓	
hiPSC-derived cardiac progenitor cells	Academic	✓		
hiPSC-derived cardiac progenitor cells	Academic	✓		
Small-molecule derived muscle progenitor cells	Academic	✓		
CRISPR/Cas9 gene modified autologous hematopoietic cells	Academic	✓	✓	
pSTAT3-inhibited iTregs	Academic	✓		
Wharton's jelly derived MSCs	Academic	✓		
Umbilical tissue-derived MSC product	Commercial	✓		
UCB-derived MSCs	Academic	✓		
AAV6 vectors for HSC gene editing	Academic	✓		
Nanoparticle-delivered CRISPR gene edited blood stem and progenitor cells	Academic	✓		
CDR-MBL CAR T cells	Commercial	✓		
Closed cell culture of iPSCs	Commercial	✓		
Closed, automated cell culture of dendritic cells	Commercial	✓		
Tissue engineered vascular grafts	Academic	✓		

Abbreviations: CAR, chimeric antigen receptor; hiPSC, human-induced pluripotent stem cell; HSC, hematopoietic stem cell; IND, investigational new drug; iPSC, induced pluripotent stem cell; MSC, mesenchymal stem cell; TCR, T-cell receptor.

[a]IND submitted in common technical document (CTD) format.

T-cells (VSTs) used to treat viral infections following hematopoietic stem cell transplantation (HSCT). In patients undergoing HSCT, new infections and reactivations of endogenous viruses remain a major source of mortality and morbidity, despite the continued development of new antiviral molecules. In the first project of PACT 1 in 2006, Baylor College of Medicine (BCM) Center for Cell and Gene Therapy produced therapeutic Epstein-Barr Virus (EBV), cytomegalovirus (CMV), and adenovirus specific T-cells (triVSTs) from HSCT donors. To generate triVSTs, EBV-transformed B lymphoblastoid cell lines (LCLs) generated from each HSCT donor were used as antigen-presenting cells (APCs). LCLs were transduced with an adenovirus vector expressing pp65 of CMV. LCLs effectively processed and presented endogenously expressed EBV antigens, as well as the pp65 transgene and virion proteins derived from the adenovirus vector to autologous peripheral blood mononuclear cells (PBMCs). After several stimulations over 3–4 weeks, sufficient triVSTs were obtained for infusion. After infusion, polyclonal "trivirus"-specific CD4+ and CD8+ T-cells expanded exponentially in the presence of virus and eliminated clinical signs and symptoms of viral disease, without causing graft versus host disease (GVHD) or any other toxicities.[1]

Although these trials illustrated the safety and clinical efficacy of small doses of VSTs, the generation of the clinical product took about 12 weeks: 6 weeks to generate the LCL, 4 weeks for triVSTs and 2 weeks for quality control (QC). Hence, in 2012 through the PACT 2 program, the BCM CPF

produced "rapidly generated multiVSTs" specific for five viruses (EBV, CMV, adenovirus, BK virus, and human herpesvirus 6 [HHV6]). PBMCs were pulsed with overlapping peptide libraries representing two or more proteins from each virus and expanded for just 10 days in the presence of cytokines using G-Rex bioreactors. These culture vessels, which were evaluated by PACT investigators, use a gas-permeable membrane that allows for large media volumes without compromising gas exchange.[2] MultiVSTs were successfully administered as prophylactic and therapeutic agents, in the absence of toxicity.[3] However, 10 days of culture followed by 14 days for QC testing is usually too long for a patient with refractory viral disease. To make VSTs available for all patients within an almost immediate time frame, multivirus-specific T-cells were evaluated as off-the-shelf products to treat partially Human leukocyte antigen (HLA)-matched recipients with viral infections in a multicenter clinical trial supported by the NHLBI and coordinated by Emmes.[4] Allogeneic VSTs were almost as effective as stem cell donor-derived VSTs, producing complete or partial responses in 92% of recipients.

In continuation of this work, PACT 3 is now supporting another project at BCM for the production of a bank of 15 allogeneic T-cell lines specific for four viruses (tetraVSTs) that can be used to treat partially HLA-matched recipients with refractory infections caused by EBV, CMV, adenoviruses, and BK virus. To further reduce the already low incidence of GVHD, tetraVSTs will be enriched for VSTs by (1) removal of CD45RA+ PBMCs that contain nonspecific bystander cells and (2) using two antigen-specific stimulation steps. This move to "off-the-shelf" cell therapies is highly desirable in the cell therapy field, as it dramatically reduces not only the time to deliver the product, but also the expense, while increasing overall feasibility. Off-the-shelf products can be generated from blood bank eligible, healthy donors selected for optimal function of their T-cell product and can be used to treat up to 30 patients without a requirement for expensive master cell bank testing. The problems facing off-the-shelf products are graft rejection and GVHD, both mediated by alloreactive T-cells in the host and donor product, respectively. Although not a significant problem using VSTs in the HSCT setting, in immunocompetent patients, graft rejection will be more powerful, whereas GVHD may be more of a problem using polyclonally activated T-cells. Currently, there is great interest in gene editing of T-cell receptors (TCRs) to prevent GVHD and HLA molecules to prevent rejection. The efficacy of these strategies in the clinic should become evident in the near future.

The University of Minnesota (UMN MCT) worked on the clinical-scale production of cGMP-compliant CD3/CD19 cell-depleted natural killer (NK) cells, and a paper has been published summarizing the evolution of NK cell manufacturing at their institution.[5] The UMN MCT also supported work on optimization of cGMP purification and expansion of umbilical cord blood-derived T-regulatory cells in support of first-in-human clinical trials to prevent GVHD in patients undergoing HSCT.[6]

CARDIOLOGY

Because adult cardiomyocytes are postmitotic, regenerative medicine approaches to treating cardiovascular disease have suffered from a shortage of suitable cells. Whereas pluripotent stem cells have the ability to be differentiated to both cardiac progenitor cells and bona fide cardiomyocytes, the scale of production of these cells has been too limited to allow for evaluation of cell replacement strategies in appropriate large animal models of heart disease and for the production of doses (hundreds of millions to billions of cells) required for clinical use. PACT supported several projects at City of Hope and University of Miami aimed at improving cell production methods for generation of replacement cells.

At the City of Hope, several projects were to support preclinical work using NIH-approved human embryonic stem cells to derive cardiomyocytes. Under PACT, these cells were developed using a refined manufacturing process. The investigators were able to develop SOPs for scalable suspension culture to produce cGMP pluripotent stem cell-derived cardiomyocytes.[7] The IND-enabling studies for this project have been completed and the IND was submitted in 2019; the clinical trial was approved in Quarter 2 2021. Human embryonic stem cell-derived cardiomyocytes (ESC-CMs) were also provided for use in preclinical studies, which showed efficacy in a nonhuman primate model of cardiac infarction.[8]

An important achievement of the University of Miami has been its support of translational medicine aiding the path from bench to bedside in the development of clinical cellular and cell-derived therapeutic products primarily but not exclusively for treatment of cardiovascular diseases. Approved projects awarded to the University of Miami under PACT 3 included the isolation and expansion of human and animal stem cells and other cell-derived biologic products, preparing them for their use in preclinical research and other IND-enabling studies that contribute to the development of clinical trials. The IND-enabling and clinical grade cellular product manufacturing performed at the University of Miami CPF included: (a) a fibroblast working cell bank for induced pluripotent stem cells (iPSC) manufacturing (b) iPSC and iPSC-derived cardiomyocytes, and (c) iPSC and iPSC derived CPCs. One of the product development projects at the University of Miami is the reprogramming of human mesenchymal stem cells (MSCs) into iPSCs using a sendai virus followed by differentiation into cardiac progenitor cells (CPCs), which will be used in a porcine cardiovascular disease model to evaluate their potential for repair of cardiac deficiencies.

The University of Miami was also awarded a developmental project to design a large-scale manufacturing strategy

to produce bone marrow-derived MSC extracellular vesicles (BMSC-EVs) for use in pre-IND studies and to overcome difficulties in manufacturing of sufficient lot sizes for use in large animal trials. The CPF adapted the Quantum Bioreactors (TerumoBCT) for large-scale expansion of bone marrow (BM)-MSCs, followed by the collection of the MSC-conditioned media and downstream isolation of EVs. Nanoparticle analysis, flow cytometry surface marker analysis, and miRNA sequencing were all used to characterize the final products.

Cardiac C-Kit + stem cells (CSCs) are a cell type currently under investigation for regenerative therapies. However, logistical challenges to cell production include slow proliferation rate, product heterogenicity, and cellular senescence. In prior research, the University of Miami basic science laboratories demonstrated that 5% O_2 was optimal for C-kit + CSC expansion. In a PACT 3 project, the CPF compared CSC products prepared under standard 21% O_2 to those prepared in 5% O_2 and observed changes in proliferation rate and cell characterization. The starting material for this project was cardiac biopsies from pediatric patients. Fresh biopsies were processed and plated in 21% or 5% O_2 and expanded to passage 1 (P1). After P1, cells were sorted for C-Kit + protein expression and further expanded to P3 before cryopreservation and phenotypic analysis by flow cytometry. Compared to adult biopsies evaluated in previous clinical development trials, pediatric biopsies were much more efficient for cell growth. Five percent oxygen was the optimal oxygen tension for cell proliferation and expansion. Surface marker analysis provided a stronger induction of endothelial surface markers in 5% O_2. In conclusion, 5% O_2 was the optimal oxygen concentration for cell expansion, however, it resulted in a final cell product with more endothelial-associated markers. Further research is required to determine the effects of this change on cell regenerative potential.

Recently, Dr. Hare and colleagues performed a meta-analysis of arrhythmia end points that showed that non-skeletal myoblast transendocardial cell therapy was associated with a significantly lower risk of sudden cardiac death or resuscitated sudden cardiac arrest, compared to control, with no proarrhythmic effects.[9,10]

Respiratory disorders

PACT, through the University of Minnesota, supported IND-enabling preclinical safety studies in sheep that demonstrated BM-derived MSCs could be safely delivered intravenously in a large animal model of acute lung injury.[11] Following a phase I dose-escalation safety study, a 60-subject, multisite phase IIa clinical trial showed that PACT-produced MSCs were well-tolerated and showed a trend for improvement in oxygenation index in the treated group.[12] A phase IIb trial jointly supported by the Department of Defense and PACT 3/NHLBI is underway at the time of writing this manuscript.

The Madison-Waisman Clinical Biomanufacturing Facility (PACT 2 CPF) manufactured the MSCs used in the phase I clinical study, which showed the feasibility, safety, and tolerance of BM-derived MSCs for obstructive chronic lung allograft dysfunction.[13]

Cell therapy manufacturing and testing

Consistent with work conducted under PACT 1 and 2, the PACT 3 program has leveraged its consortium of five centers to foster group collaboration toward advancement of cell therapy manufacturing and testing. Technical projects in PACT 1 and 2 included Endosafe assay evaluation[14]; bone marrow/Isolex evaluation[15]; validation of the shipping of human cellular products[16]; G-Rex cell culture device evaluation[2]; assays of MSC characterization and potency assay studies[17]; and optimization of cryopreservation methods for MSCs.[18] Technical projects in PACT 3 included (i) the evaluation of a cell washing device, and (ii) testing various cryopreservation media. A paper describing the first technical project is in preparation, whereas the second technical project is ongoing at the time of writing this manuscript. The CPFs also benefited through work on PACT projects, including the development of more robust internal policies for technology transfer.[19] PACT CPF principal investigators have participated and presented in the International Society of Cell Therapy (ISCT)-hosted Cell Therapy Liaison Meetings with industry and regulatory stakeholders to present challenges and needs in the cell therapy field to the FDA.

PACT education and outreach

One of the objectives of PACT is its education and outreach to the cell therapy community. The PACT program has produced web seminars since 2005. Topics have included academic and industry partnerships, early phase development, cGMP manufacturing of cardiac cells, and guidance on IND submissions. Many of these web seminars offered Continuing Education (CE) credits to attendees free of charge. A list of the PACT 3 web seminars that have been conducted are provided in Table 5.

PACT has also provided education to the cell therapy community through knowledge sharing. Early in the PACT program the CPFs chose to share template SOPs in areas that are critical to the establishment of a cGMP CPF. There have been over 85 requests for SOPs under the PACT 3 award, and over 485 requests over the span of the program, for SOPs describing Cleaning Procedures, Deviation Management, Environmental Monitoring, Personnel Training, and Quality Assurance/

Quality Control. These SOPs have been requested to aid in the preparation of facility-specific SOPs at new or established cell therapy facilities. PACT's impact has been global, with the requests for SOPs originating from 22 countries.

Information on the program has been disseminated through PACT participation and presentations at relevant scientific meetings, through the networks of the participating CPFs, and the PACT website. The requests for clinical and translational service support have come from various geographical locations throughout the United States.

PACT coordinated the 2009 publication of the book "*Cell Therapy: cGMP Facilities and Manufacturing*" with contributing authors internal and external to the PACT program. The field has advanced tremendously since then and Dr. Adrian Gee, the lead editor, realized the need for an updated and expanded edition, which PACT is also coordinating. Submission to the publisher took place in early 2021. The book is a key project representing culmination of the PACT program and a valuable resource for cell therapy researchers at various levels of interest and/or engagement in clinical product development for years to come.

PACT has collaborated with organizations and investigators to better understand the challenges and needs currently facing the cell therapy industry. PACT convened an "Expert Evaluation Panel" with broad cellular therapy expertise to provide information on gaps and opportunities of the program. In an Investigator's Meeting planned by the PACT program in 2018, a panel of investigators shared their successes as a direct result of the program and identified common and critical challenges still faced by cell therapy researchers in advancing products through the development pathway. This meeting was instrumental in identifying a need for and stimulating the expanse of regulatory services provided by the PACT program.

DISCUSSION

Since its inception in 2003, the NHLBI's PACT program has significantly impacted the support, guidance, and education of both the academic and industrial cell therapy communities. PACT has supported a wide variety of cellular therapies in preclinical and clinical applications following cGMP, GLP, and GCP guidelines. PACT has conducted primary research in areas of potency assay development, cryopreservation, cellular therapy shipping protocols, and testing novel cell therapy devices that would benefit the cell therapy community. Several investigators have returned to receive additional PACT support to continue product development, including initiation of clinical studies. The impact of individual projects, whether the work was translational, early phase clinical trials, or both, can be difficult to assess because the science is still evolving and not always linear. PACT services that

TABLE 5 List of PACT 3 web seminars

Date	Web seminar title
5/24/2021	The COVID−19 Pandemic: Challenges and Opportunities for Cell Processing Facilities (Registration open at time of writing this manuscript)
12/15/2020	Contract Manufacturing by and for Academic Institutes 179 individual registrations; 50 CE and/or SOP requests
9/3/2020	Methods for Cellular Therapies: Tracking Cells In Vivo and Assessing Biodistribution in Patients – What are your cells doing? Where do they go? 228 individual registrations; 51 CE and/or SOP requests
7/17/2020	Cell Therapy GTP and GMP Facilities: Design and Operation to Optimize Space to Meet Manufacturing Needs 217 individual registrations; 100 CE and/or SOP requests
12/10/2019	Guidance for Submission of an Initial IND Application 179 individual registrations; 66 CE and/or SOP requests
9/10/2019	Vendor Qualification 158 individual registrations; 56 CE and/or SOP requests
2/11/2019	Accelerating Your Cell Therapy: A PACT Program Update 107 individual registrations; CE not offered
11/8/2018	Issues Involved in Starting CAR T Cell Manufacturing 241 individual registrations; 90 CE and/or SOP requests
6/19/2018	Development of GMP Cell Manufacturing of Cardiac Stem Cells 190 individual registrations; 68 CE and/or SOP requests
1/16/2018	Early Phase Cell Therapy Product Development: Potency Assays 207 individual registrations; 62 CE and/or SOP requests
9/26/2017	Early Phase Cell Therapy Product Development: Quality in the Lab 217 individual registrations; 62 CE and/or SOP requests
1/16/2017	Early Phase Cell Therapy Product Development: Potency Assays 89 individual registrations; 32 CE and/or SOP requests
3/14/2017	Accelerating Your Cell Therapy 85 individual registrations; CE not offered

Abbreviations: CE, Continuing Education credit; GMP, Good Manufacturing Practice; GTP, Good Tissue Practice; PACT, Production Assistance for Cellular Therapies; SOP, Statement of Participation.

supported early trials of activated NK cells or expanded T regulatory cells as adjuvant therapies with HSCT may have very likely contributed to manufacturing feasibility, safety and efficacy of cell therapies such as gene-modified, chimeric antigen receptor (CAR)-NK cells and CAR-T regulatory cells.

Regulatory support that began in PACT 3 further rounds out the capability of the program to offer the comprehensive support that many investigators require to facilitate the FDA interactions. Peer reviewed publications, webinars, pre-IND, and IND applications for early phase trials are a testimony to that role. Although regulatory pathways have become more established over time, many investigative groups still find those pathways unclear and burdensome. PACT has been able to provide regulatory guidance to help navigate those challenges and move products forward in the development life cycle. PACT clients have found it valuable to obtain regulatory guidance on submission materials prior to FDA review, including formulation of questions to pose to the FDA, and supporting content on manufacturing, and suitability of nonclinical information in support of proposed investigational studies. Continued investigation of approaches that address these challenges throughout all stages of preclinical and clinical development, from well-defined potency assays to therapeutic biomarkers in human clinical studies, should help support studies of the safety and efficacy of cellular products. The PACT program has given significant support to these objectives.

For future programs to be successful in impacting the cell therapy field, a central coordinating center with strong understanding of the science as well as strong leadership and resources for program management is key. PACT was able to expand awareness of the program through years of outreach and presence in relevant cell therapy scientific meetings and developed a base audience. PACT's education initiatives, technical projects, web seminars, and other activities were driven by the CC but supported by the contributions of each of the CPFs as subject matter experts. As with any consortium, it is challenging to work in a collaborative nature with each individual entity having its own competing priorities and limited resources, so any opportunity to provide incentives for participating organizations is beneficial. The PACT CC kept a cumulative bibliography of publications resulting from PACT-supported projects at each CPF and metrics related to the applications and application review process. It is important that the CC establish objectives and metrics by which to track program progress and successes.

PACT had three contracts spanning 18 years, which was a key factor to success and is critical for future programs successfully accomplishing its objectives to advance the field of cell therapy. There was a 1.5-year hiatus of services between the second and third contracts, which disrupted some of the momentum into the final contract, but, overall, this duration enabled some investigators to develop their product over multiple years of support. Translational research is iterative in nature and, while the goal is to reduce the product development timeline, researchers benefit from having consistent support from a single cell manufacturing facility for its overall product development lifecycle and this also reduces the need for technology transfer or for comparability studies. The program had the benefit of two CPFs, Baylor College of Medicine and University of Minnesota, and the CC, The Emmes Company, LLC, participating from the beginning which helped in anchoring the program as other centers joined or left. It also took time to develop education and training programs as part of overall objectives. For example, the first web seminar was held only after 2 years and PACT averaged two web seminars per year in the first two iterations, but in the last iteration PACT averaged three web seminars per year.

In PACT 3, discussions began in the area of workforce training with the goal to facilitate this with local organizations and community colleges, but further efforts on this front ended when the decision was made to not renew the program. Workforce training remains a key challenge to be addressed by the cell therapy community as there remains a substantial need to supply skilled personnel for a spectrum of projects ranging from early stage academic research to biotech startup space as well as to later-stage or GMP-stage manufacturing settings. The overarching objective is to foster productive interactions between industry and workforce and, although PACT was not able to move this forward, a future program that could facilitate advancing these efforts would be extremely valuable to the cell therapy community. These activities include development of effective training programs and opportunities, fostering professional development of the workforce, easing recruitment bottlenecks due to workforce shortages, and finally contributing to the economic success of one of the nation's most competitive fields in biopharmaceutical development. To be successful, commitment to workforce training and other identified critical needs for the cell therapy community need to be a long-term vision and shared goal at the outset of the program with strong leadership from a coordinating center that can leverage the strengths of each of the participating organizations.

When the PACT program was initiated by the NHLBI in 2003, the need for complex cell manufacturing services for use in clinical trials primarily served to meet the development of cellular therapies that were adjunct to allogeneic hematopoietic cell transplants as well as the nascent field of regenerative medicine for cardiovascular disease. Thus, PACT was able to help support the rapid expansion of cell therapies for use in the treatment of blood and heart diseases. The program expanded from three to five cell manufacturing centers in order to meet demand and to expand the available expertise within the program. Another lesson learned from the PACT program is the benefit of early interactions

between investigators and GMP facilities, in order to speed the translation of basic research to clinical projects. With collaboration between novice clinically oriented investigators and facilities experienced in the manufacture of cell-based therapeutics, problems arising from dependence on clinically unsuitable raw materials and/or unscalable processes can be circumvented before they complicate clinical development. One of the more recent challenges to the PACT program and to academic cell manufacturing facilities in general is growing diversity and needs associated with specialized cell manufacturing technologies and equipment, such as 3-D printing. The ability of a few centers to have a broad range of available technologies and expertise to meet the need of all potential customers will continue to become more challenging as the state of the art in regenerative medicine expands.

Critical unmet challenges for cell therapies include the heterogeneity of cellular products due to both donor variability and cell manufacturing strategies and the limited understanding of the role that cellular therapy can play in the treatment of numerous diseases, the elucidation of mechanisms of action and potency assays for cell therapies, broad agreement on release testing requirements for autologous and allogeneic therapies, the development of fully closed systems for the production of cellular therapies at the point of care, logistics surrounding product delivery and administration, product stability over time, and the reliability of preservation techniques. Rather than being diminished by these challenges, the promise of cellular therapy has instead grown, as evidenced by the landmark regulatory approvals for CAR T cells for the treatment of hematologic malignancies.

The current successes and continued investment in research will ensure that cellular therapies continue to grow and achieve the desired goals of providing definitive benefit for heart, lung, and blood diseases. Although the PACT program ended in June 2021, programs, such as PACT, foster collaboration and address clinical and translational manufacturing, regulatory support, education and training needs, and will continue to be vital for the advancement of this field. Future programs will need to account for the growing complexity and need for specialized cellular manufacturing in order to meet the needs of academic research for regenerative medicine. The importance, however, of collaboration and leadership in a coordinated and centralized manner, as demonstrated by the successful model established by PACT, should be considered in the establishment of next-generation programs.

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CONFLICT OF INTEREST

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REFERENCES

1. Leen AM, Myers GD, Sili U, et al. Monoculture-derived T lymphocytes specific for multiple viruses expand and produce clinically relevant effects in immunocompromised individuals. *Nat Med*. 2006;12(10):1160-1166.
2. Bajgain P, Mucharla R, Wilson J, et al. Optimizing the production of suspension cells using the G-Rex "M" series. *Mol Ther Methods Clin Dev*. 2014;1:14015.
3. Gerdemann U, Keirnan JM, Katari UL, et al. Rapidly generated multivirus-specific cytotoxic T lymphocytes for the prophylaxis and treatment of viral infections. *Mol Ther*. 2012;20(8):1622-1632.
4. Leen AM, Bollard CM, Mendizabal AM, et al. Multicenter study of banked third-party virus-specific T cells to treat severe viral infections after hematopoietic stem cell transplantation. *Blood*. 2013;121(26):5113-5123.
5. Williams SM, Sumstad D, Kadidlo D, et al. Clinical-scale production of cGMP compliant CD3/CD19 cell-depleted NK cells in the evolution of NK cell immunotherapy at a single institution. *Transfusion*. 2018;58(6):1458-1467.
6. McKenna DH, Sumstad D, Kadidlo DM, et al. Optimization of cGMP purification and expansion of umbilical cord blood-derived T-regulatory cells in support of first-in-human clinical trials. *Cytotherapy*. 2017;19(2):250-262.
7. Chen VC, Ye J, Shukla P, et al. Development of a scalable suspension culture for cardiac differentiation from human pluripotent stem cells. *Stem Cell Res*. 2015;15(2):365-375.
8. Liu YW, Chen B, Yang X, et al. Human ESC-derived cardiomyocytes restore function in infarcted hearts of non-human primates. *Nat Biotechnol*. 2018;36(7):597-605. Erratum. In: Nat Biotechnol. 2018;36(9):899.
9. Schulman IH, Khan A, Hare JM. Interdisciplinary Stem Cell Institute at the University of Miami Miller School of Medicine. *Circ Res*. 2018;123(9):1030-1032.
10. Fernandes GC, Fernandes ADF, Rivera M, et al. A meta-analysis of arrhythmia endpoints in randomized controlled trials of transendocardial stem cell injections for chronic ischemic heart disease. *J Cardiovasc Electrophysiol*. 2019;30(11):2492-2500.
11. Asmussen S, Ito H, Traber DL, et al. Human mesenchymal stem cells reduce the severity of acute lung injury in a sheep model of bacterial pneumonia. *Thorax*. 2014;69(9):818-825.
12. Matthay MA, Calfee CS, Zhuo H, et al. Treatment with allogeneic mesenchymal stromal cells for moderate to severe acute respiratory

distress syndrome (START study): a randomised phase 2a safety trial. *Lancet Respir Med*. 2019;7(2):154-162.
13. Keller CA, Gonwa TA, Hodge DO, Hei DJ, Centanni JM, Zubair AC. Feasibility, safety, and tolerance of mesenchymal stem cell therapy for obstructive chronic lung allograft dysfunction. *Stem Cell Transl Med*. 2018;7(2):161-167.
14. Gee AP, Sumstad D, Stanson J, et al. A multicenter comparison study between the Endosafe® PTS™ rapid-release testing system and traditional methods for detecting endotoxin in cell-therapy products. *Cytotherapy*. 2008;10(4):427-435.
15. McKenna DH Jr, Adams S, Sumstad D, et al. CD34+ cell selection using small-volume marrow aspirates: a platform for novel cell therapies and regenerative medicine. *Cytotherapy*. 2010;12(2):170-177.
16. Whiteside TL, Griffin DL, Stanson J, et al. Shipping of therapeutic somatic cell products. *Cytotherapy*. 2011;13(2):201-213.
17. Bloom DD, Centanni JM, Bhatia N, et al. A reproducible immunopotency assay to measure mesenchymal stromal cell-mediated T-cell suppression. *Cytotherapy*. 2015;17(2):140-151.
18. Pollock K, Sumstad D, Kadidlo D, McKenna DH, Hubel A. Clinical mesenchymal stromal cell products undergo functional changes in response to freezing. *Cytotherapy*. 2015;17(1):38-45.
19. Landin A, Mailloux A, Kelley L. Incorporating gene editing source materials into the cell and gene therapy manufacturing workflow. *PACT Newsletter*. 2020;15(3):2-5.

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