



**2013**

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February 20, 2013

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Submitted electronically to: [mondorot@nhlbi.nih.gov](mailto:mondorot@nhlbi.nih.gov)

Re: Request for Information (RFI): Production Assistance for Cellular Therapies (PACT) (NOT-HL-12-165).

Dear Dr. Mondoro:

The American Society of Hematology (ASH) appreciates the opportunity to provide input in the deliberations of the National Heart, Lung, and Blood Institute (NHLBI) regarding the renewal of the Production Assistance for Cellular Therapies (PACT) program in response to the RFI NOT-HL-12-165 issued on January 13, 2013.

ASH represents more than 14,000 clinicians and scientists worldwide committed to the study and treatment of blood and blood-related diseases. These diseases encompass malignant hematologic disorders such as leukemia, lymphoma, and multiple myeloma and non-malignant conditions such as sickle cell anemia, thalassemia, aplastic anemia, venous thromboembolism, and hemophilia. In addition, hematologists have been pioneers in the fields of stem cell biology, regenerative medicine, bone marrow transplantation, transfusion medicine, gene therapy, and the development of many drugs for the prevention and treatment of heart attacks and strokes. ASH membership is comprised of basic scientists, physician scientists, and physicians working in diverse settings, including universities, hospitals and private practices.

Hematologists are currently working on some of the most costly and devastating medical problems that affect health care in the United States. Our members are pioneers in development of cellular therapies for chronic and acute hematologic diseases that have been translated into other fields of medicine. Hematologists are developing novel treatments for anemia associated with chronic diseases like cancer and chronic kidney disease. They are also devising alternatives to blood transfusions and enhancements of bone marrow transplantation through the use of umbilical cord blood, stem cells and other technologies.

Recent impressive advances in treating chronic myeloid leukemia, multiple myeloma, sickle cell anemia, thrombosis, and other hematologic disorders have all depended on support from the NIH and the NHLBI. Importantly, the new therapy related to molecular correction of diseases, “gene therapy,” is increasingly a standard approach to many genetic diseases of the blood. This modality relies on extensive *ex vivo* manipulation of blood stem cells in specialized cell processing laboratories.

ASH strongly supports renewal of the PACT program and urges the NHLBI to continue this highly successful initiative that has become a valuable resource for investigators conducting research in the area cellular therapies for blood and other diseases. Below are ASH’s comments that address the specific questions posed in the RFI.

### **The PACT Program Remains Necessary**

PACT was initiated to bridge “The Valley of Death” in the development of cell therapy. The valley lies between the pre-clinical studies that show promising benefit and the early phase clinical trials necessary to validate the approach and open the way to further development and the involvement of commercial entities. Bridging the valley requires extensive Good Laboratory Practice (GLP) and current Good Manufacturing Practice (cGMP) resources.

Although the field of cellular therapeutics is burgeoning with some, albeit limited, interest by pharmaceutical and biotechnology companies, the need for a PACT-like program remains greater than ever. None but the largest academic institutions can afford to commit the long-term resources required for GMP facilities required for the manufacture, testing and release of cellular products that meet all necessary U.S. Food and Drug Administration (FDA) guidelines. While establishing infrastructure for cGMP can often be achieved, it is important to bear in mind that cGMP is a *process*. It requires continuous large scale efforts to provide highly trained personnel who can develop, write, validate, follow and revise Standard Operating Procedures, validate equipment and air and facility cleanliness, provide quality assurance and quality control and review batch records for product release. The required high staffing levels can only be cost-effective if they are constantly employed in product manufacture/testing/release, so that very high fixed costs can be distributed among many products rather than a few. It is noteworthy that the fixed costs of a GMP facility greatly exceed the marginal costs of product manufacture. Consequently, small scale institution-based facilities can rarely be sustained long term.

Fortunately, it is now feasible to freeze and store almost all cell products made by PACT. Those that cannot be frozen are sufficiently stable for shipping within the United States. Thus, a limited number of central facilities can provide the manufacturing needs of the nation.

PACT has succeeded very well in its task. It has manufactured a range of blood and marrow-derived products that have been used by many NHLBI and other NIH investigators to bring their therapeutic products to the clinic. Several of these studies are already showing promising clinical data and may improve current medical therapy for otherwise intractable diseases.

During its existence, PACT has also helped to develop a cadre of highly trained and experienced individuals invested in the development of new cell therapeutics whose combined skill set is unequalled anywhere in the world and who can provide exceptional assistance to new clinical investigators to successfully transition their approach from the laboratory to the clinic. This intellectual resource should be retained.

### **Continuing Contributions of PACT**

To maintain its role as a resource to the scientific community, ASH suggests that PACT continue making the following contributions:

1. PACT should continue in its present role of developing and manufacturing promising pre-clinical cellular agents. In particular, PACT should continue to work with investigators and use GLP to develop specific pre-clinical products so that they can be manufactured under GMP conditions using the most appropriate scalable techniques for clinical use.
2. PACT should continue its education role and work closely with the relevant Societies such as ASH and federal agencies such as the FDA to guide the safe and effective development of the field.
3. PACT should continue its collaborative efforts to validate GMP cell culture methodologies and perform studies comparing the clinical activities of particular cell types generated through different manufacturing processes.
4. PACT should continue to manufacture master banks and reagents that may be used by many investigators in the field.

### **New PACT Contributions**

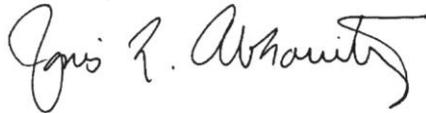
To ensure that PACT remains a valuable resource that meets the evolving needs of the scientific community, ASH suggests the following additional contributions that PACT should offer in the future:

1. PACT should be expanded to add new Centers that bring novel skills, for example, using induced pluripotent stem (iPS)-derived cells for *specific* applications.
2. PACT may also expand its reach so to include manufacturing of products used for the treatment of non-hematological disorders such as solid cancers. This would likely require additional/joint funding from other Institutes but be a more efficient use of NIH resources than the alternative of establishing a separate parallel program for the same purpose.
3. PACT should consider taking on a role as a cell-banking facility for products with clinical benefit and whose activity does not require exact tissue matching with the recipient, for example mesenchymal stromal cells and virus-specific T-cells for immunocompromised hosts.

4. PACT should provide additional training and guidance for the preparation of regulatory submissions and reports beyond their current commitments to manufacturing issues.
5. PACT should *not* be diverted into performing generalized or early pre-clinical studies of potentially promising broad approaches to cell therapies, such as iPS. The early pre-clinical development phase of cellular therapies is better supported by existing translational research grant mechanisms. PACT *should*, however, work on the development of specific products for specific clinical applications.

The American Society of Hematology looks forward to working with the NHLBI to make sure the PACT program is renewed and maintained as a valuable resource for the scientific community. ASH will be happy to provide further information and be a resource for the NHLBI. Please contact ASH Senior Manager for Scientific Affairs, Ulyana V. Desiderio, PhD, at (202) 776-0544 or [udesiderio@hematology.org](mailto:udesiderio@hematology.org) for any additional information.

Sincerely,

A handwritten signature in black ink, appearing to read "Janis L. Abkowitz". The signature is fluid and cursive, with a large initial "J" and a long, sweeping underline.

Janis L. Abkowitz, MD  
President