preimmune fetal sheep, resulted in up to 5% human hematopoietic engraftment. More than 20% albumin-producing human parenchymal hepatic cells with absence of cell fusion as well as substantial numbers of human cardiomyocytes in both atria and ventricles of the sheep heart were detected still over one year following USSC transplantation. No malignant cell transformation was observed in any of these animals.

21

CORD BLOOD CRYOBIOLOGY: IMPACT ON TRANSPLANT OUTCOMES

Creer, M.H. Department of Pathology and Pediatrics, St. Louis University, St. Louis Cord Blood Bank, St. Louis, MO.

The therapeutic potential of cord blood (CB) for hematopoietic stem/progenitor cell (HSC) transplantation is primarily limited by the number (dose) of functionally viable HSC administered to the transplant recipient. The process of cryopreservation and thawing of CB products is the single greatest and most variable source of HSC loss from collection to infusion and the effects of cryopreservation and thaw on CB HSC function are inherent in all published comparisons of CB versus BM or PBSC transplant outcome. We performed a series of studies to examine the effects of cooling rate (CR) and type of cryoprotectant (DMSO, propanediol) on CB HSC cell number (TNC and CD34), viability (trypan blue, 7-AAD) and function (CFU assay) post-thaw. Varying the CR from −1 to −20 deg. C/min. had little effect on recovery (%) of CB HSC number and trypan blue viability (%), however, CB HSC function (CFU recovery (%)) decreased markedly at CR above −5 deg. C/min. Monitoring of the CR of cord blood units is subject to artifacts arising from alterations in thermistor probe placement necessitating careful review of cooling curves and on-site validation of the cryopreservation system. Frozen CB units placed in liquid N_2 must occasionally be transferred to other locations or temporarily removed from liquid N_2 for retrieval of attached segments exposing the unit to potential warming effects (PWE). Transfer of CB units in Styrofoam containers with liquid N_2 or segment removal in liquid N_2 vapor does not cause any detectable loss of HSC number, viability or function. Similarly, repeated exposure of frozen CB units to 10 consecutive 1 min. intervals at room temperature also had no significant effect on HSC number, viability or function. We conclude that transient warming during CB unit transfer or segment removal does not result in measurable PWE.

22

Implementation of the FDA Regulatory Approach to Cells and Tissue: Focus on Cord Blood

Lazarus, E. Division of Human Tissues, Office of Cellular, Tissue, and Gene Therapies, Center for Biologics Evaluation and Research, FDA.

How is cord blood regulated?

In response to the initiative to "reinvent" the regulation of human tissue, the FDA published the Proposed Approach to Regulation of Cellular and Tissue-Based Products (Federal Register 2/28/1997). To implement this approach, three new rules are to be codified in 21 CFR 1271:

Establishment Registration and Listing
Donor Eligibility
Current Good Tissue Practices (cGTP)

All manufacturers of human cells, tissue, and cell and tissue-based products (HCT/P), including cord blood, will be required to comply with these regulations when finalized. HCT/Ps that have a metabolic function such as cord blood require additional controls; these products are also regulated as biologics under the authority of section 351 of the Public Health Service Act.

Cell or tissue products requiring FDA premarket approval meet any of the following criteria:

- Expanded, activated, genetically modified or otherwise more than minimally manipulated
- Combined with a drug or device, with some exceptions
- Labeled or advertised for non-homologous use, such as HPC delivered for cardiac repair
- Clinical effect is systemic or dependent upon the metabolic activity of the cells, except if for autologous use, or use in a first or second-degree blood relative. Example: allogeneic, unrelated donor cord and peripheral blood stem/progenitor cells

Phase-in of FDA approval requirements for some hematopoletic progenitor cell products (HPC)

Allogeneic unrelated minimally manipulated HPC for hematopoietic reconstitution require assurance of clinical safety and effectiveness. Cord blood and peripheral blood stem/progenitor cell products from unrelated donors are subject to "phase-in" of IND and licensure requirements. As described in the Federal Register notice entitled "Request for Proposed Standards for Unrelated Allogeneic Peripheral and Placental/Umbilical Cord Blood Hematopoietic Stem/Progenitor Cell Products; Request for Comments" published 1/20/1998, standaros may be developed for these HPC products if data exist to show safety and effectiveness when manufactured in accordance with certain defined product specifications and process controls.

Finalization and Implementation of 21 CFR Part 1271: current status

Finalizing the three rules that together will be codified as 21 CFR Part 1271 is a current FDA priority. The establishment registration and listing final rule was published in January 2001. The establishment registration and listing interim final rule, published in January 2004, explains that all HCT/P establishments are now required to register and list as of March 29, 2004, with the exception of those manufacturing human heart valves and dura mater. This interim rule will be revoked when all of Part 1271 becomes effective.

The final donor eligibility rule was published on May 25, 2004, and becomes effective on May 25, 2005. It is accompanied by draft guidance that provides recommendations for complying with the requirements in the donor eligibility rule. Comments on the draft guidance should be received by August 23, 2004 (90 days from the publication date) to ensure consideration in the final guidance. The rule is available on FDA's website at www.fda.gov/OHRMS/DOCKETS/98fr/97N-484S-nfr0001.pdf and the guidance is available at www.fda.gov/cber/gdlns/tissdonor.pdf. Publication of the final GTP rule is expected soon. The changes to the final rules address many of the concerns raised by cell therapy and blood bank professional associations and establishments, submitted as comments to the docket.

Possible issues for international exchange with the U.S.

Non-U.S. manufacturers are required to annually register with FDA if their HPC products are used in the U.S. These manufacturers must complete the form 3356 and indicate a U.S. Agent. All donor testing must be performed in CLIA accredited laboratories using FDA cleared/approved test kits. Currently there are more than 40 registered HPC facilities outside of the U.S.

Summary

Implementation of the regulatory approach to human cell and tissue products is nearing completion. The period of enforcement discretion for unrelated donor cord blood is ongoing, pending determination of whether there are adequate data to support a standards-based approach to licensure. Cord blood manufacturers currently must register with the FDA, and will be required to comply with DE and GTP requirements when finalized and effective.

Information Available

The website at www.fda.gov/cber/tiss.htm has links to the downloadable Form 3356 (Registration/listing), all published documents and letters; and relevant meeting minutes, summaries, transcripts, and presentations. The e-mail address for registration questions is tissuereg@cber.fda.gov.