

Re: Clare Pomeroy Award

Nominee's name: Philip H. Coelho

Nominated by: George Barry

Product name: BioArchive System, introduced in 1998

Product description: Robotic cryogenic system for the Controlled Rate Freezing, LN2 storage and retrieval of cord blood stem cell units

Background / historical perspective

Prior to the advent of Cord Blood banking, mammalian cells were routinely frozen in a variety of ways (-30°C mechanical freezer, -80° C mechanical freezer, nitrogen controlled rate freezer) and stored at -80° C or -120°C mechanical storage freezers or -135°C, -196°C nitrogen vapor storage dewars. Very little effort was expended to seek an optimized method to achieve the highest post-thaw cell viability because the cells were either used for research purposes or, as in the case of frozen red blood cells, there were so many cells that small (10-30%) losses were of no consequence to the patient. This situation changed dramatically, beginning in 1993 as a result of four factors:

- Following the first successful transplant, in 1992 The New York Blood Center (NYBC), under the direction of Dr. Pablo Rubinstein, established the first public cord blood bank, the NYBC National Cord Blood Program (NCBP) which collected its first donated cord blood unit in 1993 and provided the first unrelated transplant in August 1993.
- Banking of HLA typed units of hematopoietic stem cells sourced from cord blood (CBSCU) began and the economic viability of this venture, and clinical benefit to patients, required the stored cells to be viable, post thaw, more than a decade after storage.
- The dose of viable stem cells (number/patient weight) was identified as critical to timely engraftment and patient survival.
- Using practices common for freezing mammalian cells for a little as six months, losses in cell viability of 50%, or more were common---a catastrophic situation for an ablated patient undergoing hematopoietic reconstitution.

The Problem

It soon became clear that new technologies had to be developed that would provide pharmaceutical grade Good Manufacturing Practices (GMP) for processing and banking HLA typed CBSCUs that would assure cell viability when required by a matching patient---perhaps decades later. The fact that collected volumes of cord blood varied widely---from 30 mL to 300 mL---significantly complicated the standardization of every aspect of the processing, cryogenic freezing and storage of the CBSCU. Initially, the collected cord blood would be placed in large freezing bags and aluminum canisters, frozen in -80° C freezers and stored in racks of ~10 units in conventional LN2 Dewars. The manual transfer of units from the -80° C freezer to the conventional LN2 Dewar and, subsequent retrieval for shipment to transplant centers required removal of entire racks of CBSCU units into the ambient air in order to retrieve the chosen one, followed by a return to cryogenic temperatures of the other units for re-storage. The multiple transient warming events (TWEs) that occur during these transfers reduce the colony forming activity of the cells and lead to delayed engraftment in patients. These losses are proportional to the number of TWE exposures and their durations.

The Solutions

First, in 1994, and working with Dr. Pablo Rubinstein, Mr. Coelho developed the first processing bag set to reduce the frozen volume, adding hetastarch followed by centrifugation to remove excess red blood cells and plasma and achieve a uniform final volume of 20 mL containing essentially all the stem and progenitor cells (US 5789147). This invention allowed the automation of cord blood banking to develop. For example, as this 20 mL volume would be consistent for all units, a universal 5 mL mixture of specially formulated cryoprotectants could be pharmaceutically manufactured in quantity that would optimize the cryopreservation of CBSCUs.

Second, as all cryoprotected cord blood units would now occupy the same volume (25 mL) Mr. Coelho, in 1995, developed a 25 mL freezing bag with a geometry that would allow precise, identical freezing curves for each unit optimized for the highest cell viability (US 6146124). These CBSCUs would be housed within a dedicated, magnetic stainless steel canister that could be engaged by a robotic arm for transfer of the units to and from storage under LN2 (US 213334).

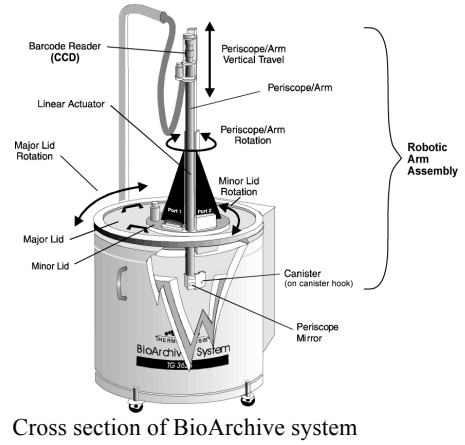
Third, Mr. Coelho developed the BioArchive System that inventories up to 3626 of these cord blood stem cell unit canisters under LN2 (US 5638686). This robotic system also performs, and electronically records, the controlled rate freezing of each unit in the gas phase above liquid nitrogen and robotically transfers the unit to its assigned storage address under liquid nitrogen within the same Dewar.



Freezing bag and canister



BioArchive System



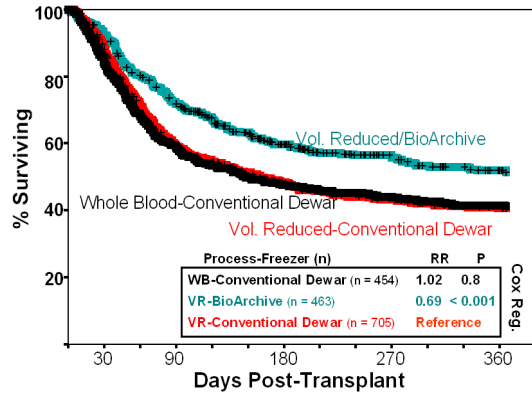
Cross section of BioArchive system

Cryobiologists have long been aware that biological activity hibernates at the intrinsic temperature of liquid nitrogen (-196°C) that is maintained by the chilling effect of the continuously evaporating nitrogen --- exactly matching the rate of heat invading the vacuum jacketed dewars. Considering the substantial expense required to bank many thousands of HLA typed CBSCUs, and potential risks should these units not contain sufficient numbers of viable cells upon thaw, it became advisable to store all samples at -196°C±0°C (under the liquid nitrogen). Further, considering the patient harm that would occur if the wrong CBSCU were transplanted, the ability to have error-free tracking of inventory.

In order to satisfy both of these urgent needs, the BioArchive robotic arm confirms the identity of a CBSCU when it enters the controlled rate freezing (CRF) module and assigns it an address under LN2. After freezing the CBSCU is robotically transferred to this address. When retrieving a desired CBSCU from its address in liquid nitrogen, the robotic arm first confirms its identity by reading the canister barcode under LN2 and then transports the unit into insulated sleeves positioned within a retrieval module. Thus, CBSCUs processed in the BioArchive System are not exposed to the frequency or severity of TWEs that occur with conventional dewars and manual transferring of units into and out of storage racks.

Performance, market acceptance and clinical outcomes

After extensive testing, NYBC's National Cord Blood Bank reported to the FDA that post thaw cell viability of CBSCUs processed in the BioArchive was 96 +/- SD 4.8%. Subsequently, the FDA allowed these CBSCUs to be transplanted in humans in 1999. Since then, 81 of the largest cord blood banks in thirty countries have upgraded from conventional, manually operated nitrogen dewars to the BioArchive System. Worldwide, a total of 208 BioArchives with a collective storage capacity of over 750,000 CBSCUs were in operation by January 2010. It is estimated that at least 75% of the more than 30,000 transplants provided worldwide have come from cord blood banks that have adopted the BioArchive technology. In 1996, NYBC's NCBP reported improved survival (p <0.001) of patients that received a CBSCU processed in the BioArchive system when compared to patients that received a CBSCU processed at NCBP prior to their adoption of the BioArchive technology.



Sincerely,

George Barry
co-founder, Syngeneis Inc.