CELL & GENE THERAPY INSIGHTS

SUPPLY CHAIN FOCUS: BIOPRESERVATION & COLD CHAIN LOGISTICS

CHANNEL CONTENT

INTERVIEW

How will COVID-19 impact the cord blood banking sector?

WOUTER VAN'T HOF holds a PhD in Cell Biology from Utrecht University in the Netherlands, and has over 15 years of biotech experience in the USA in translational research and development of adult stem cell therapies, including bone marrow stromal cells (MSC) and HPC, cord blood. He is currently Cord Blood Bank Director of the Cleveland Cord Blood Center (CCBC). Under his direction, CCBC obtained FDA approval for the manufacture and distribution of HPC, Cord Blood under federal license, as one of only eight nationally licensed cord blood banks in the USA. As Cord Blood Bank Director he oversees Laboratory Operations, including CMC, Process Validation, Aseptic Processing, and GMP compliance. In addition, Wouter leads the Cell Therapy Incubator (CTI), a new CCBC initiative facilitating internal and external programs for broader development of cord blood cell-based therapies in regenerative medicine. From 2002 to 2013, he was a Director at Athersys, Inc., with responsibility for technology transfer, product and process development, preclinical safety, and was deeply involved in regulatory discussion for clinical study design and management of a GVHD prophylaxis trial. He was the scientific lead on the completed Phase 1 safety study in HSCT support for the MultiStem Product. During his academic career, Dr Van't Hof was an Assistant Professor of Cell Biology in Medicine, Department of Medicine, Division of Pulmonary and Critical Care Medicine, and Assistant Professor of Genetic Medicine, Institute of Genetic Medicine, Weill Medical College of Cornell University.

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Q What are you working on right now at your cord blood bank?

WVH: My main responsibility in my day job as Cord Blood Bank Director at the Cleveland Cord Blood Center is ensuring that the laboratory operations for cord blood processing, archiving and distribution are functioning properly, and remain in sync with the upstream cord blood collections and the downstream quality review for timely product release for hematopoietic cell transplant. As the only public cord blood bank in the State of Ohio, we procure cord blood at 5 collection sites: two in Cleveland, OH, two in Atlanta, GA, and one in San Francisco, CA. The other locations were chosen to increase collection of cord blood units from minority groups that remain underserved in the cord blood inventories. Since its start in 2008, CCBC has collected more than 70,000 cord blood units. On a daily basis these collected units are shipped to the processing facility in Cleveland, OH, for centralized processing, cryopreservation and frozen storage. CCBC currently has over 10,000 frozen clinical-grade units in inventory and listed in the NMDP and WMDA searchable databases. To date, we have shipped more than 670 cord blood units to transplant centers throughout the USA and in 17 countries world-wide. We are one of only 8 FDA licensed cord blood banks in the USA and remaining compliant and dealing with regulatory inspections requires ongoing attention. Here I am very fortunate that our small organization does an outstanding job in systematically and efficiently dealing with licensure and accreditation expectations. I am very proud of our CCBC staff, some of whom have been with CCBC from the very early days in 2008 and 2009, much longer than my own involvement. With the compliance programs on track and well monitored, the door opens for me to work on areas of organizational need and professional interest.

Q Can you describe those mentioned incremental cord blood needs and interests?

WVH: Another core aspect of our mission is to make cord blood that is not used for processing available for research and development. Our center has provided over 11,500 research-grade units to investigators in both academic and biotechnology organizations. We believe this is crucial, both for the future of our cord blood bank and for the industry. Along this line, CCBC, which is a non-profit entity, established two social enterprise subsidiaries in 2020, to focus on the next iteration of its mission. Enabling the use of donated cord blood, beyond HCT, into the bigger realm of regenerative medicine is a major objective of these new efforts. So, the other part of my day job is leading the Cell Therapy Incubator (CTI), one of the two new CCBC subsidiaries. The CTI is housed in a

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separate facility with GMP capability, built for execution of programs that increase utilization of collected cord blood, and/or support development of new cord blood based cell therapy products or technologies. Initial CTI projects are producing non-clinical grade isolated CD34 cells from cord blood. We see increased demand and opportunity for this as a consistent source material in the biotech environment, with a growing number of companies developing cord blood derived NK cells, Tregs and other specialty products. Ultimately, we want to support manufacture of clinical grade CD34 or cord blood derived cell products. For now, the nonclinical production arm boosts higher utility of collected cord blood, which is a cornerstone of the CCBC mission. In these beginning stages of the subsidiary, I am pursuing new collaborations and contracts. With new research funding opening up for COVID-19, we are receiving many requests for our clinical grade materials, so that is keeping us busy at the moment.

Q Can you outline the technical procedures in your cord blood cell banking and processing work, including those relating to biopreservation?

WVH: Our processes are based on US regulatory and international accreditation compliant procedures and technologies, standard in the industry, with certain specific iterations. We only collect cord blood via umbilical cord puncture in utero, rather than from the delivered placenta, using a single use FDA cleared collection bag set containing CPD anticoagulant. This approach minimizes contamination risk during collection. It also allows for collection at shorter time after delivery, with better chance of obtaining the required volume and cell numbers. If those requirements are met, collected cord blood is then processed. CCBC uses the AXP AutoXpress™ System from Thermogenesis. This is a semi-automated process using centrifugation to separate cord blood into three separate fractions, red blood cells, white blood cells, and a RBC/plasma fraction obtained by volume reduction of the white cell fraction. The white blood cell fraction, containing the desired hematopoietic stem and progenitor cells, becomes a minimally manipulated product, specified as HPC, Cord Blood. This

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final product is formulated in a 25 mL volume, supplemented with 10% DMSO and 1% dextran. The freezing bag itself is divided into a 5 and a 20 mL part, both sealed to allow future use separately, where desired. Importantly, before freezing, each HPC, Cord Blood unit is placed into a sealed overwrap bag to minimize any cross-contamination risk during storage. We must keep in mind that product sterility testing is not completed until 2 weeks after freezing, and that there is a 5–10% baseline for cord blood contaminations, mostly related to collections. This physical cord blood quarantining is a very important aspect of inventory protection and is now demonstrating its relevance in the context of the current COVID-19 pandemic.

As is standard in our field, cryopreservation must be initiated within 48 hours of the time of cord blood collection. The start is defined as the insertion of the canister with the processed unit into the automated, controlled-rate freezing element of the BioArchive® System from Thermogenesis. BioArchives® are big liquid nitrogen units or dewars that accommodate long-term storage of up to about 3,600 units in liquid nitrogen at -196°C, with continuous monitoring. Associated computer modules assign a specific address to each frozen unit inside the freezer inner storage structure, allowing for controlled retrieval. Each stored product is tested for purity, identity, sterility, and potency. Upon batch record review, units complying with donor eligibility and product requirements are released from administrative quarantine and made available for search by transplant centers. We ship the majority of our units through the National Marrow Donor Program logistics system. There is obviously much more underlying detail, but this is the gist of the technical aspects around our inventory and its use.

Q You mentioned COVID-19. Can you frame for us the potential threat it presents to the cord blood banking field?

WVH: As for anybody else, all of our staff are directly impacted by the federal, state and local stay at home directions. We have implemented a minimal staffing strategy to ensure sufficient staff presence on site to monitor and manage our liquid nitrogen storage systems, and to accommodate any cord blood unit requests for transplant. This has worked out well, and we have continued to ship out units efficiently, a few of those within 24 hours of receiving the request. This process requires final review by operations, medical and quality staff members, most working from home, but it is good to see we can handle this under the current societal constraints caused by the pandemic.

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With respect to our products, the general threat of COVID-19, as with any tissue, blood or cell contaminant, is in theory very serious and could endanger all ongoing collections, our future products, and their use. We don't think that's what is actually transpiring. At this time, (early May 2020) outside of the risk for staff in delivery wards, the reality looks like the cord blood industry might hopefully be spared from major harm. COVID-19 is widely understood to not migrate from the mother via the placenta to the cord blood, minimizing risk for the baby. This is a very different scenario from the Zika virus threat a few years back. Absence of COVID-19 in cord blood also means it remains safe to collect and process donated cord blood and it justifies continued cryopreservation of cord blood collected during the active pandemic. Our cord blood collection sites have mostly remained open and actively collecting. Processing at our center in Cleveland has also managed to continue under minimal staffing strategies, with appropriate and workable social distancing procedures. We have been encouraged by production rates remaining very similar as to prior to the pandemic. This may not be the case for all public cord blood banks.

A hidden threat could be that with emergence of more sensitive tests, this coronavirus might in the future actually be found in cord blood stored during the pandemic, with different associated risks. First, in each BioArchive® unit, all frozen units are submerged in a singular liquid nitrogen supply, not in the liquid nitrogen vapor phase. In theory, over the commonly long storage times of cord blood, virus could leak from contaminated frozen cord blood bags, compromising an entire inventory within a shared BioArchive® unit. This is a possible, but very unlikely risk scenario. It would require virus to survive long-term in liquid nitrogen and pass through the walls of two different types of bags. As mentioned earlier, all cord blood units are individually wrapped within protective overwrap bags, so the risk for spread of infectious organisms from contaminated bags and subsequently into 'clean' products is really very minimal. In terms of use of the products, coronavirus contaminated units obviously would not be acceptable for transplant, especially in immune-compromised recipients. Transmission of infectious agents from tissue or blood cell donors to recipients is a major regulatory concern, and COVID-19 would fall right under that. So if coronavirus would be detected in cord blood, we may be asked to include coronavirus testing for product release and reject at risk units. That could have a great impact on units produced since late 2019. On a side note, but related to this topic, current prophylaxis strategies for transplant include more potent combinations of antibiotic, antifungal and antiviral agents. This allows transplant physicians nowadays more aggressive risk-benefit considerations with 'risky' cord blood products, within reason, and especially for patients in immediate critical need. Such considerations are made, for example, for cord blood carrying CMV risk. There also appears to be different responses to COVID-19 between children and adults, and the risk-benefit balance may have different answers for different age groups. Again, these are theoretical considerations, I am not a transplant physician, and in no way should

"...protecting our bank from the COVID-19 impact will involve closely following new regulatory guidance and ... technology development..."

this be construed as a defensive or self-serving statement, advocating risky strategies to benefit use of potentially coronavirus-tainted cord blood. On the contrary. But things do change over time, and a current contamination risk, perceived or not, may become less of an acute problem – for example, with advancement of antiviral agents.

Q What's the current consensus of opinion in terms of whether COVID-19 is having, or will have, an impact, and what steps are you and others in the field taking now to respond?

WVH: If anything, believe it or not, the coronavirus pandemic might actually result in broader use of cord blood as a transplant strategy. Procurement of adult hematopoietic stem cell products, which are bone marrow or mobilized peripheral blood derived, is impacted more directly by coronavirus. The involved collection procedures for adult grafts include more virus exposure risk between donors and collectors. Adult HSCT products are mostly used 'freshly', within short times (hours to days) after collection and with less opportunity for testing prior to transplant. Donations for bone marrow and peripheral blood have gone down, in large extend due to travel restrictions not allowing donors to get to collection centers. However, cord blood, as a frozen and tested product, obtained prior to the COVID-19 pandemic, remains readily available for safe use without virus transmission risk. It is too early to tell how this will play out, as all transplants have largely been put on hold by the worldwide lockdowns and stay at home directions in March and April of 2020. Any new trends in cord blood transplant as a consequence of COVID-19 will unlikely become evident before transplant centers open back up again sometime in 2020. Meanwhile, protecting our bank from the COVID-19 impact will involve closely following new regulatory guidance and keeping an eye on technology development for coronavirus testing in people and products. Finally, the scrutiny from our past regulatory and accreditation reviews, and numerous inspections, has taught us how to implement appropriate documentation and control systems. This will ensure required safety and activity of our cord blood products, even for those manufactured during a global threat of an infectious virus. I must tell you that some of these inspections are no picnic, and again, kudos to our dedicated staff. But under current circumstances, it is encouraging to know that we are following due process, to the best of our knowledge and in line with industry standards. We are controlling what is within our area of control. This awareness provides a great morale boost under strain, be it caused by Zika, COVID-19 or any future challenge.

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