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Cord blood expansion has arrived

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In this issue of *Blood*, Horwitz et al[1] report the results of an important phase 3 trial comparing a standard unmanipulated single or double umbilical cord blood (UCB) transplantation (UCBT) to a single UCB unit that was expanded ex vivo for 21 days with nicotinamide in combination with stem cell factor, Flt3 ligand, interleukin-6, and thrombopoietin (omidubicel).

Omidubicel resulted in superior neutrophil engraftment (12 vs 22 days), faster platelet recovery (55% vs 35% recovery to 20 000 by day +42), lower incidence of viral and fungal infections, and more time out of hospital in the first 100 days posttransplant compared with patients who received unmanipulated UCBT. Lymphocyte subset analysis revealed faster B-cell and natural killer (NK) cell recovery in omidubicel recipients. These results will be submitted for review shortly to the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), and omidubicel may become the first licensed standard-of-care expanded UCB product for clinical use.

Ever since the first UCBT, performed by Gluckman and colleagues in 1988, high rates of delayed or failed engraftment have been a major issue, given the inherently limited number of stem and progenitor cells in a single UCB unit compared with bone marrow or peripheral blood progenitor cell grafts. Barker and team in Minnesota pioneered the use of 2 unmanipulated UCB units to enhance engraftment in adults, thus allowing for more patients to receive this lifesaving therapy. However, even with a double UCBT, the median time to neutrophil engraftment is significantly delayed (26 days) compared with recipients of a sibling or unrelated transplant (16-19 days), resulting in higher treatment-related mortality.[2] To overcome this challenge, several expansion strategies have been developed to reduce the time to neutrophil and platelet engraftment in UCBT recipients (see table). Given concerns that a single expanded UCB unit may not retain the pluripotent stem cells necessary for long-term engraftment, these studies included the infusion of 2 UCB units, where 1 unit was expanded ex vivo and the second infused without further manipulation. Delaney et al used a notch-ligand–based system,[3] de Lima et al used mesenchymal stem cell (MSC)-based cocultures,[4] and Wagner et al used SR1 aryl hydrocarbon antagonists.[5] These studies showed faster engraftment, with early and short-term engraftment mediated primarily by the expanded UCB unit, and long-term engraftment supported by the unmanipulated unit.

Gamida Cell has developed a novel culture system using nicotinamide, a vitamin B-3 derivative and master regulator of nicotinamide adenine dinucleotide (NAD)-related signaling pathways directly involved in control of redox-sensitive enzymes that acts as an epigenetic modifier of hematopoietic cells.[6] UCB-derived hematopoietic progenitor cells cultured with nicotinamide and cytokines were enriched in phenotypically primitive $CD34^+CD38^-$ cells with enhanced migration toward the bone marrow, resulting in better engraftment.[6] Mechanistically, the investigators showed that the expansion of the UCB stem cells and inhibition of differentiation by nicotinamide was related to inhibition of the catalytic activity of sirtuin (SIRT1), a class III NAD^+-dependent histone deacetylase.[6] They developed a 21-day culture procedure in which the $CD34^+$ UCB cells were expanded, and the $CD34^-$ T cells were frozen and reinfused with the expanded product following ablative therapy. Their first study was conducted in the double UCBT setting, where 1 unit was expanded with nicotinamide and infused together with a second unmanipulated unit. Interestingly, unlike in the double UCB expansion studies discussed herein, the nicotinamide-expanded UCB unit resulted in long-term engraftment of 7 years or longer in some patients. These promising results formed the basis for the current trial with 1 nicotinamide-expanded UCB unit as the sole hematopoietic support. Horwitz et al are to be congratulated for their perseverance in completing this phase 3 multicenter trial with a logistically complicated protocol design involving central manufacturing facilities and patients across multiple continents. The nicotinamide-expanded hematopoietic stem cells, infused together with the $CD34^-$ T-cell fraction, resulted in robust and durable engraftment of the single expanded UCB unit in this study.

UCB expansion clinical trials

Reference/y	Compound	Modality: expansion
Delaney et al[3]/2010	Notch ligand	1 UCB in double UCBT
de Lima et al[4]/2012	MSC coculture	1 UCB in double UCBT
Wagner et al[5]/2015	StemRegenin 1	1 UCBT unit in double UCBT
Horwitz et al[11]/2018	NiCord	Single UCBT (phase 1/2)
Cohen et al[7]/2020	UM171	Single UCBT

Challenges with this approach include a 10% manufacturing failure rate and a 21-day manufacturing period, resulting in 14% of patients not being able to receive the therapy, primarily due to disease progression. Future iterations of this approach will likely involve shorter culture durations or frozen off-the-shelf expanded products to extend this potentially lifesaving therapy to more patients.

Currently, the number of UCB units in the global UCB bank inventories exceeds 1.5 million, but many of these units are too small to support hematopoiesis, particularly for adults. UCB expansion technologies as reported here and by others[7] may provide a paradigm-changing opportunity to use smaller and better HLA-matched units for UCBT; they also set a benchmark for the expansion of other important UCB populations such as MSCs, NK cells,[8] or T cells.[9,10] Indeed, promising results with genetically engineered UCB NK cells targeting $CD19^+$ cancers,[8] UCB-derived virus-specific T cells,[9] and T-regulatory cells[10] support the use of UCB units in the global inventory for the treatment of patients with cancer in the coming decades.

Conflict-of-interest disclosure: E.J.S., K.R., and The University of Texas MD Anderson Cancer Center (MDACC) have an institutional financial conflict of interest with Takeda Pharmaceutical for the licensing of the technology related to chimeric antigen receptor–NK cells. MD Anderson has implemented an Institutional Conflict of Interest Management and Monitoring Plan to manage and monitor the conflict of interest with respect to MDACC's conduct of any other ongoing or future research related to this relationship. E.J.S., K.R., and The University of Texas MD Anderson Cancer Center have an institutional financial conflict of interest with Affimed GmbH. Because MD Anderson is committed to the protection of human subjects and the effective management of its financial conflicts of interest in relation to its research activities, MD Anderson is implementing an Institutional Conflict of Interest Management and Monitoring Plan to manage and monitor the conflict of interest with respect to MD Anderson's conduct of any other ongoing or future research related to this relationship. E.J.S. participates on scientific advisory boards for Bayer, Novartis, Magenta, Adaptimmune, Mesoblast, and Axio. K.R. participates on scientific advisory boards for GemoAb, AvengeBio, Kiadis, GlaxoSmithKline (GSK), and Bayer. ■

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HEMATOPOIESIS AND STEM CELLS

Comment on Thoms et al, page 1441

Transcriptional circuit dynamics in HSPCs

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In this issue of *Blood*, Thoms et al[1] report that chromatin accessibility at regulatory regions of a heptad of transcriptional factors (TFs; LYL1, TAL1/SCL, LMO2, FLI1, ERG, GATA2, and RUNX1) displays distinct patterns at major stages of hematopoiesis and can thereby predict cell identity.

Hematopoiesis is strictly regulated by transcriptional networks, consisting of TFs, regulatory regions, and complexes of multiple transcriptional regulators interacting with each other.[2] Regulatory regions are generally located in noncoding DNA sequences including intergenic and intragenic regions, and their epigenetic states such as DNA methylation and histone modifications dynamically control chromatin accessibility in a cell type–specific manner, and also contribute to cell fate decisions.[3] Aberrant expression of key hematopoietic TFs or alterations in their regulatory regions, caused via genetic or nongenetic dysregulation, can rewire transcriptional networks and eventually lead to leukemogenesis.[4] Although much work has been conducted to study the various effects of individual TFs or their regulatory regions on hematopoiesis and