Cord Blood Stem Cell Therapy for Acquired Immune Deficiency Syndrome

Gabriel Gonzalez,^{1,2} Elizabeth J. Shpall,^{2,3} Joseph C. Gathe, Jr.,⁴ and Richard R. Behringer^{1,2}

Cord blood stem cell transplantation is routinely used to treat hematopoietic diseases. Individuals who are homozygous for the $\Delta 32$ polymorphism of the CCR5 locus, encoding a co-receptor for HIV-1, are normal and are resistant to HIV infection. Here we suggest that public cord blood repositories are likely to contain CCR5 homozygous units that could be used as a therapy for HIV-infected individuals.

HUMAN IMMUNODEFICIENCY VIRUS-1 (HIV) infection of T-cells, macrophages, and dendritic cells of the immune system leads to the development of acquired immune deficiency syndrome (AIDS), a pandemic that kills millions of people each year. Although highly active antiretroviral therapy (HAART) drugs can significantly extend the life of HIV patients, there is currently no cure for HIV infection. Here we propose that umbilical cord blood stem cells present in public cord blood banks that are homozygous for a gene polymorphism that renders them resistant to HIV infection may provide a novel therapy for AIDS.

According to the UNAIDS/WHO, there were ~30–36 million people worldwide infected with HIV in 2007. In that same year, an estimated ~2.5 million people became newly infected by HIV. Interestingly, there are some individuals who are resistant to HIV infection. A subset of these individuals was found to have a 32-bp deletion ($\Delta 32$) in both alleles of the CCR5 G protein-coupled receptor gene [1–3]. HIV gains entry into cells by binding to membrane proteins CD4 (cluster of differentiation 4) and a co-receptor, predominantly CCR5 or CXCR4 [4]. Different HIV strains have specificity for CCR5 (R5), CXCR4 (X4), or both CCR5 and CXCR4 (X4R5) co-receptors [4]. R5 is the predominant strain found in the early phases of HIV infection.

The CCR5 $\Delta 32$ allele causes a truncation and functional inactivation of the co-receptor protein [1–3]. This allele occurs at high frequency in certain human populations [5]. The CCR5 $\Delta 32$ allele occurs at a frequency of ~10% in populations of European descent [5]. For example, the allele frequency is 8% in Spain, 11% in Britain, 14% in Iceland, and 21% in Ashkenazi Jews. The prevalence and spread of the $\Delta 32$

allele in Europe and Western Asia have been suggested to be due to protection from small pox [6]. In the United States, the CCR5 $\Delta 32$ allele is estimated to occur at a frequency of 19% in individuals of European descent [7]. Although the CCR5 $\Delta 32$ allele produces a nonfunctional protein that is not present on the plasma membrane, individuals who are homozygous for the CCR5 $\Delta 32$ polymorphism appear healthy [8].

Homozygosity for CCR5 $\Delta 32$ confers resistance to HIV infection by R5 strains, whereas heterozygosity may delay the development of AIDS [1,3]. In vitro studies suggest that the truncated CCR5 receptor may also have dominant negative effects on wild-type CCR5 and CXCR4, potentially conferring resistance to X4 and X4R5 HIV strains [9]. The resistance of CCR5 $\Delta 32/\Delta 32$ individuals to HIV offers clues for developing therapies for the treatment of HIV infection and AIDS. Indeed, gene and drug therapies to interfere with CCR5 function are currently under development [4,10]. Here we propose a stem cell therapy for AIDS.

The blood from the placenta and umbilical cord after separation from a newborn baby is collected noninvasively as a source of hematopoietic stem cells (HSCs), that is, cord blood stem cells, capable of reconstitution of the hematopoietic system after transplantation into histocompatible recipients [11]. Cord blood stem cells are now routinely collected for storage and potential future personal use by families or donated to public cord blood stem cell banks for research and treatment of hematopoietic and other diseases [11]. Because cord blood-derived HSCs are less mature in comparison to adult bone marrow-derived HSCs, transplantation requires less precise histocompatibility matching between donor and recipient [11]. Thus, the number of recipients for a cord

¹Department of Genetics, ²Center for Stem Cell and Developmental Biology, ³Department of Stem Cell Transplantation and Cellular Therapy, University of Texas M.D. Anderson Cancer Center, Houston, Texas.

⁴Therapeutic Concepts, PA, Houston, Texas.

blood HSC allotransplant is potentially greater than that for an adult bone marrow allograft. Because the *CCR5* $\Delta 32$ polymorphism is present at a relatively high frequency in specific human populations, we predict that *CCR5* $\Delta 32/\Delta 32$ cord blood units should be and will be continuously present at a predictable frequency (1–3%) in the current cord blood banks where allele frequencies are high [5]. Transplantation of *CCR5* $\Delta 32/\Delta 32$ cord blood stem cells into HIV-infected individuals should produce HIV-resistant blood cells, alleviating or potentially curing the development of AIDS.

The potential use of cord blood stem cells for the treatment of AIDS opens up important points for discussion. First, HIV-infected individuals would need to be human leukocyte antigen (HLA) typed which is not routinely performed. Second, partial engraftment by the cord blood stem cells may be sufficient to alleviate T-cell deficiency because the donor tissue is resistant to HIV infection and would have a selective advantage. Perhaps one cord blood unit might even be sufficient for treating more than one patient. In addition, myeloablative treatment of HIV-infected individuals prior to transplantation may or may not be necessary; safer nonmyeloablative regimens could potentially be used to facilitate engraftment of the *CCR5* $\Delta 32/\Delta 32$ cord blood stem cells. Indeed, promising findings have recently been obtained regarding the feasibility of HSC transplantation into HIV-infected individuals being treated for lymphoma [12]. Third, the concept of stem cell therapy for HIV treatment can be extended to the use of *CCR5* $\Delta 32/\Delta 32$ adult HSCs (e.g., bone marrow) as donor tissue but would require a more rigorous HLA match and intrusive manipulation of donors to collect stem cells. Fourth, an HIV-infected patient treated with a *CCR5* $\Delta 32/\Delta 32$ cord blood or bone marrow allograft would be trading the consequences of HAART therapy for immune suppression therapy to prevent transplantation disease. In addition, in rare cases, *CCR5* $\Delta 32/\Delta 32$ resistance to HIV infection has been demonstrated to be incomplete and associated with X4 strains [13]. Finally, the *CCR5* alleles in human embryonic stem cells or induced pluripotent stem (iPS) cells could be genetically converted to the $\Delta 32$ allele, that upon differentiation would provide a source of $\Delta 32/\Delta 32$ HSCs for transplantation. In particular, the generation of $\Delta 32/\Delta 32$ iPS cells from individuals for differentiation into HSCs would provide an autograft for HIV infection therapy. In summary, we suggest that cord blood stem cells and other types of stem cell therapies may have great potential for the treatment of HIV infection and AIDS.

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Address reprint requests to:

Dr. Richard R. Behringer

Department of Genetics

University of Texas, M.D. Anderson Cancer Center

1515 Holcombe Boulevard

Houston, TX 77030

E-mail: rrb@mdanderson.org

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