Can Therapeutically-Rational Exchange (T-REX) of Thalassemic Red Blood Cells Improve the Clinical Course of *Plasmodium falciparum* Malaria?

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In 2007, a hematopoietic stem-cell transplant of "mutant" homozygous CCR5 cells successfully blocked cell-entry of the human immunodeficiency virus. Fortunately, the legacy of this historic cell therapy-"the Berlin patient" breakthrough-is still advancing medicine. Lessons learned: We should respect and exploit the genetic engineering of human evolution, identify disease-resistant cells, and create cell banks and donor registries that advance life-saving cell therapies. For malaria, "therapeutically-rational exchange" (T-REX) refers to using special malaria-resistant cell variants, such as thalassemic red blood cells (RBCs) for RBC exchange transfusions, instead of using ordinary, non-descript "standard-issue" units of blood. Regarding terms, "selective allogeneic variant exchange" (SAVE) of cell variants refers to replacing disease-susceptible "normal cells" with special disease-resistant "mutant cells" that evolved to prevent human extinction. Hence, using T-REX of thalassemic RBCs for patients infected with *Plasmodium falciparum* represents a malaria-specific SAVE.

As expected from malaria-driven evolution, all thalassemic RBCs are malaria-resistant (are protective); "the malaria hypothesis" emerged because thalassemic alleles were found to be prevalent where malaria has been endemic [1]. Regarding protection, the binding of parasitized RBCs to endothelial cells is reduced in malaria patients having α- or β-thalassemia [1]. For T-REX, blood banks can, at most, provide three thalassemic variants because the blood-donation process excludes unqualified donors. A thalassemic individual healthy enough to donate RBCs may (1) have β-thalassemia trait, (2) have α-thalassemia trait, or (3) be a silent carrier of α-thalassemia [1, 2]. Hence, where public health officials seek to reduce malaria morbidity and mortality via T-REX, blood banks first need to identify thalassemia units or other malaria-resistant units using hemoglobin electrophoresis or high performance liquid chromatography (HPLC). Fortunately, the prevalence of thalassemia can be substantial: for the mild α-thalassemia, 10%–20% in Sub-Saharan Africa, the Middle East, India, and Southeast Asia; and for β-thalassemia, 1%-20% in the Mediterranean and parts of Sub-Saharan Africa [1]. By testing tubing segments from RBC units using hemoglobin electrophoresis or HPLC, malaria-protective RBCs can be easily identified and made available for T-REX.

In conclusion, T-REX of malaria-resistant RBCs is an exceptionally simple SAVE that may substantially reduce malaria morbidity and mortality. Hence, T-REX of thalassemic RBCs and several other malaria-resistant RBC variants should be evaluated in a timely manner [3-5]. Blood-bank/transfusion-medicine specialists and technicians worldwide can easily offer T-REX if properly supported by their medical institutions in terms of staff and blood-bank enhancements. Of note, services required to perform appendectomies on patients with parasite-induced appendicitis far exceed the additional resources needed to offer T-REX. Furthermore, just as donors of life-saving cells, tissues, or organs have been successfully recruited in the past, T-REX donors can also be actively recruited to donate periodically or as required. Hence, even if the initial "passive prevalence" of local malaria-resistant RBC variants in blood banks is low, donor registries and active recruitment can increase availability of malaria-resistant RBCs and make T-REX feasible. Historically, citizens have enthusiastically embraced opportunities to donate blood.

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