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.
Peer-review: Externally peer-reviewed.


Conflict of Interest: Dr. Ryan Jajosky is the CEO and part-owner of Biconcavity Inc. Dr. Philip Jajosky is CMO and part-owner of Biconcavity Inc. Dr. Audrey N. Jajosky has no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

References
4. Jajosky RP, Jajosky AN, Jajosky PG. To prevent or ameliorate severe Plasmodium falciparum malaria, why not evaluate the impact of exchange transfusions of sickle cell trait red blood cells? Transfus Apher Sci 2018; 57: 63-4. [CrossRef]