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Therapeutically-rational exchange (T-REX) of Gerbich-negative red blood cells can be evaluated in Papua New Guinea as "a rescue adjunct" for patients with Plasmodium falciparum malaria

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Abstract

"Conventional exchange transfusion"—that delivers nondescript "standard issue" units of red blood cells (RBCs)—is used worldwide to rescue dying *Plasmodium falciparum (Pf)* malaria patients. Recently, exchanging special malaria-resistant RBCs (T-REX) has been recommended to prevent random delivery of malaria-susceptible RBCs that promote *Pf* infection. Fortunately, Papua New Guinea (PNG) is well positioned to help optimize exchange as "a rescue adjunct" because (a) Gerbich-negative (GN) RBCs that resist *Pf* invasion are prevalent in PNG; (b) with international support, PNG has conducted outstanding malaria research; (c) PNG's scientists feel studies of GN RBCs can advance malaria therapeutics; and (d) with blood-bank support, evaluating exchange of GN RBCs is feasible in PNG. An exchange-transfusion study of GN RBCs might attract international sponsorship given the threat of expanding drug-resistance as well as growing recognition that advancing transfusion medicine and expanding blood donation could especially help *Pf*-infected children—immediately.

1 INTRODUCTION: TERMINOLOGY AND THE NEED FOR BETTER "RESCUE ADJUNCTS"

The Gerbich blood group antigens that determine a person's Gerbich phenotype are controlled by the glycophorin-C gene (*GYPC*). To avoid confusion that can be caused by different terms that are essentially synonymous, here we use terms adopted in past publications.[1–7] The malaria-resistant Gerbich-negative (GN) red blood cell (RBC) variant known as "the GN phenotype" is often called "GYPCΔex3" because the GN phenotype is encoded by the *GYPC* gene with exon 3 deletion.[3] For example, in an article describing the

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protection provided by the GN phenotype, Zimmerman et al. noted: “it is clearly important to investigate how GYPCΔex3 influences malaria pathogenesis”.[4] Maier et al. noted: “The GYPCΔex3 allele reaches a high frequency (46.5%) in coastal areas of Papua New Guinea (PNG) where malaria is hyperendemic”.[3] In contrast, Serjeantson et al. did not use the “GYPCΔex3” symbol: “Gerbich-negative erythrocytes showed increased deformability compared with Gerbich-positive cells, suggesting at least one mechanism by which a selective advantage for the Gerbich-negative phenotype could be affected in malarious areas”.[8] Potentially confusing for physicians, the symbol “GYPCΔex3” can refer to either the genotype or the GN phenotype. Perhaps this sentence is helpful: The GYPCΔex3 gentoype encodes a RBC phenotype having a special GYPC RBC surface receptor that resists invasion of *Plasmodium falciparum (Pf) parasites*. Here, clinicians can view different terms as being essentially equivalent: GYPCΔex3 = GN RBCs = a special GYPC receptor = “the Gerbich-negative phenotype.” In general, articles about Gerbich blood-group antigens use additional terms and abbreviations.

Regarding exchange-transfusion terms, exchange of malaria-resistant GN RBCs can be called “therapeutically-rational exchange” (T-REX) of GN RBCs or GN T-REX.[5–7] The special acronym “T-REX” was created because clinicians may not appreciate that, for more than 40-years, all exchange transfusions for *Pf*-malaria patients had transfused nondescript “standard issue” units of RBCs that randomly delivered malaria-susceptible RBCs that can promote *Pf*-disease progression. Because T-REX refers to exchanging only malaria-resistant RBCs, the clinical impact of T-REX might differ substantially from that of conventional “standard issue” exchange. Regarding the key terms, clinicians need to know (a) T-REX = exchange of special malaria-resistant RBCs and (b) malaria-resistant GN RBCs might be called “GYPCΔex3 RBCs.”

Regarding the rationale for evaluating the clinical impact of GN T-REX, it seems prudent to translate the “inborn protection” of GN RBCs into an RBC transfusion therapy. Also, at the molecular level, we do not fully understand how special RBCs “genetically engineered” by malaria-driven evolution have prevented human extinction. Of note, the malaria-resistant “sickle trait” RBC—that contains hemoglobin-AS (HbAS)—is probably the best known RBC genetic variant found in malaria-endemic regions. One interesting explanation for how sickle trait has promoted human survival is that HbAS RBCs have a special microRNA distribution that inhibits *Pf*-parasite growth.[9, 10] Studies have also found that *Pf*-infected HbAS RBCs are less cytoadherent (less “sticky”) resulting in less RBC sequestration which, in turn, may explain why sickle-trait patients are less likely to develop cerebral malaria (CM) and other life-threatening complications caused by microvascular obstruction.[11, 12] In his review, Isbister emphasized malaria-related RBC “sludging” and “rheology” when explaining that exchange transfusion is indicated for fulminant malaria because *Pf*-infected RBCs can “interact with host cells by excessive binding in the microvasculature leading to occlusion”.[13] Interestingly, in the past 130 years, clinicians may have unknowingly and randomly rescued some *Pf*-malaria patients by transfusing malaria-resistant HbAS RBCs. This is possible given that healthy persons with sickle-trait RBCs donate blood which explains why HbAS RBCs are found in blood banks and in post-transfusion patients with “transfusion-acquired hemoglobinopathies”.[14]

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Regarding T-REX of GN RBCs as "a candidate rescue adjunct" for *Pf*-malaria patients, based on decades of survival data, it seems most prudent to assume—until proven otherwise—that donated malaria-resistant RBC variants can save lives. Because *Pf* malaria continues to cause profound suffering and death—and because expanding drug resistance is a threat—scientists have been warning that better adjuncts are desperately needed.[15–19] Because severe malaria can be lethal despite artemisinin derivatives, Varo et al. have urged research specifically to identify new adjunctive therapies.[17] Since CM is especially gruesome and lethal, evaluating adjuncts that might prevent CM has been recommended.[15, 16, 19] In addition to explaining how sequestration of *Pf*-infected RBCs within the microvasculature of the brain and "hemostatic dysfunction" seem linked to CM, O'Sullivan et al. noted "development of adjunctive therapies that can attenuate CM progression clearly represents a major unmet need".[16] Of course, even simple transfusion can successfully rescue some *Pf*-malaria patients, as noted since 1892.[20] Regarding exchange transfusion, although journals often insist authors submit only new and unique findings, for 40 years, clinicians—presumably feeling compelled—have repeatedly published remarkably similar case reports describing how exchange transfusions dramatically rescued their near-death *Pf*-malaria patients. [21–30] Unfortunately, "standard issue" transfusions do not always rescue *Pf*-infected patients. So, instead of transfusing "standard issue" units, some have argued that transfusing malaria-resistant group-O RBCs, for example, is likely to be more effective than transfusing malaria-promoting RBCs.[7, 31] Regarding optimizing transfusions for *Pf*-malaria patients, we feel it is most prudent to assume—until proven otherwise—that (a) any given malaria-resistant RBC variant is likely to be more therapeutic than any malaria-promoting RBC phenotype and (b) exchange transfusion will be more effective than simple transfusion. These assumptions seem logical and prudent based on decades of epidemiologic, clinical, and laboratory data.

2 THE RATIONALE FOR T-REX OF GN RBCs

We feel T-REX might be markedly more effective than simple transfusions of GN RBCs because, in addition to simply delivering uninfected, malaria-resistant donor GN RBCs, exchange removes "sticky" *Pf*-infected RBCs that can cause microvascular occlusion and death. Clinicians should be aware that RBCs remain cytoadherent even after drugs have successfully killed the *Pf* parasites.[32] Hughes et al. noted that because a patient's RBCs remain "sticky" long after the parasites are dead, "adjunctive therapy strategies that can also reverse cytoadherence may also be advantageous in addressing the high mortality seen in severe malaria".[32] Also encouraging, Serjeantson noted that GN RBCs "showed increased deformability".[8] And so, GN T-REX might substantially (a) reduce RBC cytoadherence and (b) increase RBC deformability—two rheologic benefits for *Pf*-malaria patients who are at risk for microvascular occlusion.

Regarding one specific molecular mechanism, GN RBCs may resist onset of severe *Pf* infection by blocking one of the invasion pathways used by *Pf* parasites. On the *Pf* parasite, the RBC-binding antigen called "EBA140" cannot bind to the unique GYPC receptor on GN RBCs—a finding scientists consider to be "compelling evidence" that GN RBCs emerged in Melanesians via selection by severe malaria.[3]

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Regarding encouraging epidemiologic and mortality data, Serjeantson reported: "*P. falciparum* and/or *Plasmodium vivax* infection in Gerbich-negative subjects was 5.7% compared with 18.6% in those who were Gerbich positive".[8] That finding suggests GN RBCs might explain PNG's relatively low malaria-mortality rate compared to Africa. For Melanesian children with severe *Pf* malaria, Manning et al. noted a low mortality (<1%) in a hospital setting while "Case fatality rates in African children with severe *falciparum* malaria lie between 3% and 50%" and added "This difference could reflect protective genetic factors".[33] Perhaps the key "protective genetic factor" is the GYPCΔex3 gene allele.[2] The substantial prevalence of GN RBCs in PNG might also explain an apparent paradox: PNG's low malaria-mortality rate despite PNG's high frequency of malaria drug-resistance.[33–35] This disparity explains why scientists feel some Melanesians must enjoy genetic protection.[33–35] Perhaps the protection provided by GN RBCs outweighs the drug-resistance of some *Pf*-parasite strains in PNG.[33–35] If GN patients are substantially protected even when infected with drug-resistant *Pf* parasites, using GN T-REX may be an especially valuable rescue adjunct if *Pf*-parasite drug-resistance becomes more problematic.

3 THE FEASIBILITY OF GN RBC T-REX IN PNG

Simple transfusion has been used adjunctively to treat malaria patients since 1892.[20] Since 1974, conventional exchange transfusion has been used to rescue severely ill *Pf*-malaria patients.[21] Now, to optimize exchange-for-malaria, we have recommended that T-REX be evaluated.[5–7, 36–39] Fortunately, in 1981, a clinical study that evaluated exchange transfusions of two different malaria-resistant RBC variants was successfully conducted by pediatricians in Nigeria.[40] Given the advances in medical care since 1981, evaluation of T-REX is surely feasible in PNG decades after exchange transfusions of malaria-resistant RBC genetic variants proved to be both safe and effective in sub-Saharan Africa.[40]

Also fortunate, researchers appreciate that PNG is "a prime location for studies of interactions between different parasite species, and of the biology of local human genetic adaptation and its implications for malaria morbidity and mortality".[41] In recent decades, global health scientists from the United States, Spain, France, Switzerland, New Zealand, and Australia have collaborated with PNG malaria researchers. Clearly, clinicians and researchers in PNG are well positioned to evaluate the impact of GN T-REX as a non-drug rescue adjunct. Fortunately, T-REX studies have the potential to not only optimize patient care but to clarify disease mechanisms and advance transfusion medicine.

Regarding the prevalence of GN blood donors in PNG, a prevalence of 11% was noted in the 2009-Vol. 49 supplement published by *Transfusion* that included the oral plenary session abstract SP184 titled "Distribution of Gerbich Negative Blood Donors in Port Moresby, Papua New Guinea".[42] This 11% prevalence among healthy PNG blood donors suggests GN T-REX might be feasible in PNG even without active recruitment of GN donors.[42] The presenter, Halverson, noted "an 11% prevalence of the Gerbich negative phenotype is a significant number in the Port Moresby population".[42] Among Melanesians in PNG, Booth and McLoughlin reported "Over 50% of members of certain population groups are Gerbich negative".[43] Serjeantson found that "The Gerbich-negative phenotype occurs in about 10% of Melanesians living in the northern provinces".[8] Maier et al. noted "The GYPCΔex3

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allele reaches a high frequency (46.5%) in coastal areas of Papua New Guinea".[3] From an evolution-oriented perspective, the high GN prevalence in PNG's malaria-endemic regions is not surprising since GN RBCs may have substantially promoted human survival by resisting invasion by *Pf* parasites as well as by being more deformable.[3, 8]

4 CONCLUSIONS

We agree with Patel et al. who collaborated with the Papua New Guinea Institute of Medical Research: They concluded the clinical impact of Gerbich-negative red blood cells should be studied.[2] Relevant to their recommendation, physicians are promoting evaluation of T-REX of malaria-resistant RBC variants; and, fortunately, GN therapeutically-rational exchange transfusion (T-REX) should be safe and feasible in PNG given the success of exchange transfusions of malaria-resistant RBC genetic variants in Nigeria.[5–7, 36–40] Presumably reassuring for clinicians in PNG, researchers have noted (a) PNG is an ideal setting for GN research, (b) GN RBCs seem to protect against severe *Pf* malaria, and (c) clinical studies of GN RBCs in PNG have been recommended.[2–4]

With hospital support and technical assistance from blood bank and transfusion medicine specialists, clinicians in PNG have the opportunity to evaluate T-REX of GN RBCs as "a rescue adjunct" for patients with severe *Pf* malaria. Assessing the therapeutic potential of exchanging GN RBCs seems prudent because (a) *Pf* malaria is still lethal and (b) optimizing "rescue adjuncts" can help PNG (and other nations) prepare for the further evolution of drug-resistant *Pf* parasites. We agree with Patel et al. who concluded that the link between GYPCΔex3 and malaria morbidity in young children "requires further study".[1] Zimmerman et al. similarly noted: "it is clearly important to investigate how GYPCΔex3 influences malaria pathogenesis".[4] We concur and feel GN T-REX is the simplest and most direct way to assess the impact of GYPCΔex3 RBCs on *Pf*-malaria morbidity and mortality.

Finally, malaria researchers, molecular geneticists, and evolutionary biologists in PNG and elsewhere should carefully consider how a GN T-REX project in PNG might clarify *Pf*-disease mechanisms. Furthermore, the incentive- and reward-based recommendations of Bates et al. imply that if a transfusion project can reduce *Pf*-malaria mortality, such success might substantially promote transfusion medicine and blood donation in PNG and, ideally, attract international sponsors.[44] The successful 1981 Nigerian study of exchange transfusions of malaria-resistant RBCs surely means GN T-REX is feasible in PNG.[40] Given that PNG's malaria researchers want clinical studies of GN RBCs, physicians in PNG should feel justified in asking for support if they decide to evaluate GN T-REX. Clinicians should feel comfortable: T-REX is simply a way to optimize exchange-for-malaria via thoughtful, prudent selection of donor cells.

CONFLICT OF INTERESTS

Dr Ryan Jajosky is the CEO and part-owner of Biconcavity Inc. Dr Philip Jajosky is CMO and part-owner of Biconcavity Inc. Biconcavity Inc. is a biotechnology research and development company exploring drug-linked erythrocytes. Biconcavity does not have any interest in malaria. Dr Audrey Jajosky does not have any disclosures.

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