

Pathogen Reduction of Whole Blood and Red Blood Cells

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Disclosures

- Principal Investigator of a US government funded clinical trial of Miarsol whole blood pathogen reduction technology
- Consultant/Professional Fees:
 - Ashland Global
 - Ortho Clinical Diagnostics

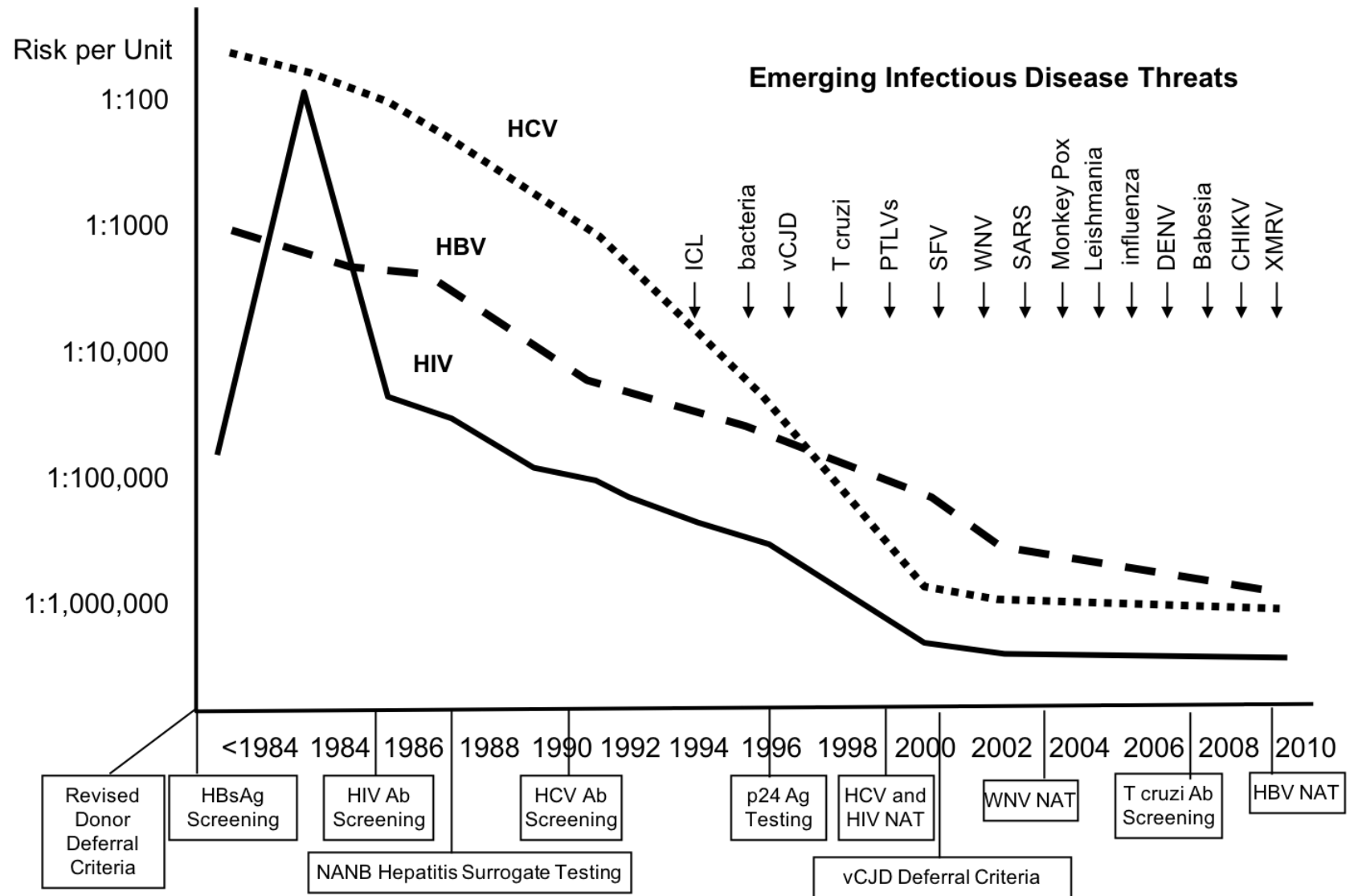
Objectives

- Review the need and challenges for whole blood (WB) and red blood cell (RBC) pathogen reduction technology to reduce transfusion transmitted infections
- Assess the two primary WB or RBC pathogen reduction technologies
 - Cerus INTERCEPT
 - Terumo BCT Mirasol
- Understand the current obstacles and long-term goals of WB and RBC pathogen reduction technology

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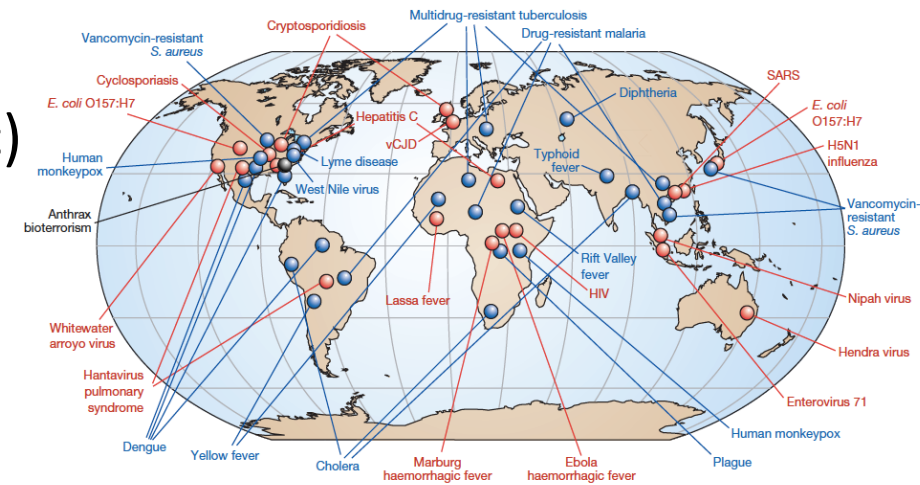
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Risk of Transfusion Transmitted Infections



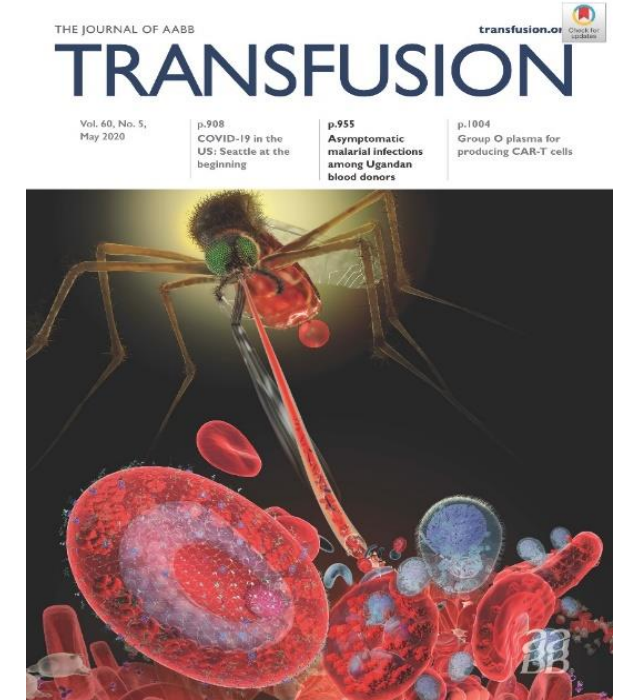
Transfusion-Transmitted Infections (TTIs) in Low-Income Countries

- TTIs are extremely common
- ~5 - 10% of transfusions lead to TTIs (WHO)
- Up to 1% of new HIV infections per year may be attributable to transfusions (UNAIDS)
- Despite screening for HIV, HBV, HCV and syphilis, TTIs continue to be a persistent problem
 - Many pathogens not screened
 - Screening failures (no NAT, limited QA programs, etc)
 - Emerging infectious diseases



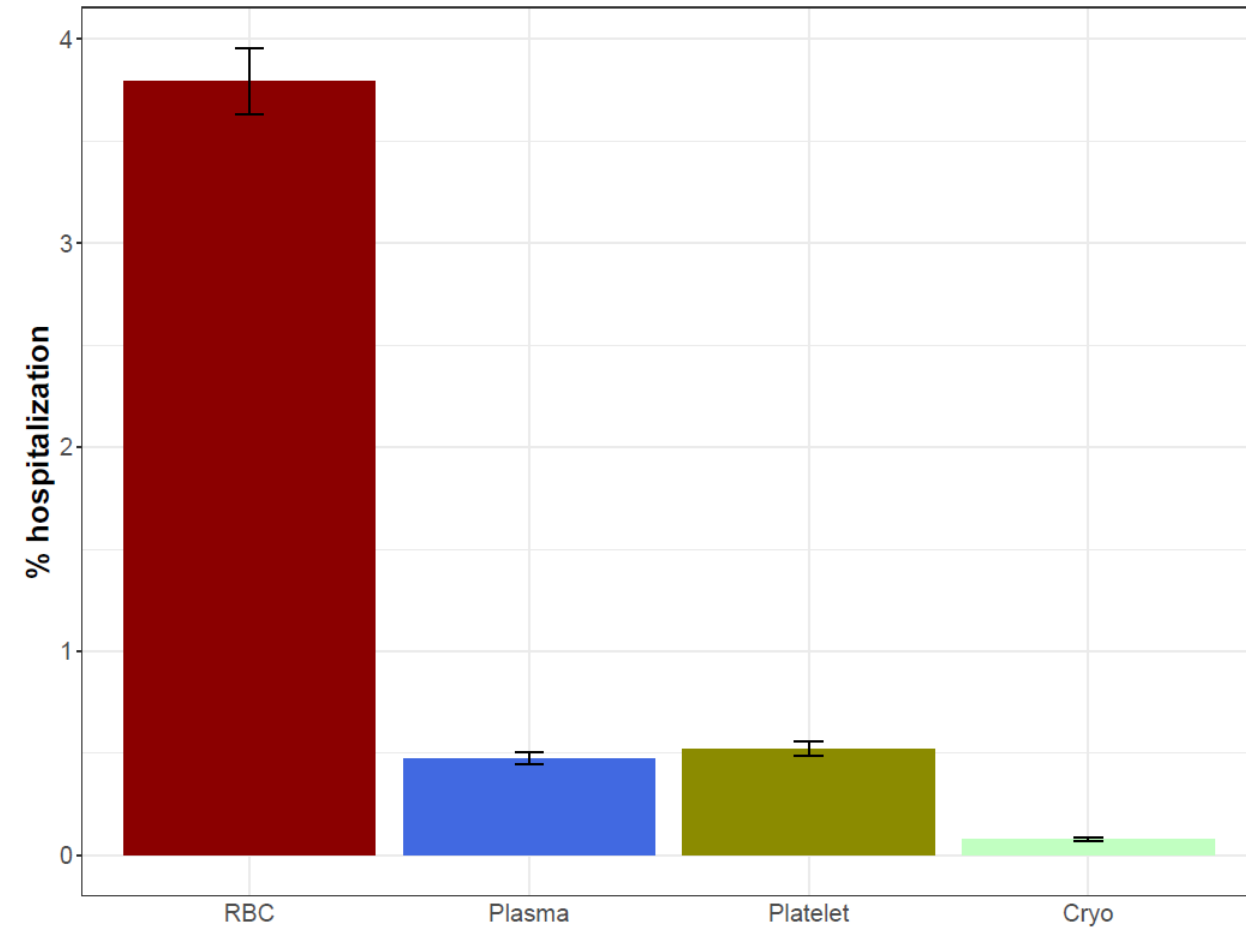
Platelet vs. RBC Pathogen Reduction

- Infectious risk
 - Platelets: Bacteria
 - RBCs: Malaria
Babesia
Viruses
- Pre-exposure prophylaxis and post-exposure prophylaxis for HIV increase the risk of transfusion transmitted HIV despite NAT testing
- Transfusion-associated graft vs. host disease

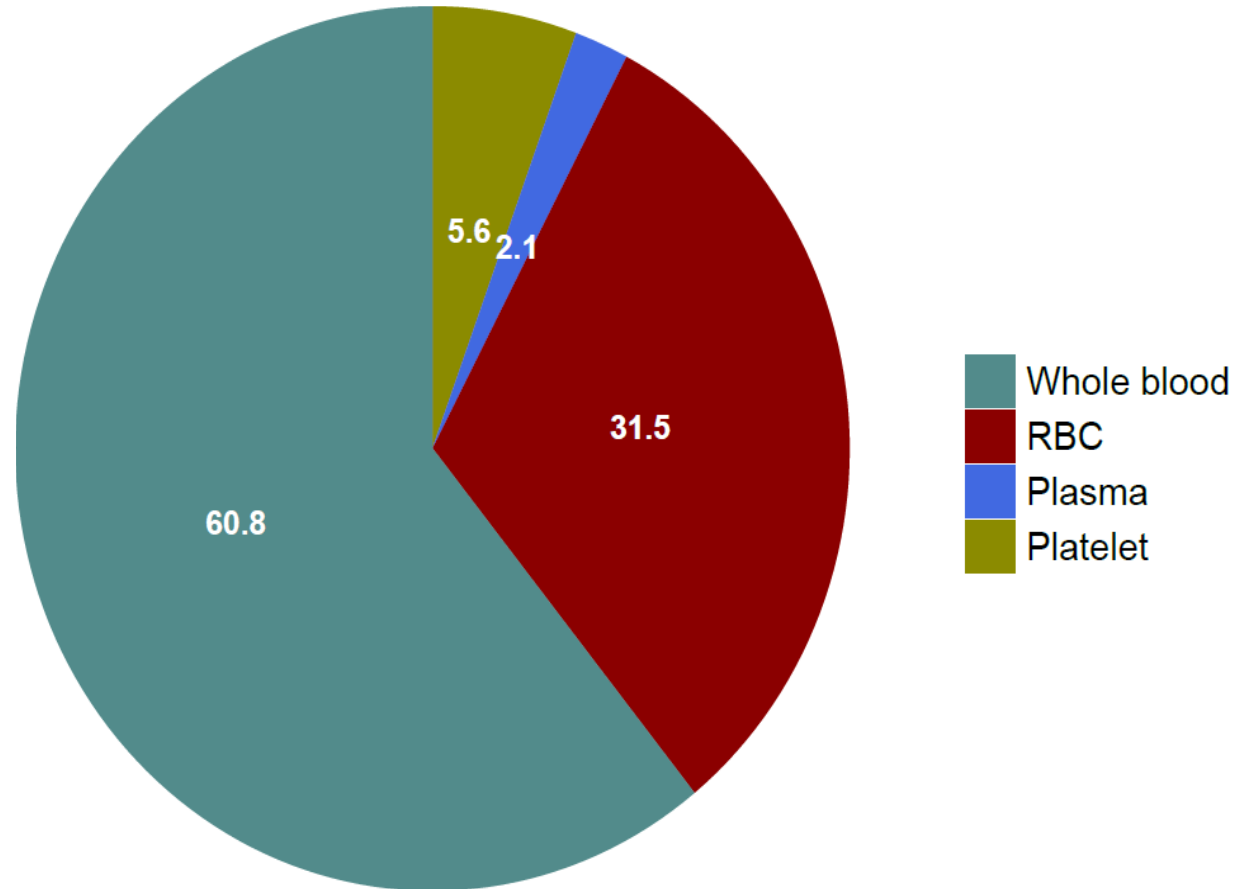


WB and RBC Transfusions

US Hospitalizations

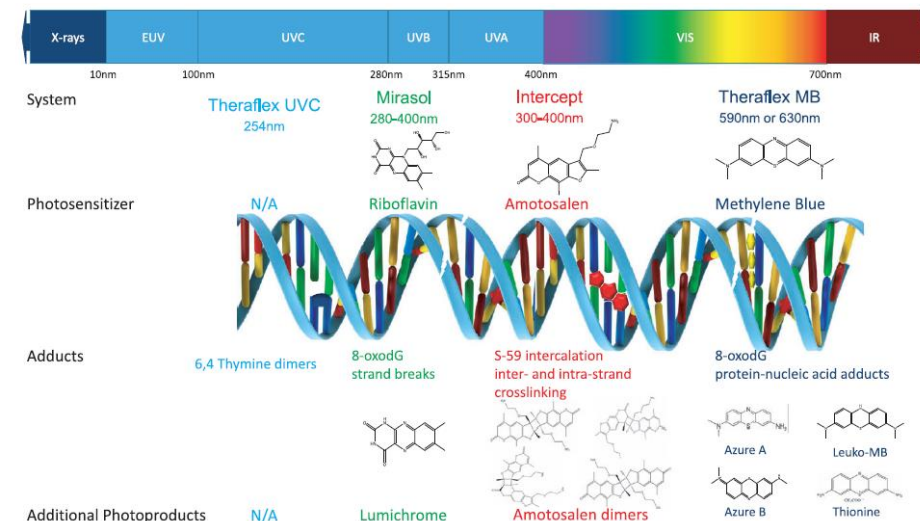


Uganda Blood Distribution



Challenges of WB and RBC Pathogen Reduction

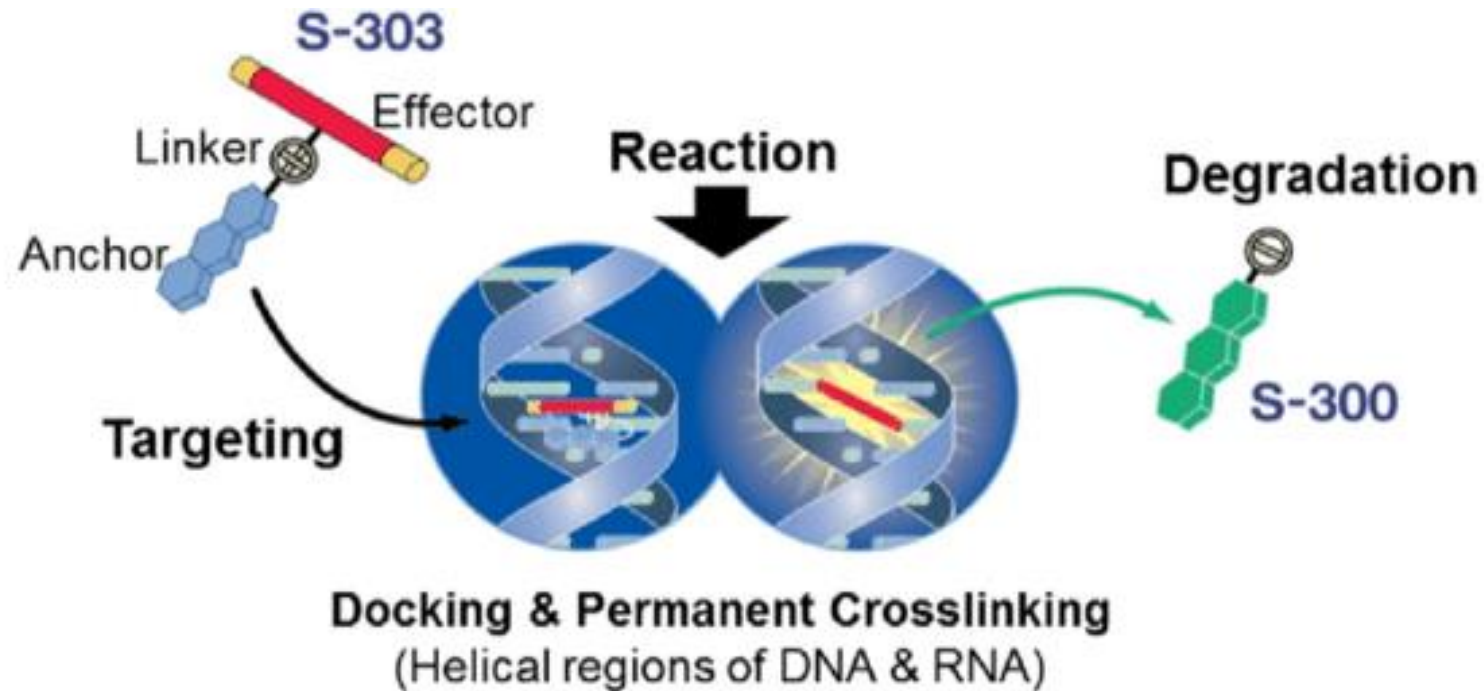
- Light activated methods are difficult because hemoglobin absorbs light near the same wave length as psoralens
- Many photochemicals depend on oxygen dependent chemistry to complete their inactivation; RBC hemoglobin that has significant quantities of bound oxygen → increased reactive oxygen species and undesirable side effects (e.g., RBC membrane damage)
- Slight modifications to RBC membranes that lead to increased protein binding (e.g., stickiness, etc.)
- Non-light activated compounds use alkylating agents (e.g., S-303) and are indiscriminate
 - Binding to cell proteins and membrane components permanently alters them and create new antigen targets on these cell surfaces (i.e., neoantigens).



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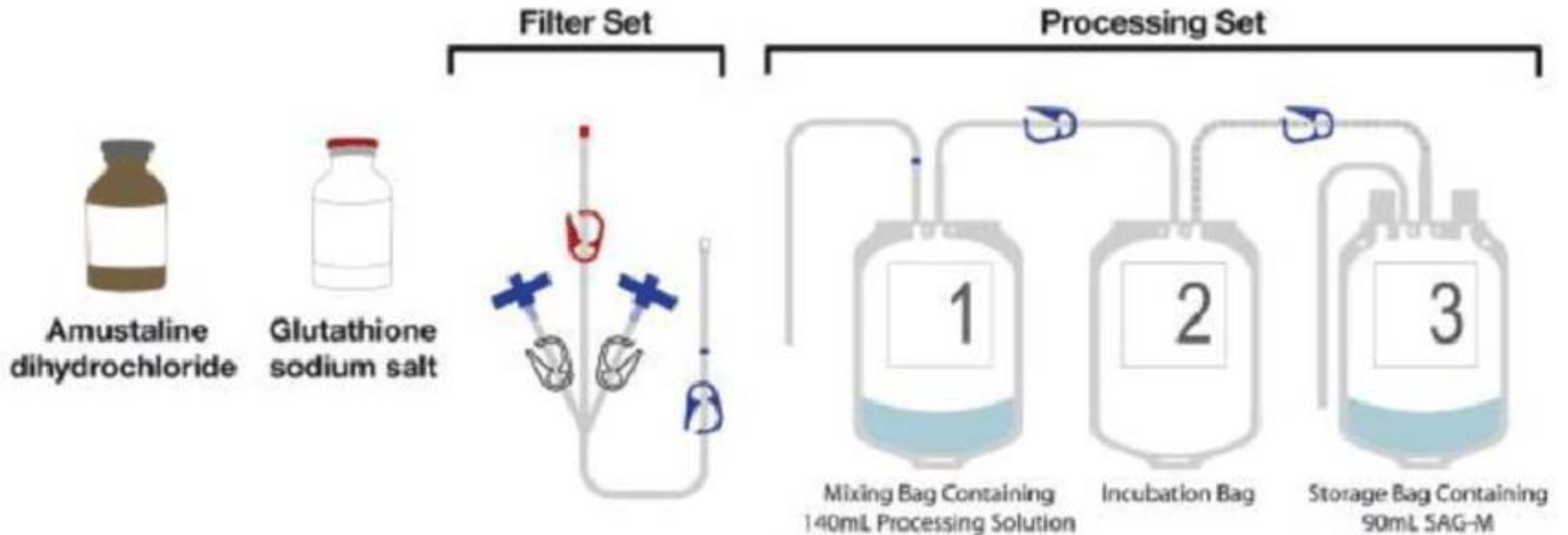
INTERCEPT RBC Mechanism of Action



Amustaline (S-303) is a highly-soluble alkylator – 3 components

- Acridine anchor – targets nucleic acids and intercalates between target base pairs
- Effector – covalently bonds guanine bases
- Linker

INTERCEPT RBC Inactivation System



Prevalence of natural and acquired antibodies to amustaline/glutathione pathogen reduced red blood cells

Christof Geisen¹  | Anne North² | Lisa Becker¹ | Veronika Brixner¹  |
Melissa von Goetz² | Laurence Corash²  | Richard J. Benjamin²  |
Nina Mufti² | Erhard Seifried¹ 

INTERCEPT Pathogen Reduction Efficacy

Type	Characteristic	Organism	Log reduction ^a
Bacterial	Gram-negative	<i>Yersinia enterocolitica</i> [63]	$\geq 6.8 \pm 0.2$
		<i>Serratia marcescens</i> [63]	5.1 ± 0.1
		<i>Escherichia coli</i> [63]	$\geq 6.7 \pm 0.1$
		<i>Salmonella choleraesuis</i> [65]	3.9 ± 0.1
		<i>Pseudomonas fluorescens</i> [65]	3.0 ± 0.1
		<i>Klebsiella oxytoca</i> [65]	$\geq 6.3 \pm 0.3$
	Gram-positive	<i>Staphylococcus epidermidis</i> [63]	$> 7.1 \pm 0.1$
		<i>Staphylococcus aureus</i> [36]	$> 5.1 \pm 0.3$
Viral	Enveloped, ssRNA (+)	Cell-associated human immunodeficiency virus [63]	$> 5.9 \pm 0.1$
		Bovine viral diarrhoea virus (BVDV; hepatitis C model) [63]	$> 4.8 \pm 0.0$
		Zika virus (ZIKV) [62]	$> 5.99 \pm 0.2$
		Chikungunya virus (CHIKV) [58]	$> 5.8 \pm 0.2$
		Dengue virus (DENV) [57]	$> 6.61 \pm 0.2$
		Vesicular stomatitis virus (VSV) [109]	5.7 ± 0.2
	Enveloped, dsDNA	Duck hepatitis B virus (DHBV; hepatitis B model) [59]	$> 5.1 \pm 0.2$
		Cytomegalovirus (HSV model for CMV) [36]	≥ 6.0
	Non-enveloped, sdRNA	Bluetongue virus (BTV) [63]	$\geq 5.0 \pm 0.1$
	Non-enveloped, dsDNA	Human adenovirus 5 (AD5) [63]	$> 7.4 \pm 0.2$
Protozoal	Non-enveloped, ssRNA (+)	Feline calicivirus (FCV) [64]	$> 6.8 \pm 0.1$
	Intra-erythrocytic parasite	<i>Babesia microti</i> [70]	$> 5.0 \pm 0.2$
		<i>Plasmodium falciparum</i> [110]	$> 7.9 \pm 2.3$

INTERCEPT RBC: Clinical Pathway

Phase I and II: Healthy Blood Donors	Recovery & Lifespan (n=27) Prototype Completed	Recovery & Lifespan (n=26) Completed	In Vitro Characterization (Grifols Sets) (n=67) Enrollment Complete	In Vitro Characterization (Fenwal Sets) (n=65) Enrolment Complete	Recovery and Survival (Fenwal Sets) (n=24) Protocol Approved
Phase III Patients	STARS Acute Transfusion (CV Surgery) (n=51) Completed	SPARC Chronic Transfusion (Thalassemia) (n=81) Completed			
Phase II and III Patients	ReCePI Acute Tx (CV Surgery, n≥292) Enrolling	RedeS (n=6-800) Acute (28d) Complete Chronic (28d +6m) (n=140) Enrolling RCE¹ (n=20) Enrolling			
Phase IV Patients	CLI 00140 HV-7 (n=860) Design submitted	US Study (Fenwal Sets) (n=TBD) Anticipated	= BARDA Funded		



US in vitro, pathogen inactivation, compound development and clinical studies funded by BARDA (initial \$183M contract)

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Mirasol Whole Blood Mechanism of Action

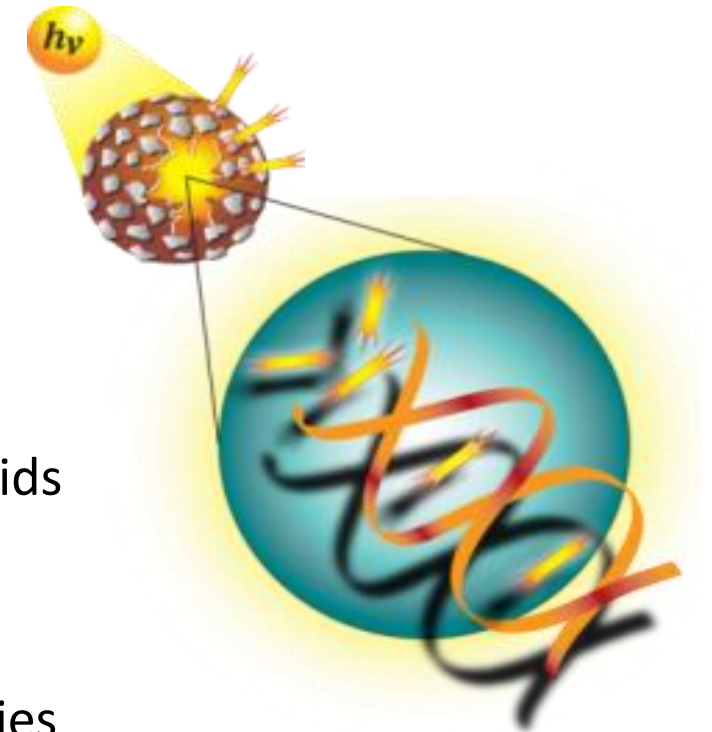
The Mirasol System inactivates pathogens and WBCs by altering their nucleic acids in two primary ways:

UV light only: reversible inactivation

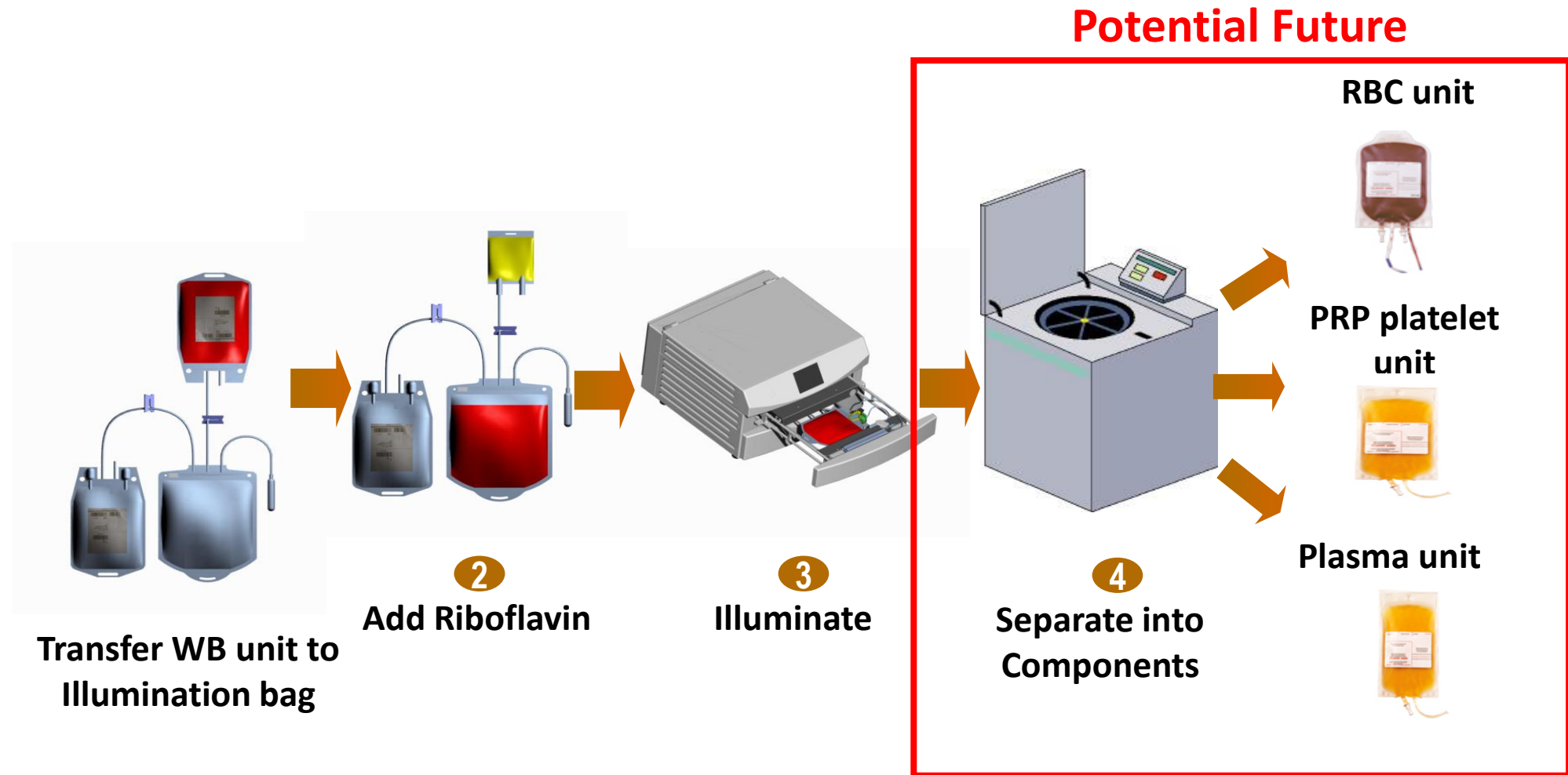
- UV light alone breaks chemical bonds in the nucleic acids of pathogens and WBCs

UV light + riboflavin: irreversible inactivation

- Riboflavin (vitamin B2) molecules form complexes with nucleic acids
- UV light from the Mirasol Illuminator activates the riboflavin molecule in the complex
- Photoactivated riboflavin induces release of reactive oxygen species that leads to damage of nucleic acids (guanine bases), making pathogens unable to replicate



Mirasol Whole Blood Pathogen Reduction System



Mirasol Pathogen Reduction Efficacy

Bacteria	Log Reduction
B. Cereus	5.3
E. coli	4.9
K. pneumoniae	>5.0
P. fluorescens	2.7
S. aureus	4.1
S. epidermidis	3.2
S. liquefaciens	5.9
S. pyogenes	>5.0
Y. enterocolitica	4.4

Virus	Log Reduction
HIV	4.5
HCV	2.7
CMV	>6.0

Parasite	Log Reduction
Babeisia microti	>5.0
Babesia divergens	7.3
Leishmania donovani	2.3
Plasmodium falciparum	>6.4
Trypanosoma cruzi	>3.5

Effect of *Plasmodium* inactivation in whole blood on the incidence of blood transfusion-transmitted malaria in endemic regions: the African Investigation of the Mirasol System (AIMS) randomised controlled trial

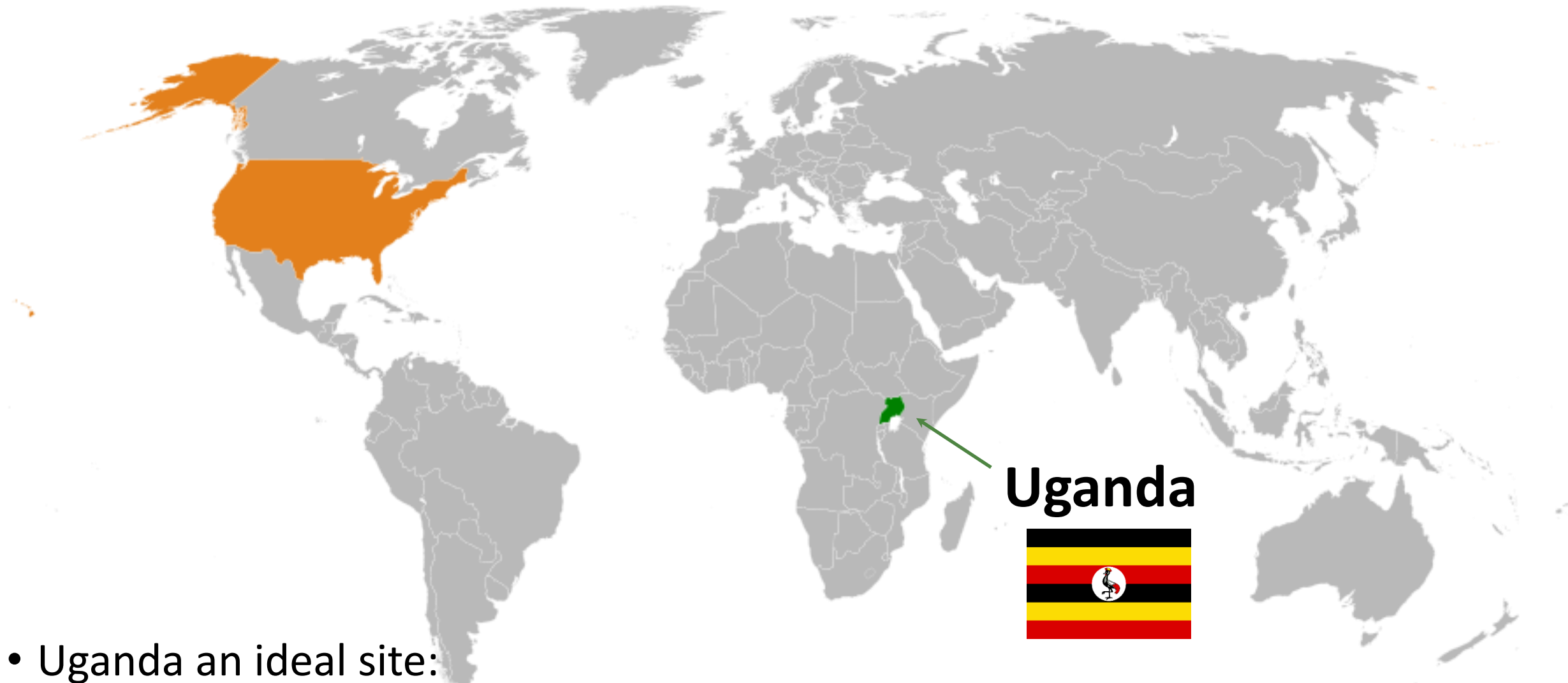
Jean-Pierre Allain, Alex K Owusu-Ofori, Sonny Michael Assennato, Susanne Marschner, Raymond P Goodrich, Shirley Owusu-Ofori

- Single-center randomized trial of 226 participants in Ghana
- Incidence of transfusion-transmitted malaria ($p = 0.039$)
 - Pathogen-reduced arm: 1/28 [4%]
 - Control arm: 8/37 [22%]

This trial did not assess other TTIs or adverse outcomes that can only be evaluated with larger and longer trials.

Critical knowledge gaps

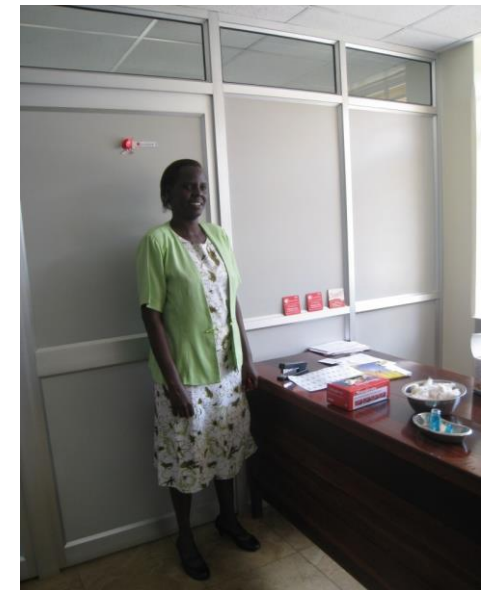
- Does Mirsaol have sufficient log kill to prevent transfusion transmission of TTIs?
- Is Mirasol PRT able to prevent the transmission of TTIs (e.g., HIV, HBV, HCV, HEV, HHV-8, or bacteria) *in vivo*, in addition to malaria?
- Is it feasible and sustainable to implement Mirasol PRT in low-resource settings?
- Clinical data showing reduced transfusion transmission and number of preventable cases is the best way to answer these questions.



- Uganda an ideal site:
 - Uganda's blood testing and storage infrastructure is functional, though resource-limited
 - Higher rate of TTIs presents a greater opportunity for health benefits, and also a greater challenge for PRT

Uganda Blood Transfusion Services

- National system
- 100% anonymous, voluntary donors
- Repeat donors: 58%
- TTI testing on donations
 - HIV – antigen/antibody (0.71%)
 - anti-HCV (1.76%)
 - HBsAg (2.41%)
 - Syphilis (RPR)
- HIV
 - Population: 7%
 - Blood donors: 0.71%



STUDY PROTOCOL

Open Access

The Mirasol Evaluation of Reduction in Infections Trial (MERIT): study protocol for a randomized controlled clinical trial



Ronnie Kasirye¹, Heather A. Hume², Evan M. Bloch³, Irene Lubega¹, Dorothy Kyeyune⁴, Ruchee Shrestha³, Henry Ddungu⁵, Hellen Wambongo Musana¹, Aggrey Dhabangi⁶, Joseph Ouma¹, Priscilla Eroju¹, Telsa de Lange⁷, Michael Tartakovsky⁷, Jodie L. White³, Ceasar Kakura¹, Mary Glenn Fowler³, Philippa Musoke⁸, Monica Nolan¹, M. Kate Grabowski³, Lawrence H. Moulton⁹, Susan L. Stramer¹⁰, Denise Whitby¹¹, Peter A. Zimmerman¹², Deo Wabwire¹, Isaac Kajja¹³, Jeffrey McCullough¹⁴, Raymond Goodrich¹⁵, Thomas C. Quinn^{3,9,16}, Robert Cortes¹⁷, Paul M. Ness³ and Aaron A. R. Tobian^{3,18*} 



Study Design

- Prospective, randomized, double-blind, controlled trial at Mulago Hospital Complex and Kawempe Hospital
- Eligible patients randomized 1:1 to receive Mirasol-treated WB vs. standard WB transfusions
- Hypothesis: Mirasol treatment will reduce the combined incidence of transfusion-transmitted infections including HIV, HBV, HCV, HEV, HHV-8, malaria, and bacteria in recipients of transfusions using Mirasol-treated FWB
- The increase in hemoglobin among recipients post-transfusion will be equivalent between Mirasol treated WB and the current standard WB
- Enroll 2000 patients receiving FWB transfusions (1350 participants already enrolled)



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Challenges for WB and RBC Pathogen Reduction

- WB and RBC PRT is primarily a proof of principle concept that needs continual development
- The current processes are relatively slow and time consuming. Higher throughput and more automated methods are needed
- Pathogen reduction will likely not be 100% effective for all agents
- Many pathogen reduction methods alter the cellular quality and lead to lower increments
- The economics of PRT needs to be evaluated (e.g., how much are hospitals willing to spend)

Advantages and Goals of WB and RBC Pathogen Reduction

- PRT offer a generalized, proactive mechanism to reduce or eliminate the threat of emerging infectious disease transmission by transfusion
- PRT will permit safer blood for use in situations when there is no time for screening (e.g., pandemic preparedness)
- PRT may allow certain donor screening tests to be eliminated



EDITORIAL

Quest for the holy grail: pathogen reduction in low-income countries

“A low-cost, easy-to-use technology that can inactivate WBCs and a wide array of pathogens, including known emerging and unidentified threats, in whole blood could potentially have a dramatic public health impact...”

Summary and Conclusions

- WB and RBC pathogen reduction technology (PRT) is critically needed, but much more difficult to implement than platelet or plasma PRT
- Cerus INTERCEPT and Terumo BCT Mirasol technologies have substantial pathogen log reduction, but continual development is needed
- PRT needs to be economically feasible so all countries are able to benefit

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