Pathogen Reduction of Red Cell Concentrates

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Disclosures

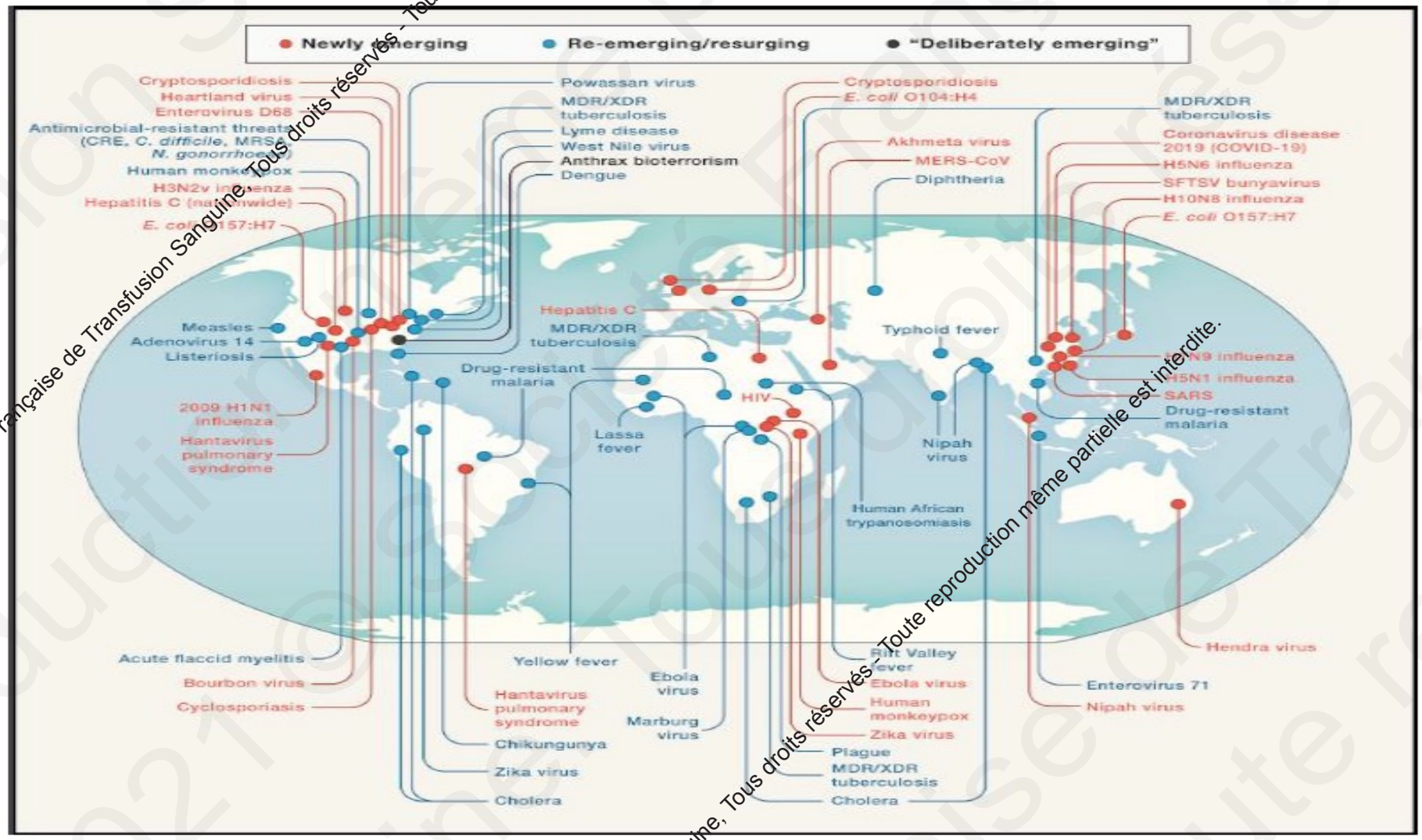
- Employee of Cerus Corporation
- Professor, Laboratory Medicine, University of California, SF
- Principal Investigator HHS/BARDA Contract for Pathogen Reduced RBC
- Principal Investigator HHS/FDA Contract for Development of New Compounds for Whole Blood Pathogen Reduction

Agenda

- Rationale for pathogen reduction, emerging pathogens, and pandemic preparedness
- Technology
  - Riboflavin + UVB
  - Amustaline-GSH
- Clinical experience
- Conclusions

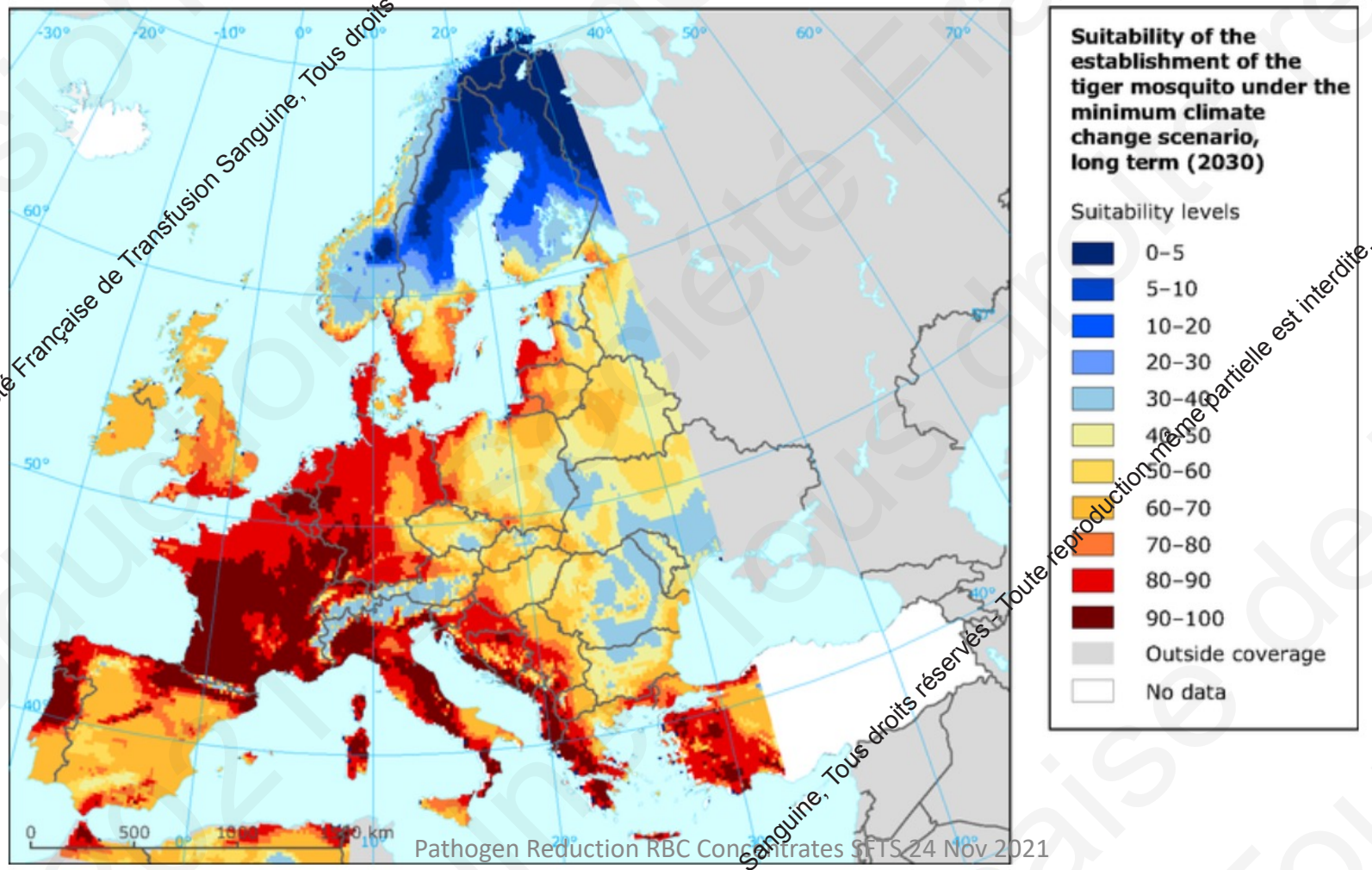
History of Global Emerging and Re-Emerging Pathogens Entering Humans and the Blood Donor Population

Morens and Fauci 2020 Cell ; 182:1077-1092



Suitability of Climate in Europe for the Asian Tiger Mosquito Climate Change is Changing the Range of Insect Vectors

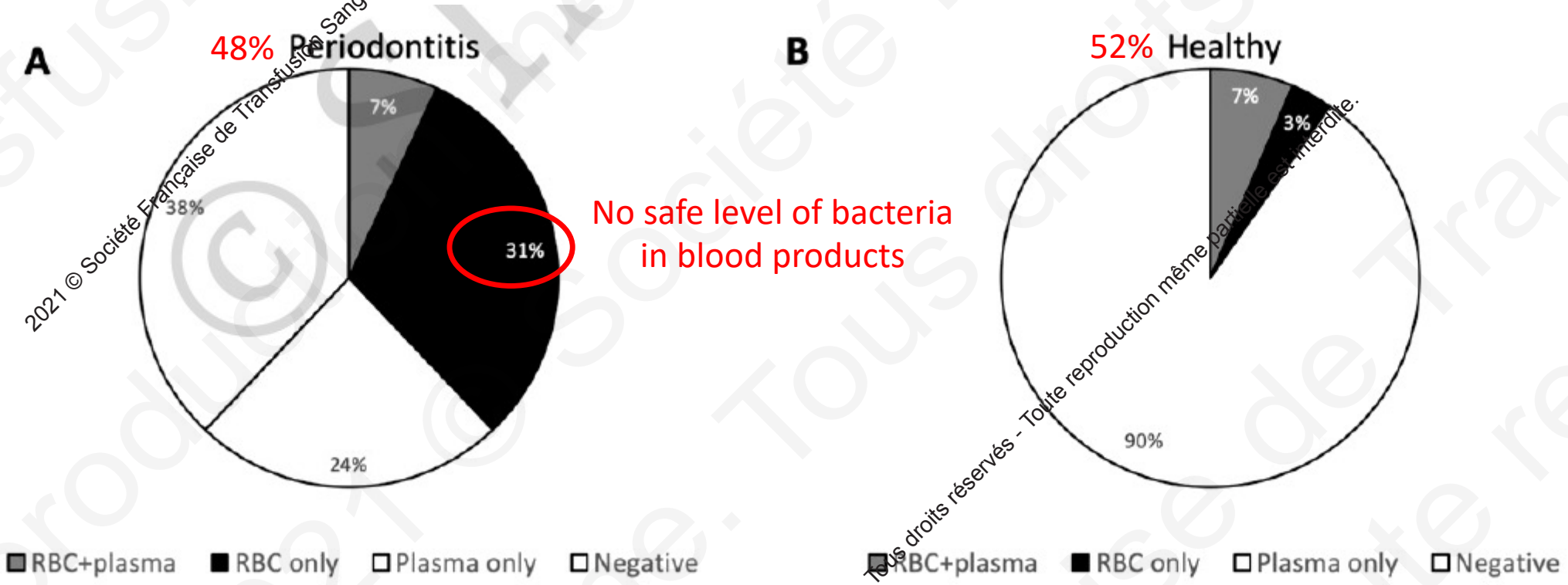
Transmits 25 different arboviruses



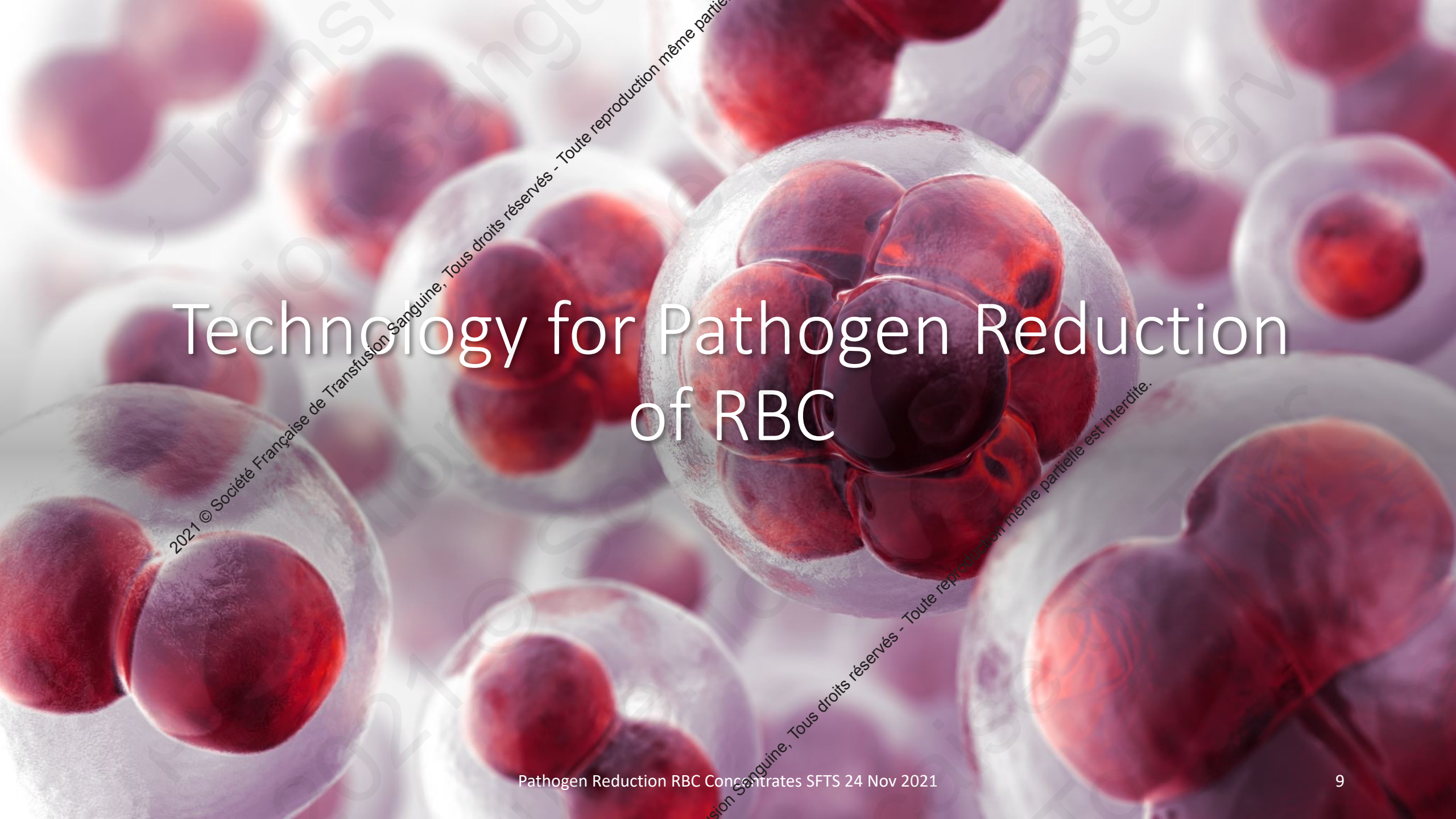
Bacteria in RBC Concentrates- Unrecognized Donor Risk of Periodontitis

Periodontitis increases risk of viable bacteria in freshly drawn blood donations

Christian Damgaard[1,2], Susanne G. Sækmose[3], Martin Nilsson[4], Mogens Kilian[5], Claus H. Nielsen[1,2], Palle Holmstrup[1]



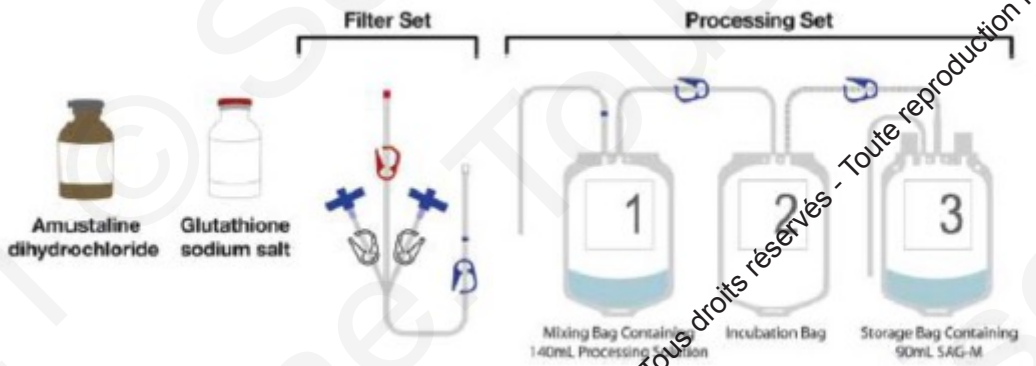
No safe level of bacteria in blood products



Technology for Pathogen Reduction of RBC

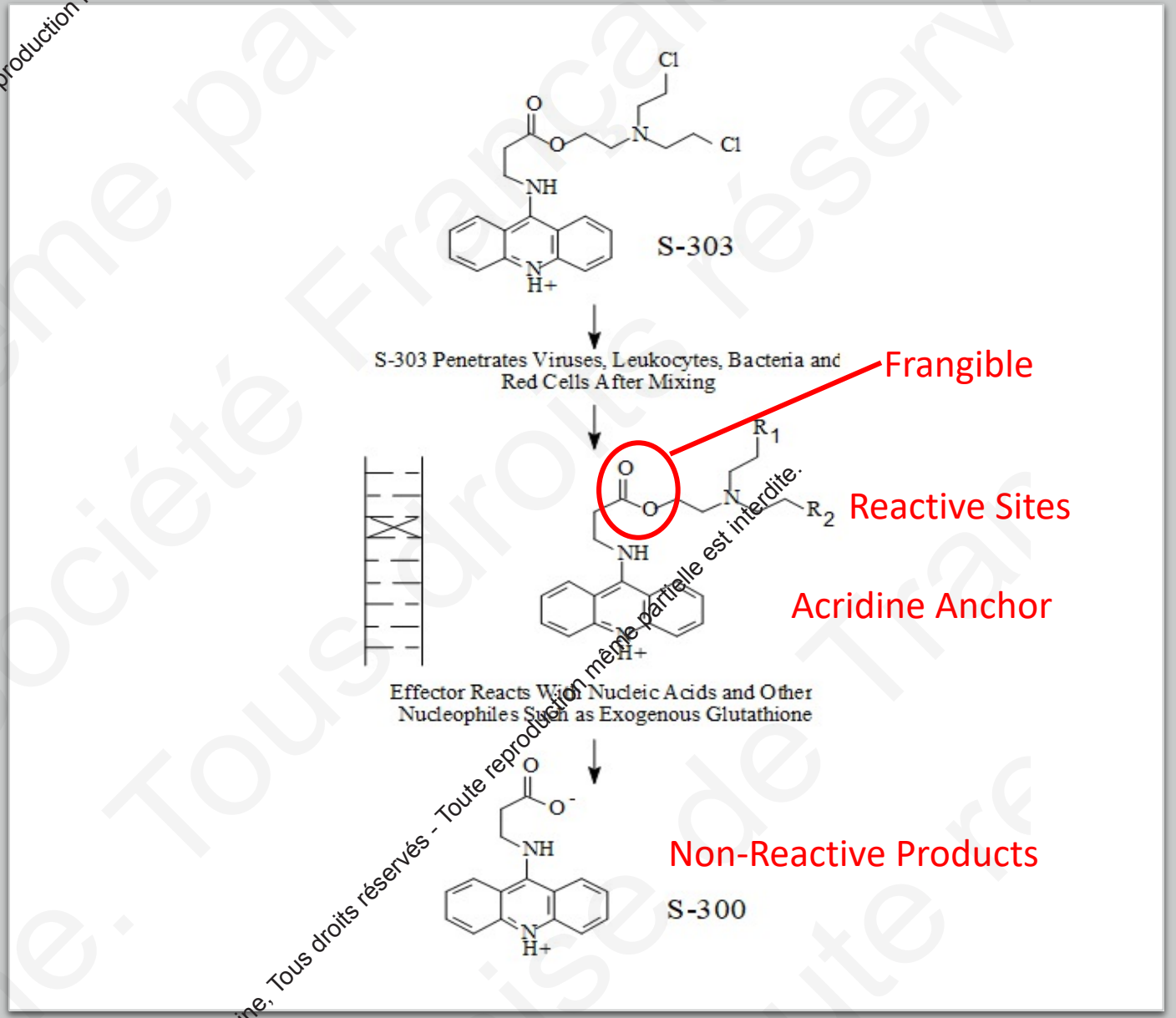
Amustaline-GSH

Amustaline- GSH Pathogen Reduction



S-303 MECHANISM OF ACTION

- Specific adduct formation by alkylation
- Does not require reactive oxygen species
- Degradation to inactive by-products



Riboflavin-UV

Improving the safety of whole blood-derived transfusion products with a riboflavin-based pathogen reduction technology

Susan Yonemura,[1] Suzann Doane,[1] Shawn Keil,[1] Raymond Goodrich,[1,2] Heather Pidcoke,[1] and Marcia Cardoso[3]

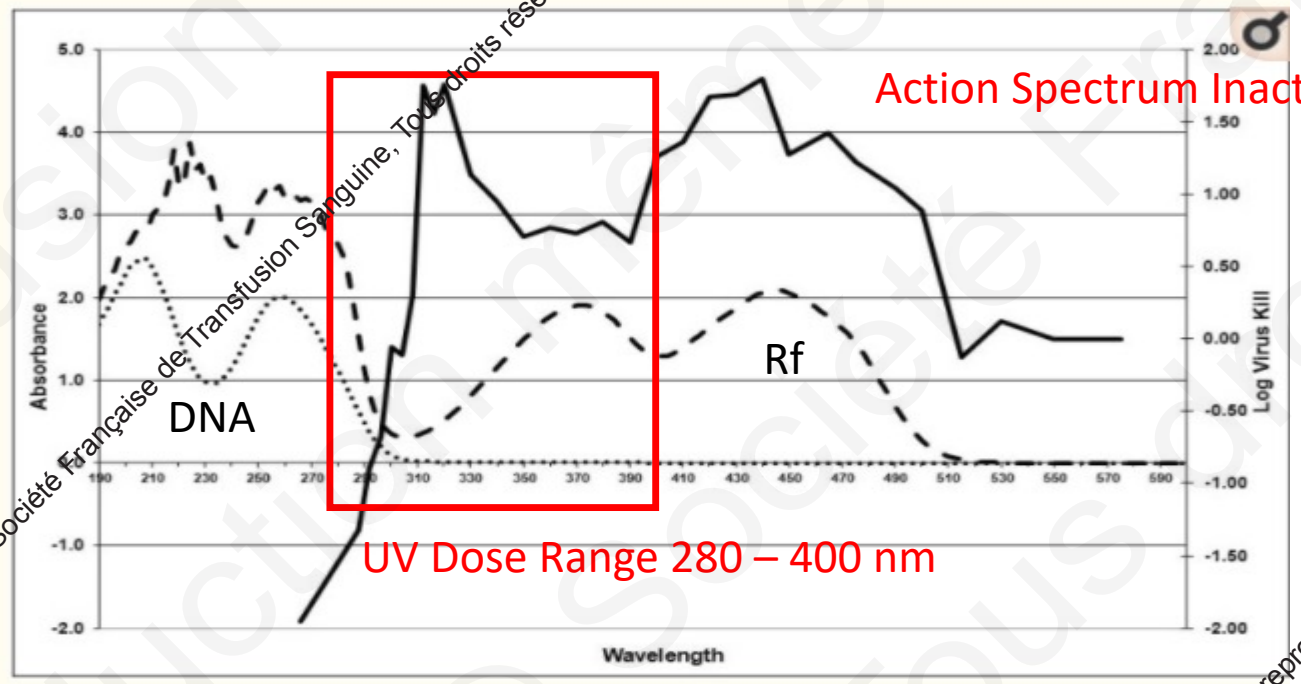


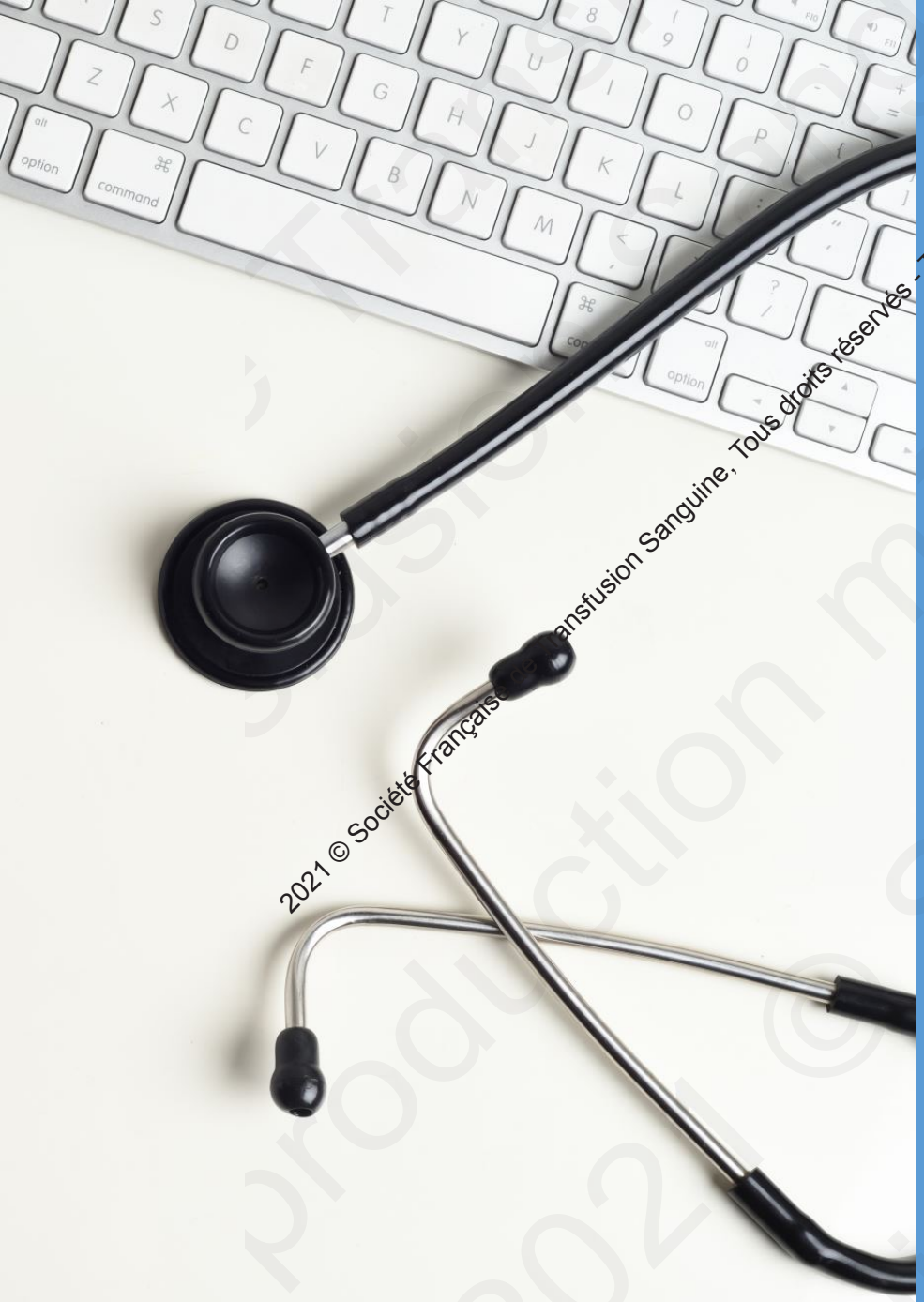
Figure 1

Light absorption and virus inactivation in solution as a function of wavelength of light.

Solid line: action spectrum (virus inactivation *vs* wavelength); dotted line: absorption of 1 mg/mL DNA in saline; dashed line: absorption of 200 μM riboflavin in saline.

Chemical and Biological Mechanisms of Pathogen Reduction Technologies

Janna M Mundt,* Lindsay Rouse,[1] Jeroen Van den Bossche,[1] and Raymond P Goodrich[1]



Clinical Data

Pathogen Reduction Technology: Clinical Trials

- Amustaline-GSH
  - Phase 2: radiolabel post transfusion recovery and lifespan 35-day RBC
  - Phase 3
    - EU: Acute anemia – cardiovascular surgery (n = 52)
    - EU: Chronic anemia – transfusion dependent thalassemia (n = 80)
    - US: Acute anemia – all cause of acute anemia ongoing (n = 600)
    - US: Acute anemia – cardiovascular surgery, ongoing (n = 290)
- Riboflavin-UVB
  - Phase 2: radiolabel post transfusion recovery and lifespan 21-day RBC
  - Phase 3: prevention of transfusion transmitted plasmodia by WB

Amustaline-GSH RBC Clinical Data

Red blood cell concentrates treated with the amustaline (S-303) pathogen reduction system and stored for 35 days retain post-transfusion viability: results of a two-centre study

J. A. Cancelas,[1] J. L. Gottschall,[2] N. Rugg,[1] S. Graminske,[2] M. A. Schott,[3] A. North,[3] N. Huang,[3] N. Mufti,[3] A. Erickson,[3] S. Rico[3] & L. Corash[3]

	Test mean (SD) (n = 26)	Control mean (SD) (n = 26)	Mean difference (Test–Control)	95% CI of Mean treatment Difference (Test–Control)[a]
24-h post-transfusion recovery (%)	83·2 (5·2)	84·9 (5·9)	−1·8	−3·6, 0·0
Life span (days)	62·8 (10·6)[b]	75·1 (13·7)	−12·3	−17·4, −7·2
T_{50} (days)	33·5 (7·1)[b]	39·7 (10·2)	−6·2	−9·7, −2·6
$AUC_{0\text{-last}}$ (surviving cells × days)	22·6 (1·9)	23·1 (2·2)	−0·6	−1·4, 0·3

- No difference in 24-hour post transfusion recovery
- Difference in survival, but within physiologic ranges
- No difference in area under the curve (AUC)

Red blood cell concentrates treated with the amustaline (S-303) pathogen reduction system and stored for 35 days retain post-transfusion viability: results of a two-centre study

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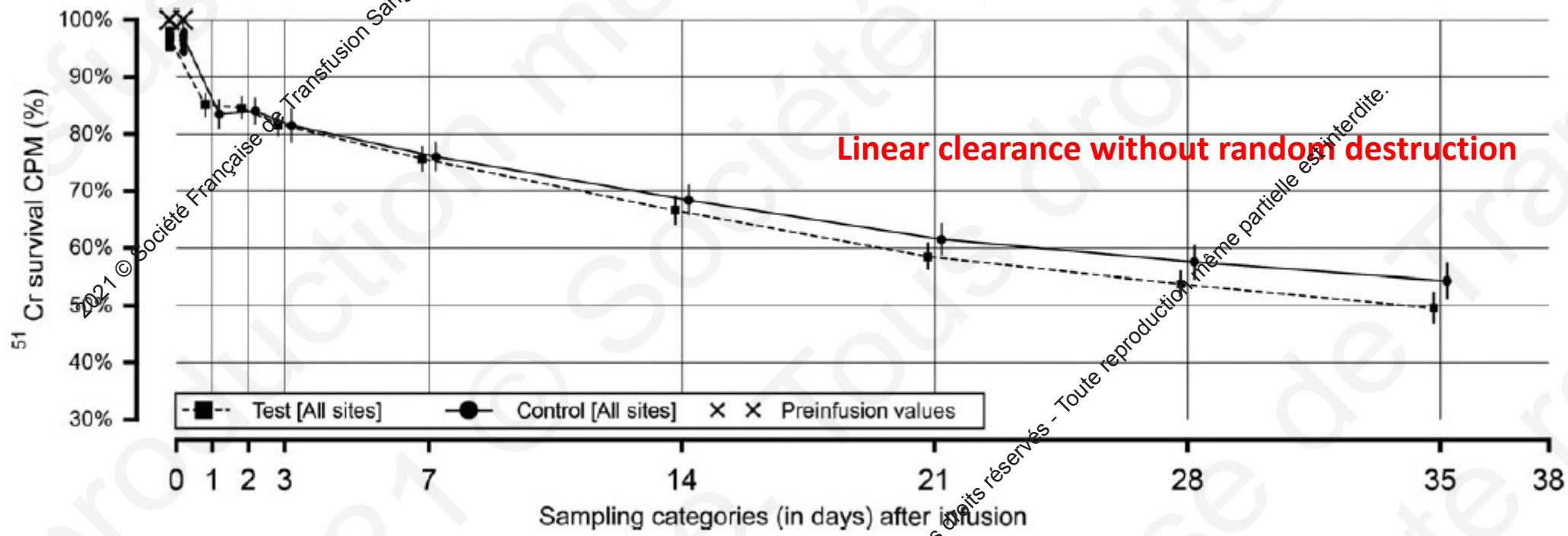
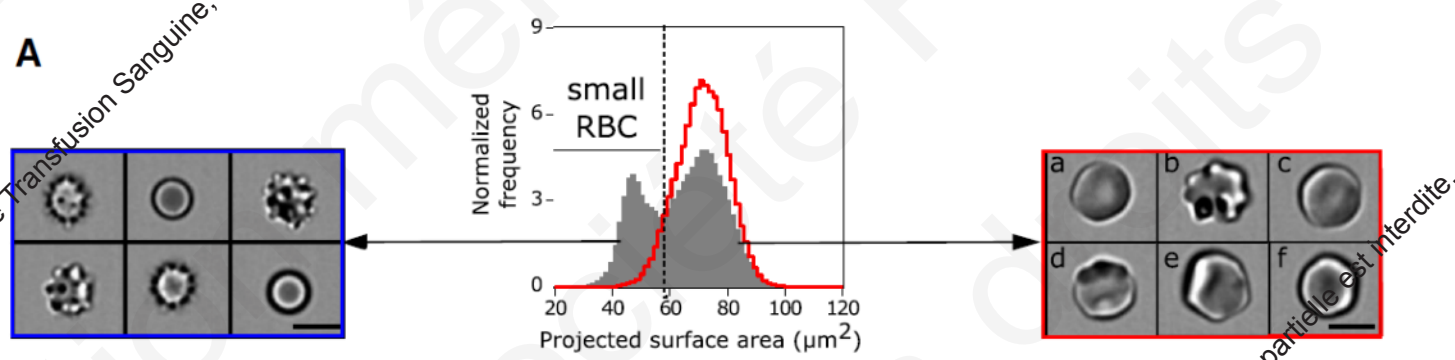


Linear clearance without random destruction

Spherocytic shift of red blood cells during storage provides a quantitative whole cell–based marker of the storage lesion



Rapid clearance of storage-induced microerythrocytes alters transfusion recovery

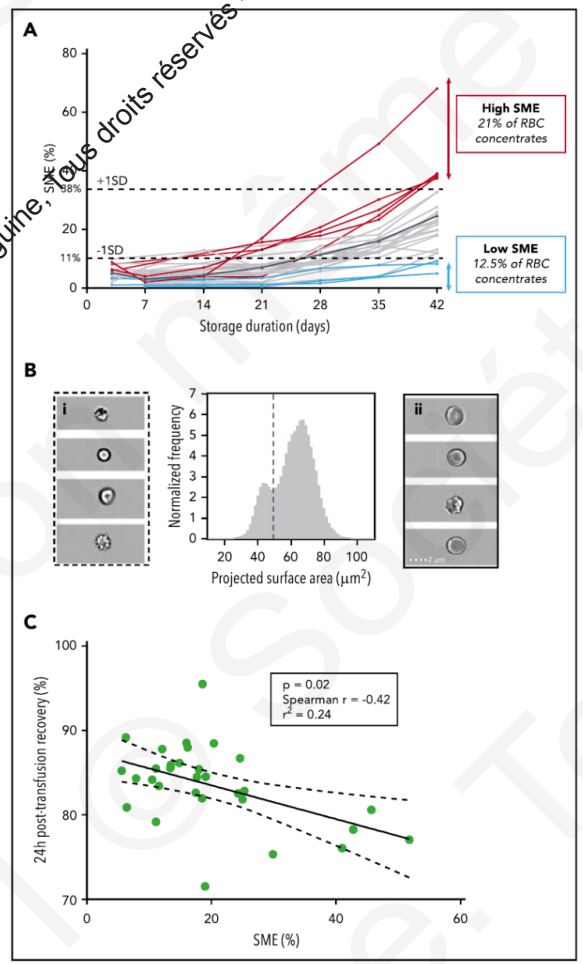
Camille Roussel,[1-4,*] Alexandre Morel,[1,2,5,*] Michaël Dussiot,[1,2,*] Mickaël Marin,[2-4] Martin Colard,[1,2] Aurélie Fricot-Monsinjon,[2-4] Anaïs Martinez,[1,2] Charlotte Chambrion,[2-4] Benoît Henry,[2-4] Madeleine Casimir,[1,2] Geoffroy Laville,[2-4] Mallorie Dépond,[2-4] Safi Dokmak,[6] François Paye,[7] Alain Sauvanet,[6] Caroline Le Van Kim,[2-4] Yves Colin,[2-4] Sonia Georgeault,[8,9] Philippe Roingeard,[8,9] Steven L. Spitalnik,[10] Papa Alioune Ndour,[2-4] Olivier Hermine,[1,2,5] Eldad A. Hod,[10] Pierre A. Buffet,[2-4,11,†] and Pascal Amireault[1-4,†]

cerus

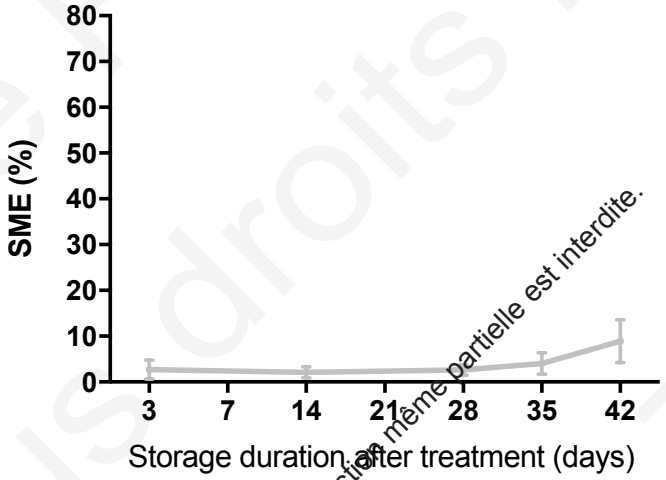
TRANSFUSION MEDICINE

Rapid clearance of storage-induced microerythrocytes alters transfusion recovery

Figure 2. Proportion of SMEs at the end of storage correlates with 24-hour posttransfusion recovery in healthy human volunteers. (A) Quantification of SMEs upon storage of RBC concentrates in SAGM solution (n = 24) between days 3 and 42 (mean value in solid black line). Low (blue lines) and high proportions of SMEs (red lines) defined by proportions of SME < −1 SD (11%) and > +1 SD (38%) at the end of storage, respectively. (B) Representative normalized frequency plot for RBC concentrate at the end of storage in AS-3 showing a well-demarcated subpopulation of SMEs. Subpopulation of SMEs contains spherocytes, spherocechinocytes, and type III echinocytes (i), whereas normal-sized RBCs (ii) contain discocytes and type I and II echinocytes. (C) Correlation between 24-hour posttransfusion recovery and proportions of SMEs quantified by imaging flow cytometry at the end of storage (n = 31; P = .02; Spearman r = −0.42; r² = 0.24).



Amustaline GSH RBCs show lower SME's than conventional stored RBC



Red blood cells treated with the amustaline (S-303) pathogen reduction system: a transfusion study in cardiac surgery

Veronika Brixner,[1] *Arnold-Holger Kiessling*,[2] *Katharina Madlener*,[3] *Markus M. Müller*,[1] *Johannes Leibacher*,[1] *Sarah Dombos*,[1] *Iuliia Weber*,[1] *Hans-Ulrich Pfeiffer*,[1] *Christof Geisen*,[1] *Michael Schmidt*,[1] *Reinhard Henschler*,[4,5] *Anne North*,[6] *Norman Huang*,[6] *Nina Mufti*,[6] *Anna Erickson*,[6] *Christine Ernst*,[6] *Salvador Rico*,[6] *Richard J. Benjamin*,[6] *Laurence M. Corash*,[6] and *Erhard Seifried*[1]

- Population: Elective adult cardiovascular surgery patients
- Intervention: Amustaline-GSH RBC Concentrates in SAGM
- Comparison: Conventional RBC Concentrates in SAGM
- Primary Outcome: Hemoglobin content of RBC Concentrates
- Timing: 7 days of RBC transfusion support, immune surveillance through day 90

In Vitro Efficacy

Parameter	TEST (n)	CONTROL (n)	Treatment Difference - P
Hemoglobin Content (g)	53.6 ± 5.6 (389)	56.3 ± 6.0 (365)	-2.6, -1.9: p < 0.001
Hemoglobin EOS QC (g)	53.1 ± 5.7 (301)	55.8 ± 5.9 (261)	-2.8, -1.92: p < 0.001
Hemolysis EOS QC (%)	0.28 ± 0.12 (301)	0.35 ± 0.16 (261)	-0.09, -0.04: p < 0.001
ATP EOS (umol/g)	2.8 ± 0.9 (294)	2.4 ± 0.7 (262)	0.33, 0.59: p< 0.001
Plasma free HB EOS (g/dL)	1.42 ± 0.64 (263)	1.79 ± 0.88 (225)	-0.49, -0.23: p < 0.001
Plasma Protein (mg/dL)	68.0 ± 25.6 (301)	228.8 ± 34.7 (298)	-166, 156: p < 0.001

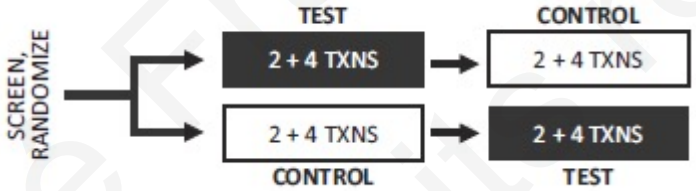
Clinical Outcomes

OUTCOME	TEST (25)	CONTROL (26)	P-VALUE
Renal Failure	5 (20%)	3 (11.5%)	0.412
Hepatic Failure	1 (4%)	0	0.371
6 MWT – day 1 (m)	44.8	53.1	0.472
6 MWT – day 13 (m)	95.5	97.7	0.626

Yesim Aydinok,[1] Antonio Piga,[2] Raffaella Origa,[3] Nina Mufti,[4] Anna Erickson,[4] Anne North,[4] Katie Waldhaus,[4] Christine Ernst,[4] Jin-Sying Lin,[4] Norman Huang,[4] Richard J. Benjamin[4] and Laurence Corash[4]

Amustaline-glutathione pathogen-reduced red blood cell concentrates for transfusion-dependent thalassaemia

STUDY DESIGN: Randomized Crossover 12 transfusions 80 Patients TDT



- Population: Transfusion Dependent Thalassemia
- Intervention: Amustaline-GSH RBC
- Comparison: Conventional RBC
- Outcome: Hemoglobin Use Over 6 months
- Timing: 6 Months Transfusion Support

VARIABLE HEMOGLOBIN CONTENT OF RBC COMPONENTS

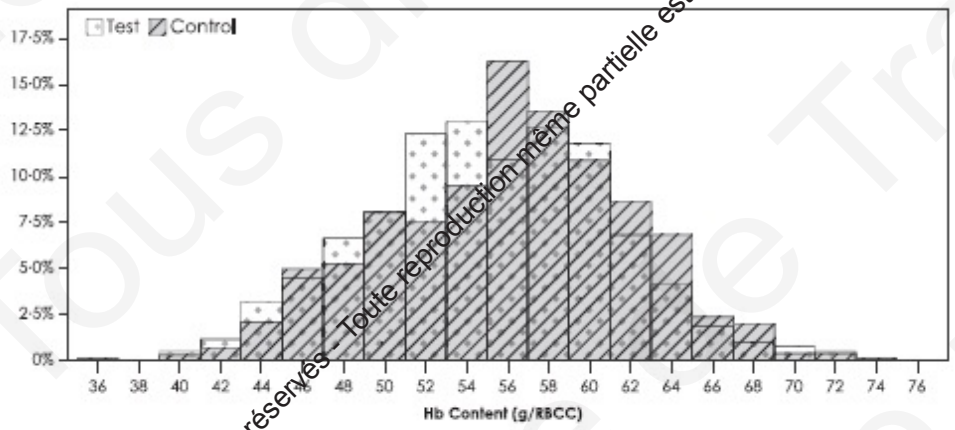


Fig 3. Haemoglobin content of test and control RBCC. The proportional (%) distributions of total haemoglobin (Hb) content (g) for 1024 Test (dots) and 1008 Control (diagonal) red blood cell concentrates (RBCC) are shown.

Primary Endpoint: Hemoglobin Use per Day per Kg

1 g of hemoglobin = 3.7 mg Fe

Hemoglobin Use of A-GSH RBC was not-inferior

Haemoglobin use (g/kg/day) for the ITT populations in the efficacy evaluation period (transfusions 3, 4, 5 and 6).*

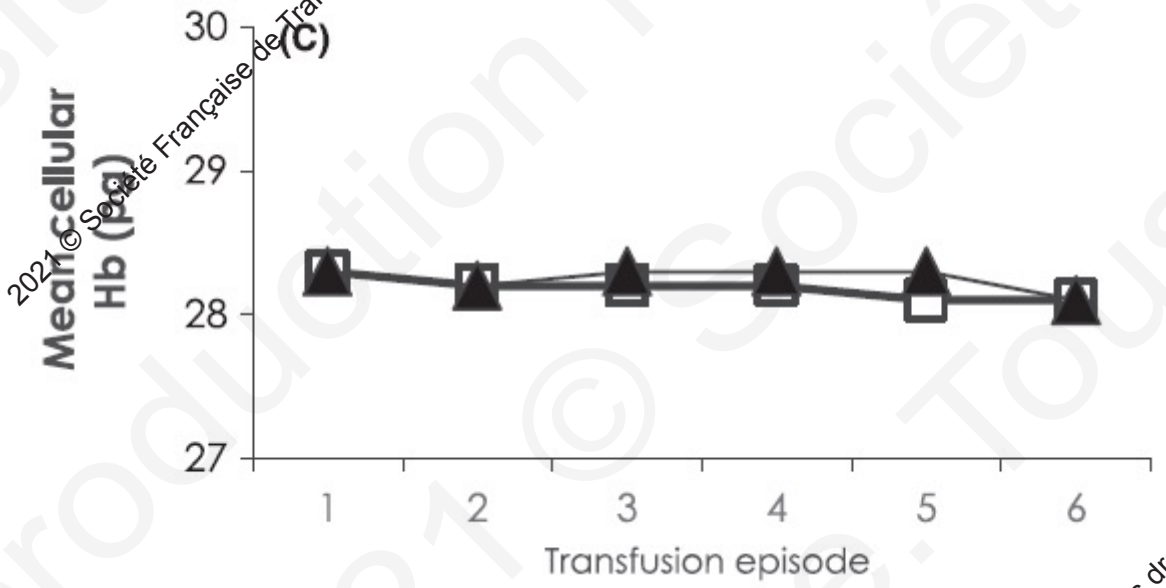
	Non-splenectomized		Splenectomized		ITT population§§		
	Test	Control	Test	Control	Test	Control	*P*
ITT (*n*)	40	40	40	40	80	80	
Dose†	471 (81)	461 (96)	451 (47)	461 (59)	461 (67)	461 (79)	0·950
Interval†	17·6 (3·0)	18·4 (3·4)	20·7 (3·5)	21·0 (3·5)	19·2 (3·6)	19·7 (3·6)	0·032
Hb use†	0·135 (0·03)	0·130 (0·03)	0·091 (0·03)	0·092 (0·03)	0·113 (0·04)	0·111 (0·04)	0·373

Parameter	Test (*n* = 1024)	Control (*n* = 1008)	Difference (CI)†	*P*‡
RBCC volume (ml)	271·4 (19·0)	278·9 (22·2)	−7·5 (−9·3, 5·7)	<0·001
RBCC Hct (%)	60·5 (2·4)	59·0 (2·8)	1·5 (1·7, 1·7)	<0·001
RBCC Hb content (g)	54·6 (5·9)	55·6 (5·9)	−1·0 (−1·5, −0·5)	<0·001

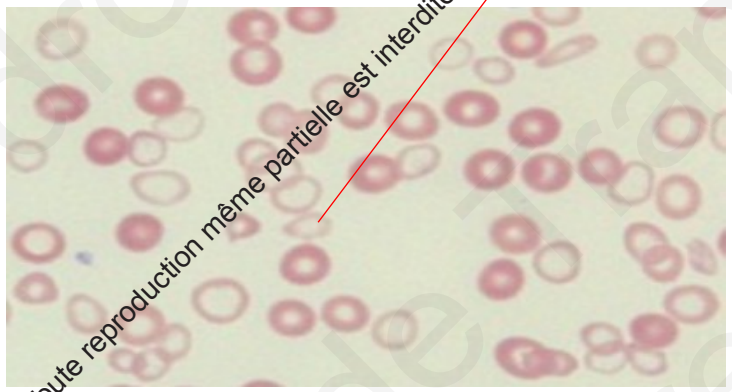
MCH as an Index of RBC Production Suppression

Decrease Erythroid Hyperplasia

- **MCH of Endogenous Thalassemia RBCs is < 25 pg**
- **Endogenous RBC Production was effectively suppressed**



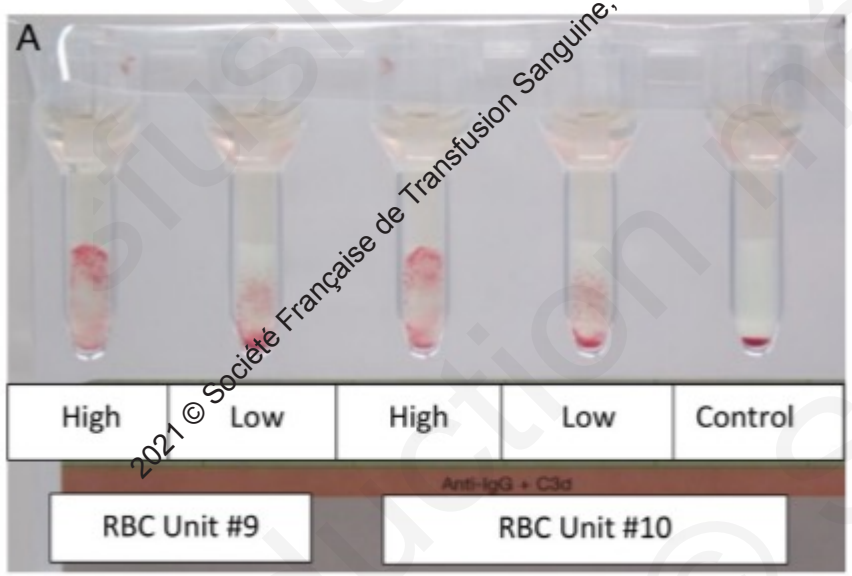
Pre-transfusion patient mean corpuscular haemoglobin (MCH, pg) are indicated for all Test (▲) and Control (□)

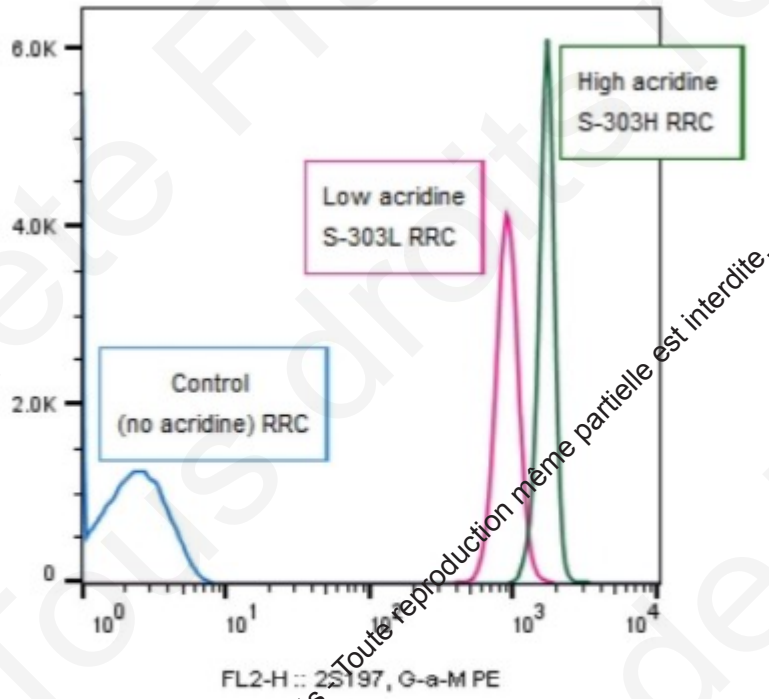


Thalassemia RBC

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

Christof Geisen[1] | Anne North[2] | Lisa Becker[1] | Veronika Brixner[1] | Melissa von Goetz[2] | Laurence Corash[2] | Richard J. Benjamin[2] | Nina Mufti[2] | Erhard Seifried[1]





SAMPLE ID	PE Molecules/Cell
Control RRC	42
S-303L RRC	15643
S-303H RRC	29721

Cell panels with varying levels of S-303 adducts to detect antibodies to S-303 RBC

Patient number	Reactivity, initial screen: S-303H RRC	Reactivity, initial screen: S-303L RRC	Antibody class/subclass	Antibody titer: S-303H RRC	Antibody titer: S-303L RRC	Specificity by inhibition assay
General hospitalized patients						
1	++	–	IgG, non $G_{1,3}$/non G_4	4	neg	Acridine
2	–	++	IgG, non $G_{1,3}$	neg	8	Unidentified
3	++	–	IgG, non $G_{1,3}$/non G_4[a]	4	neg	Acridine
4	++++	+++	IgG, non $G_{1,3}$/non G_4	8	8	Acridine
5	+	–	IgG, non $G_{1,3}$	1	neg	Acridine
6	+++	+	IgG, non $G_{1,3}$/non G_4	4	neg	Acridine
7	++	+	IgG, non $G_{1,3}$	2	neg	Acridine
8	+	–	IgG, non $G_{1,3}$	2	neg	Acridine
9	+	++	IgG, non $G_{1,3}$/non G_4	4	4	Acridine
10	+++	–	IgM	16	neg	Acridine
11	+/–	+	IgG, non $G_{1,3}$/ possible G_4	4	nt	Acridine
12	+/–	–	IgG, non $G_{1,3}$/non G_4	4	neg	Acridine
Hemoglobinopathy patients						
13	++++	+++	possible IgM	8	neg	Acridine
14	+++	++	probable IgM	8	neg	Acridine
15	–	++	IgG, non $G_{1,3}$	neg	1	unidentified
16	++++	+++	IgG, non $G_{1,3}$	32	neg	acridine
			IgM	16	neg	
17	+/–	+++	IgG, non $G_{1,3}$	nd	nt	unidentified

- 10,721 sera from transfused hospitalized patients
- 998 Chronically transfused patients
- 17 positive sera detected. primarily non-$IgG_{1,3}$ all low titer
- 0.15% incidence of native Abs
- Primarily anti-acridine specific

TABLE 3 Patient characteristics in clinical studies using the current generation of amustaline/GSH RBC concentrates

Diagnosis	STARS[6] Cardiac surgery	SPARC[5] Thalassemia	Total
Number screened for natural S-303 antibody	87	86	173
Patients transfused with amustaline/GSH RBC concentrates in test arm	25	81	106
Mean (range) exposure to amustaline/GSH RBC (# of concentrates)	2.9 (1-7)	12.5 (3-18)	(1-18)
Mean (SD) S-303 epitopes/RBC (n = 12) on Day 2 post manufacture[a]	9064 (1005)	13151 (919)	-
Mean (SD) S-303 epitopes/RBC (n = 12) on Day 35 post manufacture	5033 (841)	7035 (639)	-
Patients with natural S-303 specific antibodies at screening	0	0	0
Patients with S-303-specific antibodies at Day ~90 post transfusion	0	0	0

- Patients Exposed to S-303 RBC in Clinical Trials: No Immune Responses Observed
- 81 transfusion dependent thalassemia patients transfused for six months
- Large phase registry study for chronically transfused patients is expected as part of post marketing surveillance

Riboflavin UV Clinical Data

Red blood cells derived from whole blood treated with riboflavin and ultraviolet light maintain adequate survival in vivo after 21 days of storage

Jose A. Cancelas,[1] Sherrill J. Slichter,[2,3] Neeta Rugg,[1] P. Gayle Pratt,[1] Shawnagay Nestheide,[1] Jill Corson,[2] Esther Pellham,[2] Marty Huntington,[4] and Raymond P. Goodrich[5]

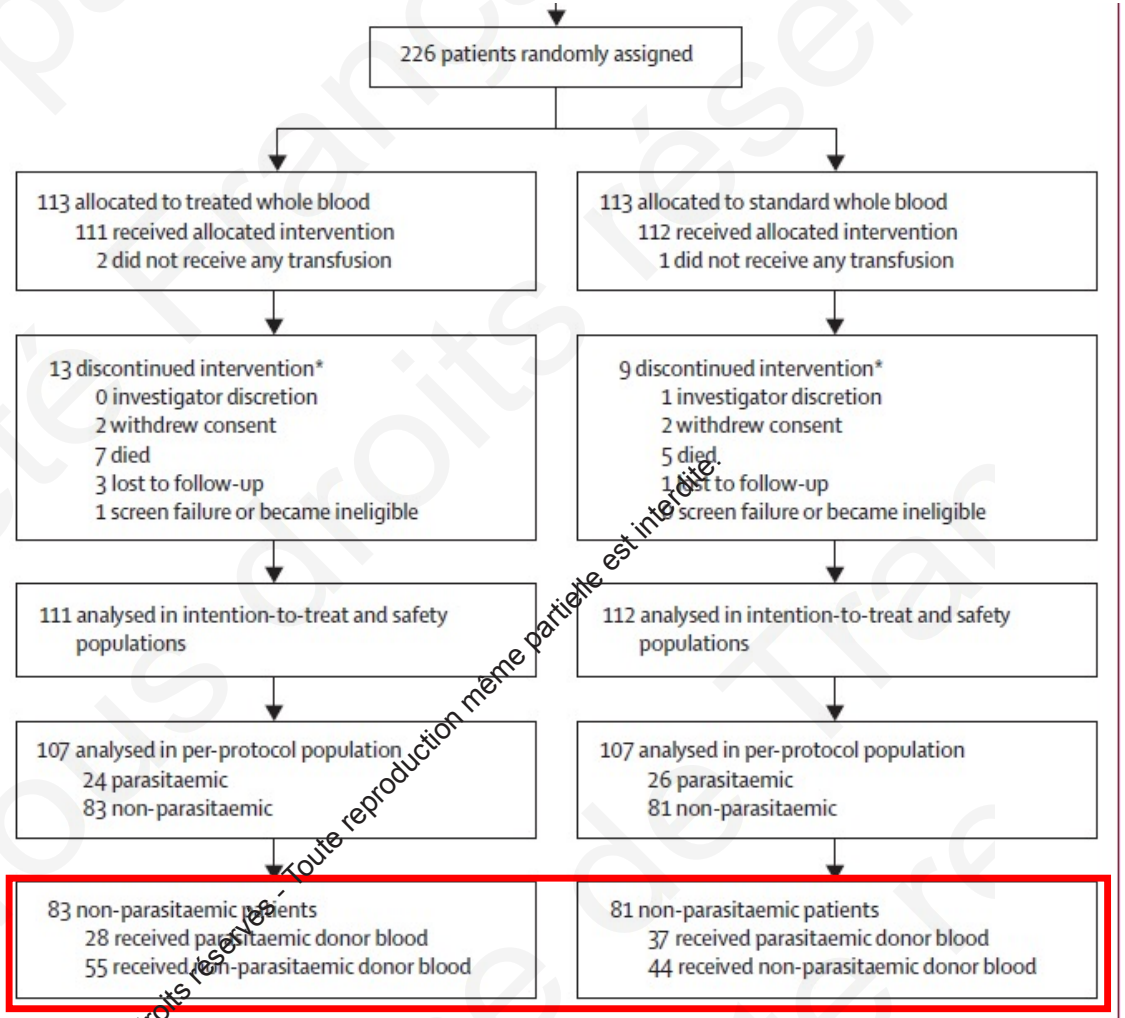
TABLE 1. 24-hour RBC recoveries and linear and exponential survivals

	All subjects		
Collection order	Mirasol treated	Untreated control	Difference
Number	24	24	24
24-hr RBC recovery (%)			
Mean (±SD)	82.5 (±3.9)	91.7 (±6.8)	−9.2 (±6.6)
95% CI†	80.9 to 84.2	88.8 to 94.6	−12.0 to −6.4
Subjects with RBC recovery ≥75%‡, n (%)	23 (95.8)	24 (100.0)	
RBC survival (days)			
Mean (±SD)	60.5 (±5.6)	81.6 (±15.5)	−21.1 (±12.1)
95% CI†	58.1 to 62.8	75.6 to 88.1	−26.2 to −16.0
T_{50} (days)			
Mean (±SD)	22.6 (±4.3)	35.8 (±7.9)	−13.2 (±7.0)
95% CI†	20.8 to 24.4	32.5 to 39.1	−16.2 to −10.3

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 Maxwell, Raymond P Goodrich, Shirley Owusu-Ofori

- Population: Plasmodia negative + Anemia
- Intervention: Riboflavin-UV WB Plasmodia + Donors
- Comparison: Conventional WB Plasmodia + Donors
- Outcome: Transfusion Transmitted Plasmodia
- Timing: Transfusion with 28 day follow up
- Design: Randomized, Controlled



Prevention of Transfusion Transmitted Malaria

	Parasitaemic whole blood transfused (exposed patients; n=65)*		Non-parasitaemic whole blood transfused (non-exposed patients; n=99)*		p value
	Treated patients (n=28)	Untreated patients (n=37)	Treated patients (n=54)	Untreated patients (n=45)	
Transfusion-transmitted malaria (≥2 parasitaemic samples, with allelic matching criteria)	1 (3·6%; 95% CI 0·1–28·2)	8 (21·6%†; 95% CI 9·8–38·2)	NA	NA	0·039‡
Transfusion-transmitted malaria (≥2 parasitaemic samples, no allelic matching criteria)	3 (10·7%; 95% CI 2·3–28·3)	13 (35·1%†; 95% CI 20·2–52·5)	1	0	0·024‡
Single parasitaemic samples	11	10	3	4	0·0049§
No parasitaemic samples	14	14	50	41	<0·0001§

The results of this primary endpoint analysis are for the total of 164 non-parasitaemic patients at day 0. NA=not applicable. *37 (57%) of 65 samples from exposed patients were parasitaemic post-transfusion *vs* eight (8%) of 99 in non-exposed patients (p<0·0001 for comparison between exposed and non-exposed patients receiving treated or untreated whole blood). †Absolute risk difference estimate: –18·1% (95% CI –33·0 to –3·1) for transfusion-transmitted malaria defined with allelic matching and –24·4% (–43·6 to –5·2) for transfusion-transmitted malaria defined without allelic matching. ‡p value for comparison between exposed patients transfused with treated *vs* untreated whole blood. §p value for exposed *vs* non-exposed patients receiving treated or untreated whole blood.

Table 2: **Distribution of parasitaemic samples in exposed and non-exposed patients receiving treated or untreated whole blood**

The incidence of TT Malaria was reduced by Riboflavin-UVB Treatment of Whole Blood

Summary and Conclusions

- Riboflavin-UV RBC is in clinical development, no ongoing trials at present
- Amustaline-GSH RBC completed clinical trials for CE mark registration
  - Dossier submitted to TUV and Competent Authority for MDR review
  - Initial indication is for anemia due to ineffective RBC production
  - Pathogen and leukocyte inactivation are effective
  - Post-transfusion RBC viability is within therapeutic range for 35-day RBC
  - RBC components contain adequate levels of hemoglobin
  - Amustaline-GSH RBC were non-inferior for support of transfusion dependent thalassemia in a blinded RCT
  - Immune responses are infrequent, and thus far not physiologically active
  - Post marketing immune surveillance and registry are required

THANK YOU, TOGETHER WE CAN MAKE A DIFFERENCE
EFS is an important collaborative partner