EMERGING TECHNOLOGIES: PLASMA, RBC & WHOLE BLOOD

CLAUDIA S. COHN, MD, PHD
ASFA 2016
DISCLOSURES

• I have received research support and Honoraria from Fresenius Kabi
• I have received research support from Octapharma
• I have been an invited guest at a Cerus Research conference
• I have received research funding from Ortho Diagnostics and consulting fees
Landsteiner discovers ABO blood types

1900

Plasma collection begins

1920

Plastic blood bags patented

1950

Hepatitis B testing begins

1972

HIV testing begins

1985

Leukoreduction begins

1986

Enhance transfusion safety

1989

Artificial blood developed

1990

2000-?

From Medical Laboratory Observer
William B. Lockwood, PhD, MD
From: Protecting the Blood Supply From Emerging Pathogens: The Role of Pathogen Inactivation
Jean Pierre Allain Transfusion Med Reviews 2005
US FDA TRALI Fatalities

ARC & others implement male-predominant plasma transfusion strategy

PLASMA PREPARATIONS TO MITIGATE RISKS

• Octaplas (Octapharma) – solvent detergent treated pooled plasma (SD Plasma)

• Pathogen inactivation:
  • Amotosalen/psoralen – Intercept (Cerus)
  • Riboflavin – Mirasol (Terumo)
  • Methylene blue – Theraflex MB (Macopharma)
OCTAPLAS – (SD PLASMA)

• Manufactured from human plasma collected in US licensed centers
• All plasma tested
  • Viral markers
  • Parvovirus B19
  • Hepatitis E and Hepatitis A
• ABO blood group pools
• Solvent detergent treated
ABO groups

630 – 1,520 donors

- Solvent: TnBP
- Detergent: Tween-80 or Triton X-100

SD Removed by Oil and Solid Phase Extraction

Aliquot into 200 ml units
PRION REMOVAL

- Affinity ligand column for selective binding of prion protein (PrPSc)
- Prions reduction: >5 logs
- Product insert does not make claims regarding prion removal

OCTAPLAS VS PLASMA UNIT
OCTAPLAS UNIT

• Benefits:
  • Lipid enveloped viruses inactivated –
    • HIV
    • HBV
    • HCV
    • Chikungunya virus
    • West Nile virus
    • Zika virus
    • Non-enveloped viruses reduced by screening
  • Dilution of HLA and HNA antibodies through pooling reduces TRALI risk
  • Dilution of allergens reduces risk of allergic reactions
  • Most coagulation factors present at reduced albeit acceptable levels
OCTAPLAS UNIT

• Disadvantages:
  • Protein S – should not be used in Protein S deficient patients
  • Plasmin inhibitor – increased risk of hyperfibrinolysis
  • Ineffective inactivation of nonenveloped viruses (hepatitis A and parvovirus)
  • Increased cost
<table>
<thead>
<tr>
<th>Study</th>
<th>Design and N</th>
<th>Clinical Setting</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hellstern et al.</td>
<td>Prospective; N=30</td>
<td>Coagulopathy</td>
<td>Decrease in PT, increase in fibrinogen and antithrombin</td>
</tr>
<tr>
<td>Solheim et al</td>
<td>Prospective; comparison of FFP, octaplas and 'no plasma' N=66</td>
<td>Open heart Surgery</td>
<td>No clinical difference</td>
</tr>
<tr>
<td>Williamson et al</td>
<td>Prospective; octaplas vs FFP; N=55</td>
<td>Coagulopathy in liver disease, liver transplant and TTP</td>
<td>Equal correction of coagulation parameters, equal clinical efficacy</td>
</tr>
<tr>
<td>Haubelt et al.</td>
<td>Prospective; octaplas vs FFP; N=47</td>
<td>Open heart Surgery</td>
<td>No clinical difference</td>
</tr>
<tr>
<td>Demeyere et al</td>
<td>Prospective; cotaplas vs 4-factor PCC; N=20</td>
<td>Reversal of oral anti-coagulants in urgent cardiac surgery</td>
<td>PCC reverses faster and with less bleeding than SD-plasma</td>
</tr>
<tr>
<td>Lerner et al.</td>
<td>Prospective; SD-plasma vs FFP; N=45</td>
<td>Coagulopathy</td>
<td>No clinical difference, no difference in PT correction</td>
</tr>
</tbody>
</table>
Reviewed Octaplas literature since 2007 – no meta analysis possible due to heterogeneity of studies. Selected only three studies selected that compared Octaplas to FFP.

- Effective in clinically improving bleeding episodes in TTP patients
- No differences in clinical outcomes noted
- Rate of adverse events was lower for Octaplas
  - Transfusion associated infections
  - TRALI
  - Other adverse events

“While there is no evidence to suggest worse outcomes, the routine use of Octaplas as initial treatment for TTP can still not be recommended based on our update.”
OCTAPLAS: SUMMARY

- Widely used in Europe
- Clinically equivalent to FFP for coagulation metrics
- No reports of TRALI associated with Octaplas
- General reduction in other adverse events
PLASMA PREPARATIONS TO MITIGATE RISK

• Octaplas (Octapharma) – solvent detergent treated pooled plasma (SD Plasma)
• Pathogen inactivation:
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  • Riboflavin – Mirasol (Terumo)
  • Methylene blue – Theraflex MB (Macopharma)
INTERCEPT BLOOD SYSTEM FOR PLATELETS AND PLASMA: AMOTOSALEN + UVA

UVA Illumination

Amotosalen (S-59)

Targeting Guanine

Intercalation

Crosslinking

Helical region of single- or double-stranded DNA or RNA

Multiple crosslinks block strand separation and replication
COMPLETED PRE CLINICAL SAFETY STUDIES: AMOTOSALEN

- Acute toxicity
- Sub-chronic toxicity
- Chronic toxicity
- Safety pharmacology
- Distribution – Metabolism
- Occupational Exposure

- Reproductive
  - Fertility
  - Teratology
  - Perinatal
  - Developmental

- Genetic toxicity
- Carcinogenicity

North et al, Transfusion 51:2208, 2011
INTERCEPT: PATHOGEN INACTIVATION

**Enveloped viruses**
- HIV-1*
- HIV-2*
- HBV*
- DHBV
- HCV*
- BVDV
- HTVL-I*
- HTLV-II
- CMV
- WNV*
- SARS
- Vaccinia
- Chikungunya
- Dengue
- Influenza virus (H1N1) Avian flu
- Virus (H5N1)

**Non-enveloped viruses**
- Bluetongue virus, type 11
- Simian Adenovirus-15
- Feline calicivirus
- Parvovirus B19
- Human adenovirus 5

**Spirochetes**
- Treponema pallidum
- Borrelia burgdorferi

**Protozoa**
- Trypanosoma cruzi*
- Plasmodium falciparum
- Leishmania sp.
- Babesia microti

**Leukocytes**

**Gram-negative bacteria**
- Klebsiella pneumoniae
- Yersinia enterocolitica
- Escherichia coli
- Pseudomonas aeruginosa
- Salmonella choleraesuis
- Enterobacter cloacae
- Serratia marcescens

**Gram-positive bacteria**
- Staphylococcus epidermidis
- Staphylococcus aureus
- Streptococcus pyogenes
- Listeria monocytogenes
- Corynebacterium minutissimum
- Bacillus cereus (vegetative)
- Lactobacillus sp.
- Bifidobacterium adolescentis
- Propionibacterium acnes
- Clostridium perfringens

* Currently Tested in Routine Blood Bank Practice
INTERCEPT AND ZIKA VIRUS

Inactivation of Zika virus in plasma with amotosalen and ultraviolet A illumination

PROTHROMBIN TIMES FOR SUBJECTS VS. TIME
INTERCEPT FROZEN PLASMA
## INTERCEPT PLASMA IN TTP

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intercept</th>
<th>Control</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission rate within 30 days of first TPE</td>
<td>82.4%</td>
<td>88.9%</td>
<td>0.658</td>
</tr>
<tr>
<td>Median time to remission (days):</td>
<td>3-31+</td>
<td>3-13</td>
<td>0.530</td>
</tr>
<tr>
<td>All patients (range)</td>
<td>3-13</td>
<td>3-13</td>
<td>0.718</td>
</tr>
<tr>
<td>Among patients with remission (range)</td>
<td>n = 14</td>
<td>n = 16</td>
<td></td>
</tr>
<tr>
<td>Relapse rate (among patients with remission)</td>
<td>35.7%</td>
<td>37.5%</td>
<td>1.000</td>
</tr>
<tr>
<td>Median time to relapse (days):</td>
<td>2-23</td>
<td>4-34</td>
<td>0.784</td>
</tr>
<tr>
<td>Among patients who relapsed (range)</td>
<td>n = 5</td>
<td>n = 6</td>
<td></td>
</tr>
<tr>
<td>No difference:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total # TPE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume of FFP/patient</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume of FFP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># units of FFP</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Photochemically treated fresh frozen plasma for transfusion of patients with acquired coagulopathy of liver disease.


### PRIMARY DIAGNOSIS AT STUDY ENROLLMENT

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Intercept no. (%); n = 60</th>
<th>Control no. (%); n = 61</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhosis</td>
<td>45 (75)</td>
<td>47 (77)</td>
</tr>
<tr>
<td>Acute hepatitis</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>1 (2)</td>
<td>9 (15)</td>
</tr>
<tr>
<td>Multisystem organ failure</td>
<td>0 (0)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Warfarin reversal</td>
<td>2 (3)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Other</td>
<td>11 (18)</td>
<td>11 (18)</td>
</tr>
</tbody>
</table>

*Mintz PD. Blood 2006; 107:3753-3760*
CHANGE IN PT AND PTT ADJUSTED FOR FFP DOSE AND PATIENT WEIGHT ONE HOUR AFTER 1RST TRANSFUSION

<table>
<thead>
<tr>
<th>Test</th>
<th>Intervention</th>
<th>Mean dose-adjusted change +/- SD, seconds/ml/kg</th>
<th>P value (2-tailed test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT</td>
<td>Intersol (N=58)</td>
<td>0.31 +/- 0.60</td>
<td>.676</td>
</tr>
<tr>
<td></td>
<td>FFP (N=58)</td>
<td>0.35 +/- 0.52</td>
<td></td>
</tr>
<tr>
<td>PTT</td>
<td>Intersol (N=56)</td>
<td>0.32 +/- 0.75</td>
<td>.398</td>
</tr>
<tr>
<td></td>
<td>FFP (N=55)</td>
<td>0.37 +/- 6.01</td>
<td></td>
</tr>
</tbody>
</table>

- PT: Intersol found to be non-inferior to FFP
- PTT: Wide variance in PTT response did not allow equivalence to be confirmed
QUANTITATIVE AND QUALITATIVE ANALYSIS OF COAGULATION FACTORS IN CRYOPRECIPITATE PREPARED FROM FRESH-FROZEN PLASMA INACTIVATED WITH AMOTOSALEN AND ULTRAVIOLET A LIGHT

PLASMA PREPARATIONS TO MITIGATE RISK

• Octaplas (Octapharma) – solvent detergent treated pooled plasma (SD Plasma)
• Pathogen inactivation:
  • Amotosalen/psoralen – Intercept (Cerus)
  • Riboflavin – Mirasol (Terumo)
  • Methylene blue – Theraflex MB (Macopharma)
The Mirasol system inactivates disease-causing agents by altering their nucleic acids in two primary ways:

1. UV light only: reversible inactivation
   - UV light alone breaks chemical bonds in the nucleic acids of pathogens

2. UV light + riboflavin: irreversible inactivation
   - Riboflavin molecules form complexes with nucleic acids
   - UV light activates the riboflavin molecule in the complex
   - Photoactivated riboflavin induces a chemical alteration to nucleic acids, making pathogens unable to replicate
<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Toxicity*</td>
<td>Negative</td>
</tr>
<tr>
<td>Neoantigenicity*</td>
<td>Negative</td>
</tr>
<tr>
<td>Ames Mutagenicity†</td>
<td>Negative</td>
</tr>
<tr>
<td>CHO Clastogenticity†</td>
<td>Negative</td>
</tr>
<tr>
<td>Cytotoxicity†</td>
<td>Negative</td>
</tr>
<tr>
<td>Reproductive Toxicity*</td>
<td>Negative</td>
</tr>
<tr>
<td>Subchronic Toxicity*</td>
<td>Negative</td>
</tr>
<tr>
<td>MMN Genotoxicity*</td>
<td>Negative</td>
</tr>
<tr>
<td>Blood Compatibility†</td>
<td>Passed</td>
</tr>
<tr>
<td>Leachables and Extractables†</td>
<td>Passed</td>
</tr>
</tbody>
</table>
MIRASOL EFFECTIVE AGAINST CLINICALLY RELEVANT PATHOGENS

Kill Performance for Viruses:
~2–6 log (99.0-99.9999%)
Demonstrated by infectivity assay (TCID$_{50}$)

Transfusion-transmitted CMV is prevented following of transfusion of 6 log PFU of Murine CMV or 6 log of infected leukocytes (Mirasol treated)

Kill Performance for Bacteria:
~2–5 log (99.0-99.9999%)
Demonstrated by high titer studies.

These organisms account for > 80% of septic events reported in surveillance studies
Mirasol has been shown to be more effective than bacterial culture methods

Kill Performance for Parasites:
≥ 3.0 to ≥ 5.0 (≥99.9% to ≥99.999%)

Babesia and Orientia were tested in an animal infectivity model. No disease transmission observed with treated products

Slide from J. McCullough
MIRASOL-TREATED FFP USED SUCCESSFULLY IN TREATMENT OF PATIENTS WITH TTP¹

- The Institute for Hematology and Transfusion Medicine in Poland followed six patients with TTP who received a total of 711 Mirasol-treated FFP units:

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of patients</th>
<th>No. of procedures</th>
<th>No. of Mirasol-treated FFP units administered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acquired TTP</td>
<td>2</td>
<td>Patient 1: 50 TPE procedures (458 units)</td>
<td>634</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patient 2: 18 TPE procedures (176 units)</td>
<td></td>
</tr>
<tr>
<td>Hereditary TTP</td>
<td>4</td>
<td>77 prophylactic transfusions</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(to the 4 patients)</td>
<td></td>
</tr>
</tbody>
</table>

- No transfusion-related adverse reactions were observed in any of the patients receiving prophylactic transfusions of Mirasol-treated FFP

¹Letowska, et al., 2012
PI PLASMA SUMMARY

- Pathogen Inactivation: Inhibits DNA replication
- Hemostasis:
  - Average clotting factor activities 75% – 85% of untreated plasma
  - Clinically equivalent to plasma in trials testing coagulation test corrections and bleeding outcomes
- Mitigates TA-GVHD risk.
Comprehensive US government program for dried plasma development

Anthony E. Pusateri,1 Michael B. Given,2 Victor W. Macdonald,3 and Mary J. Homer4

• DOD and Biomedical Advanced Research and Development Authority are sponsoring development of 3 dried plasma products.
TRANSFUSION RISKS: PLASMA AND RBC
RBC/WHOLE BLOOD PREPARATIONS TO MITIGATE RISK

• Pathogen inactivation:
  • S303 – Intercept (Cerus)
  • Riboflavin – Mirasol (Terumo)
INTERCEPT RBC – Mechanism of Action

- S-303 is a nucleic acid-targeted alkylator that quickly diffuses into viruses, bacteria, parasites and blood cells
- Glutathione (GSH) is used to quench side reactions of the effector with other biological materials
RBC Viability – 35 Day Storage: RCT Cross Over Design 27 Healthy Subjects

<table>
<thead>
<tr>
<th></th>
<th>S-303</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-hour Recovery</td>
<td>87.9 ± 8.4%</td>
<td>89.8 ± 7.0%</td>
</tr>
<tr>
<td>Median Lifespan</td>
<td>32.8 ± 6.1 days</td>
<td>39.5 ± 6.4 days</td>
</tr>
</tbody>
</table>

- 24-hour recovery comparable between Test and Reference RBC (meets FDA criteria)
  - Mean > 75%, SD < 9%, LB 95% CI > 70%
- Median lifespan of Test RBC shorter, but within published reference range (28 to 35 days) for 35 day storage RBC
<table>
<thead>
<tr>
<th></th>
<th>S-303 (N=74)</th>
<th>Reference (N=74)</th>
<th>p-Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint</td>
<td>16 (22%)</td>
<td>15 (21%)</td>
<td>0.02‡</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>0</td>
<td>2 (2.7%)</td>
<td>0.25</td>
</tr>
<tr>
<td>Renal Failure</td>
<td>16 (22%)</td>
<td>14 (19%)</td>
<td>0.84</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td></td>
<td>0.50</td>
</tr>
<tr>
<td>RBC Volume Transfused</td>
<td>1073</td>
<td>1031</td>
<td>0.74</td>
</tr>
<tr>
<td>Immune response to S-303 RBC</td>
<td>0/74</td>
<td>0/74</td>
<td></td>
</tr>
</tbody>
</table>
Cardiac Surgery Study: Adverse Events
Benjamin et al. Transfusion; 2005; 45:1739-1749

<table>
<thead>
<tr>
<th></th>
<th>S-303 (N=74)</th>
<th>Control (N=74)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>74 (100%)</td>
<td>72 (97%)</td>
<td>0.50</td>
</tr>
<tr>
<td>Related AE</td>
<td>2 (2.7%)</td>
<td>1 (1.4%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Maximum Severity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 0</td>
<td>0 (0%)</td>
<td>2 (2.7%)</td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>2 (2.7%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>8 (11%)</td>
<td>19 (26%)</td>
<td>0.03†</td>
</tr>
<tr>
<td>Grade 3</td>
<td>45 (61%)</td>
<td>35 (47%)</td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td>19 (26%)</td>
<td>18 (24%)</td>
<td></td>
</tr>
</tbody>
</table>

Due to differences in Grade 3 arrhythmias with associated hypokalemia, not attributed to treatment
INTERCEPT RBC: PLANNED EU PHASE 3 STUDIES

CHRONIC ANEMIA
Transfusion-dependent thalassemia major patients (n=50)

1° efficacy endpoint = Hemoglobin usage
1° safety endpoint = Immunogenicity with repeat exposure

Each patient is on study ~12 months

ACUTE ANEMIA
Elective cardiovascular surgery patients, first time CABG or valve repair (n=50)

1° endpoint = Hemoglobin change per unit
Exploratory clinical endpoints and safety

* Day of surgery plus 6 days post-op.
RIBOFLAVIN AND UV LIGHT:
MIRASOL AND WHOLE BLOOD
Treatment of Whole Blood with the Mirasol System

Objective is to provide a Cost-Effective, Logistically Viable Pathogen Reduction and White Cell Inactivation Process for All Blood Products
RIBOFLAVIN AND UV: MIRASOL

Treatment of blood with a pathogen reduction technology using ultraviolet light and riboflavin inactivates Ebola virus in vitro

Andrew P. Cap,1 Heather F. Pidcocke,1 Shawn D. Keil,2 Hilary M. Staples,3 Manu Anantpadma,3 Ricardo Carrion Jr.,3 Robert A. Davey,3 Ashley Frazer-Abel,4 Audra L. Taylor,5 Richard Gonzales,2,5 Jean L. Patterson,9 and Raymond P. Goodrich2

CONCLUSION: Our in vitro results demonstrate that the UV+RB treatment efficiently reduces EBOV titers to below limits of detection in both serum and whole blood. In vivo testing to determine whether UV+RB can improve convalescent blood product safety is indicated.
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
AIMS

- Enrolled patient in need of two whole blood transfusions
  - Excluded if symptomatic for malaria or currently treated with anti-malarials
- Randomized to receive:
  - Untreated whole blood
  - Mirasol treated
- Units screened for parasites retrospectively
- Pre- and post-transfusion blood samples tested (days 0, 1, 3, 7, and 28) for parasite genome and related assays
- Primary endpoint: Incidence of transfusion-transmitted malaria in non-parasitemic recipients exposed to parasitemic whole blood
AIMS RESULTS

- 8/37 developed transfusion-transmitted malaria in untreated group
  
  versus

- 1/28 developed transfusion-transmitted malaria in Mirasol group

- Safety profile and clinical outcomes were similar in both groups.
INTERCEPT PLATELET AND PLASMA USE

- Routine use at over 100 centers in 18 countries
- Kits sold to produce >1.7 million units of INTERCEPT platelets & plasma
- INTERCEPT safety and efficiency established in routine use
MIRASOL SYSTEM ACTIVITIES AROUND THE WORLD
(JANUARY 2013)

- Over 160 Mirasol Illuminators placed in 25 countries
- Over 320,000 Mirasol disposable sets distributed for platelets and plasma treatments
- Post-market surveillance on 32,000+ platelet and 44,000+ FFP transfusions, with no Mirasol system related serious adverse events reported
THANK YOU
QUESTIONS

• ????????
### SUMMARY OF EVIDENCE FOR LEUKOCYTE INACTIVATION BY INTERCEPT

<table>
<thead>
<tr>
<th>Assay Systems</th>
<th>Significant Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In vitro</strong></td>
<td></td>
</tr>
<tr>
<td>LDA1 for viable T cells</td>
<td>Validated inactivation of $&gt; 10 \times 5.4\pm0.3$ T cells/mL</td>
</tr>
<tr>
<td></td>
<td>$&gt; 3000$-fold efficacy margin based on dose-response experiments</td>
</tr>
<tr>
<td>DNA modification</td>
<td>One amotosalen adduct per 83 bp</td>
</tr>
<tr>
<td>PCR2</td>
<td>Amotosalen-DNA adducts inhibit PCR amplification</td>
</tr>
<tr>
<td>Cytokine synthesis</td>
<td>Eliminated during storage</td>
</tr>
<tr>
<td>Early Antigen Presentation</td>
<td>Severely inhibited after treatment</td>
</tr>
<tr>
<td><strong>In vivo</strong></td>
<td></td>
</tr>
<tr>
<td>TA-GVHD animal model3</td>
<td>Photochemical treatment prevents TA-GVHD in a murine transfusion model</td>
</tr>
</tbody>
</table>
HISTORY OF BLOOD: SAFETY DRIVES PROGRESS