

Cryopreserved Platelets (CPP) ATACCC 2009



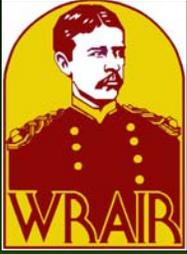
VICTOR W. MACDONALD, PH.D.

Director, Division of Military Casualty Research

Former Chief, Department of Blood Research

Walter Reed Army Institute of Research

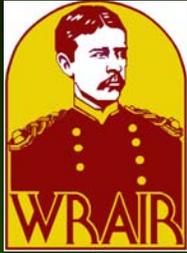
Silver Spring, MD 20910



Cryopreserved Platelets (CPP) Disclaimer



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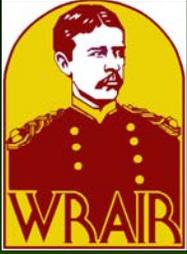
Driven by Military Need



- Approximately 50% of battlefield deaths are attributable to hemorrhage.
- Up to 35% of hemorrhagic deaths may be preventable with improved management of hemorrhage at all points from point of wounding to combat support hospital.

Needs include:

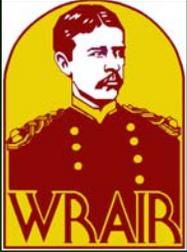
- Improved use of available products (PRBC, plasma, and cryoprecipitate) – Level 2b and Level 3
- Availability of platelets or platelet substitute – Level 3



Treatment Goals - Trauma



- Stop bleeding & restore vascular volume
 - Tourniquet
 - Hemostatic bandages & surface agents
 - Systemic hemostatic agents
 - Crystalloids & Colloids
- Restore vascular volume & normal clotting function
 - Blood components
 - Plasma, cryoprecipitate, red cells, platelets
 - Fresh whole blood
- Normalize oxygen carrying capacity
 - Red cells or artificial oxygen carrier



Continuum of Health Care (blood products)



Level 1- Combat Medic and Battalion Aid Station



Level 2a- Medical Company



Level 2b- Forward Surgical Team/ Forward Resuscitative Surgical Suite

- Type O PRBC
- Thawed Plasma
- Untested fresh Whole Blood



Blood product availability

None

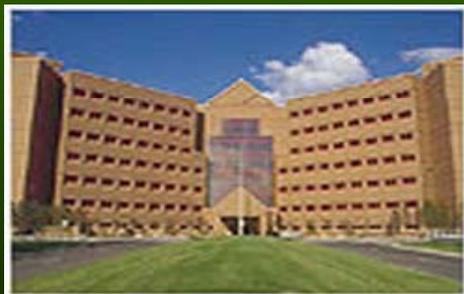
Type O PRBC

All Approved Products

- Type-specific PRBC
- FFP
- Thawed Plasma
- Untested fresh whole blood and apheresis platelets



Level 3- Combat Support Hospital

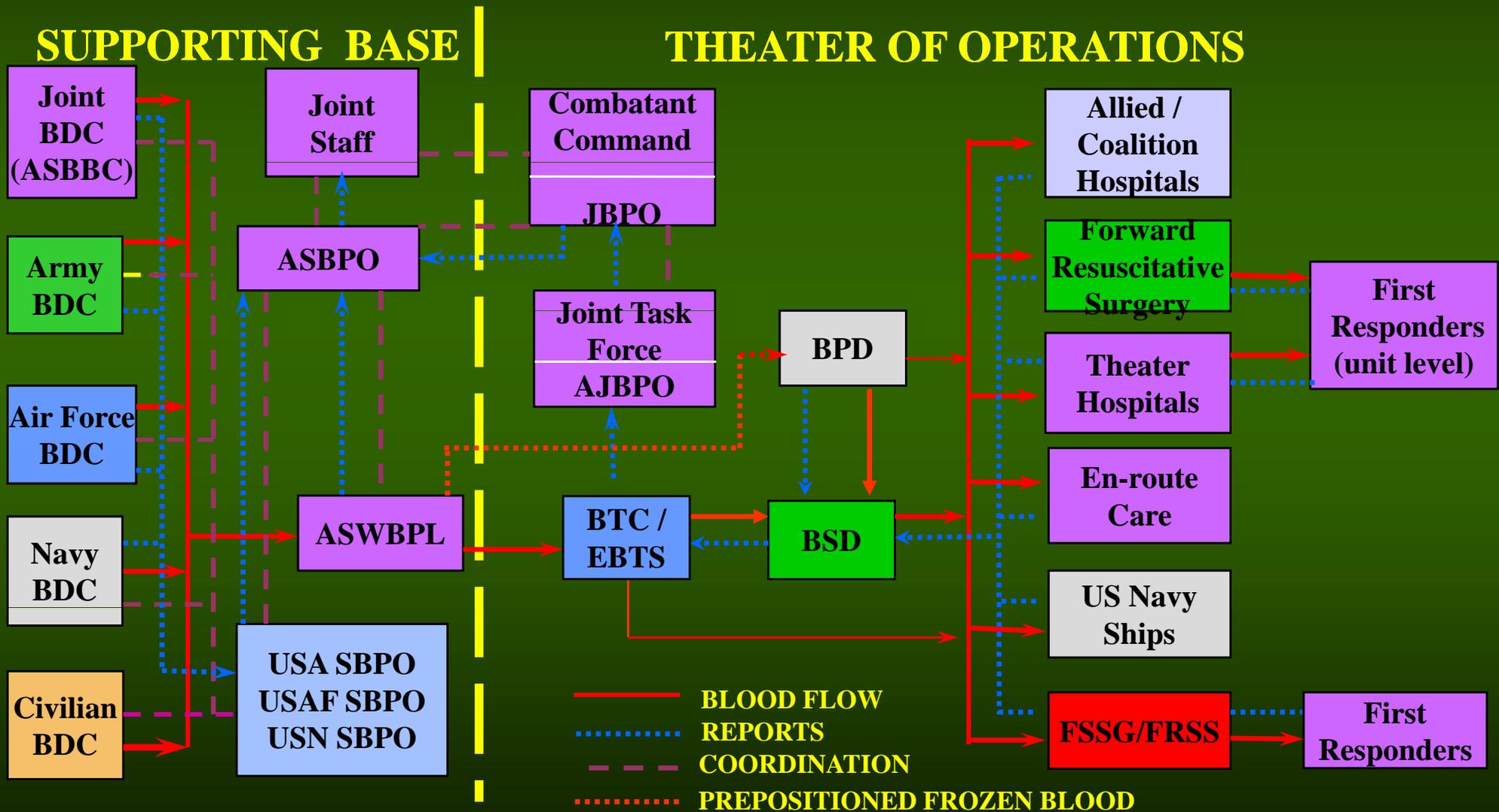


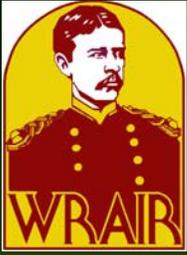
Level 4/5- OCONUS/CONUS Major Medical Centers



BLOOD DISTRIBUTION SYSTEM

Armed Services Blood Program



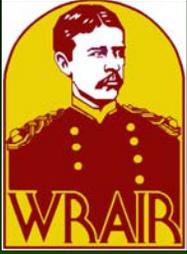


Platelet-Derived Systemic Agents

Current Source of Platelets



- Fresh, whole blood (Level 2b and 3)
 - Intensive use beginning in Spring 2004. Coincided with more stable environment and personnel in “Green Zone.”
 - Available in Afghanistan and Iraq.
 - FDA-approved blood donor screening not available in theater
- Platelet apheresis (Level 3)
 - Deployed
 - Jan 2005 – Green Zone in Baghdad
 - Jun 2005 – Balad in northern Iraq
 - Jun 2007 – Afghanistan
 - FDA-approved blood donor screening not available
- Cryopreserved platelets
 - Dutch military deploys CPP to and uses CPP (reconstituted in plasma) in Balkans and Afghanistan as part of NATO mission.

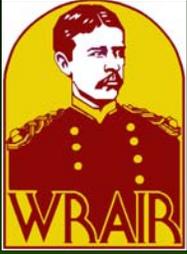


Platelet-Derived Systemic Agents

Platelet Replacement Alternatives



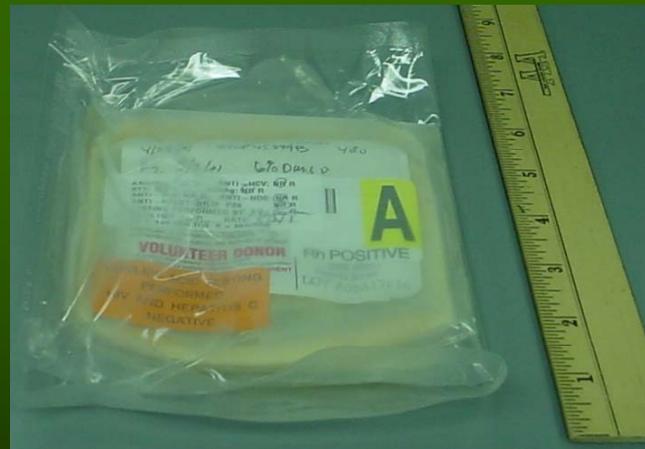
Potential Solution	Comments
Cryopreserved Platelets (CPP)	<ul style="list-style-type: none"> • More mature than lyophilized platelets • Best characterized relative to range of platelet characteristics and functions relative to lyophilized platelets • Requires deployment of -65°C (possibly -20°C) storage
Lyophilized Platelets	<ul style="list-style-type: none"> • Two potential products <ul style="list-style-type: none"> – Thrombosomes™ (Cellphire, Inc) – Stasix™ (Entegriion, Inc) • Early in development • Uncertain characteristics and effects
Continued deployment of platelet apheresis	<ul style="list-style-type: none"> • FDA-approved donor screening not available • Difficult to supply in remote austere environments
Use of fresh whole blood	<ul style="list-style-type: none"> • FDA-approved donor screening not available • Performance effect on donors (generally other soldiers) • Limited capability in mass casualty situations

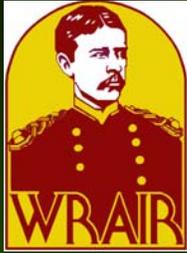


Blood Products in Development



Cryopreserved (Frozen) Platelets (CPP)



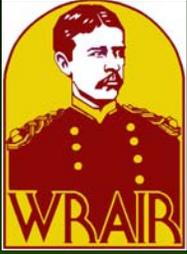


Frozen Platelet Product

Military Need & Desired Characteristics



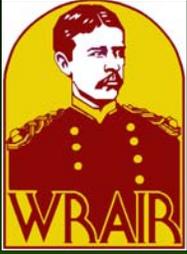
- Blood Bank Product that is fully tested, characterized, and licensed product to replace traditional liquid preserved platelets (LPP) in locations where transfusion transmitted disease (TTD) testing is unavailable.
- Efficacy $\geq 70\%$ equivalent clotting efficacy of liquid-preserved platelets measured by Aggregometry .
- Deployable to Level 3 Medical Treatment Facility (MTF).
- Shelf-stable at $\leq -65^{\circ}\text{C}$ for $\geq 2\text{y}$; at -20°C for $\geq 4\text{wk}$.
- Ready for infusion after rapid thaw without washing.



DMSO Cryopreserved Platelets



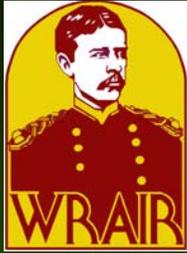
- Proposed Indication: Adjunct in treatment of massive hemorrhage associated with platelet deficiency or platelet dysfunction.
- Preparation: Standard blood bank procedures
- Dose: 1 unit (10 mL to 15 mL), containing up to 3×10^{11} human platelets with 6% DMSO added, centrifuged to remove most supernatant, cryopreserved at -65°C (or -20°C), and resuspended in 10 ml saline or plasma.
- Treatment Course: One unit administered intravenously via a blood administration set for thrombocytopenia or thrombocytopathy. Repeat dose as clinically indicated.



Development Strategy & Progress



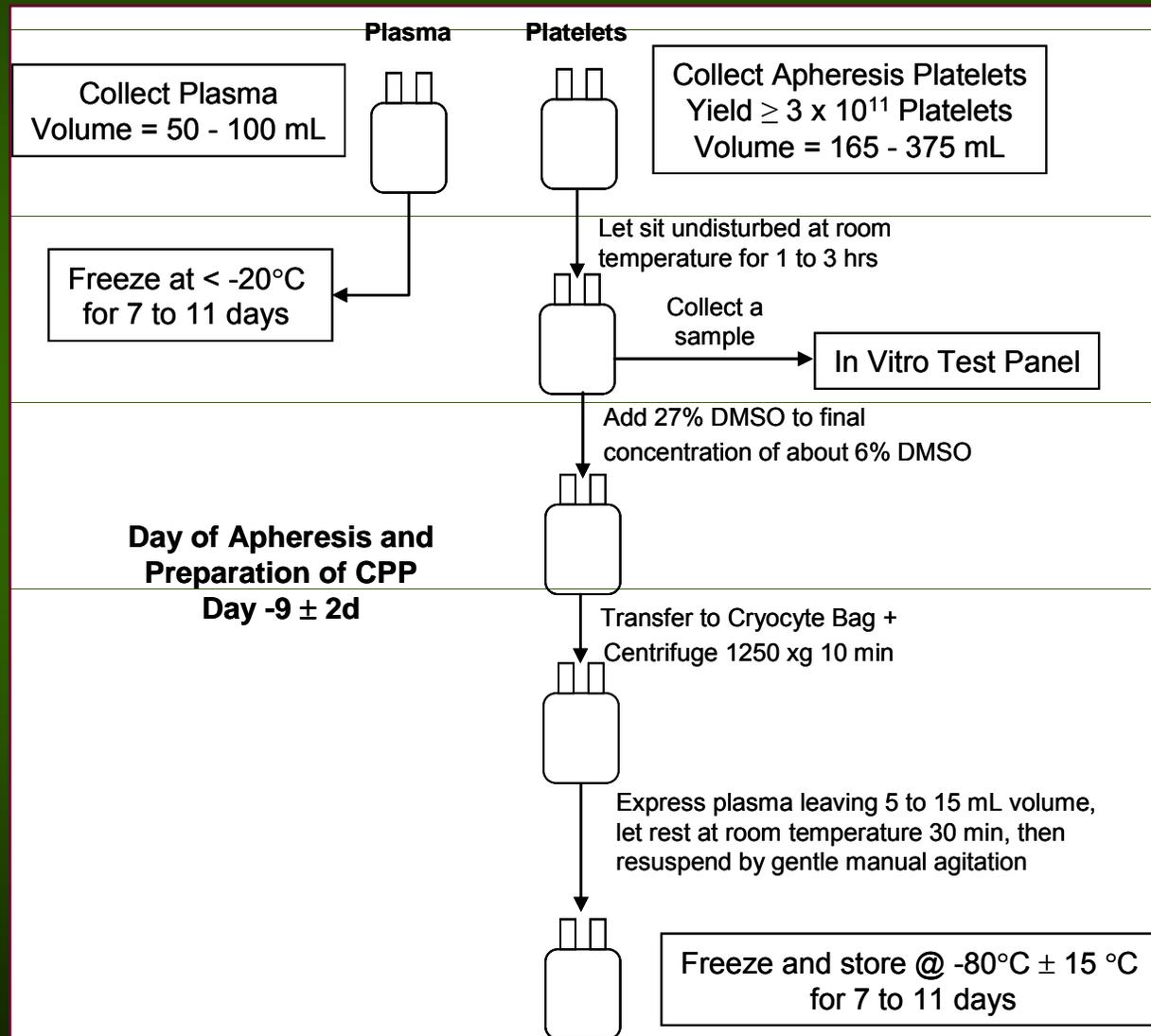
- Integrated Product Team (IPT)
 - Chartered and Functioning.
- Standardized Manufacturing Process
 - Master Batch Record complete and transferred.
- Validation Studies
 - Correlation demonstrated for In Vitro characteristics of CPP manufactured at two sites.
- Phase 1 Clinical Trial
 - FDA approved IND 19 June 2009 to Compare recovery and survival of autologous CPP with fresh platelets.
 - Begin at DHMC 10 August 2009

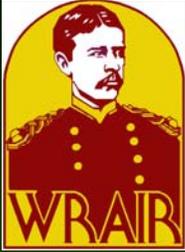


CPP

Summary of Platelet Processing (1)

Apheresis and Cryopreservation



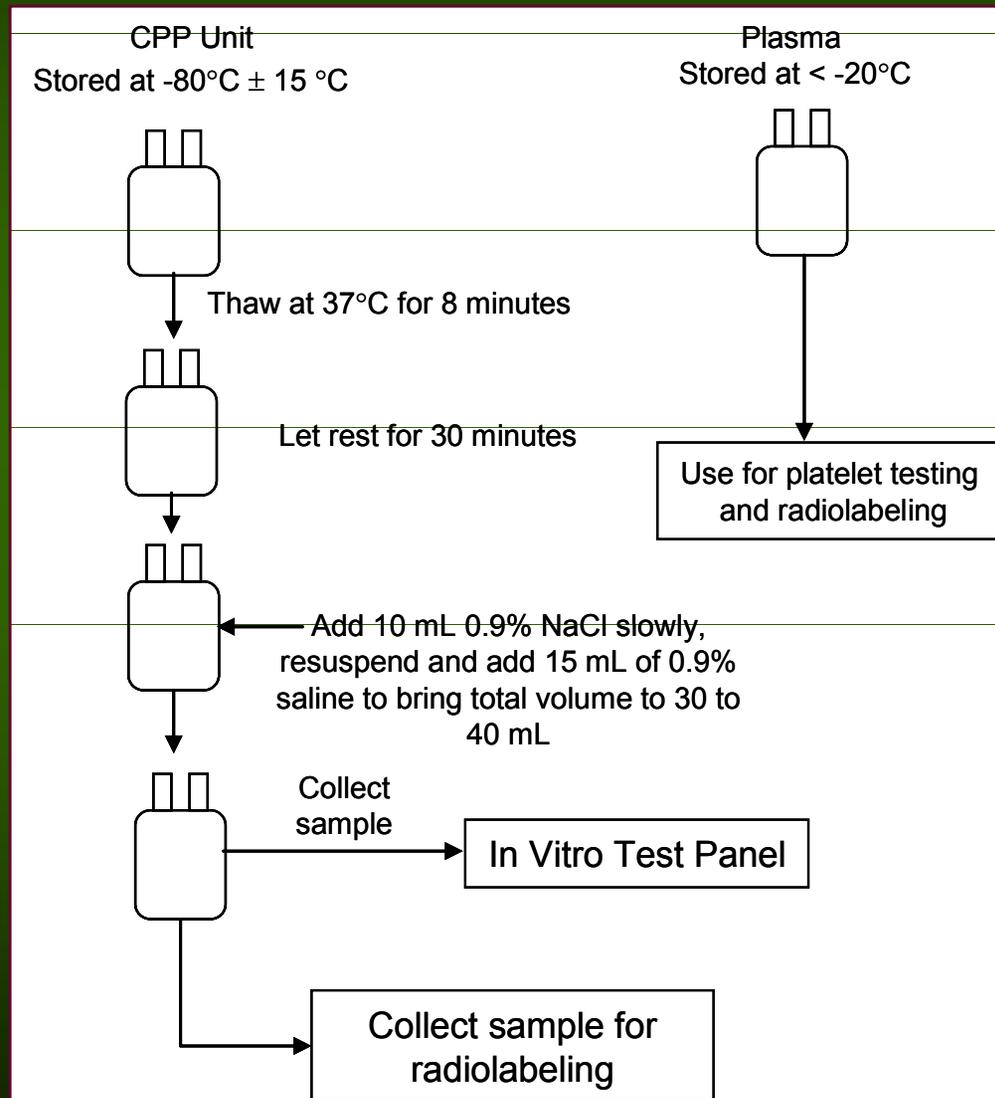


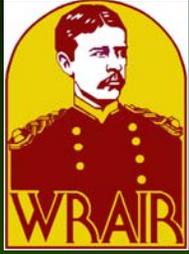
CPP

Summary of Platelet Processing (2)



Thawing and Reconstitution





CPP Validation Data (1)



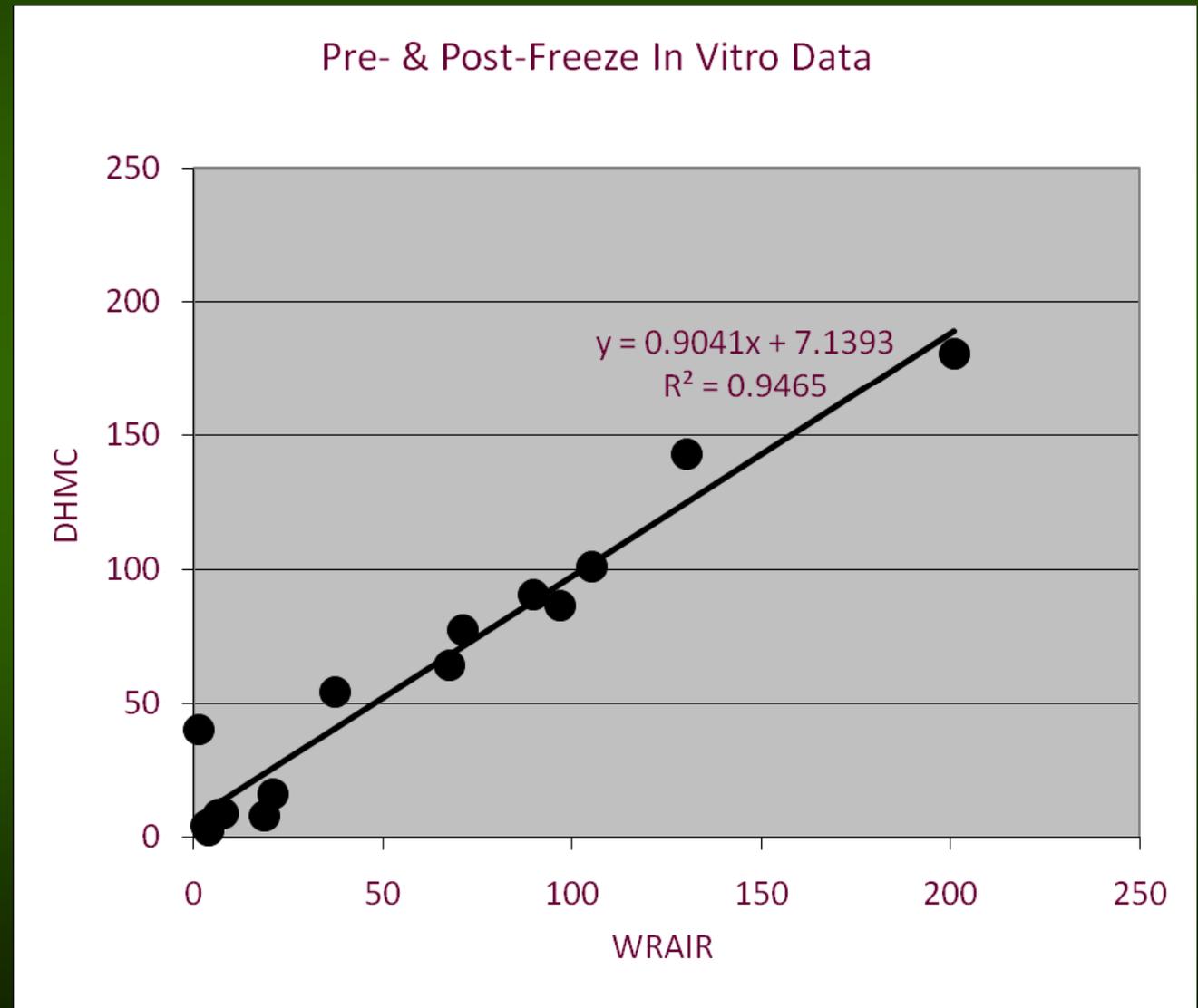
Raw Correlation Matrix:

(Mean Values for CPP)

- Morphology
- MPV
- ESC
- HSR
- Aggregation ADP/Epi
- Aggregation Collagen
- P-Selectin
- Annexin V Binding

WRAIR $n=10$

DHMC $n=9$

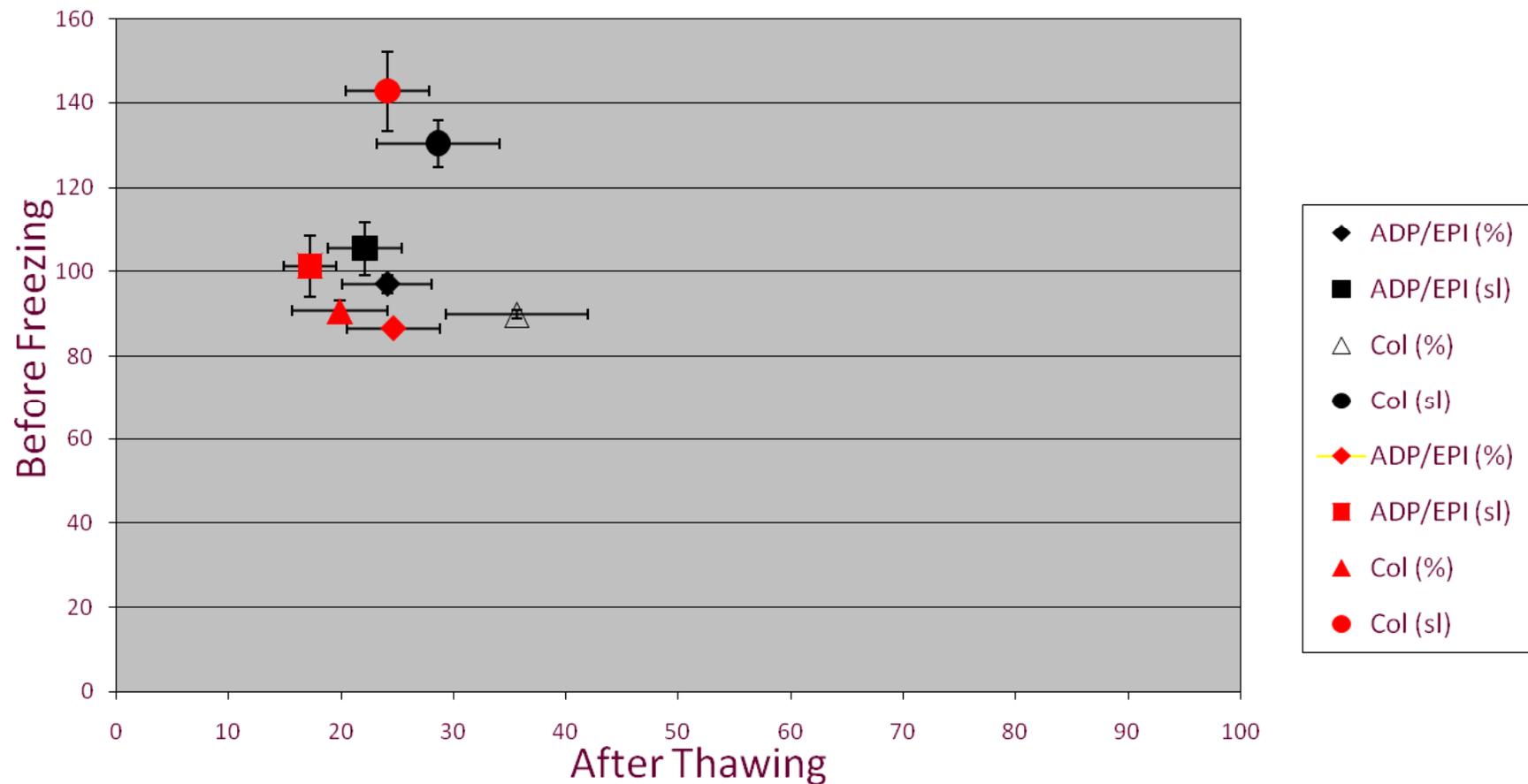


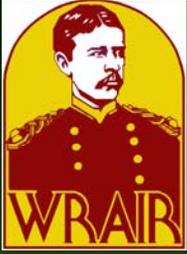


CPP Validation Data (2)



In Vitro Platelet Aggregation





Experimental Function Data



In Vitro clot formation and strength measurement

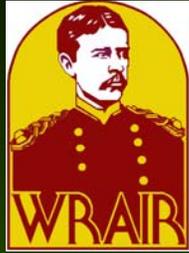
Thromboelastograph (TEG[®]), Hemoscope[™] (Haemonetics Corp.)

	TEG MA (mm)	TEG r-time (sec)	PFA-100 CT (sec)
Pre-Freeze	67.1 ± 1.0	15.6 ± 1.0	83 ± 6
Post-Freeze	60.8 ± 1.2	8.9 ± 0.4	147 ± 20

In Vitro simulation of vascular injury

PFA-100[®], Siemens



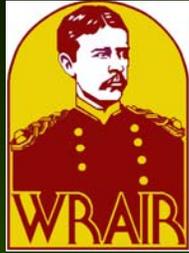


Development Strategy

Pre-Phase 3



- cGMP validation of process & product.
- Validate -65°C for cryopreservation temperature & time.
- Test *in vitro* characteristics of CPP initially stored at -65°C and then at -20°C for up to 4 weeks.
- Phase 1/2 study of CPP to reduce bleeding time in thrombocytopenic cancer patients.



Development Strategy

Phase 3



- BLUF
 - Require FDA approval for an indication allowing use in trauma.
 - CPP has been developed with funding from ONR since 1972.
 - Clinical experience with cryopreserved platelets (similar but not identical to CPP) since 1972 strongly suggests that this product is safe and effective.
- Potential surrogate studies for massive bleeding
 - CPP versus LPP in CABG patients in a multi-center study similar to Khuri, et al. (1999).
 - CPP versus LPP in burn patients (debridement or grafting).
- Unless FDA approves a surrogate clinical trial group for trauma, a Phase 3 prospective randomized multi-center trauma trial will have to be conducted.



Khuri et al: CPP versus LSP

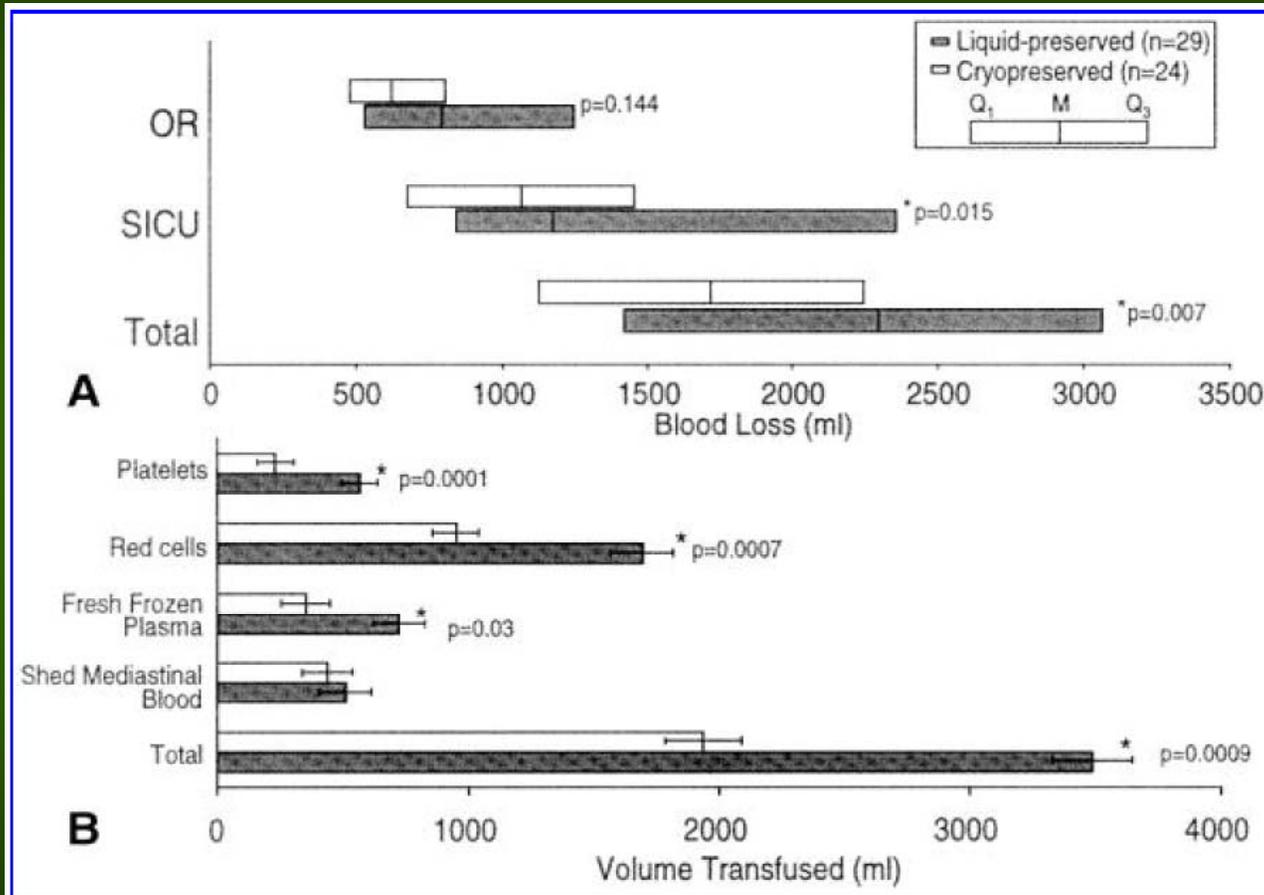
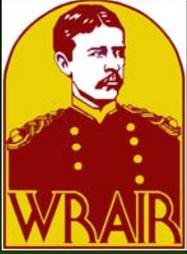


Figure 2A. Blood loss measured in the operating room (OR), blood loss measured in the surgical intensive care unit (SICU), and combined total blood loss in patients who received liquid-preserved platelet transfusions and in those who received cryopreserved platelet transfusions. Data are shown as median and IQR. M, Median; Q1, 25th percentile; Q3, 75th percentile. B, Volumes of transfused blood products received by the same groups. Data are shown as mean ± SEM.

BLUF: CPP appear to be superior to LPP for management of post-operative, non-surgical bleeding occurring in conjunction with cardio-pulmonary bypass (CPB) surgery.

- ✓ Prospective, randomized, controlled, blinded study of CPB patients (n=53) who experienced non-surgical bleeding during and after surgery.
- ✓ Patients had similar characteristics pre-op.
- ✓ Throughout the intra-operative and post-operative courses, all individuals involved with ordering blood products were blinded to the type of platelets.

Khuri et al: J Thorac Cardiovasc Surg, Volume 117(1). January 1999. 172-184



DMSO Cryopreserved Platelets

Baltimore Cancer Research Center



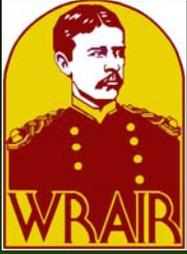
- In 1979 approximately 1600 units of [5% DMSO] frozen platelets were transfused including 225 transfusions of autologous platelets administered to 45 patients with leukemia (frozen at least 3-years)
 - “... essentially no side effects following transfusion.”
 - Post-transfusion increments highly consistent ... averaging two-thirds of the recovery obtained with fresh platelets with accompanying shortening of the bleeding time.
 - Technology is simple, cost effective, and reproducible and is suitable for use in more general blood bank settings.



DMSO Cryopreserved Platelets Dutch Military Frozen Blood Bank



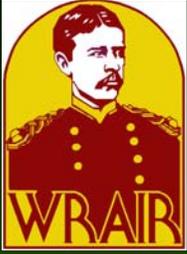
- Since 2001, frozen blood bank used by Dutch military hospitals in the Balkans and Afghanistan.
- Over 400 units of DMSO (6%) cryopreserved platelets (reconstituted in FFP) used in military combat casualties (33 US) with no adverse events reported in uncontrolled use.
- Use of cryopreserved platelets (reconstituted with FFP) in an elderly woman with pelvic gunshot wounds and a young soldier with idiopathic thrombocytopenic purpura during peace-keeping operations in Bosnia.
 - Both with “unstoppable” bleeding.
 - Barely detectable rise in platelet counts after transfusion.
 - Bleeding in the 2 study participants halted within 20 minutes of transfusion of 1 apheresis unit ($\sim 3 \times 10^{11}$ platelets/U) of cryopreserved platelets.



Systemic PDHA Outlook



- Freeze-dried platelet products as currently formulated may be limited to acute applications.
 - May have longer-term pro-coagulant activity.
- Cryopreserved platelets appear more native-like and remain effective longer after infusion.
- Major issue for deployment: Storage Temperature
 - Prefer capability for long-term storage at $\leq -65^{\circ}\text{C}$
 - Desire capability for limited deployment at -20°C
 - Require comparisons of $\leq -65^{\circ}\text{C}$ vs -20°C storage
- Estimated approval: 2014/2015 time-frame



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QUESTIONS?