

Conservation des concentrés plaquettaires à 4°C : une solution d'avenir ?

Dr Tom Scorer

Surgeon Commander, Royal Navy

Haematology Consultant, University Hospital, Plymouth

XXXème Congrès - Marseille
de la Société Française de Transfusion Sanguine

Du 24 au 26 novembre 2021



Déclaration de conflits d'intérêts

Nom : Tom Scorer

☐ **J'ai, ou ai eu** durant les trois dernières années, une affiliation, des intérêts financiers ou autres intérêts avec un organisme industriel ou commercial de type :

- ☐ Rémunération / Bourse / Honoraires
- ☐ Orateur / Consultant
- ☐ Autre :

Nom de l'organisme / des organismes :

✓ **Je n'ai pas de conflit d'intérêt**



Bleeding = Preventable death

- No. 1 cause of preventable death
- Transfusion saves lives
 - 20 x Survival benefit – within 13 mins
- Platelets – reduce mortality

REGULAR ARTICLE



Platelet transfusions improve hemostasis and survival in a substudy of the prospective, randomized PROPPR trial

Jessica C. Cardenas,^{1,2} Xu Zhang,³ Erin E. Fox,¹⁻³ Bryan A. Cotton,¹⁻³ John R. Hess,⁴ Martin A. Schreiber,⁵ Charles E. Wade,¹⁻³ and John B. Holcomb,¹⁻³ on behalf of the PROPPR Study Group



Acosta JA, et al. J Am Coll Surg 1998

Eastridge BJ, et al. J Trauma Acute Care Surg 2012;73: S431-7

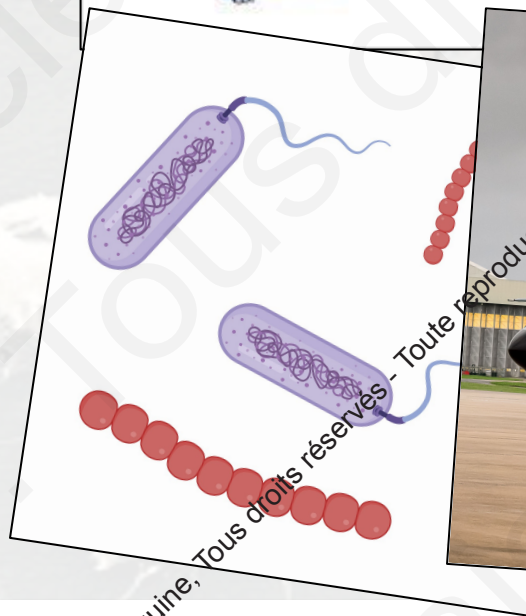
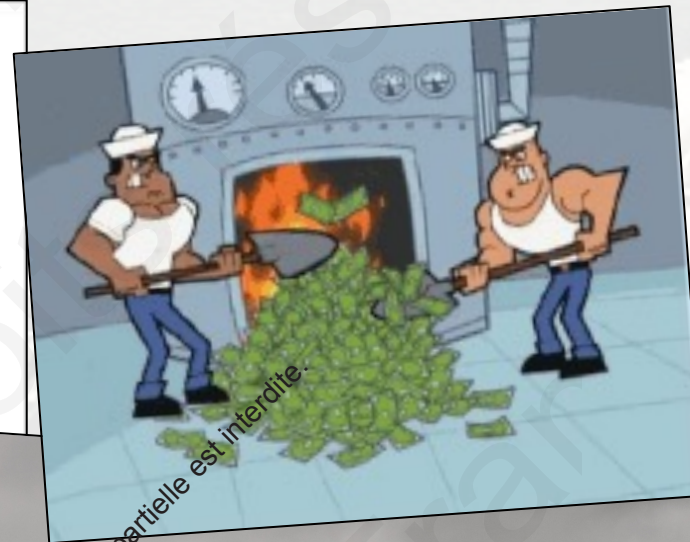
Peralta et al. Int J Crit Illn Inj Sci. 2016 Oct-Dec; 6(4): 188–193.

Cardenas et al. Blood Adv. 2018 Jul 24; 2(14): 1696–1704.

Platelets are Challenging...

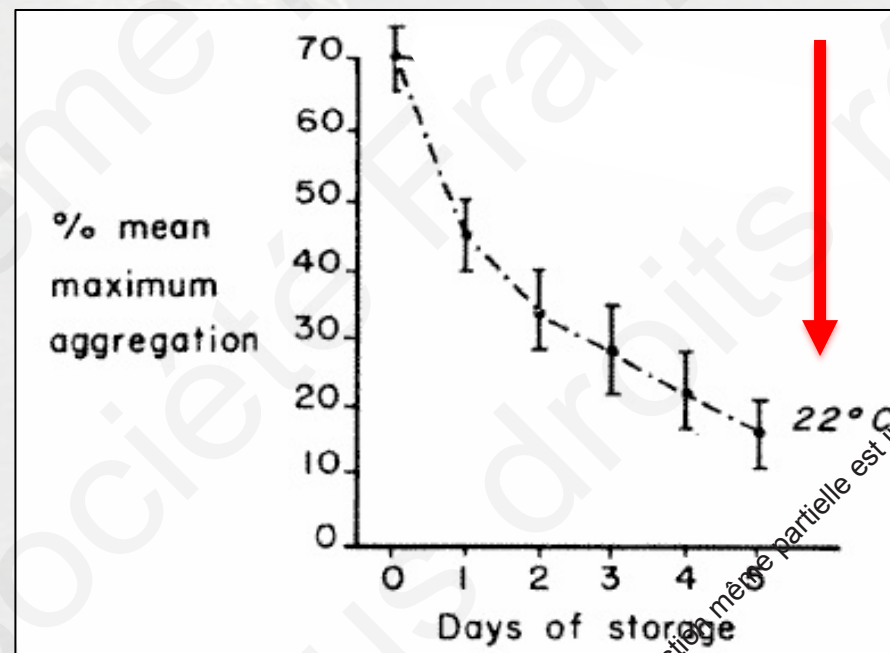
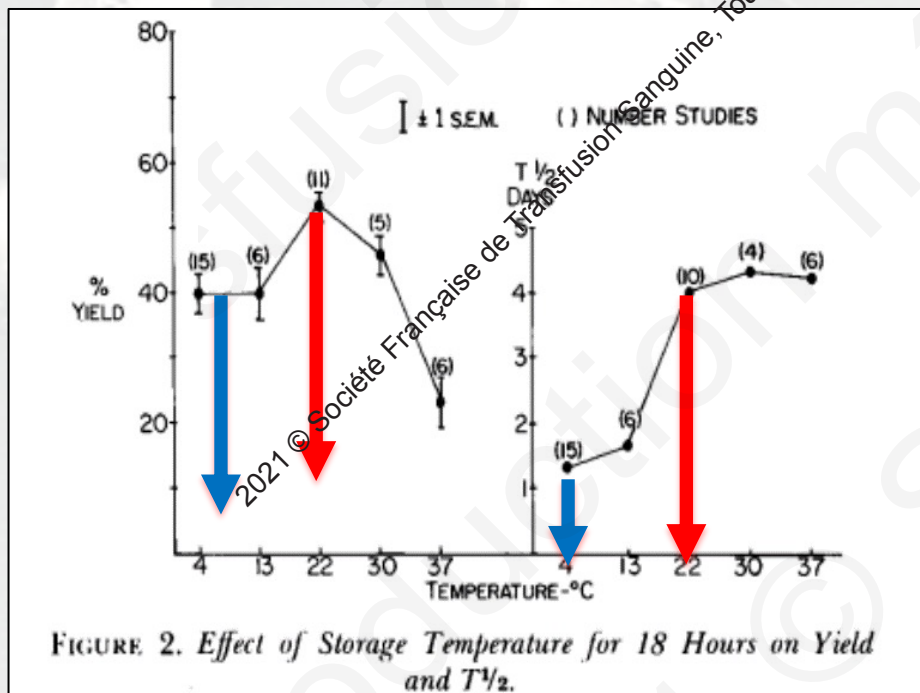
Standard of Care Stored at 22°C - Warm

- Require an incubator agitator
- Safety
 - Greatest infection risk
 - 1:5000 bacterial contamination
- Short shelf life 5-7 days
 - Wastage = 4% - 25%
 - UK >10,000 units = £2million pa.
 - US >200,000 units = \$1 billion pa.
- Resupply (cost / frequency)
 - Flights every 5 days – £70K ea.



Warm Platelets Survival vs Function

***in vivo* survival best warm**



**Platelet
Function
Declines
with warm
storage**

The standard of care platelet product is optimized to prevent bleeding in thrombocytopaenic patients

Becker, G.A et al.(1973) *Transfusion*, **13**, 61-68.

Valeri, C.R. (1974a) *The New England journal of medicine*, **290**, 353-358

Seghatchian J et al. (1997) *Transfusion Medicine* **11** (2) 130-144

Bikker, A (2016) *Transfusion*, **56**, 1030-1037

Murphy, S et al. *NEJM* 1969;280(20);1094-1098



Cold Stored Platelets Evidence

- Reduced bacterial proliferation
- Respond to inhibition
- Improved aggregation responses
- Stronger clot formation
- Enhanced function - arterial shear
- Logistical benefits

REVIEW

Manufacturing variables and hemostatic function of cold-stored platelets: a systematic review of the literature

Thomas Scorer^{a,1,2,3}, Ashleigh Williams,⁴ Kristin Reddoch-Cardenas^{a,3}, and Andrew Mumford¹

Therapeutic Utility of Cold-Stored Platelets or Cold-Stored Whole Blood for the Bleeding Hematology-Oncology Patient

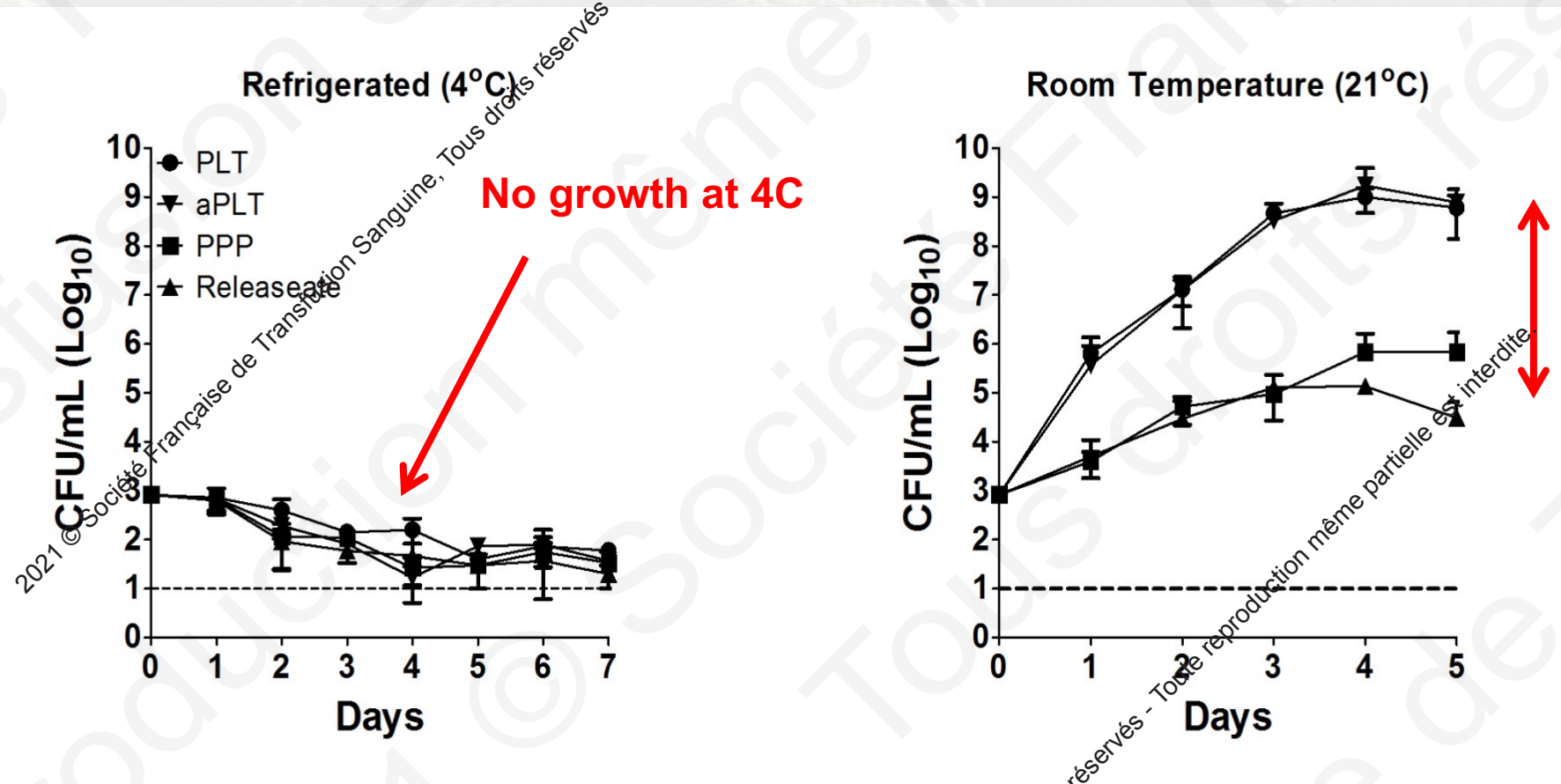
Thomas G. Scorer, MBBS, FRCPath^{a,b,*},
Kristin M. Reddoch-Cardenas, PhD^c, Kimberly A. Thomas, PhD^d,
Andrew P. Cap, MD, PhD^c, Philip C. Spinella, MD, FCCM^d



Enables PLT transfusion in more remote and constrained settings

Cold Stored Platelets

Safety – Bacterial contamination

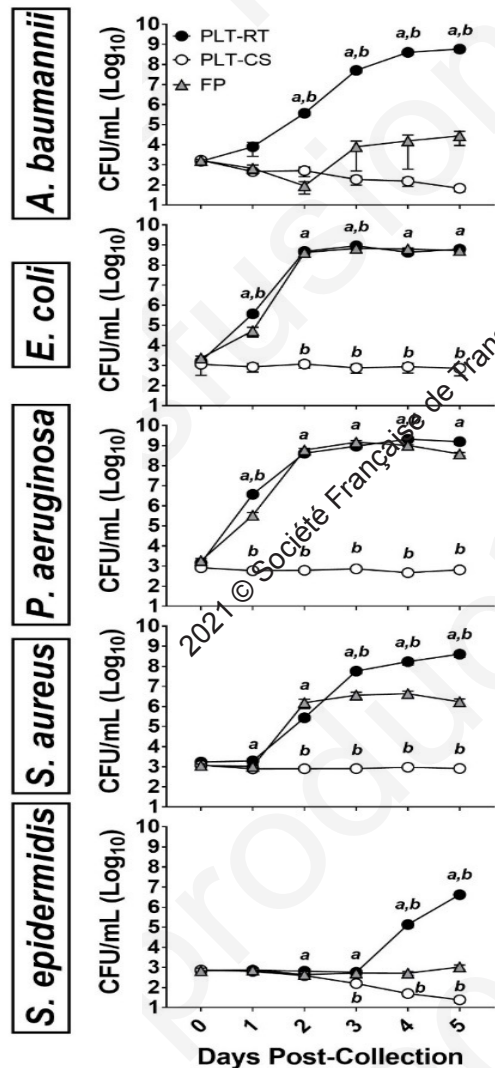


Refrigeration lowers risk of bacterial contamination & sepsis.

PLT at RT feed bacterial growth (lactate).

Cold Stored Platelets

Safety – *Refrigeration is SAFER*

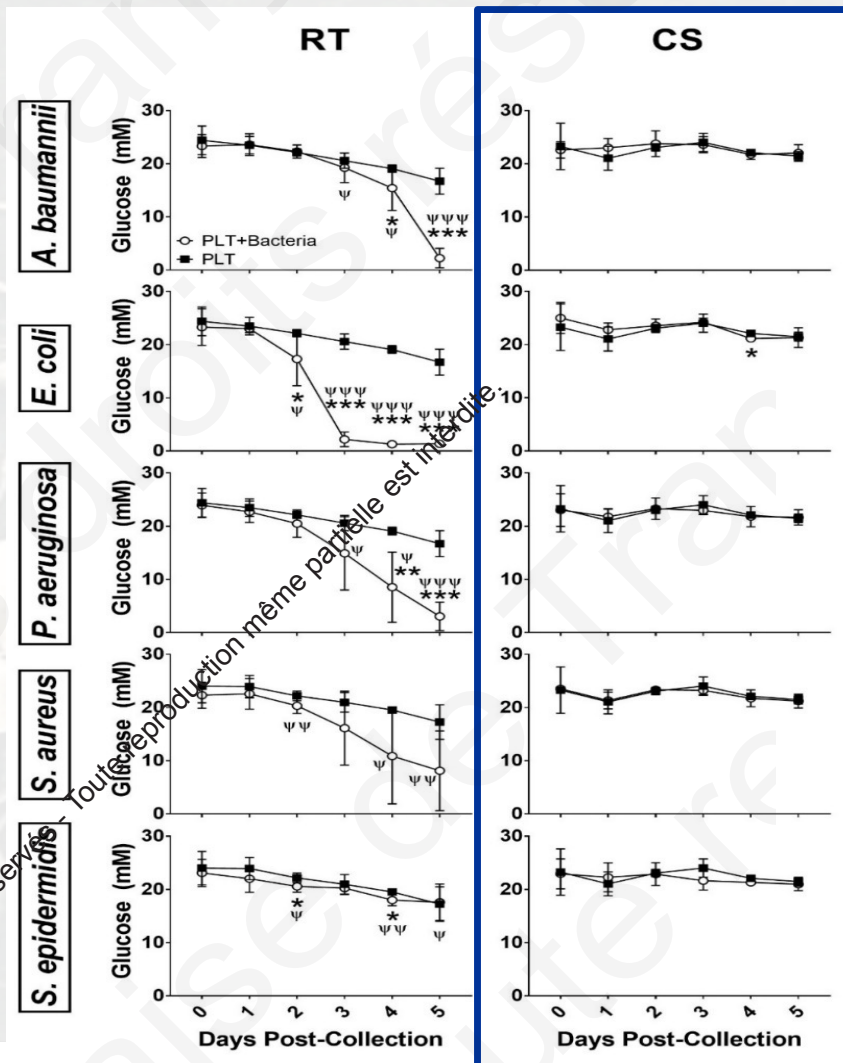


**PLT stored at RT
feed bacteria!**

**All bacteria: more
growth @ RT, but...**

***A. baumannii*, *S. aureus*, *S. epidermidis* grow
better w/ RT PLT
than in RT plasma!**

**Cold storage slows
metabolism & growth,
reduces glucose
consumption.**



Safety: refrigerated platelets respond to physiologic inhibitory signals

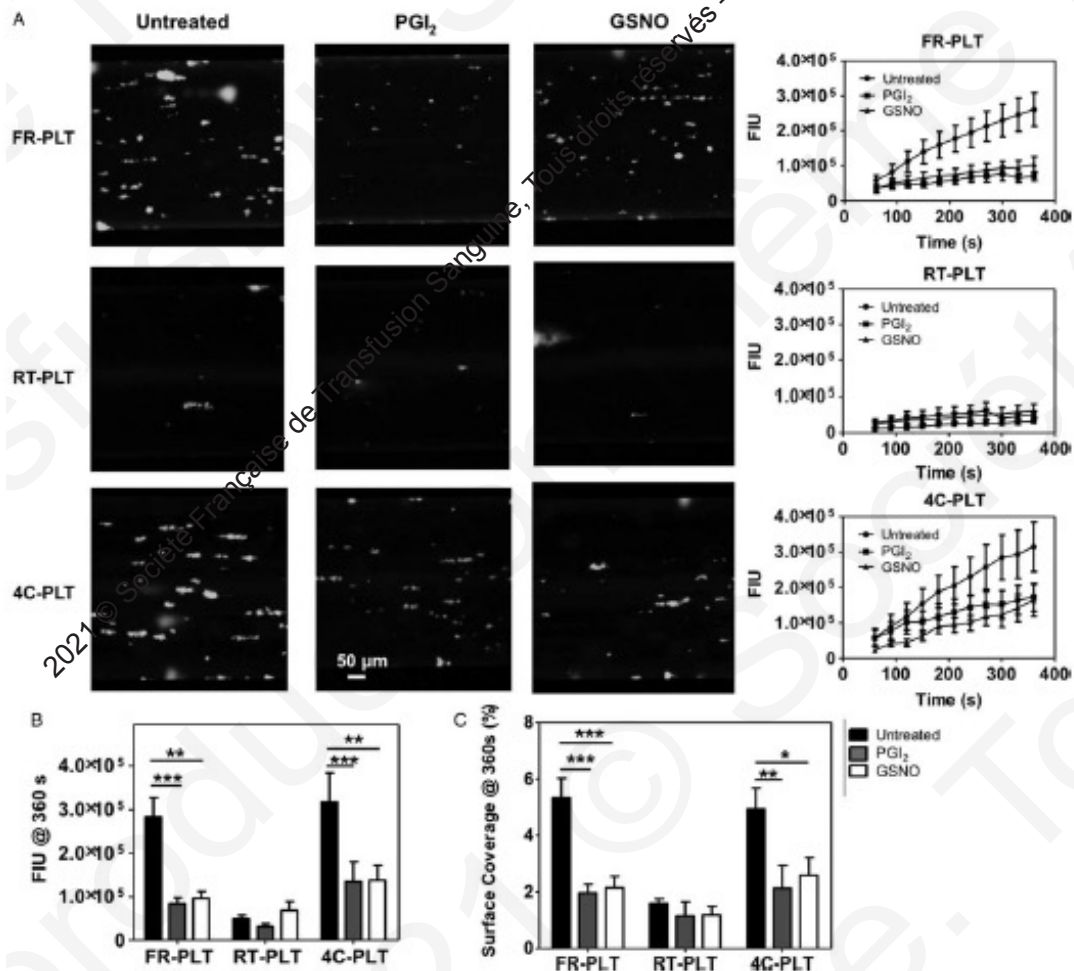
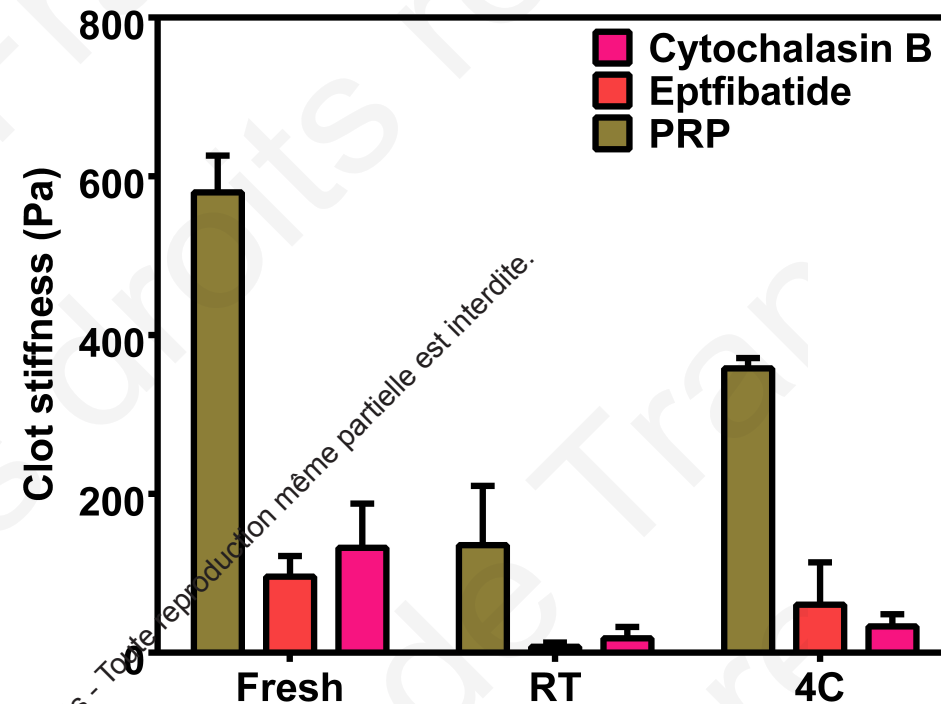
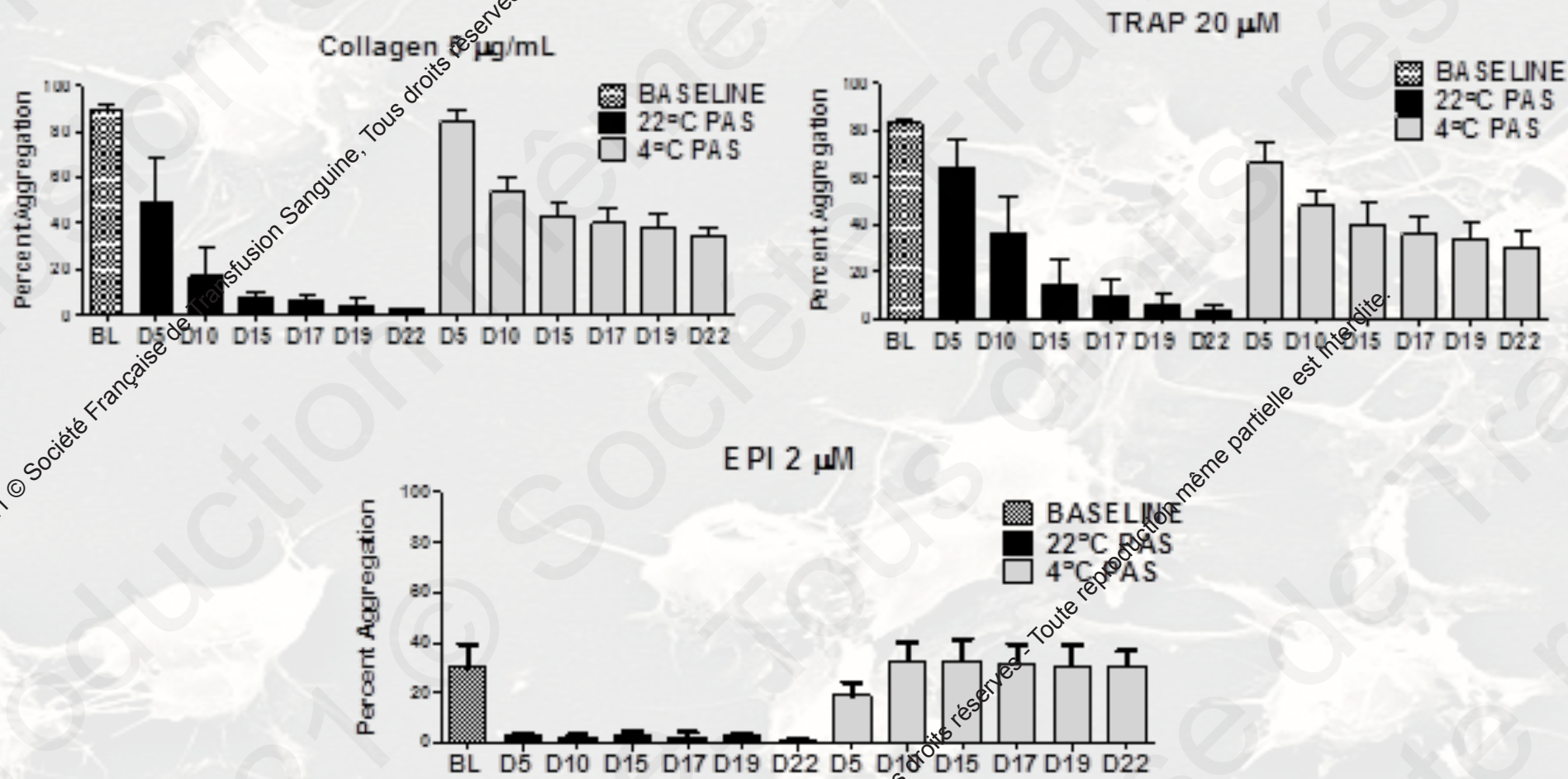


FIG. 5. Platelet adhesion under high shear with and without inhibitors. A, Micrographs of Fresh, 4C, and RT platelets either untreated, GSNO-treated, and PGI₂-treated are shown after 360 s of perfusion. Average fluorescence intensity unit (FIU) traces (n = 4) are shown for (B) Fresh, (C) 4C, and (D) RT. E, Surface coverage and (F) FIU at 360 s are represented as mean ± SEM (n = 4) with Untreated in black, PGI₂ in gray, and GSNO in white. (B–F) are represented as Untreated (●), PGI₂ (■), and GSNO (▲). The micrographs are cropped and enlarged; however image size proportionality was maintained between images and timepoints. Images were pseudocolored to aid in visualization.

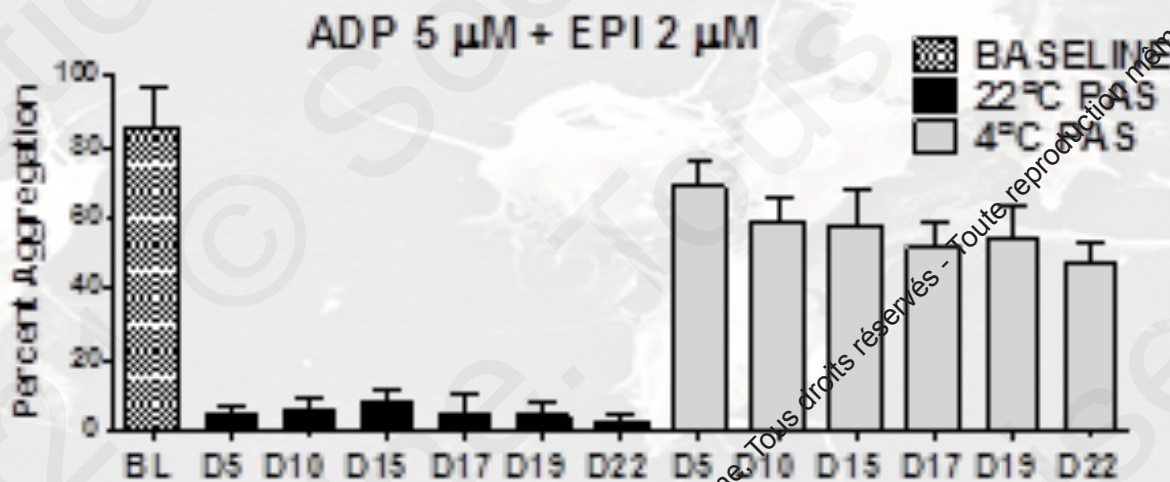
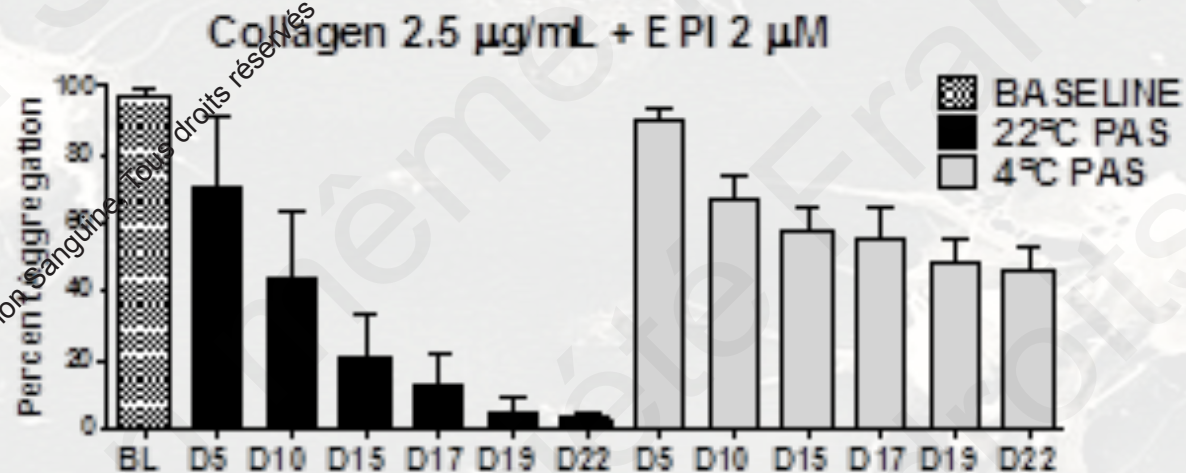


Aggregation response to multiple agonists *well preserved in PAS at 4°C*



Getz Transfusion 2016

CSP retain greater response to dual agonists



Getz Transfusion 2016

Cold Storage - Results Consistent

- Aggregation
- Adhesion under flow, spreading, anti-PLT drug reversal
- Clot strength
- Clot retraction
- Clot architecture
- Thrombin generation
- TEG/ROTEM
- Mitochondrial function
- Apoptosis activation
- Membrane integrity
- Granule content
- Response to regulatory stimuli
- RNA preservation
- Inflammatory potential (TXA2 and sCD40L release)
- Bacterial growth
- **In vivo (rat) hemostasis (histology, intravital microscopy)**
- **Clinical bleeding**



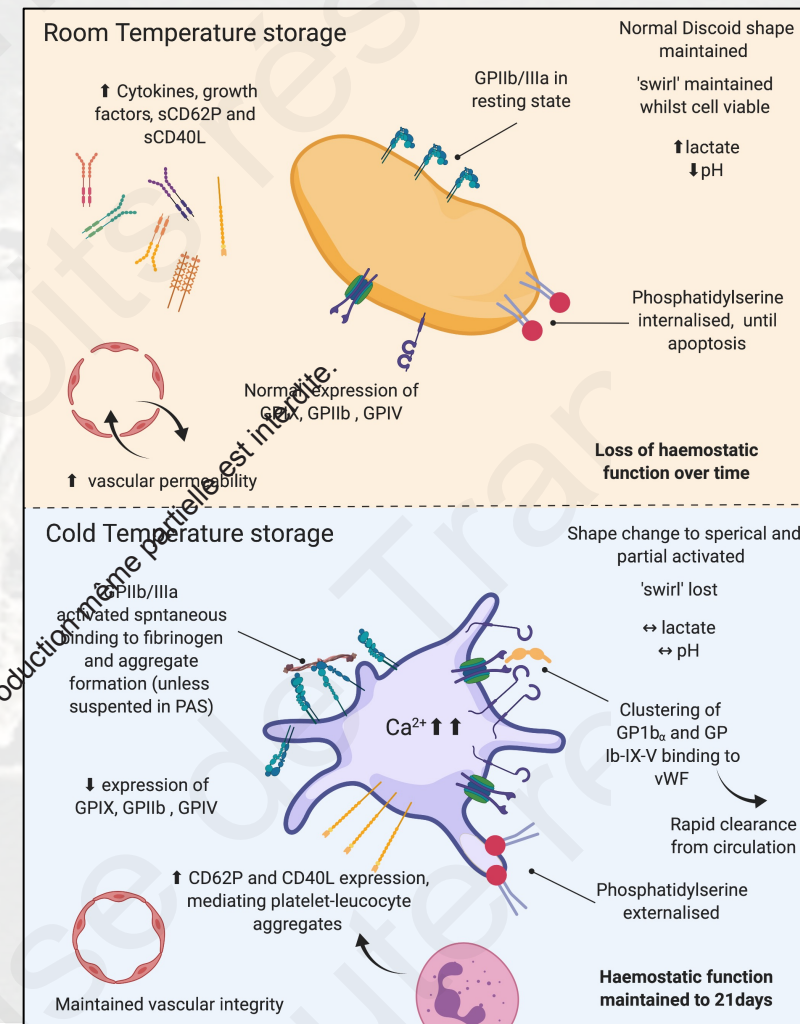
4C better

**Current practice focuses on
Quality (pH), HSR,
morphology...**

Do CSP correct dysfunction?

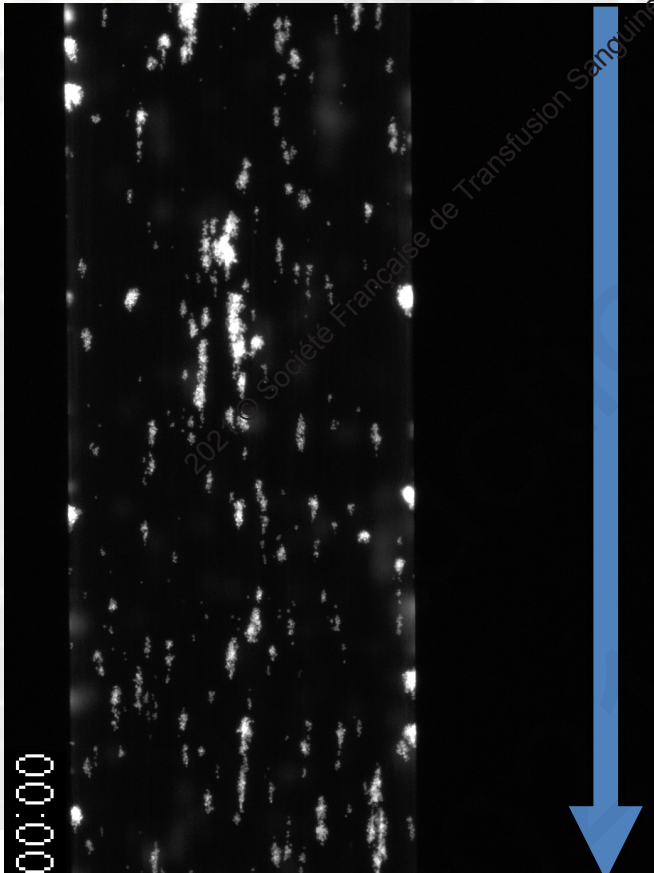
Can cold stored platelets correct platelet dysfunction?

1. Anti-platelet medication - *in vitro* drug spiking
2. Cardiopulmonary bypass – *in vitro* model
3. Patients post cardiac bypass – *ex vivo* analysis



CSP reverse thrombocytopeny *in vitro* models

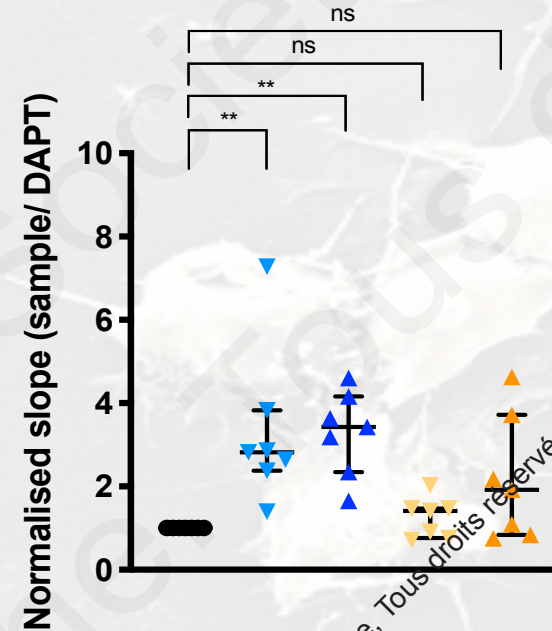
BIOFLUX System
Arterial Shear rate



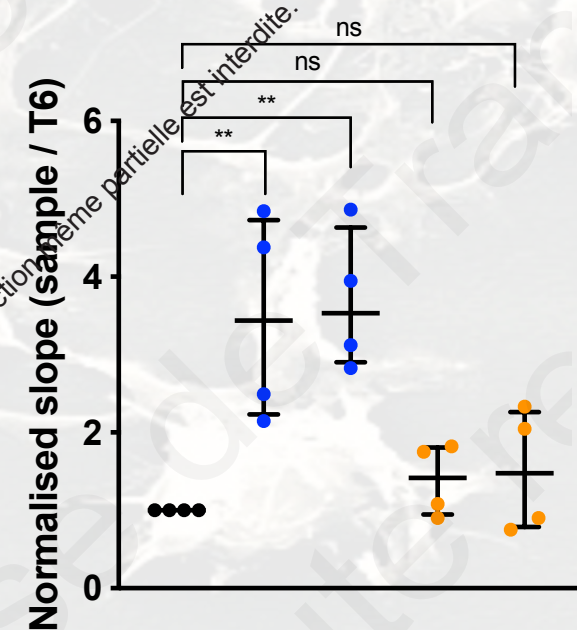
Flow direction

Rate of surface area coverage
Increased with mixing CSP, but not RTP

Ticagrelor and Aspirin



Cardiac bypass model



• DAPT ▽ DAPT + 1 ATD CSP ▽ DAPT + 1 ATD RTP
 ▲ DAPT + 2 ATD CSP ▲ DAPT + 2 ATD RTP

• T6 • T6 + CSP <7d • T6 + RTP <7d
 • T6 + CSP >7d • T6 + RTP >7d

Study Aim

Cold Platelets in Cardiac Surgery (CoPiCS) Study

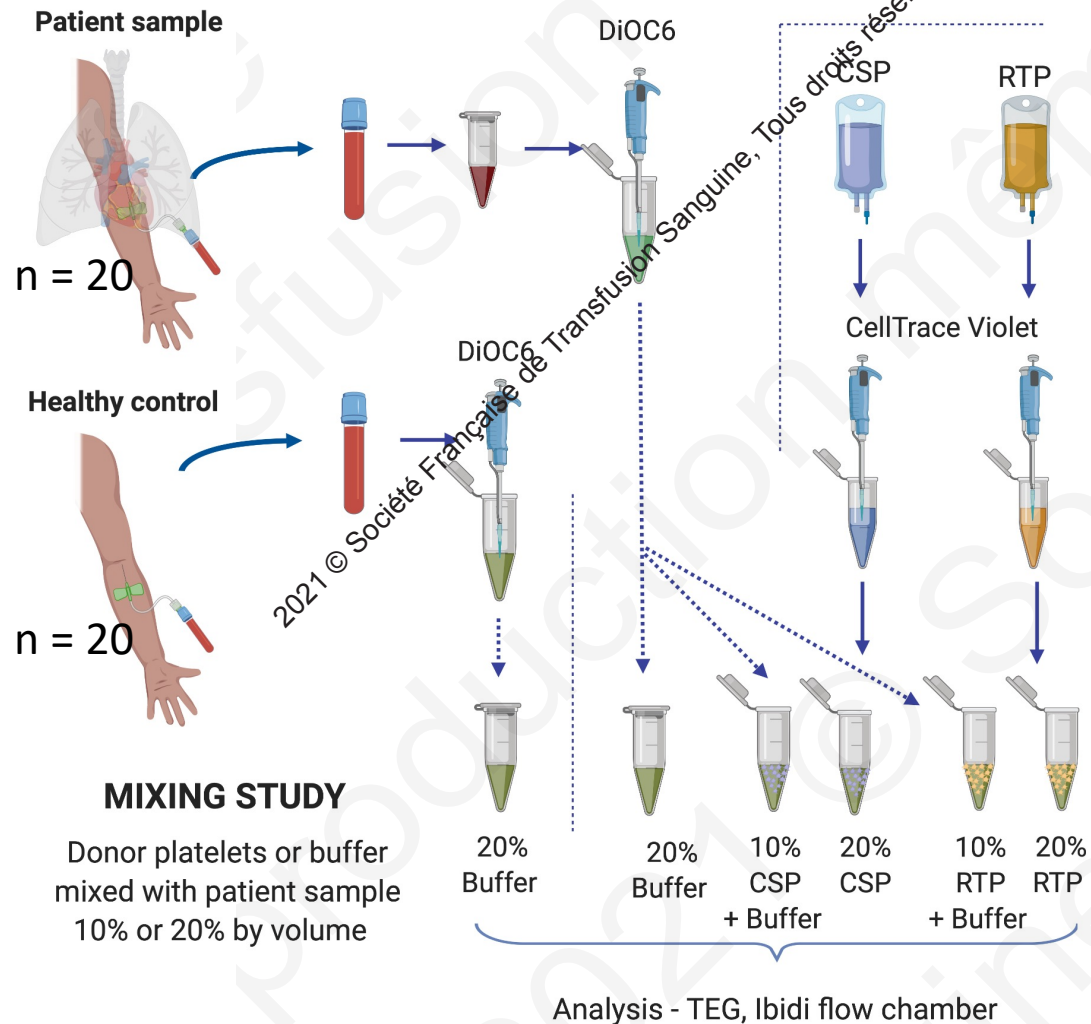
Can cold stored platelets correct platelet dysfunction?

1. Anti-platelet medication - *in vitro* drug spiking
2. Cardiac bypass – *ex vivo* model
3. Patients post cardiac bypass – *ex vivo* analysis

- Physiologically relevant
 - Novel - Ibidi Flow Chamber assay



General Study design



Cardiac Surgery patients
“all comers” n = 20

16 male, 4 female, mean age 62.4yrs

7 concurrent anti-PLT medication

Valve, CABG, complex

CPB – mean 62.3 mins

Cross clamp time – mean 63.4 mins

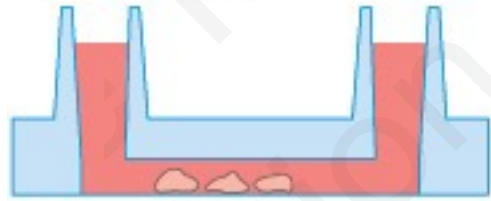
Analysis

TEG – venous shear

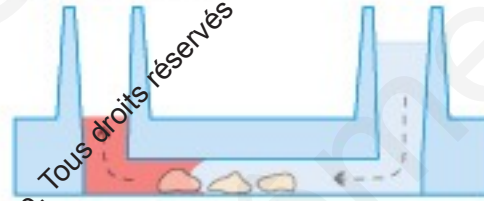
Flow chamber assay – arterial shear

Ibidi Flow chamber assay

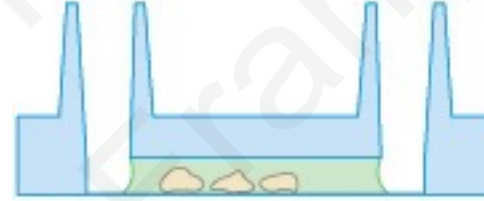
Sample infused at arterial shear



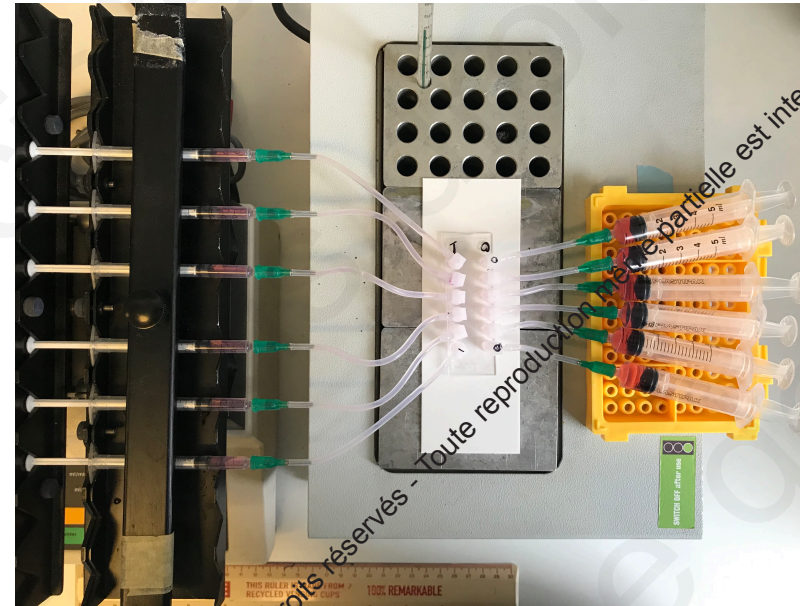
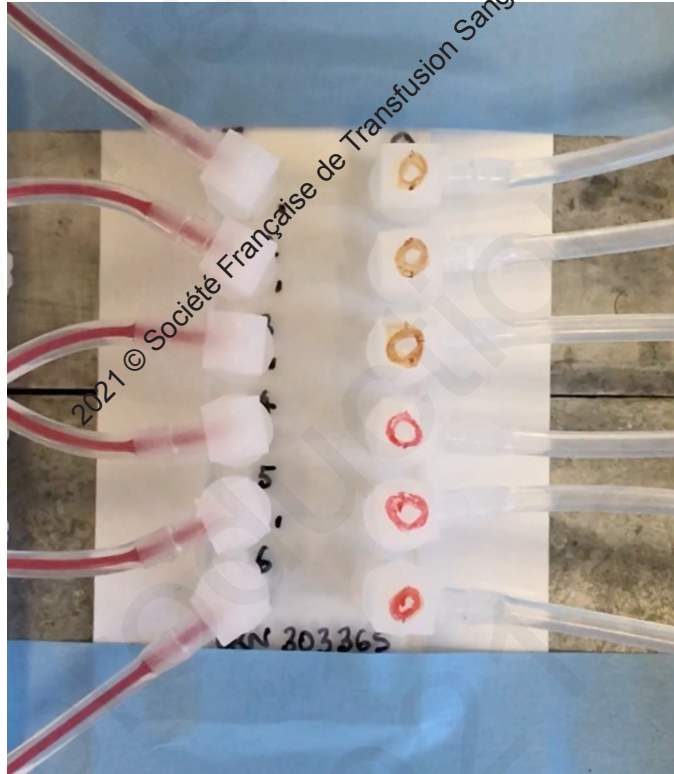
Washed

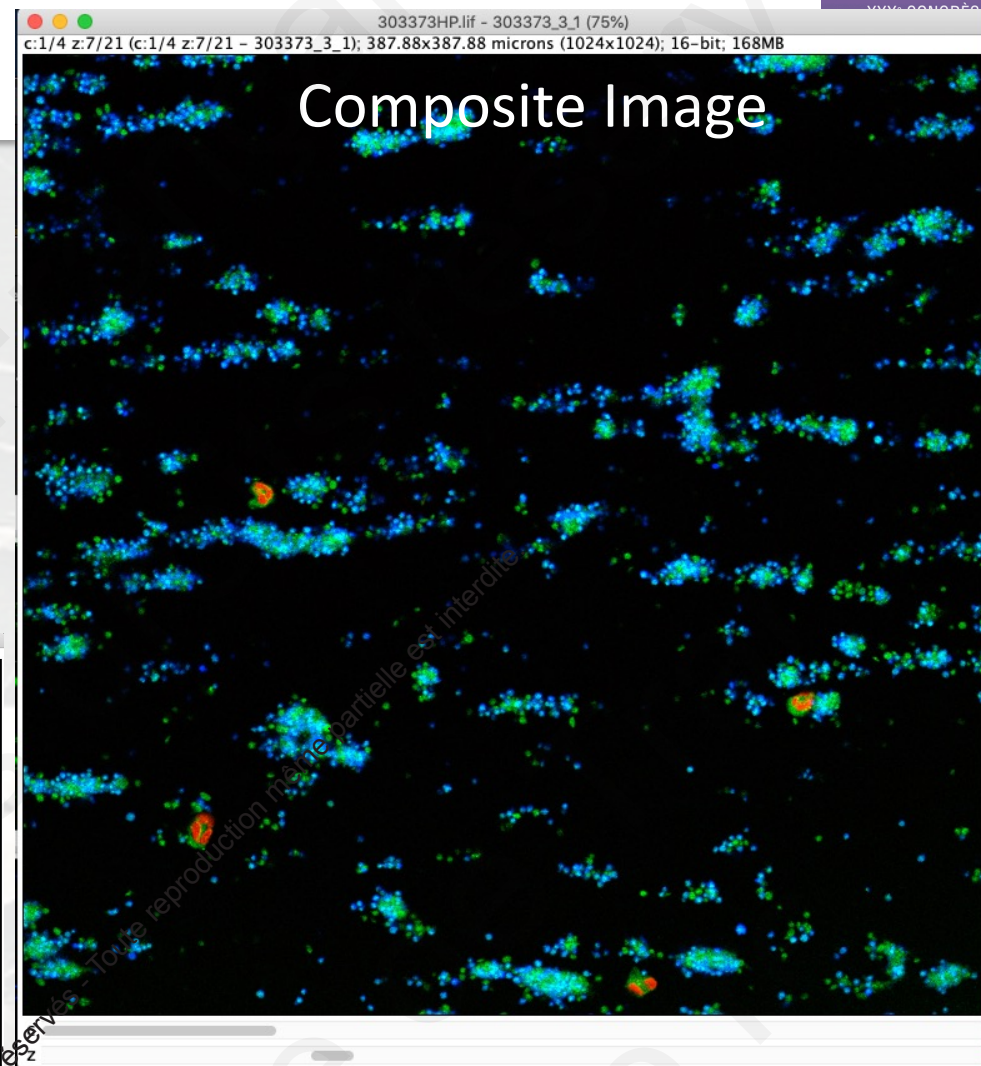
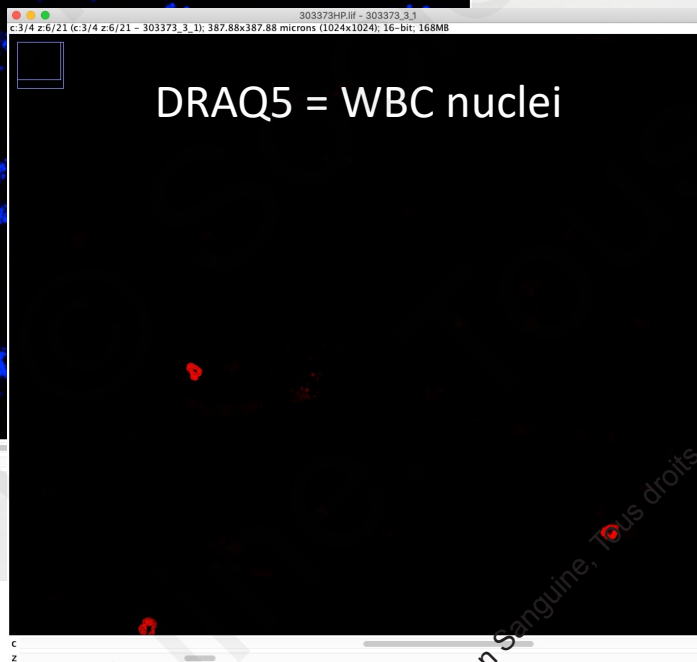
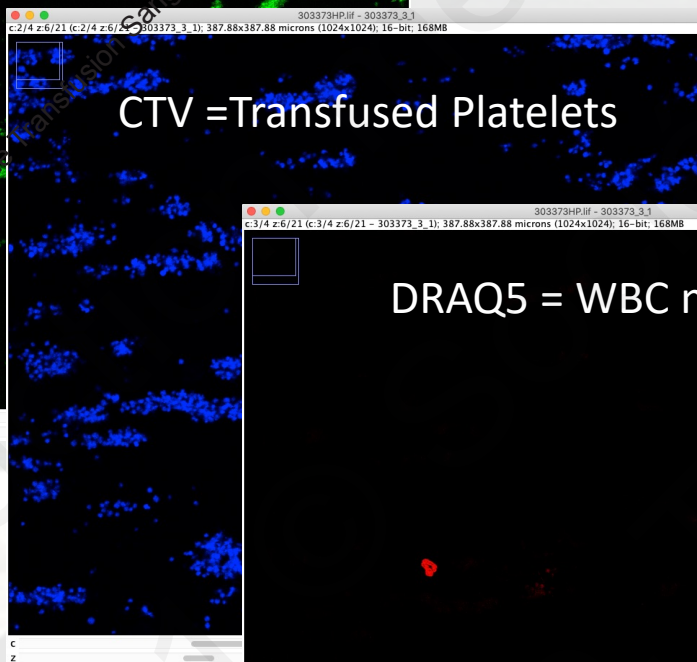
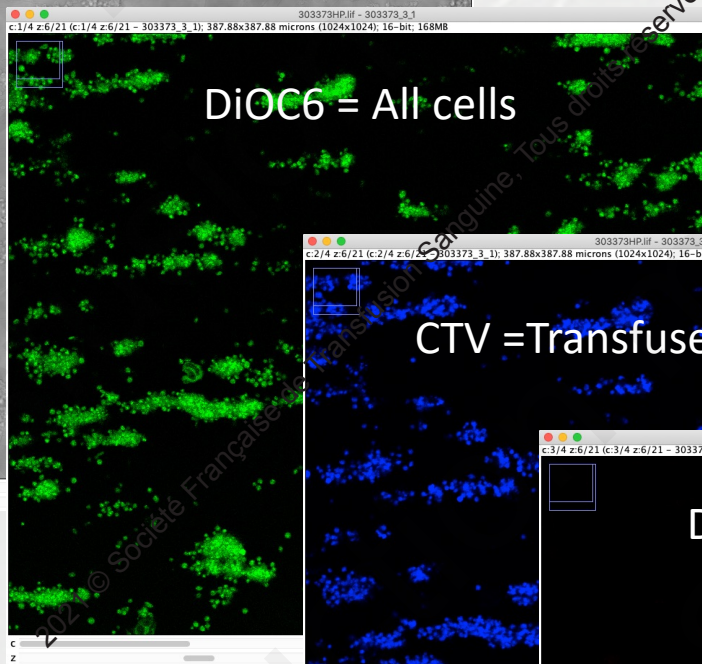
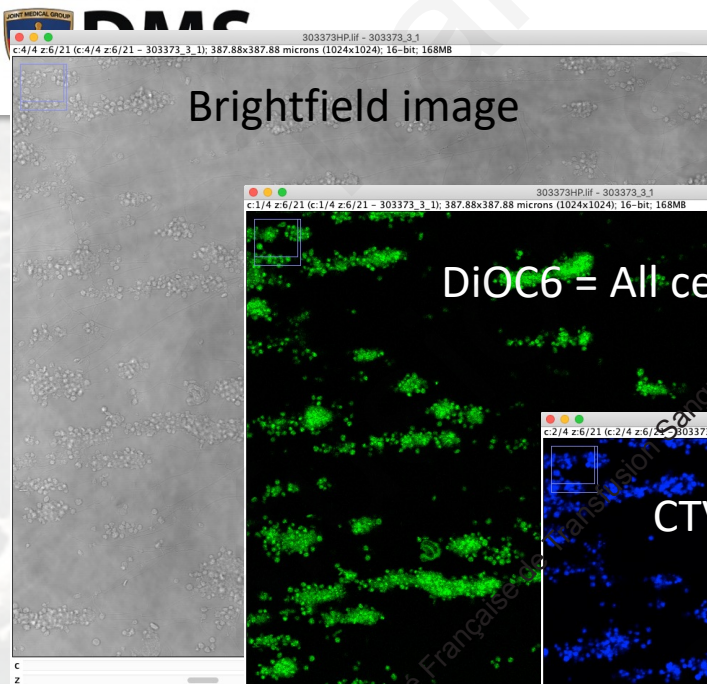


Fixed



Imaged

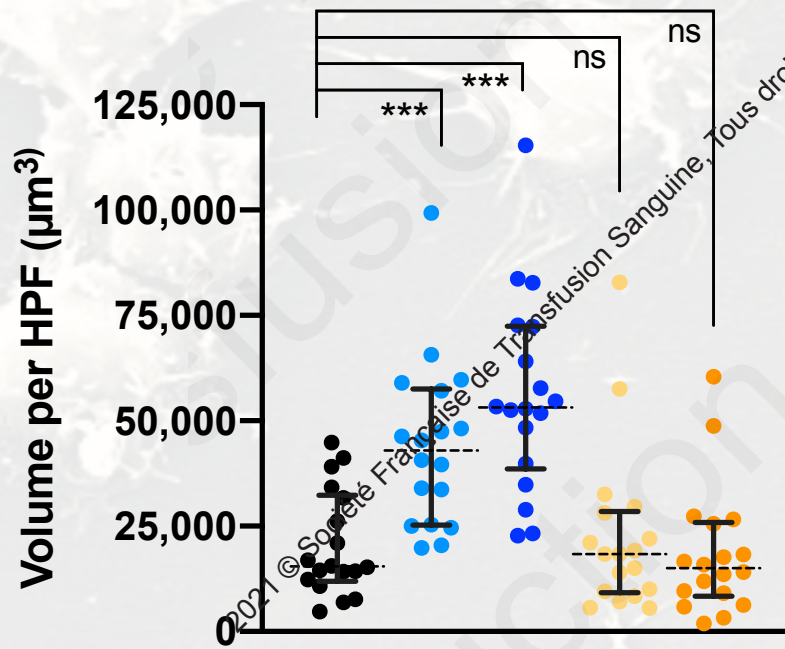




3D Images acquired as a z-stack

Results – Clot Volume

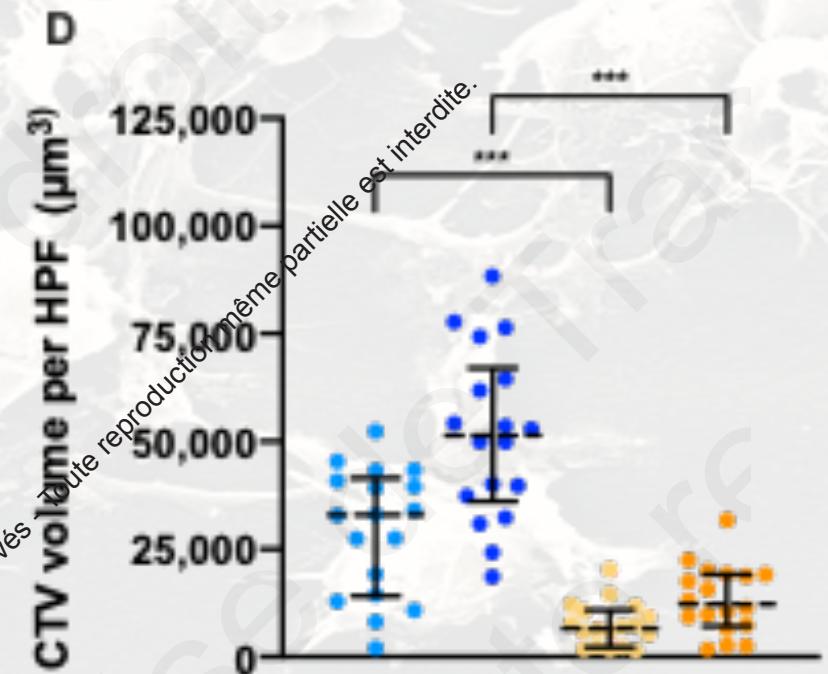
Greater clot volume with CSP (P < 0.001)



- Patient
- Patient + CSP 10%
- Patient + CSP 20%
- Patient + RTP 10%
- Patient + RTP 20%

Predominant contribution is increased aggregation
Directly attributed to CSP

Clot volume is due to CSP





CSP – logistical advantages

Can stored alongside Red Blood Cells or WB

- No agitator
- No incubator
- Prolonged storage times – 14-21 days

Enable platelet transfusion in more remote and constrained settings



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DoD Clinical Experience implements CSP in DCR: JAN 2016



Shelf life 3d in 2016, validation to 5d

Shelf life extension to 10d JUN 2017

Shelf life extension to 14d FEB 2019

First CSP transfusion: 15 APR 2016

**CSP used in Damage Control Resuscitation (DCR) along
with RTP**


UNITED STATES CENTRAL COMMAND
7115 SOUTH BOUNDARY BOULEVARD
MACDILL AIR FORCE BASE, FLORIDA 33621-5101

9 February 2019

MEMORANDUM FOR DIRECTOR, JOINT BLOOD PROGRAM, USCENTCOM

SUBJECT: Cold Stored Platelet (CSP) Life Extension Authorization

Ref(s): (a) OSD (HA) Policy 10-002
(b) CDR Signed CCSG Position Paper dated 14 June 2017, Non-FDA Approved CSP Shelf Life Extension

1. In accordance with reference (a) and approved by Commander, U.S. Central Command via reference (b), the use of CSPs stored up to fourteen days for emergency transfusion is authorized. All requirements for non-FDA approved blood product transfusions as outlined in reference (a) must be part of transfusion practice and overseen by the Joint Blood Program Officer.

2. The Blood Program Officer may submit to the U.S. Central Command Surgeon a request to extend further to eighteen days (or beyond) following appropriate evaluation of CSP transfusion with fourteen-day storage to ensure CSP efficacy and lack of complications. Appropriate quality assurance information must be included with that request to make a data driven, informed decision that is directed at optimizing morbidity and mortality in combat casualties through best transfusion practices. Reference (b) limits us to 15 days, so extension to 18 days will require CENTCOM CDR involvement again.

3. My point of contact is Mr. Ray Huntsinger, who can be reached at 312-529-0345 or by electronic mail at charles.r.huntsinger.civ@mail.mil.

CALDERJEFFREY
Y.S.1096662188
J. SCOTT CALDER
Colonel, USAF, MC, SFS
Command Surgeon

Digitally signed by
CALDERJEFFREY Y.S.1096662188
Date: 2019.02.09 12:49:28
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Validation Summary and Approval

Cold Storage of Apheresis Platelets Validation

Facility

BSD
Bagram Airfield
APO AE 09354

Purpose

To assess the validity of storing apheresis platelets at refrigerated temperatures while maintaining the safety, purity, and potency of the blood component. Current research indicates that platelets stored at refrigerated temperatures causes partial activation of platelets and leads to improved hemostatic function in cases of acute hemorrhage.

This validation will determine if this blood component can safely be stored in the current operational environment. Successful validation will demonstrate that cold storage of apheresis platelets meets the FDA quality control requirements for apheresis platelet components.

The following areas will be addressed: Installation Qualification, Operational Qualification and Performance Qualification. If successful, this validation will support the introduction of 5-Day Cold Storage Platelets for transfusion in cases of acute hemorrhage.

Date of Validation

23 November 2015 - 23 December 2015



UNCLASSIFIED
UNITED STATES CENTRAL COMMAND
7115 SOUTH BOUNDARY BOULEVARD
MACDILL AIR FORCE BASE, FLORIDA 33621-5101

26 June 2017

MEMORANDUM FOR DIRECTOR, JOINT BLOOD PROGRAM, U.S. CENTRAL COMMAND

SUBJECT: Cold Stored Platelet (CSP) Life Extension Authorization

Ref(s): (a) OSD(HA) Policy 10-002
(b) CDR Signed CCSG Position Paper dated 14 June 2017, Request for Non-FDA approved CSP Shelf Life Extension.

1. In accordance with reference (a) and approved by Commander, U.S. Central Command via reference (b), the use of CSPs stored up to ten days for emergency transfusion is authorized. All requirements for non-FDA approved blood product transfusions as outlined in reference (a) must be part of transfusion practice and overseen by the Joint Blood Program Officer.

2. The Blood Program Officer may submit to the U.S. Central Command Surgeon a request to extend shelf life to fifteen days following appropriate evaluation of transfusion with ten-day storage to ensure CSP efficacy and lack of complications. Appropriate quality assurance information must be included with that request to make a data driven, informed decision that is directed at optimizing morbidity and mortality in combat casualties through best transfusion practices.

My point of contact is COL Stephen Linck, who can be reached at (813) 529-0362 or by email at stephen.j.linck.mil@mail.mil.

DARIN K. VIA
CAPT, MC, USN
Command Surgeon

**Gradual increase in CSP
vs. RTP production, now
mostly CSP (>2000U total
PLT produced since 2016)**



Clinical experience DoD



Injury pattern CSP vs. RTP

- More likely to suffer blast or GSW, penetrating or multiple
- No difference in TBI distribution

CSP interventions vs. RTP:

- Less likely to be operatively managed
- No difference in TKA (most patients received in both groups), FVII (use rare); transfusions similar

CSP outcomes vs. RTP:

- No difference in VTE, arterial thrombosis, sepsis, mortality
- No difference in outcomes adjusted for ISS

Overall CSP assessment:

- **CSP-containing DCR clinical safety and efficacy similar c/w RTP-only DCR**
- **CSP 14d shelf life and bacterial safety compelling**

Characteristics	RTP	CSP	Total
Overall	161 (62.9%)	95 (37.1%)	256 (100%)
GENDER			
Male	149 (92.5%)	94 (98.9%)	243 (94.9%)
Female	12 (7.5%)	1 (1.1%)	13 (5.1%)
US_MIL			
US Mil/NATO	35 (21.7%)	11 (11.6%)	46 (18%)
Other	126 (78.3%)	84 (88.4%)	210 (82%)

Norway - Pilot RCT

PERIOPERATIVE MEDICINE

ANESTHESIOLOGY

A Pilot Trial of Platelets Stored Cold *versus* at Room Temperature for Complex Cardiothoracic Surgery

Geir Strandenes, M.D., Joar Sive Christopher K. Bjerkvig, M.D., Tr Andrew P. Cap, M.D., Ph.D., Det Einar Klæboe Kristoffersen, M.D., Rune Haaverstad, M.D., Ph.D., V Hanne Bræthøen, B.Sc., and H

ABSTRACT

Background: This pilot trial focused on feasibility and safety to provide preliminary data to evaluate the hemostatic potential of cold-stored platelets (20°C) compared with standard room temperature–stored platelets (20°C–24°C) in adult patients undergoing complex cardiothoracic surgery. This study aimed to assess feasibility and to provide information for future pivotal trials.

Methods: A single center two-stage exploratory pilot study was performed on adult patients undergoing elective or semiurgent complex cardiothoracic surgery. In stage I, a two-armed randomized trial, platelets stored up to 7 days in the cold were compared with those stored at room temperature.

Table 1. Safety Endpoints

	Room Temperature–stored up to 7 Days (n = 25)	Cold-stored up to 7 Days (n = 25)	Cold-stored for 8 to 14 Days (n = 15)
Arterial thromboembolism*	6 (24%)	6 (24%)	2 (13%)
Venous thromboembolism†	2 (8%)	0 (0%)	2 (13%)
Transfusion reaction caused by platelet transfusion	0 (0%)	0 (0%)	0 (0%)
Time to extubation, h	1.6 (5.08–21.37, 3.37–212.72)	6.6 (5.12–19.45, 3.67–349.02)	16.0 (4.28–27.27, 3.28–135.58)
Length of stay in intensive care unit, days‡	2 (1–5, 1–28+)	2 (1–6, 1–28+)	4 (2–14, 1–28+)
28-Day mortality	3 (12%)	2 (8%)	2 (13%)

The results are given as median (interquartile range, minimum, maximum) or count (percentage).

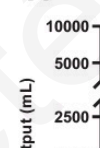
* Days from surgery: room temperature–stored up to 7 days: 3, 9, 10, 13, 16, and 22. Cold-stored up to 7 days: 2, 4, 4, 7, 8, and 14. Cold-stored from 8 to 14 days: 2 and 6.

† Days from surgery: room temperature–stored up to 7 days: 1 and 6; cold-stored for 8 to 14 days: 1 and 9.

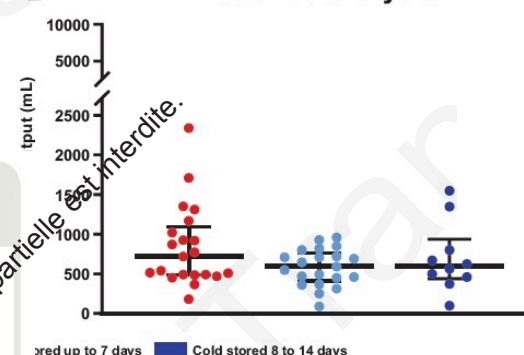
‡ One patient in the group with room temperature–stored up to 7 days, one patient in the cold-stored up to 7 days group, and two patients in the cold-stored for 8 to 14 days remained in intensive care at the conclusion of the 28-day study period. These were defined as 28 days for statistical analysis.

- Pilot trial CSP vs RTP in cardiac Sx published – Sep 20
- No difference – no safety concerns

A Intention-to-treat



B Post hoc analysis



Intention-to-treat patients (A) and post hoc analysis patients receiving 14 days cold-stored platelets (B). The dots represent the individual difference between the room temperature– and cold-stored for 7 days 15, two-tailed Mann–Whitney U test; SPSS Statistics for Windows, 4 days arm was not compared with the two stage I arms.



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Updates



- **FDA – license for CSP – stored for up to 14 days – Jan 20**
- **DoD funding CHIPS - \$26 million**



FDA grants South Texas Blood & Tissue Center first license for new process that triples shelf life of critically needed platelets

Breakthrough expected to increase availability of platelets for trauma patients and active bleeding cases

f t in G+ p @ Email Print Friendly Share

February 28, 2020 08:45 ET | Source: BioBridge Global

San Antonio, Texas, Feb. 28, 2020 (GLOBE NEWSWIRE) – The U.S. Food and Drug Administration has granted the South Texas Blood & Tissue Center (STBTC) a license to use a new process shown to almost triple the current five-day shelf life of platelets.

Platelets are a key blood component constantly in demand for treating trauma, severely bleeding patients and maternal hemorrhage, which is a special challenge for rural hospitals. There also is a growing need for platelets for use in cancer treatment, transplant surgeries and other medical conditions.

STBTC, a subsidiary of BioBridge Global, is the first blood center in the United States to receive an FDA license to produce the licensed cold-stored platelets. Cold-stored platelets are refrigerated and can be transfused up to 14 days after collection.



THE THOR NETWORK

An international multidisciplinary network of civilian and military providers ranging from first responders and medics to critical care physicians and from basic scientists to clinical trialists.

VISION: To improve outcomes from traumatic hemorrhagic shock by optimizing the acute phase of resuscitation.

MISSION: To develop and implement

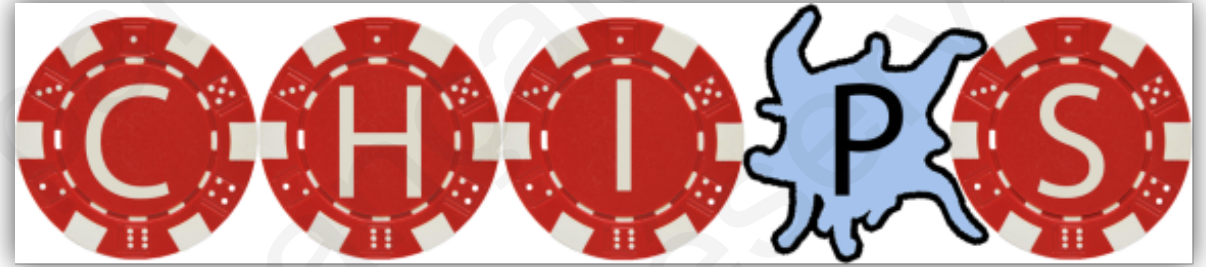
PRESS RELEASE

September 26, 2020

THOR Network investigators have been awarded over 26 million dollars by the US Department of Defense for a research program that will examine the efficacy and safety of cold stored platelets for patients with active bleeding.

The funding will support the Chilled Platelet Study (CHIPS), which is a phase III, multicenter, randomized, double blinded, adaptive, non-inferiority, storage duration ranging trial in 1000 cardiac surgery patients with active bleeding. The adaptive trial design will allow for a maximum storage duration of up to 21 days in the cold storage group. The control group will be room temperature stored platelets with a maximum of 5-7 days, and the primary outcome is a well validated 5-point bleeding score. The trial is expected to begin in the summer of 2021.

Chilled Platelets Study -



- DoD funded trial – \$26m (CI Phil Spinella)
- Phase III, multicenter, randomized, double blinded, adaptive, non-inferiority, storage duration ranging trial in 1000 cardiac surgery patients with active bleeding
 - Phase 1 are CSP non-inferior to RT platelets (day 7)
 - Phase 2 – how long in storage (to day 21) is non-inferiority maintained?
- CHIPS trials - UK site for trial – aim start Jan 22
 - Plymouth Hospitals NHS Trust ± Bristol

Welsh Blood Service (central funding)

- Phase 0 Validation for MHRA - Apr 21
 - Aim Phase 0 validation complete Feb 22
 - Additional testing – Bioenergetic profiling
 - D21, AP 100% plasma



CSP for Quality Assurance

- UK NEQAS – External Quality Assurance (EQA)
- Platelet function testing – No current EQA
- Pilot trial starting UK NEQAS and Welsh Blood service
 - Dec 2021 – Confirmatory testing and protocol development
 - Feb 2022 – Pilot EQA exercise (2-3 sites)
 - May 2022 – Larger pilot EQA with interpretation (15+ sites)
- Summer 2022 – Publish findings





DMS
Defence Medical Services

Summary



Cold stored platelets:

- Preserved haemostatic function for 14 days, 'equivalent' up to 21
 - Capable of reversing thrombocytopathy
- Reassuring clinical safety data
- Practical benefits: Cost, time, space and wastage

Time for a trial...

Time to find out if cold storage of platelets is better for bleeding?



Thank you



USAISR – COL Andrew p. Cap Medical Corps, US Army

University of Bristol - Prof Andrew Mumford

Centre of Defence Pathology & Defence Professors

DCA Pathology – Lt Col Emma Hutley

Prof. Mil. Med – Col David Woods RAMC

Prof. Mil. Anaesthesia – Col Tom Wooley RAMC

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Umang Sharma, Grantham Peltier, Colby McIntosh, Kristin Reddoch-Cardenas

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Welsh Blood Service

Chloe George

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