American Red Cross

Cold Stored Platelets

And Other Stories

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Disclosures

- I have no relevant financial conflicts to disclose.
- (Currently, the only people who wish to pay me are the Red Cross.)

Objectives

At the end of the session, the participant will be able to answer:

1) Are Cold Stored Platelets appropriate for everyone?
2) When do CSP make sense?
3) Can I get them now, or soon?

Outline

- History of Transfusion
- Platelet Biology
- Room Temperature Platelets
- Cold Stored Platelets
- Lots of studies…
- Potential Marketplace
- What's Next?

Blood transfusion is an inherently unsafe act.

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hart adapted from
ao and Sherwood
ACC 2014

A Brief History of Transfusion

- **1628** English physician William Harvey discovers the circulation of blood. Shortly afterward, the earliest known blood transfusion is attempted.
- **1665** The first recorded successful blood transfusion occurs in England: Physician Richard Lower keeps dogs alive by transfusion of blood from other dogs.
- **1667** Jean-Baptiste Denis in France and Richard Lower in England separately report successful transfusions from lambs to humans. Within 10 years, transfusing the blood of animals to humans becomes prohibited by law because of reactions.
- **1795** In Philadelphia, American physician Philip Syng Physick, performs the first human blood transfusion, although he does not publish this information.

- **1818** James Blundell, a British obstetrician, performs the first successful transfusion of human blood to a patient for the treatment of postpartum hemorrhage. (~4 oz from husband)
- **1840** At St. George's School in London, Samuel Armstrong Lane, aided by consultant Dr. Blundell, performs the first successful whole blood transfusion to treat hemophilia.
- **1873-1880** US physicians transfuse milk (from cows, goats, and humans).
- **1884** Saline infusion replaces milk as a “blood substitute” due to the increased frequency of adverse reactions to milk.

- **1900** Karl Landsteiner, an Austrian physician, discovers the first three human blood groups, A, B, and O. Landsteiner receives the Nobel Prize for Medicine for this discovery in 1930.
- **1902** Alfred Decastello and Adriano Sturli add AB.
- **1907** Hektoen suggests that the safety of transfusion might be improved by crossmatching blood between donors and patients
- **1908** French surgeon Alexis Carrel devises a way to prevent clotting by sewing the vein of the recipient directly to the artery of the donor. The procedure proves unfeasible for blood transfusions, but paves the way for successful organ transplantation, for which Carrel receives the Nobel Prize in 1912.

- **1914** Long-term anticoagulants, among them sodium citrate, are developed, allowing longer preservation of blood.
- **1932** The first blood bank is established in a Leningrad hospital.
- **1937** The first hospital blood bank in the United States is established at the Cook County Hospital in Chicago.
- **1939/40** The Rh blood group system is discovered by Landsteiner, Wiener, Levine and Stetson and is soon recognized as the cause of the majority of transfusion reactions.
- **1940** The United States government establishes a nationwide program for the collection of blood. The American Red Cross joins the effort, collecting 13 million units of blood by the end of World War II.

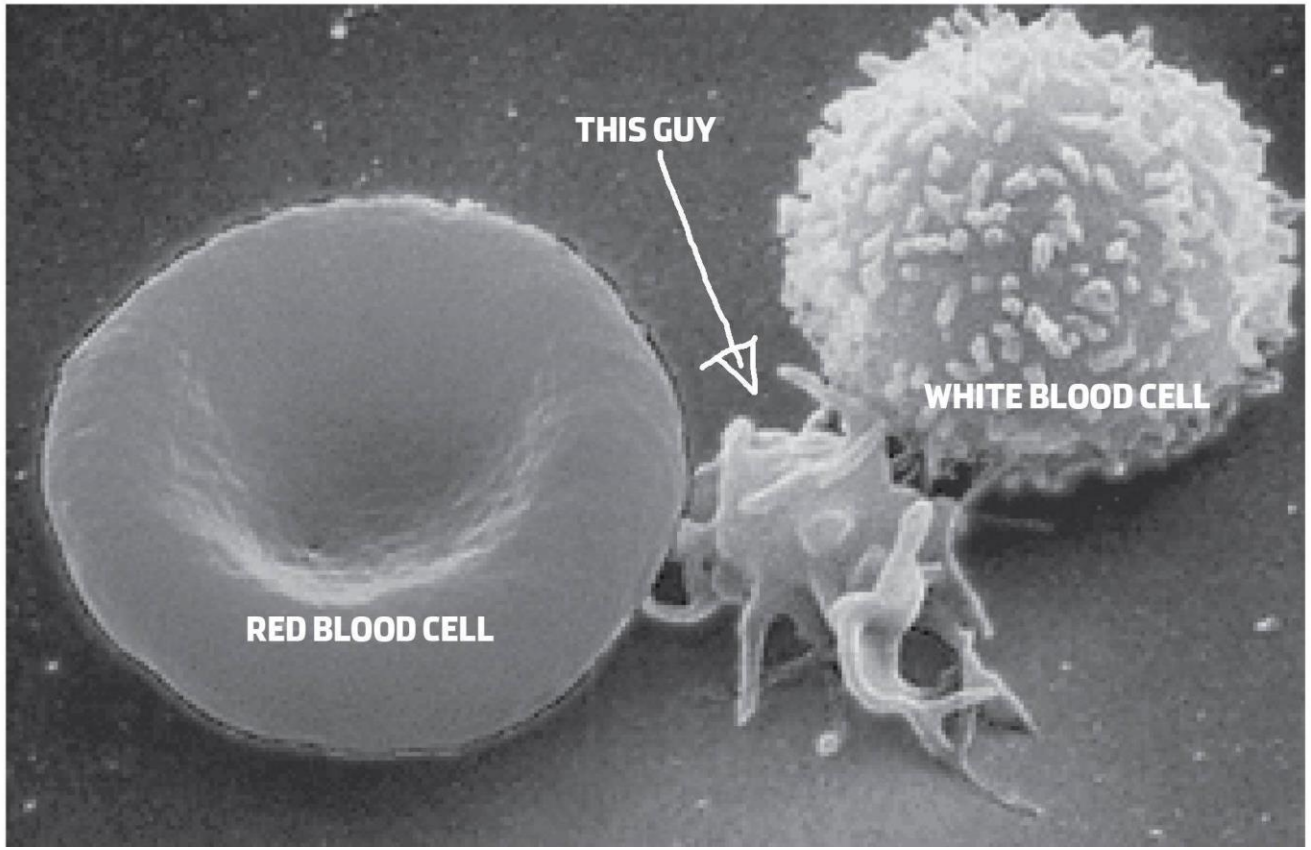
- **1943** The introduction of acid citrate dextrose (ACD) solution, which reduces the volume of anticoagulant, permits transfusions of greater volumes of blood and permits longer term storage.
- **1943** Transfusion-transmitted hepatitis is described.
- **1950** The plastic bag for blood collection is developed, replacing breakable glass bottles. This also allows whole blood to be separated into components. The refrigerated centrifuge appears in 1953.
- **1959** Max Perutz of Cambridge University deciphers the molecular structure of hemoglobin.
- **1964** Plasmapheresis is introduced.

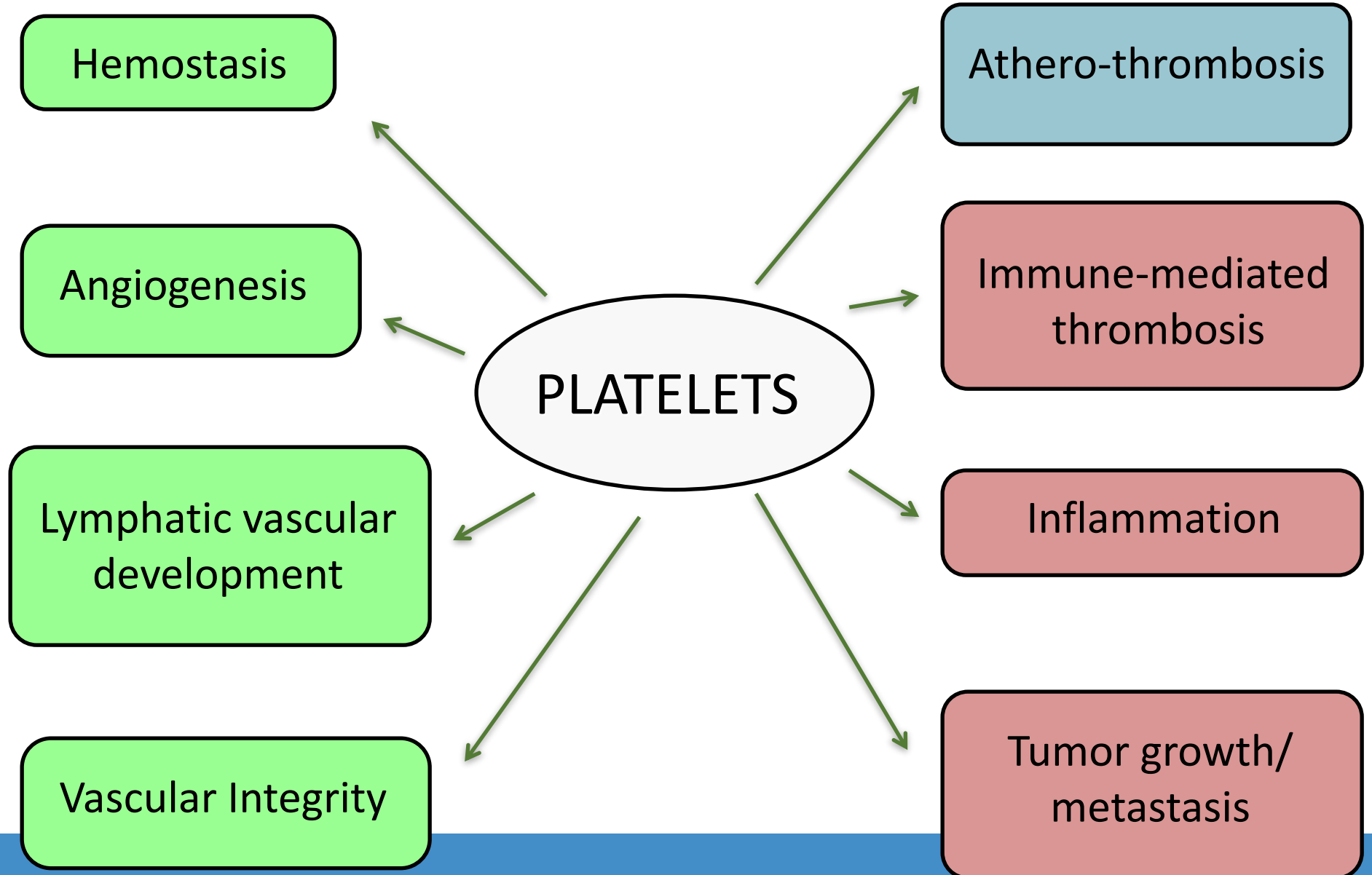
- **1967** Rh immune globulin is commercially introduced.
- **1969** Platelets are stored at room temperature.
- **1972** Apheresis is used to extract one cellular component, returning the rest of the blood to the donor.
- **1981** First Acquired Immune Deficiency Syndrome (AIDS) case reported.
- **1984** Human Immunodeficiency Virus (HIV) identified as cause of AIDS.
- **1985** The first blood-screening test to detect HIV is introduced.
- **1987** Hepatitis testing started.
- **1989** HTLV testing started.
- **1990** Hepatitis C (non-A, non-B hepatitis) testing started.

- **1992** HIV-1,2 antibody tests introduced.
- **1996** p24 antigen testing for HIV (first direct test) started.
- **1999** Nucleic Acid Amplification Testing (NAT) employs technology that directly detects the genetic materials of viruses like HCV and HIV.
- **2003** West Nile Virus testing introduced.
- **2010** Chagas disease testing started.
- **2014** Pathogen Reduction technology licensed in US.
- **2016** Zika virus testing developed and started. (Discontinued in 2022)
- **2018** Babesia tests approved by FDA (previously used as unlicensed)

What is a Platelet?

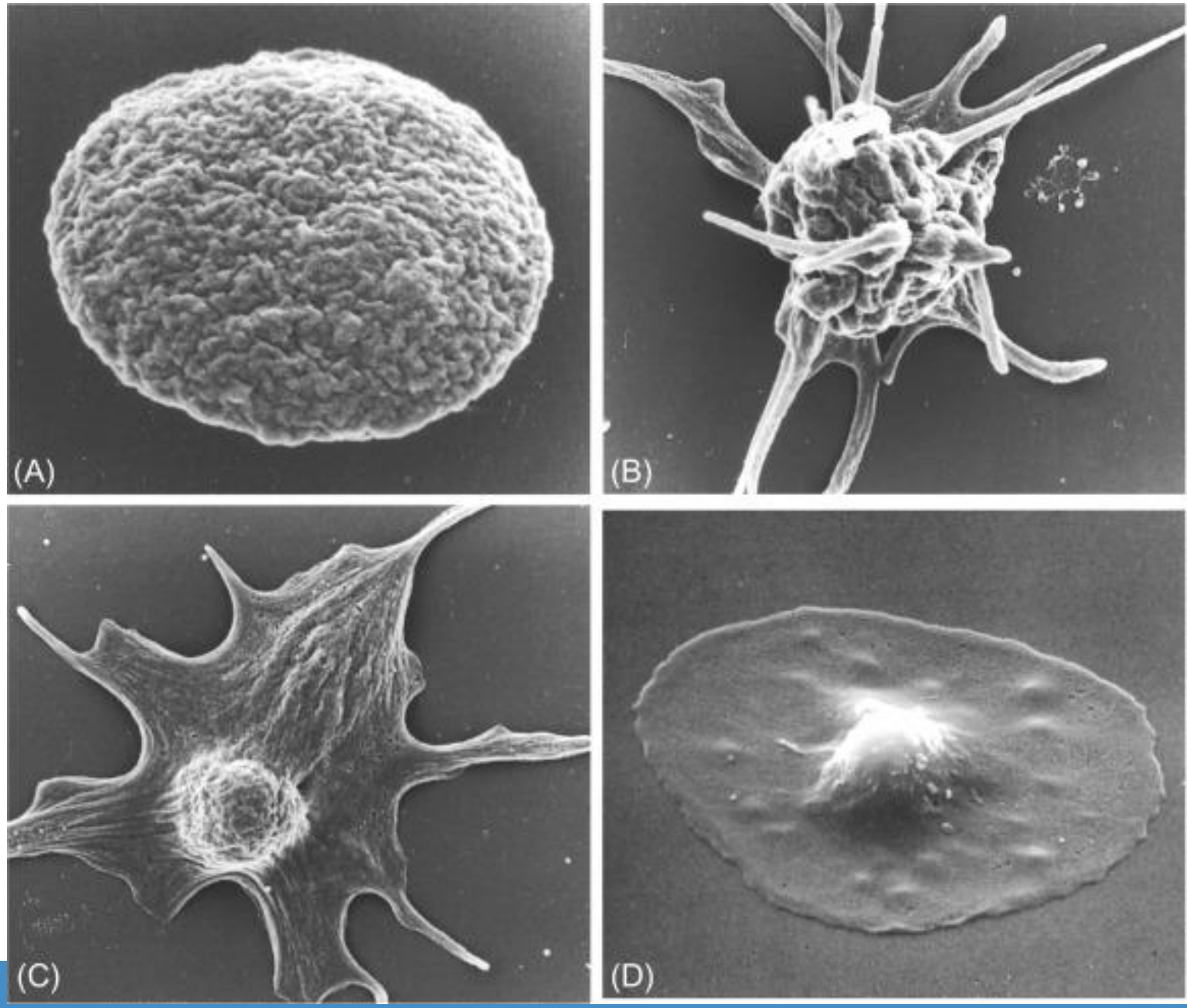
- Blood cell
- ‘Normal’ count: 100,000-600,000 per uL
  - 10,000 bleeding threshold
  - ~4.5% of all cells in body!
- 2-4 um diameter
  - RBC ~7.5, WBC ~10-14
- Primary Function: Hole-plugging
  - Small: direct
  - Large: Bricks in the Wall




Hemostasis
Angiogenesis
Lymphatic vascular development
Vascular Integrity
PLATELETS
Athero-thrombosis
Immune-mediated thrombosis
Inflammation
Tumor growth/ metastasis

Platelet Types

- Quiescent (resting)
- Activated
- Dying



QUIESCENCE

- NO and PGI_2 are released from intact endothelium
- Levels of intracellular cyclic nucleotides are elevated
- PKA and PKG suppress platelet activation

ACTIVATION

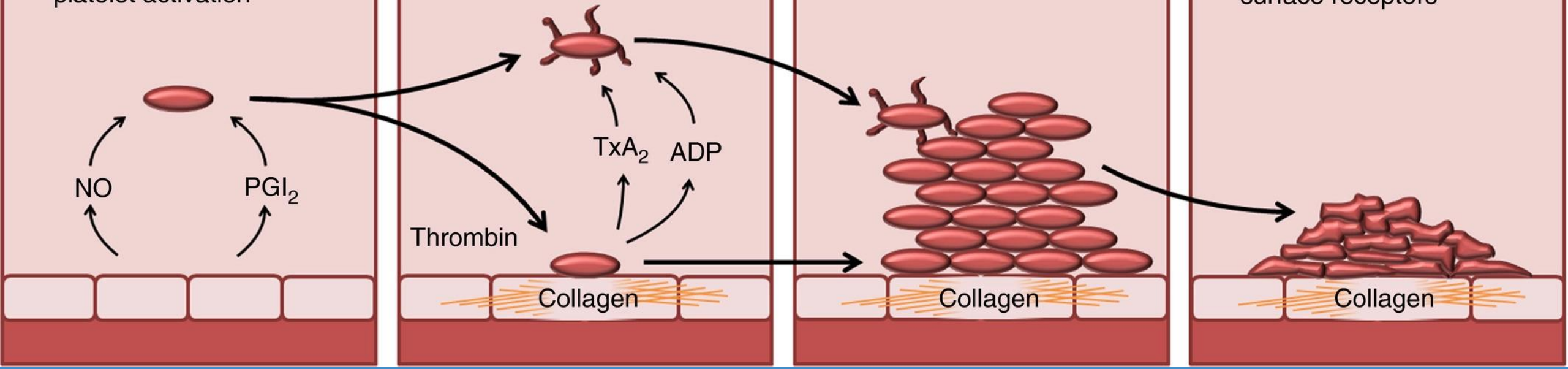
- Collagen and thrombin initiate activation following vascular injury
- Platelets secrete secondary mediators ADP and TxA_2

THROMBUS GROWTH

- PLC, PKC and PI3K support sustained platelet activation
- Integrin $\alpha_{IIb}\beta_3$ binds fibrinogen and supports aggregation

SELF-REGULATION

- ITIM-bearing negative regulators limit thrombus growth
- ESAM limits $\alpha_{IIb}\beta_3$ activation
- Desensitization of cell surface receptors



Platelet Transfusion Settings

- Platelets maintain endothelial integrity & plug gaps (~7,100 /µL/d req. for the latter)
- **Therapeutic transfusion**
  - Used for WHO Gr ≥2 bleeding in the setting of actual or functional thrombocytopenia
  - Obvious end-point – cessation of bleeding
- **Pre-procedural transfusion**
  - Considered for surgical interventions and closed procedures with a risk of hemorrhage – most thresholds based upon expert opinion
- **Prophylaxis in Hypoproliferative Thrombocytopenia**
  - Due to primary or secondary (therapy related) bone marrow dysfunction
  - 50 – 75% of platelets currently transfused to prevent bleeding
  - Presumes that maintenance of counts above a "safe" threshold will result in lower hemorrhagic morbidity/ mortality

Blood 1985;66:1105; *NEJM* 2008;359:1261.

In the Beginning…

- All blood was cold…

  and it was good.

1969: New England Journal of Medicine

Platelet Preservation – Effect of Storage Temperature on Maintenance Of Platelet Viability – Deleterious Effect of Refrigerated Storage

Murphy S. et al.

Results:

- Room temp-stored platelets (22ºC) had "normal" life-span of up to 96h
- Refrigerated platelets (4ºC) had a markedly shortened life-span

Conclusion:

- The use of cold temperatures should be abandoned in the preparation and storage of platelets for transfusion purposes.

Lessons Learned

- Room Temperature Platelets:
  - Are quiescent
  - Don’t aggregate in storage
  - Circulate well
  - Survive longer (in patients)
  - Produce higher count increments
  - Grow bacteria REALLY well
- Cold Stored Platelets
  - Are activated
  - Stop bleeding well
  - Survive longer (in storage)
  - Don’t circulate well or long

Hemostatic Function of Apheresis Platelets Stored at 4 °C and 22°C

- Compared apheresis platelets (APs) stored at both temperatures (n=5)
  - 22°C with agitation (current state)
  - 4°C with and without agitation (once and future state)
- Split into mini bags and sampled on Days 1, 3, and 5
- Evaluated platelet counts, mean platelet volume, blood gas analytes, aggregation response, thromboelastography, TxB2 and sCD40L release, activation markers and microparticle formation.
- Hypothesis: APs stored at 4°C would demonstrate more viable metabolic characteristics, perform better in functional tests, form stronger clots, and release fewer inflammatory mediators compared to APs stored at 22°C.

Reddoch, KM, et al., *Shock.* 2014 May ; 41(0 1): 54–61

Hemostatic Function of Apheresis Platelets Stored at 4 °C and 22°C

Metabolic and electrolyte levels in plasma during storage.

	Baseline	RT		4C		4C+AG	
	Day 1	Day 3	Day 5	Day 3	Day 5	Day 3	Day 5
pH	7.24±.07	7.45±.16	7.28±.08	7.45±.21	7.44±.13	7.48±.25	7.44±.15
Lactate (mg/dL)	1.77±0.6	6.85±0.8*	12.87±2.1*	4.51±0.6*	5.67±0.3*†	4.83±0.7*	6.05±0.4*†
Glucose (mg/dL)	321.5±8.1	294.0±22.1*	238.3±42.5*	310.2±14.2*	307.5±25.0*†	312.4±28.1*	303.5±24.6*†
Bicarbonate (mM)	18.04±1.6	10.06±2.9*	6.27±0.9*	14.00±1.7*δ	12.78±0.8*†	14.01±2.7*δ	12.38±1.0*†
pCO_2 (mmHg)	38.5±4.7	13.8±1.5*	13.1±.25*	24.1±4.2*δ	19.5±4.4*†	22.6±5.6*δ	18.7±4.7*†
pO_2 (mmHg)	91.8±9.7	113±17.8	132±41.2	120.4±32.7	139.8±26.8*†	116.6±31.0	128.0±29.3†
Sodium (mM)	137.5±1	139.5±3.7	140.25±1.3*	137.4±1.7	136.8±.96†	137.8±1.6	136.5±1.3†
Potassium (mM)	3.24±.18	3.34±.23	3.45±.31	3.52±.19*	3.60±.25*	3.52±.25*	3.55±.27*†
Chloride (mM)	97.6±.89	101.3±4.9	104.8±1.3*	99.2±2.8	99.7±1.2†	99.0±2.2	98.8±1.7†

*Values (mean ± SD) significant from Baseline represented by ($P < 0.05$)

δValues significant from Day 3 RT represented by ($P < 0.05$)

†Values significant from Day 5 RT represented by ($P < 0.05$)

Hemostatic Function of Apheresis Platelets Stored at 4 °C and 22°C

Conclusions:

- Apheresis Platelets stored at 4°C:
  - Maintain more viable metabolic characteristics
  - Are hemostatically more effective
  - Release fewer pro-inflammatory mediators

- These findings suggest that CSP may improve outcomes for acutely bleeding patients

Parameters:	22°C	vs	4°C	Implications:
Rate of Metabolism In Storage		>	✓	4°C: Preserved platelet viability (more stable)
Aggregation response to stimulus		<	✓	4°C: More responsive to activating stimuli
Clot strength		<	✓	4°C: Greater clot strength
Fibrinolysis		>	✓	4°C: Greater clot stability
Expression of activation markers		<		Depends on goal
Proinflammatory Mediators		>	✓	4°C: Potentially fewer side effects

REFRIGERATED PLATELETS FOR THE TREATMENT OF ACUTE BLEEDING: A REVIEW OF THE LITERATURE AND REEXAMINATION OF CURRENT STANDARDS

Heather F. Pidcoke,* Philip C. Spinella,† Anand K. Ramasubramanian,‡ Geir Strandenes,§‖ Tor Hervig,‖ Paul M. Ness,¶‖ and Andrew P. Cap*

- "We hypothesize that choices were centered on optimization of preventive PLT transfusion strategies, possibly to the detriment of the therapeutic needs of acutely bleeding patients"
- "a 'one-size-fits-all' strategy for PLT storage may not be adequate, and a reexamination of whether cold-stored PLTs should be offered as a widely available therapeutic product may be indicated."

CSP in PAS Exhibit Superior Hemostatic Potential

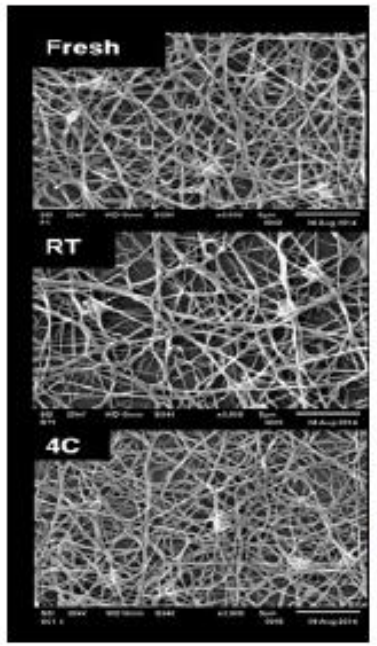
2015: Blood

Cold-Stored Platelets in PAS Exhibit Superior Hemostatic Potential

Nair PM, et al.

Conclusion:

- 4ºC platelets are hemostatically more active than the current standard-of-care and may offer a better solution for resuscitation of bleeding patients.



Nair, Haem. 2017

American Red Cross

Pathogen-Inactivated CSP

2019: Transfusion

Impact of Cold Storage on Platelets Treated with Intercept Pathogen Inactivation
Six KR, et al.

Conclusion:

- Combined effects suggest platelets demonstrate:
  - More rapid clearance time
  - Procoagulant effects *in vitro*
    - **Potential utility in acutely bleeding patients**
    - **Requires clinical studies to confirm**
- Cold storage and PRT both inhibit pathogen replication
  - **May be possible to extend storage duration**

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Pathogen Reduction

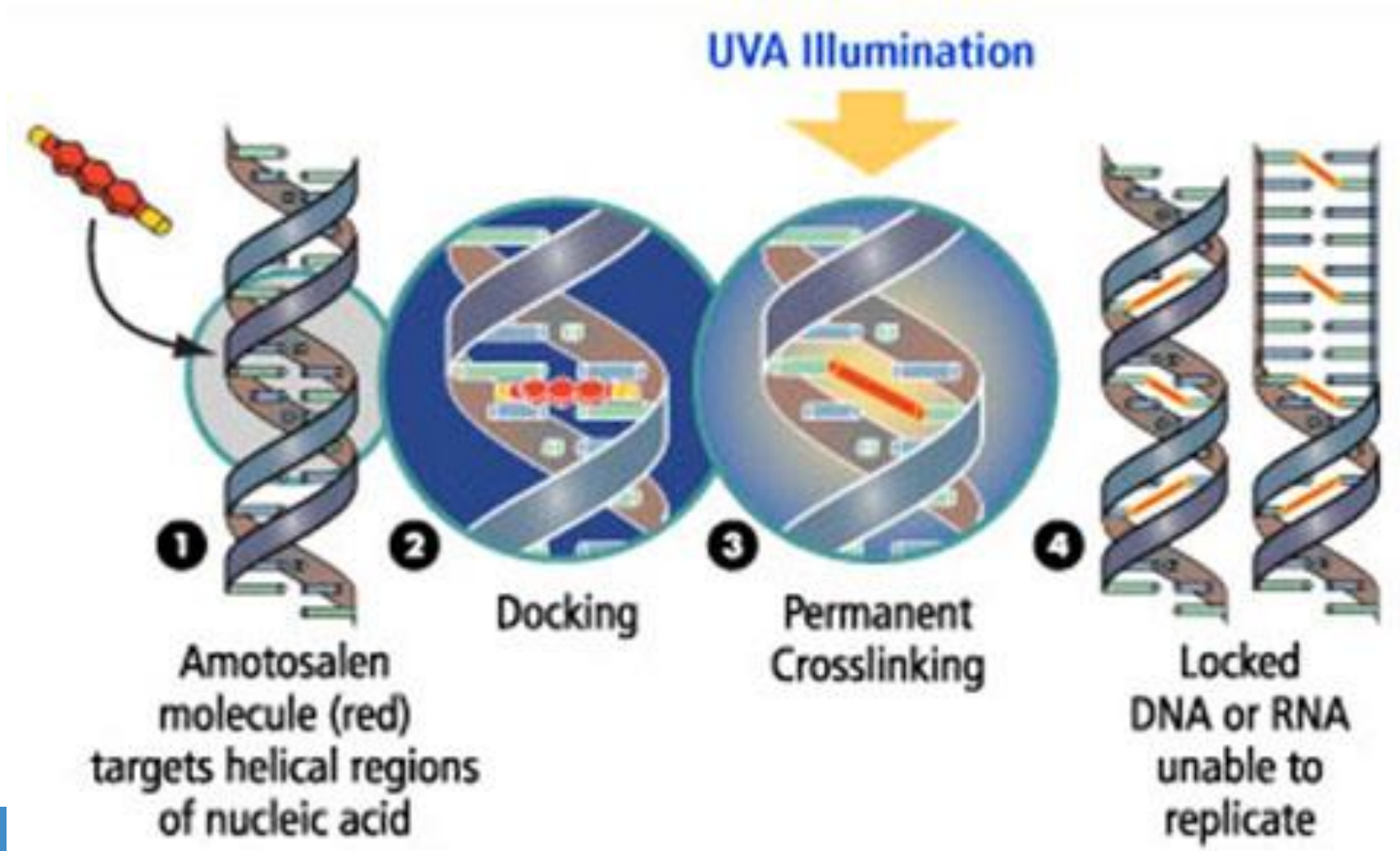


Image courtesyCerus Corp.

Figure 2: The INTERCEPT Blood System for Platelets

Using a sterile connecting device (SCD), the platelet container is sterilely connected to the INTERCEPT kit. Amotosalen (1) is added by gravity flow and the platelet mixture is illuminated with UVA light (2). Residual amotosalen and its photoproducts in the platelet mixture are reduced to low levels using a compound adsorption device (CAD) (3) before the platelets are transferred to the storage container.

Image courtesy of Cerus Corp.

Bacterial Growth Mitigation through Refrigeration

2019: Transfusion

Platelet Enhancement of Bacterial Growth During Room Temperature Storage: Mitigation Through Refrigeration

Ketter PM, et al.

Study:

- Challenged with *Acinetobacter baumanii, Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus, Staphylococcus epidermidis*
- Room temperature showed significant growth as early as Day 1, peaking at Days 3, 4
- Cold storage ablated bacterial growth, limited platelet metabolism and preserved platelet function

Conclusion:

- Data suggest that CSP present an alternative to RT to both extend storage life and reduce the risk of transfusion-related sepsis.

Use of CSP To Extend Inventories

2020: Transfusion

Transition from Room Temperature to Cold-Stored Platelets for the Preservation of Blood Inventories During the COVID-19 Pandemic
Warner MA, et al.

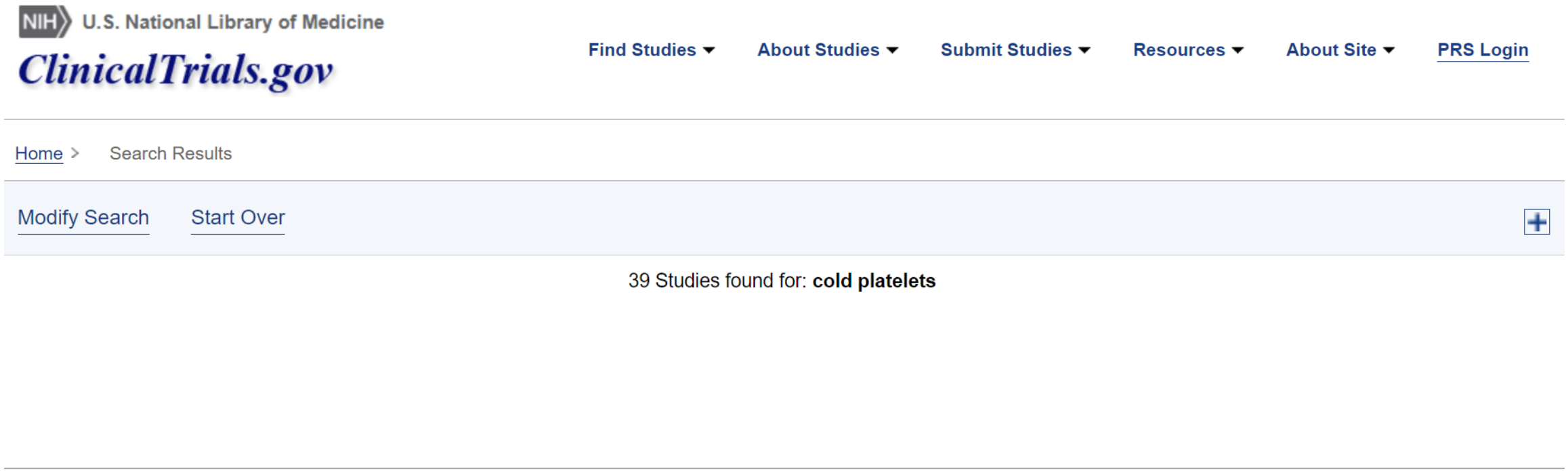
Study:

- Transitioned room temperature platelets to cold storage during period of constrained inventory
- 61 units transfused to 40 bleeding patients (cardiac, vascular, general, transplant surgery)

Conclusion:

- CSP were associated with adequate hemostasis
- No signs of patient harm
- No transfusion reactions

More to Come…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39 Studies found for: cold platelets

CHIlled Platelet Study (CHIPS Trial)

- The American Red Cross is currently manufacturing PR and LVDS-36 cold-stored platelets for the CHIPS clinical trial, led by Drs. Philip C. Spinella, Marie E. Steiner, and Nicole D. Zantek.

- Phase III, multicenter, randomized, double-blinded adaptive, non-inferiority, storage duration-ranging trial in adult and pediatric patients undergoing cardiac surgery that will compare the transfusion cold-stored (4°C) platelets at increasing storage durations to standard room temperature-stored (22°C) platelets.

What does FDA say?

October 2015:

- FDA issued a variance for use of Cold Stored Platelets with shelf-life of 3 days for trauma use only.

August 2019:

- FDA issued a variance for the DOD with shelf-life of 14 days without agitation. Cold stored platelet products will be used to treat actively bleeding patients when conventional platelet products are not available, or their use is not practical.

March 2020:

- FDA granted approval to South Texas Blood & Tissue Center to produce licensed cold stored platelets.
  - Same stipulations as DOD variance.

FDA Status

- The following exceptions or alternative procedures have been approved under 21 CFR 640.120(a) during July 2022 – December 2022.
- 1. 606.65(e)
  - One-time exception to distribute Red Blood Cells, Leukocytes Reduced, Fresh Frozen Plasma and Recovered Frozen Plasma units, that were collected from donors whose hemoglobin was determined using expired microcuvettes.
- 2. 606.65(e) & CFR 610.53(b)
  - To manufacture Apheresis Platelets, Leukocytes Reduced, stored at 1-6 °C for up to 14 days without agitation. The cold stored platelets products will be used to treat actively bleeding patients through day 14 of storage when conventional platelet products are unavailable, or their use is not practical.
- 6. 640.54(a)(2) & 606.65(e)
  - To manufacture Cryoprecipitated AHF and Pooled Cryoprecipitated AHF from Plasma Frozen Within 24 Hours After Phlebotomy (PF24).

June 23, 2023

Alternative Procedures for the Manufacture of Cold-Stored Platelets Intended for the Treatment of Active Bleeding when Conventional Platelets Are Not Available or Their Use Is Not Practical

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Guidance for Industry

This guidance is for immediate implementation.

Current FDA Status

To address the urgent and immediate need for platelets in the U.S., the guidance was issued for immediate implementation in accordance with 21 CFR 10.115(g)(2). FDA has determined that prior public participation is not feasible or appropriate. The guidance gives notice of the following exceptions and alternatives under 21 CFR 640.120(b) now available to all blood establishments:

- Alternative procedures to 21 CFR 610.53(b) and 21 CFR 606.65(e) to permit the storage of apheresis platelets at 1 to 6 degrees Celsius for up to 14 days from the date of collection when such apheresis platelets are intended for the treatment of active bleeding when conventional platelets are not available or their use is not practical.
- Exceptions to the requirements in 21 CFR 640.25(b)(1) and 21 CFR 640.25(b)(3), regarding testing for platelet count and measurement of actual plasma volume, for the manufacture of apheresis platelets stored at 1 to 6 degrees Celsius for up to 14 days from the date of collection, and intended to treat active bleeding when conventional platelets are not available or their use is not practical.

Blood establishments may implement the above exceptions and alternatives without submitting a request to FDA under 21 CFR 640.120(a).

Changes Being Effected in 30 days (CBE30) is required.

Manufacturing

- 100% plasma or FDA-approved PAS.
- If not pathogen reduced, must be in cold (1-6ºC) within 4 hours of end of collection
- If intended for PR must be in cold within 4 hours of end of PR process.
- Maximum storage time is 14 days.
- Agitation is optional (requires refrigerated rotator.)
- Storage temperature range is 1-10ºC.
- If exposed to room-temperature conditions, do not return to cold storage.

Circular of Information

- Update December 2021 COI to include:
  - “CSP are intended for the treatment of active bleeding when conventional platelets are not available, or their use is not practical.”
  - “CSP must be stored continuously at 1-6°C to control the risk of bacterial contamination for up to 14 days”.
  - “Transfusion services should establish procedures for examining CSP for visible aggregates before transfusion.”

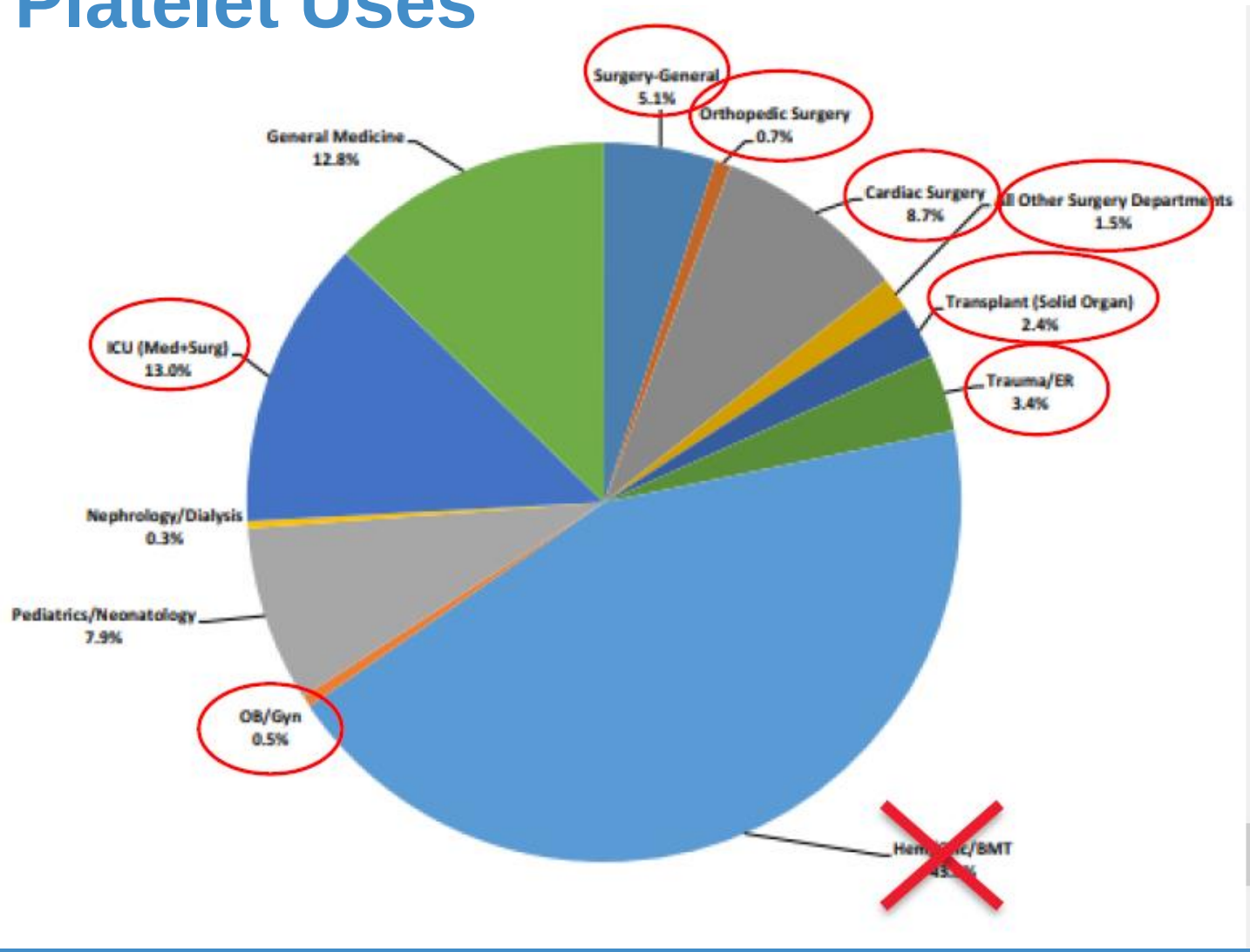
Platelet Uses

Non-Bleeding: (60-70%)

- Hem/Onc
- BMT
- Dialysis

Bleeding: (30-40%)

- Surgery
- Trauma
- OB/Gyn
- ICU



Potential Downside

- Hospitals would be required to keep a dual inventory of Platelet products
- Procedures would have to detail who/what/when

Summary

- Laboratory studies demonstrate superior in vitro hemostatic potential but reduced circulation time
  - Further research underway to:
    - Assess for safety and non-inferiority of CSP compared with RT PLT for the treatment of acute bleeding
    - Determine hemostatic ability in vivo
- Suppresses bacterial growth due to cold storage
- Maintains superior platelet viability during storage
- Extended shelf-life
  - Current variances allow for 14-day storage
    - Enhances platelet availability

ARC Plans

Do we want to produce Cold Stored Platelets? Yes!!

- Longer shelf life: At least 14 days
- Potentially better efficacy for actively bleeding patients
- Improved access to platelets, where they are logistically challenging today
- Enhanced value proposition for customers

Progress

- ARC is supporting the CHIPS trial by providing units to participating hospitals
- ARC is working toward an FDA submission, targeting July
- We plan to offer *Pathogen Reduced* Cold Stored Platelets
  - Non-PR platelets need to be put into the cold within 8-hours, limiting volume and increasing manufacturing complexity
  - Stays consistent with our Pathogen Reduction position and messaging

What's Next?

- Expanded Whole Blood (for Trauma) use
  - Expanded non-trauma Surgical
- Platelet Alternatives
  - Thrombosomes (natural and artificial lipid particles)
  - Long shelf life
  - No preparation necessary (crossmatch)
- Freeze-dried/Spray-dried plasma
  - Shelf stable for years
  - Instant availability (Just add water!)

Thank You

- Any questions?

  - matthew.coleman@redcross.org