INNOVATION

in Blood Banking and Transfusion Medicine

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Definition of Innovation

- Innovation means something more creative than improvement.
- The innovation in blood banking is expected to be the slowest relative to other scientific fields.

- The first proposed title of key lecture: “The development history of blood components, current status and future of blood transfusion”. However, the development of blood components has been too long and the need for such changes is not so great as of now.

- The future direction of research and the development of future technologies in the blood bank.
Contents

• Pathogen Reduction Technologies
• Dried Plasma
• Production of Stem Cell Based Transfusable RBCs
• The Future of Blood Group Matching
• Patient Blood Management
(I) Improving Blood Safety and Availability Through Pathogen Inactivation
Emerging Pathogens

- Emerging pathogens may cause massive disruption of the blood supply by compromising both safety and availability.
Major Emerging and Reemerging Infectious-Disease Outbreaks, Epidemics, and Pandemics, 2002 through 2015
Emerging infectious disease agents and their potential threat to transfusion safety

- 68 infectious agents
- Many are Zoonoses
  - Climate change (global warming)
  - Habitat destruction
- Global travel
- Immigration
- Risk behavior
- Bioterrorism
- Decline public health funding

Stramer et al. Transfusion, 2009: 49:1s-20s
Continual Addition of **Costly** New test

Other pathogens?

Source:
Custer B. Transfusion Medicine Reviews 2009;23(1):1
## Current status of PI

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Technology</th>
<th>Key mechanisms</th>
<th>Transfusion components</th>
<th>Licensing</th>
<th>Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerus</td>
<td>INTERCEPT®</td>
<td>Amotosalen + UVA Light (320-400 nm)</td>
<td>Platelets (apheresis or whole blood-derived)</td>
<td>CE marked (class III) 2002</td>
<td>22</td>
</tr>
<tr>
<td>Cerus</td>
<td>INTERCEPT®</td>
<td>Amotosalen + UVA Light (320-400 nm)</td>
<td>Plasma (apheresis or whole blood-derived)</td>
<td>CE marked (class III) 2006</td>
<td>13</td>
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<tr>
<td>Cerus</td>
<td>INTERCEPT®</td>
<td>S-303 (FRALE)</td>
<td>Red cells</td>
<td>n/a</td>
<td>-</td>
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<tr>
<td>Cerus</td>
<td>INTERCEPT®</td>
<td>S-303 (FRALE)</td>
<td>Whole blood</td>
<td>n/a</td>
<td>-</td>
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<tr>
<td>Terumo BCT</td>
<td>Mirasol®</td>
<td>Riboflavin + UVB Light (280-360 nm)</td>
<td>Platelets (apheresis or whole blood-derived)</td>
<td>CE marked (class IIIB) 2007</td>
<td>18</td>
</tr>
<tr>
<td>Terumo BCT</td>
<td>Mirasol®</td>
<td>Riboflavin + UVB Light (280-360 nm)</td>
<td>Plasma (apheresis or whole blood-derived)</td>
<td>CE marked (class IIIB) 2008</td>
<td>11</td>
</tr>
<tr>
<td>Terumo BCT</td>
<td>Mirasol®</td>
<td>Riboflavin + UVB Light (280-360 nm)</td>
<td>Whole blood</td>
<td>CE marked 2015</td>
<td>-</td>
</tr>
<tr>
<td>Macopharma</td>
<td>THERAFLEX®</td>
<td>UVC light</td>
<td>Platelets (apheresis or whole blood-derived)</td>
<td>CE marked (class IIIB) 2009</td>
<td>-</td>
</tr>
<tr>
<td>Macopharma</td>
<td>THERAFLEX®</td>
<td>Filtration + Methylene Blue + visible light (400-700 nm)</td>
<td>Fresh frozen plasma (apheresis or whole blood-derived)</td>
<td>CE marked (class III) 2004</td>
<td>15</td>
</tr>
<tr>
<td>Octapharma</td>
<td>Octaplas (S/D)</td>
<td>Solvent/Detergent</td>
<td>Large-pool of plasma (apheresis or whole blood-derived)</td>
<td>Licensed (in UK) 1998</td>
<td>32</td>
</tr>
<tr>
<td>VIPS</td>
<td>n/a</td>
<td>Solvent/Detergent</td>
<td>Single donation or mini-pool of plasma (apheresis or whole blood-derived)</td>
<td>CE marked 2009</td>
<td>At least 3</td>
</tr>
<tr>
<td>Vitex</td>
<td>INACTINE</td>
<td>PEN 110</td>
<td>Red cells</td>
<td>n/a</td>
<td>-</td>
</tr>
</tbody>
</table>

Source:
FDA approves INTERCEPT Blood System for Plasma (2014)
PRT using Ultraviolet Light and Riboflavin

Riboflavin + UV Light (UVA and UVB):

- Blood product
- Riboflavin (vitamin B2) solution
- UV Light

- Reduction of viruses, bacteria, parasites
- Inactivation of residual leucocytes

Steps:
1. Transfer WB unit to Illumination bag
2. Add Riboflavin
3. Illuminate
4. Separate into Components

Components:
- RBC unit
- PRP platelet unit
- Plasma unit
Theraflex UV-Platelets system

Hands-on time: 5 min
Total Process time: 8 min

Transfer to Illumination Bag < 1 min Transfer to Storage Bag

Theraflex UV-Platelets process time

Effiziente UV-C-Penetration durch dünne Schichten
Bildung 6-4 Photoprodukten

DNA (vor Bestrahlung)
Optimale UV-C-Exposition unter Agitation
UV-C-induzierte DNA-Schädigung
Dried Plasma is Reemerging, with New Technologies
Need for Dried Plasma

- FDA-approved dried plasma: not yet
- **Historical Products**
  - In WWII, pooled, lyophilized plasma: hepatitis transmission problems
  - In Korean War, but in 1953
  - By 1968, dried pooled plasma was abandoned in the US
  - In 1985, production was discontinued due to the risk of HIV infection
- **Modern Products**
  - French lyophilized plasma (FLYP)
    - In 1994, French resumed dried plasma, incorporating a robust hemovigilance program
    - Universal, minipooled (<11 donors) product, using carefully screened and monitored donors
    - Exclude plasma from women, pathogen reduction (Cerus)
    - In Europe, in America
  - German Red Cross
    - In early 1990 through 2006, SD pathogen reduced pooled lyophilized plasma
    - Since 2009, LyoPlas N-w: a single donor, quarantined lyophilized plasma
  - US DoD (IND application)
    - Lyophilized, single donor, rested plasma product manufactured from individual FFP units
    - Pooled, group AB (universal), S/D-treated, spray dried plasma products (Naval research products)
    - Single donor spray-dried plasma
Dried Plasma Target Characteristics

- **Innovative steps**
  - Balance of safety, efficacy, ease of use, minimal logistics and business case (cost)
  - Spraying dry technique
  - Requires that glass not be used

**TABLE 2. Dried plasma target characteristics**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Developmental threshold</th>
<th>Developmental objective</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA clearance</td>
<td>FDA clearance</td>
<td>FDA clearance</td>
</tr>
<tr>
<td>Efficacy</td>
<td>80% of normalized plasma activity</td>
<td>90% of normalized plasma activity</td>
</tr>
<tr>
<td>Blood group</td>
<td>ABO</td>
<td>Universal</td>
</tr>
<tr>
<td>Final transfusible volume</td>
<td>200 to 250 mL</td>
<td>200 to 250 mL</td>
</tr>
<tr>
<td>Reconstitution time</td>
<td>≤ 6 min</td>
<td>≤ 6 min</td>
</tr>
<tr>
<td>Storage temperature</td>
<td>2–8°C</td>
<td>20–24°C</td>
</tr>
<tr>
<td>Operational temperature</td>
<td>0–40°C</td>
<td>0–40°C</td>
</tr>
<tr>
<td>Shelf-life</td>
<td>1 year</td>
<td>3 years</td>
</tr>
<tr>
<td>Reconstituted shelf-life</td>
<td>24 hr</td>
<td>120 hr</td>
</tr>
<tr>
<td>Product packaging</td>
<td>≤ 48 cubic inches with ruggedized container</td>
<td>≤ 48 cubic inches with ruggedized container</td>
</tr>
</tbody>
</table>

Fig. 1. Unique ruggedized lyophilization, storage, and administration container.

Fig. 2. Packaging concept for the spray-dried, S/D-treated, pooled plasma product. The rehydration fluid is citrate-phosphate buffer, which allows maintenance of levels of coagulation factors to 7 days at 4°C after reconstitution.

Transfusion 2016: 56; s16-s23
Production of Stem Cell Based Transfusable RBCs

The first approach relies on enzymatic conversion of specific blood group antigens, that is, manipulation of the ABO system.

The second approach is to mask antigens by treatment of RBCs with polyethylene glycol.

The third approach involves *in vitro* production of RBCs with a predefined antigenic profile from genetically manipulated stem cells.
Current Trends and Future Areas of Research

- Failure of all previous artificial oxygen carrier studies
  - Perfluorochemicals (PFC)
  - Hemoglobin-based products
  - non-capsule-type hemoglobin
  - encapsulated hemoglobin

Production of RBCs from stem cells
RBC Production from Stem Cells


RBC production from human ESC by Advanced Cell Technology was nominated top 100 new technology by Discover
Differentiation, Enucleation, GMP grade massive production, Preservation

<table>
<thead>
<tr>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 days</td>
<td>7 days</td>
<td>4 days</td>
</tr>
<tr>
<td>SCF+IL-3_FIT3</td>
<td>SCF+IL-3+EPO</td>
<td>EPO</td>
</tr>
</tbody>
</table>

- IMDM 10% FBS
- SCF 5ng/ml
- IL-3 1ng/ml
- Th 1/20 signal
- Lcstimus

- Stempro SF media
- SCF 10ng/ml
- IL-3 1ng/ml
- EPO 6U/ml

- Stempro SF media
- SCF 50ng/ml
- IL-3 1ng/ml
- EPO 3U/ml

- Stempro SF media
- SCF 50ng/ml
- EPO 2U/ml
- FBS 0.05%

- Stempro SF media
- SCF 50ng/ml
- IL-3 1ng/ml
- EPO 3U/ml

- CD34+ cells
- Proerythroblast
- Basophilic normoblast
- Polychromat. n.
- Orthochromat. n.
- Reticulocyte
- Mature RBC

- Transfusion

- CB
- PB
- CD4
- CD45
- CD71
- CD73
- CD90
- CD105
- CD11b
- CD15
- CD34
- CD38
- CD49d
- CD99
- HLA-DR
- CD44
- CD29
- CD54
Erythroid differentiation and amplification

Mesoderm induction and hematopoietic commitment
Hematopoietic differentiation and enrichment
Erythroid differentiation and amplification
Erythroid maturation
Enucleation

Sturgeon CM etc. Nat Biotechnol, 2014)
RhD blood group conversion using transcription activator-like effector nucelases

Diagram of Rh genes. RhD negative status (D−) is mostly due to the complete lack of the RHD gene.
(IV)
The Future of Blood Group Matching

BLOOD GROUP GENOTYPING: THE FUTURE IS NOW
Typing for Blood Group Genes

• Traditionally has been done by phenotyping using serological methods
• Can now be done by genotyping (DNA)
  – PCR-RFLP : single nucleotide polymorphism
  – PCR-SSP or Allele Specific-PCR
  – Real Time PCR
  – DNA Sequencing
  – Microarray
  – Bead Chip Microarray
NGS in Transfusion Medicine

- The first example of NGS-base blood group genotyping: in 2011
- Potential applications of NGS-based blood group genotyping
  - Mass scale screening in donors
  - Find rare, uncommon and null blood units for patients with rare blood phenotypes
  - Enhance antigen matching between donors and multitransfused patients
- Current limitation of blood group genotyping by NGS:
  - Lower throughput
  - Higher error rate NGS technology
  - Continuously in development, has become a powerful means to decipher the genome.
- Evaluating the cost, potency and benefits of NGS technologies for clinical practices is in a large scale study
- Future developments in NGS
  - Contribute to make the gold standard for blood group typing evolve from phenotyping to genotyping
  - Make donor/patient crossmatching by NGS another example of precision medicine
The role of RBC matching

• Level 1 : ABO and RhD (Usual Matching)
• Level 2 : Extended to complete Rh (C,e,E,e) and Kell (K,k) antigen service (Partial Better Matching)
• Level 3 : Duffy(Fy^a,Fy^b), Kidd (Jk^a,Jk^b), MNS (M,N,S,s) (Extend Matching) at Immunohematology Reference Lab
• Level 4 : Do^a, Do^b, Hy, Jo^a, Lutheran(Lu^a, Lu^b)
(V)
Patient Blood Management
Patient Blood Management

Era of personalized medicine
- Personalized medicine
- Tailored medicine
- Precision medicine

1990s - 2000s
- Blood conservation
- Blood management
- Use of blood for improved patient outcome

Personalized Medicine in Transfusion
- Individualized treatment
- Customer/Patient-centered
- Be concerned in quality of life
- Maintain hemoglobin concentration, minimize blood loss, harness & optimize physiologic reserve

Whereas cancer was for many years the singular driver of personalized medicine, other areas are making inroads into this space. [Duke Center for Personalized and Precision Medicine]
The pillars of patient blood management

1st Pillar
Maintain hemoglobin concentration

2nd Pillar
Minimize blood loss

3rd Pillar
Harness & Optimize physiological reserve

Multidisciplinary team approach
Maintain Hemoglobin Concentration

- Identify causes of anemia
- Treat iron deficiency anemia
- Stimulate erythropoiesis

Can be successfully achieved without transfusion

**Circulation.** 2007 Nov 27;116(22):2544-52.

**JAMA.** 2017 May 23;317(20):2097-2104.
Minimize Blood Loss

• Blood-sparing surgical techniques
• Early hemostatsis
• Cell savers
• **Goal (Thromboelastography)-guided transfusion**
• Utilization of pharmacologic/hemostatic agents
Harness & Optimize Physiological Reserve

- Assess patient’s **reserve and risk factors** (cardiovascular disease, elderly orthopedic patients, etc.)

- **Restrictive transfusion** (Hb < 7.0 g/dL) vs **Liberal transfusion** (Hb 8.0-10.0 g/dL)

- Optimize cardiac output and ventilation/oxygenation

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**Table 3.**
Clinical factors that may increase the critical haemoglobin concentration

<table>
<thead>
<tr>
<th>(1)</th>
<th>Reduced oxygen delivery.</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a)</td>
<td>Decreased cardiac output.</td>
</tr>
<tr>
<td>(i)</td>
<td>Pre-morbid disease e.g., ischaemic heart disease, valvular heart disease.</td>
</tr>
<tr>
<td>(ii)</td>
<td>Hypovolaemia e.g., increased capillary leak.</td>
</tr>
<tr>
<td>(iii)</td>
<td>Arrhythmias e.g., atrial fibrillation.</td>
</tr>
<tr>
<td>(iv)</td>
<td>Pulmonary embolism.</td>
</tr>
<tr>
<td>(v)</td>
<td>Specific heart muscle disease e.g., systemic inflammatory response syndrome (SIRS) related cardiomyopathy.</td>
</tr>
<tr>
<td>(b)</td>
<td>Hypoxaemia secondary to acute respiratory failure.</td>
</tr>
<tr>
<td>(c)</td>
<td>Acute lung injury (ALI)/Acute respiratory distress syndrome (ARDS).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(2)</th>
<th>Increased oxygen consumption.</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a)</td>
<td>Pain, stress, anxiety.</td>
</tr>
<tr>
<td>(b)</td>
<td>Shivering.</td>
</tr>
<tr>
<td>(c)</td>
<td>Fever.</td>
</tr>
<tr>
<td>(d)</td>
<td>Severe infection.</td>
</tr>
<tr>
<td>(e)</td>
<td>Sepsis/Systemic inflammatory response syndrome (SIRS).</td>
</tr>
<tr>
<td>(f)</td>
<td>Trauma.</td>
</tr>
<tr>
<td>(g)</td>
<td>Surgery.</td>
</tr>
<tr>
<td>(h)</td>
<td>Burns.</td>
</tr>
<tr>
<td>(i)</td>
<td>Adrenergic drug infusions.</td>
</tr>
<tr>
<td>(j)</td>
<td>Work of breathing e.g., during weaning.</td>
</tr>
<tr>
<td>(k)</td>
<td>Convulsions.</td>
</tr>
</tbody>
</table>
What Lies Ahead: The Global View

• The promising benefits of PBM strategies will be increasingly viewed and adopted by clinicians
• It will be promoted and supported by the regulatory bodies as a standard of care for all patients
• The patient-centered approach for the best clinical outcome will be provided in transfusion medicine
• PBM will most plausibly become implemented on a national level through education and reimbursement.
Summary

Western Desert, Egypt, 1940

Blood Program in the Korean War

Severance Hospital Blood Bank