DETERMINATION OF SUITABILITY OF RBCS FOR TRANSFUSION AND ANIMAL MODELS FOR SHOCK/TRAUMA

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CONFERENCE GOAL

- Inform FDA/CBER on potential alternative criteria to license RBC storage solutions since the current approach does not account for direct measures of efficacy or toxicity.
  - Need to understand transfused RBC physiology
  - Explore candidate measures of RBC efficacy and toxicity
    - Develop panels of measures with metabolomics and systems biology principles
  - Test RBC quality measures in animal models for validation
    - Small then large animals
  - Develop appropriate RBC transfusion indications for clinical trial methodology
  - Perform trials to assess if RBC quality metrics are surrogates for clinical outcomes.
    - Trials in large animals or humans
    - Trials in multiple disease states
      - RBC quality panels may be different according to disease state
CONFERENCE GOAL

- Seems daunting and perhaps impossible due to complexity and interactions between
  - Donor variability
  - Collection
  - Processing
  - Storage conditions
  - Patient conditions

- Will never be perfect

- MUST MUST MUST improve RBC licensing criteria past current standards

- A little better is better than nothing at all

- Incremental improvements are valuable
INFLUENCE OF TRANSFUSED RBC PHYSIOLOGY UPON RECIPIENT OXYGEN DELIVERY

- ALLAN DOCTOR, MD

- RBCs comprise a key node in regulation of $O_2$ delivery
  - Match regional blood flow and tissue respiration
  - Stored RBCs strongly influence vasoregulation and paradoxically, in certain circumstances may impair $O_2$ delivery homeostasis

- Transfusion Decision Making (and ability to study transfusion efficacy) requires precise understanding of:
  - Anemia tolerance (physiologic reserve, supply dependency, specific vital organ threats)
  - Illness trajectory & likelihood of transfusion harms
  - Sequencing of transfusion with other interventions supporting $O_2$ delivery
  - Ability to monitor $O_2$ delivery (components) as well as the dynamic reflexes that comprise homeostasis
Conceptual Evolution: Hormesis & Salutary effects of Anemia?

metabolic response to diminished $O_2$ delivery improves resilience to other physiologic challenges (preconditioning)
RELATIONSHIP BETWEEN BLOOD FLOW, [HB] AND O$_2$ DELIVERY

BLOOD FLOW, NOT O$_2$ CONTENT, IS THE PRINCIPLE DETERMINANT OF O$_2$ DELIVERY

Erzurum. PNAS 2007;104:17593-17598.
INSIGHTS INTO RED CELL QUALITY A CENTURY OF ANALYSIS

JIM ZIMRING, MD, PHD

- Survival and Recovery and hemolysis measures are suboptimal metrics for efficacy and safety of RBC units
  - Don’t reflect actual efficacy
  - Partial safety analysis

- RBCs need to remain in circulation to deliver oxygen – yes

- Remaining in circulation does not mean they deliver oxygen

- Attention on what predicts “Good vs poor storers”
  - May be misguided
  - Don’t know if the good storers have more efficacious RBCs.
INSIGHTS INTO RED CELL QUALITY A CENTURY OF ANALYSIS

JIM ZIMRING, MD, PHD

- Different patient disease states may require different panel of RBC quality metrics
  - Hemorrhagic shock
  - Septic Shock
  - Hypoproliferative anemia
  - Chronic anemia-hemoglobinopathies
FDA EVALUATION OF RED CELL PRODUCTS
JARO VOSTAL, MD, PHD

- Current process is designed to evaluate red cell products that are similar to conventional red cell products-
  - need to expand process to better evaluate very novel RBC products

- In vitro studies are not predictive of clinical performance-
  - need better pre-clinical tests that correlate with clinical outcomes

- In vivo studies are focused on red cell kinetics in circulation but not on oxygen delivery
  - need pre-clinical and clinical methods to evaluate oxygen delivery (in vitro tests and validated animal models)
CLINICAL USE OF RBCS FOR TRANSFUSION
JOHN HESS, MD, MPH, FACP, FAAAS

- RBC Transfusion is decreasing
  - Moving from “just in case to just in time”
- Demographic bind
  - 50% of RBC use for > 65 years of age, this population will double from 2000 to 2025
- Increased plasma and platelet use has reduced RBC transfusion in severe bleeding
- RBCs, plasma, and whole blood now being used prehospital in few large trauma programs
Donor variability in survival and recovery of RBCs

RBC processing also causes variability in survival and recovery of RBCs
  - Irradiation, Frozen, standard RBCs

- RBC licensing criteria should provide a reasonable level of assurance of RBC efficacy and safety
- Current evaluation criteria, though somewhat arbitrary, have served us well – changes should be evidence-based
- Biomarkers should reflect RBC function and clinical outcomes
- Assays should be reproducible and methods standardized
- The ideal evaluation criteria and the appropriate statistical treatment are neither identified nor obvious (or they would have been adopted years ago)
PREDICTIVE CLINICAL VALUE OF IN VITRO MEASURES OF RED CELL QUALITY

JASON ACKER, PHD

- RBC units should not be treated as if they are all the same

- Quality metrics
  - Biochemical
    - ATP, 2,3 DPG, lipodmic, metabolomic profiles, oxidative injury markers
  - Biophysical
    - Deformability, osmotic fragility, hemolysis
  - Unit characteristics
    - Hb, volume, residual WBCs, etc...

- RBC quality metrics affected by
  - Donor characteristics
  - Collection and processing methods
  - Storage conditions
  - Recipient characteristics

- Need to determine which RBC quality metrics will affect patient outcomes
SWINE MODELS FOR SHOCK/TRAUMA
MIKE DUBICK, PHD, FCCM, FACN

- Swine models are primary models used for trauma-hemorrhage studies
  - Hemodynamic similarity to humans
  - More hypercoagulable compared to humans
  - Reproducible models between centers
  - Transgenic swine may allow for human RBC transfusion
NON-HUMAN PRIMATE TRANSFUSION MODELS
SYLVAIN CARDIN, PHD

- Rhesus Macaques
  - Phylogeny – except ape species closest to humans
  - Extremely high protein homology to include coagulation proteins
  - Xenocompatibility: human products accepted in macaques
  - Hemodynamics, hemostasis, immune response very similar to humans
- Limitations
  - Regulatory scrutiny – high
  - Logistic burden on animal lab staff - high
  - Cost- high
GAPS AND FUTURE DIRECTIONS

- Start with low hanging fruit
  - Prohibit cherry picking in licensing studies

- Identify most likely **candidate surrogate measures** of efficacy and toxicity

- Perform **small animal study** to determine which panel RBC quality metrics are associated with oxygen delivery or toxicity

- Test the panel of RBC quality metrics in **large animal models** to determine if RBC quality panel improves oxygen delivery, reduces toxicity, improves outcomes
  - Trauma-hemorrhage
  - Sepsis
  - Hypoproliferative anemia

- Surrogates markers that correlate highly with outcomes can be considered as FDA licensing criteria.

- Animal model studies could also be required for licensing
GAPs AND FUTURE DIRECTIONS

- Whole blood licensing
  - Whole blood use is increasing across the US for hemorrhagic shock
  - New methods of storing/processing are being developed
  - Platelet function not circulation time

- Whole blood availability is increasing
  - Group O whole blood has been permitted by AABB as universal donor
    - Safer than ABO compatible products
  - Storage to 14-21 days at 4C has superior hemostatic function vs platelets at 22C to 5 days
    - In vitro studies
  - Clinical program use is exploding
    - Pittsburgh, Mayo clinic, Kentucky, Camden NJ
    - San Antonio and Houston coming on line soon.
IF NEW CRITERIA IS DEVELOPED......

- Should previously licensed products be required to meet new criteria
- Is it appropriate to hold new products to one standard when products in clinical use have been held to a different standard??