

The Science & Speculations of TRALI

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Critical Care

Research Group

Why? How? What?

- 1. seeds of the hypothesis**
- 2. proposed mechanism**
- 3. current evidence**

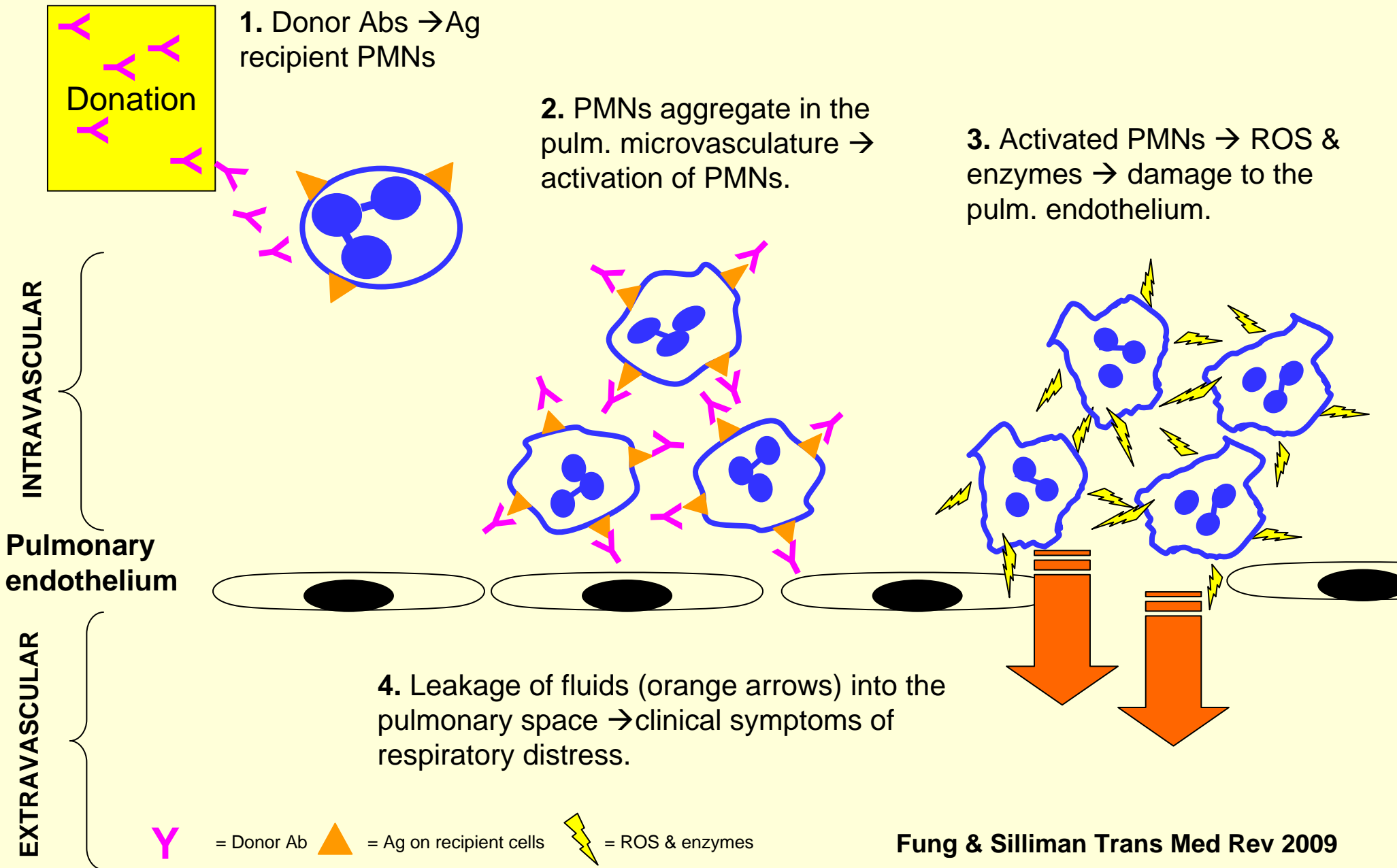
Seeds of: Ab hypothesis

- 5 cases all had leukoagglutinating or lymphocytotoxic Ab
(*Popovsky et al 1983 Am Rev Resp Disease*)
- 36 cases,
89% donor leukocyte Ab (HLA or HNA)
(*Popovsky et al 1985 Transfusion*)

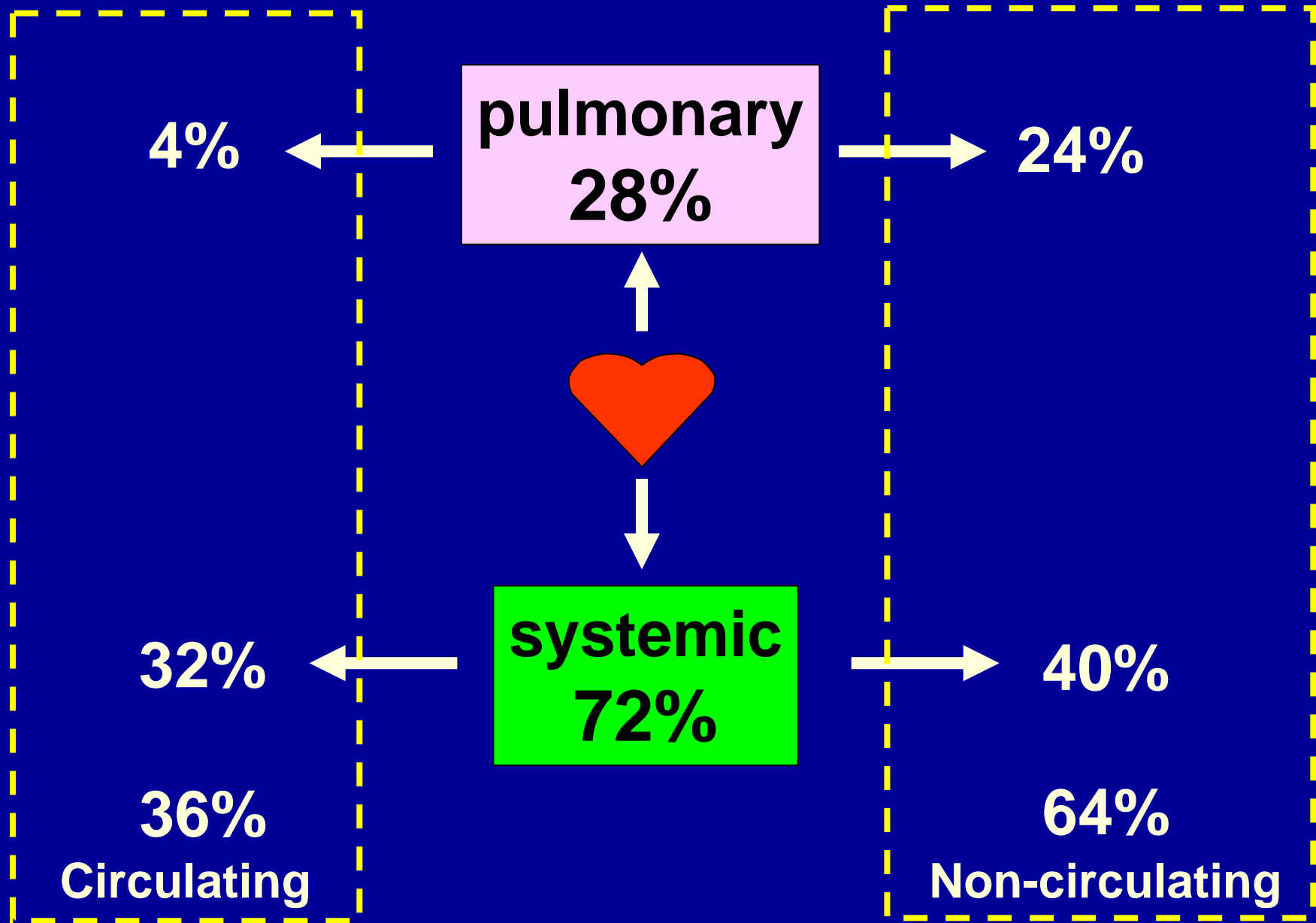
1st hypothesis

**Ab mediated
or Immune**

Antibody Mediated TRALI



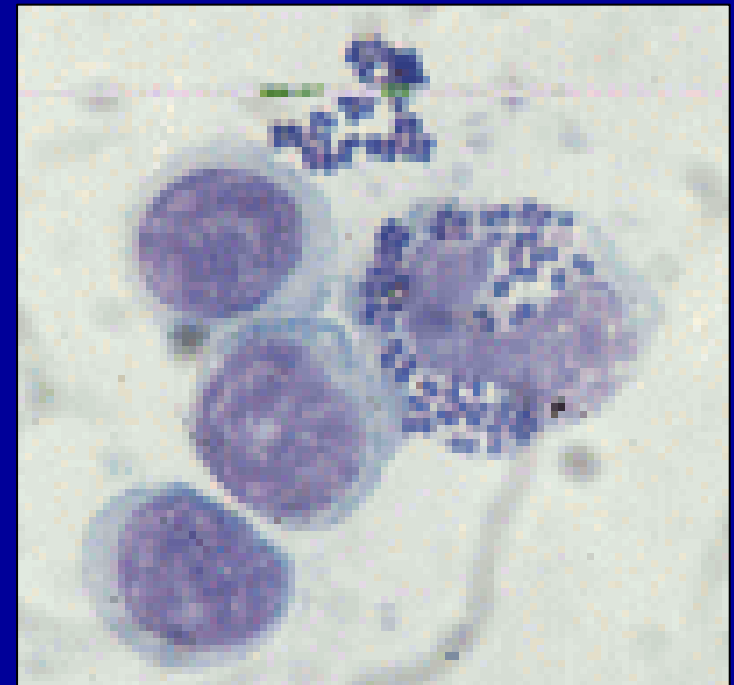
Neutrophils (PMNs) Distribution



Neutrophil Function

Innate immunity

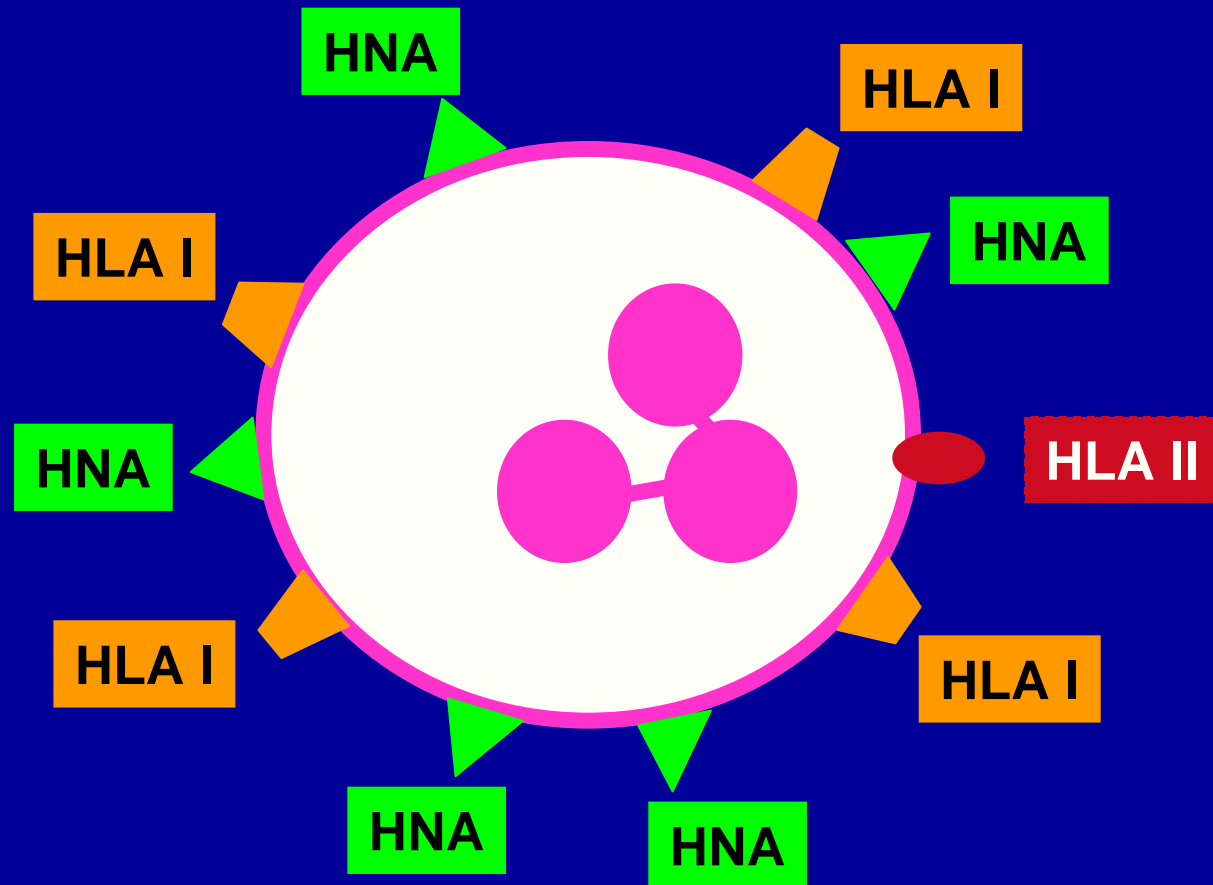
- Migrate to site
- Phagocytise & destroy pathogens by
 - release of enzymes from intracellular granules
 - release of oxygen radicals
- Control infection



Antigens on Neutrophils

HNA = Human Neutrophil Antigen

HNA - 1a
- 1b
- 1c
HNA - 2a
HNA - 3a
- 3b
HNA - 4a
HNA - 5a



Ab associated with TRALI

Ab in donations

- HNA-3a (5b) (*Nordhagen 1986, Vox Sang, Daveron 2002, Kopko 2004, Ganguly 2004*)
- HNA-2a (*Van Buren 1990, Bux 1996*)
- HLA-B35 (*Eastlund 1985*)
- HLA-A2 (*Jensen 1990, Bux 1996, Leach 1998, Win 2001, Kopko 2004*)
- HLA-DR (*Flesch 2002, Kopko 2003, Nishimura 2003*)

1.

Screen for leukocyte Ab?

Does the patient have PMN Ab's?

Do the donations have PMN Ab's?

Screen patient & donations for Ab using:
GIFT & GAT for HNA & HLA
HLA class I & II (LCT, ELISA, flow, luminex)

Any Ab detected → ASSOCIATED

BUT are the Ab IMPLICATED ?

2.

How do we confirm an Ab is IMPLICATED?

Does the patient's leukocyte have the cognate Ag?
(phenotyping or genotyping)
→ the Ab has a potential target



Seeds of : 2 event hypothesis

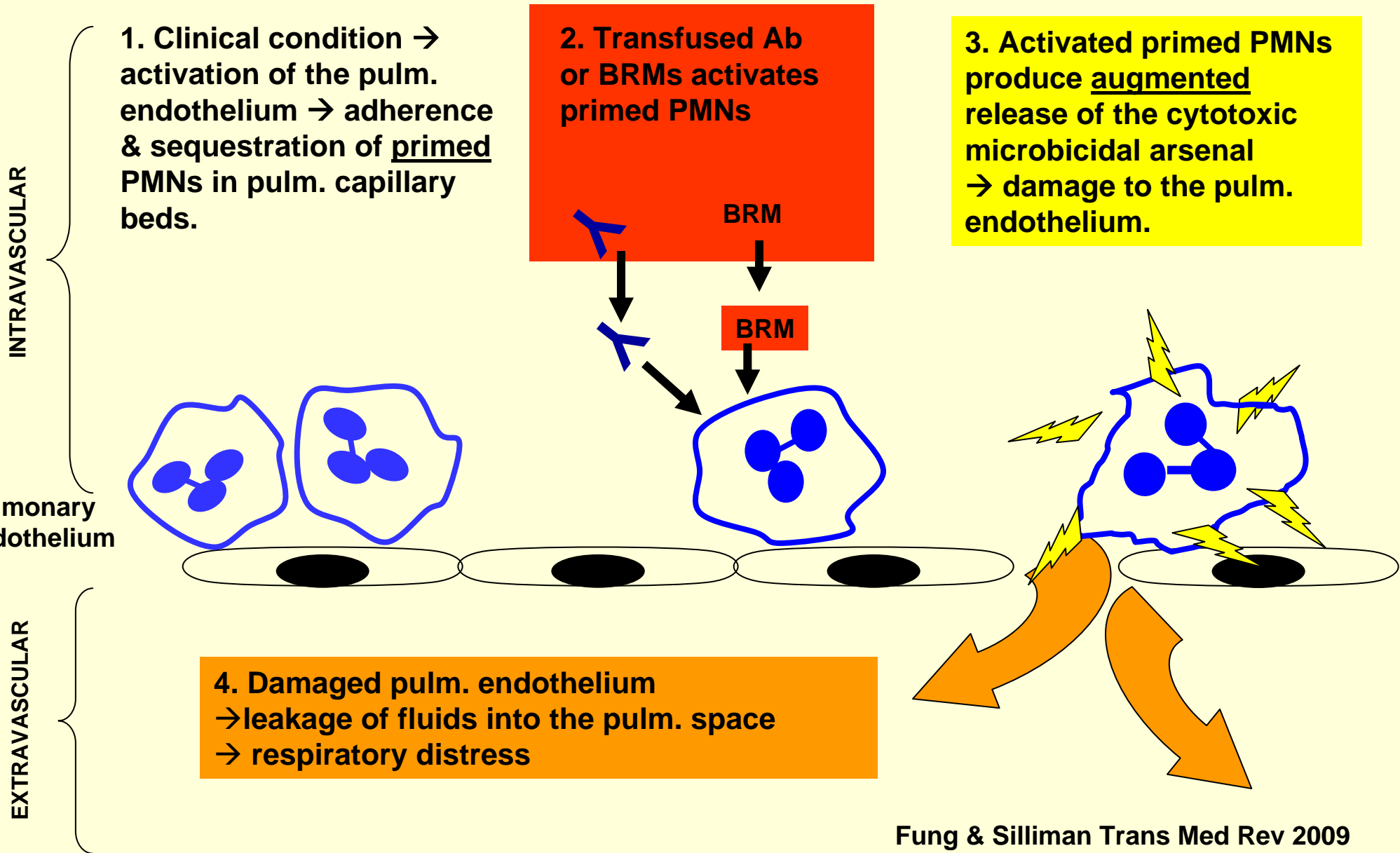
- TRALI cases have no leukocyte Ab
- Why do leukocyte Ab cause TRALI in some patients & not others?

- TRALI clinically identical to ARDS
- Only the sick (priming event) get transfused (2nd event)

2nd hypothesis

**2 event or
priming**

2. Priming or 2 Event Mechanism



Priming refers to the process whereby the PMNs response to an activating stimulus is potentiated.

Effects of priming

a.Reduced deformability

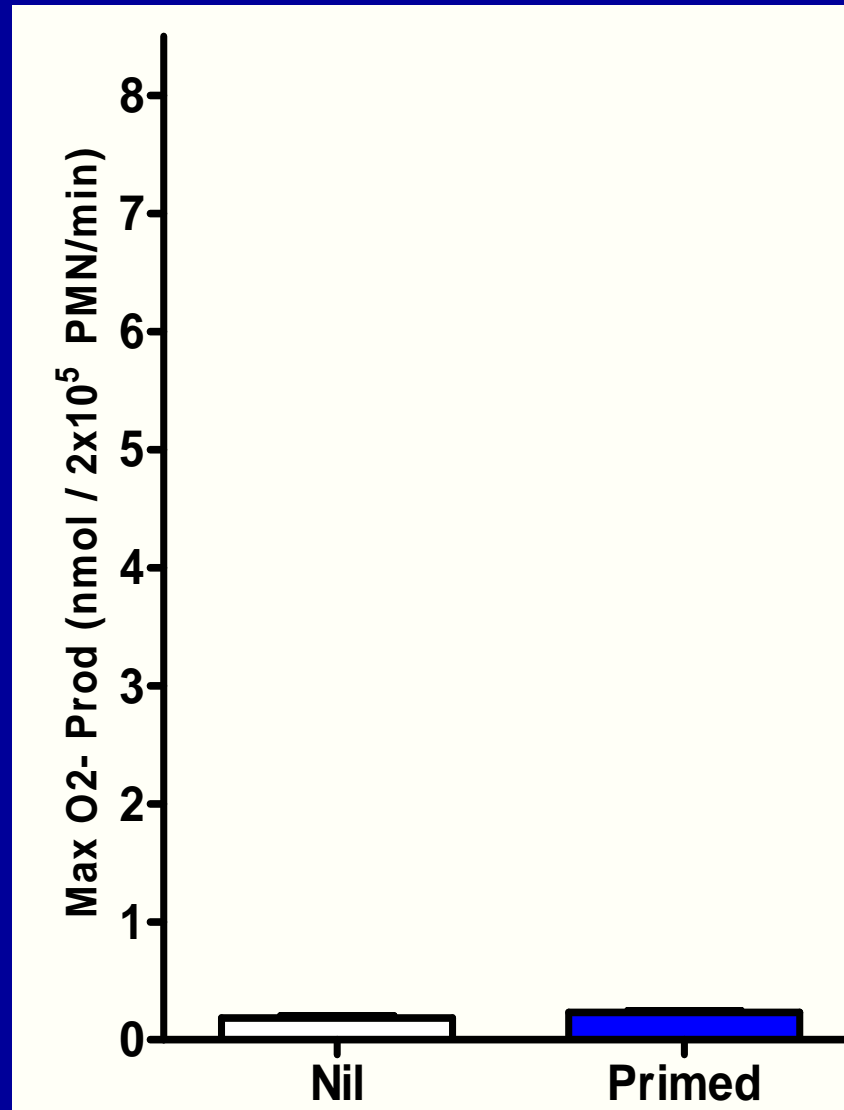
b.Delayed apoptosis

c.Augmented respiratory burst

d.Changes in surface molecule expression

e.Is reversible

c. Priming - augments respiratory burst



Evidence for: non-immune insult

- Stored blood components contain agents that prime PMN (*Silliman et al 1992 Vox Sang*)
- Lipids generated during storage of platelets prime PMNs (*Silliman et al 1996 Transfusion*)
- Stored RBC activate human PMN (*Zallen et al 2000 Shock*)
- Plasma from stored PRBC delay PMN apoptosis & primes for cytotoxicity (*Biffi et al 2001 J Trauma*)
- sCD40L in stored blood primes neutrophil (*Khan 2006 Blood*)

Animal models of TRALI

Animal models of TRALI

Ex-vivo

**isolated and perfused
animal lung**

**transfusion of human
neutrophils and anti-
neutrophil Ab**

rabbits



rats



dogs



baboons



Ex-vivo

RABBIT (*Seeger et al Blood 1990*)

human PMN + anti-HNA3a + C' → rise vas. permeability



**2 event
mechanism**

In-vivo

MOUSE

(Looney et al JCI 2006 & 2009)

+ MAb → ALI & high mortality



2 event

Critical Care Research Group, The Prince Charles Hospital

Australian Red Cross Blood Service

University of Queensland



John-Paul TUNG
PhD Candidate

Ovine (large animal) 2 event model of TRALI



**Tung, J. et al. (2009 HAA meeting, Transfusion Medicine)
(manuscript under review)**

1 st event + 2 nd event	n	oedema	hypoxemia	TRALI	
				pos	%
saline + saline	3	1	0	0	0%
saline + d1-PLT-S/N	3	2	1	1	33%
saline + d5-PLT-S/N	3	2	0	0	0%

1st. In-vivo 2 event large animal TRALI model
1st. Whole blood platelet

Do lymphocytes have a role in the pathogenesis of TRALI?

BALB/c or **CB.17 SCID** mice



Rectal temps → shock

30' 60' 90' 120'

34-1-2s iv
(10ug, 50ug, 100ug
200ug or 500ug)

120min

•% Pulmonary PMN counts (cytospin)

•Wet/Dry Lung Ratio → measure of edema

•Morbidity/mortality

Fung et al. (ASH 2009 Annual Meeting Abstracts) Blood 114:641

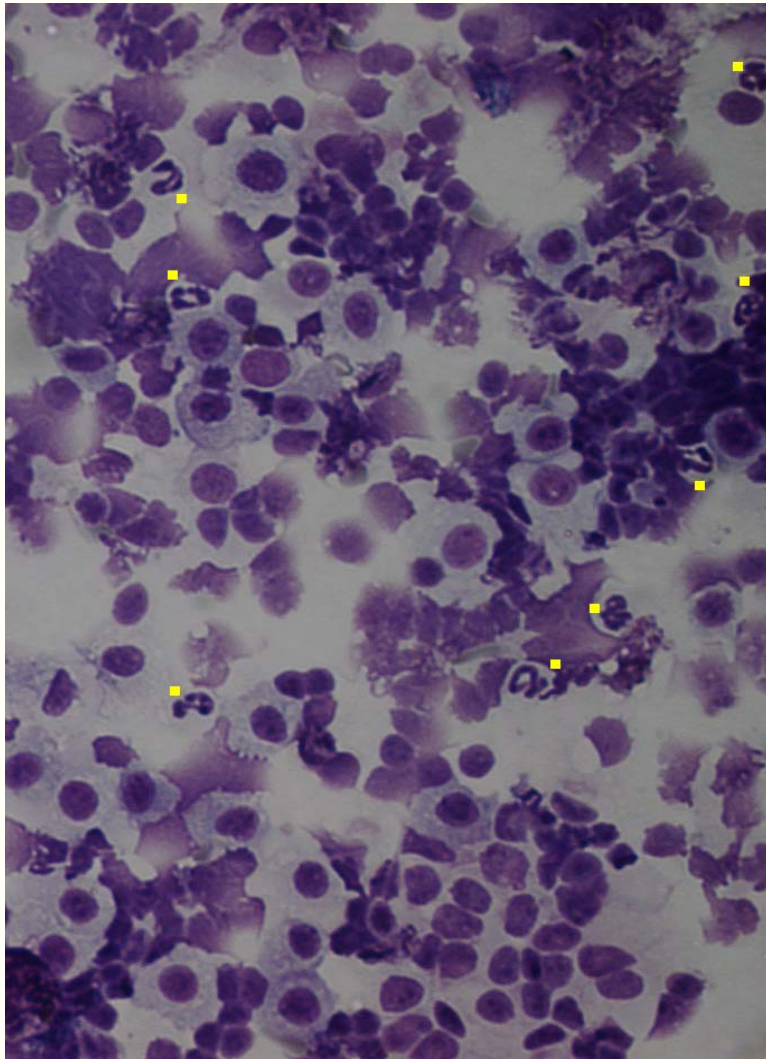


Leading with Innovation
Serving with Compassion

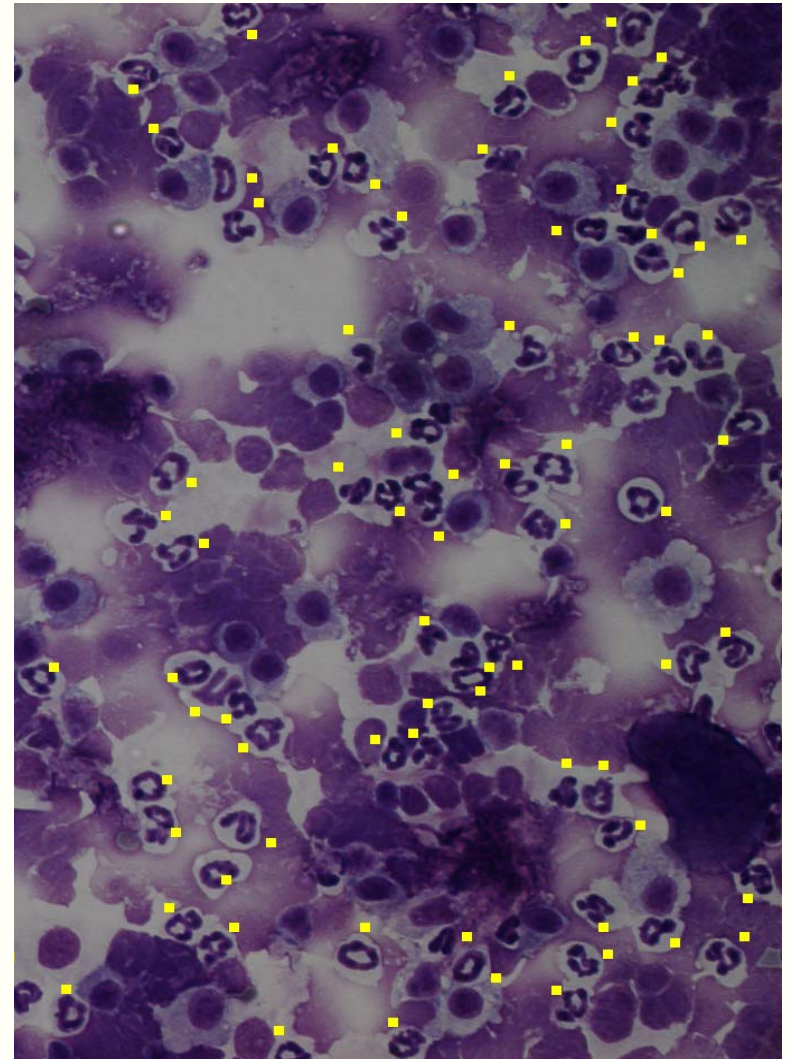
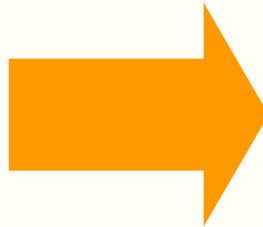
ST. MICHAEL'S HOSPITAL

A teaching hospital affiliated with the University of Toronto

SCID + 100ug 34-1-2s

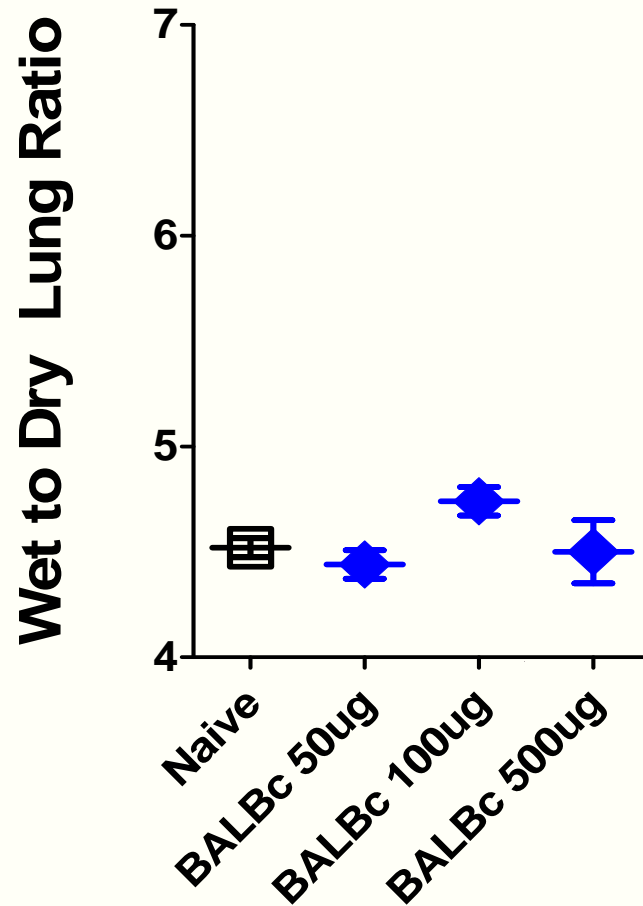


5min post



60min post

34-1-2s induced ALI in SCID



Mouse TRALI Summary

	BALBc	SCID
Pulmonary PMN accumulation	Yes	Yes
Hypothermia	++	++++
ALI (wet to dry lung ratio)	No	Yes
Mortality	0%	20-40%

(Fung et al Manuscript under review 2010)

Lessons from TRALI

TRALI = serious complication of transfusion

hypothesised mechanisms

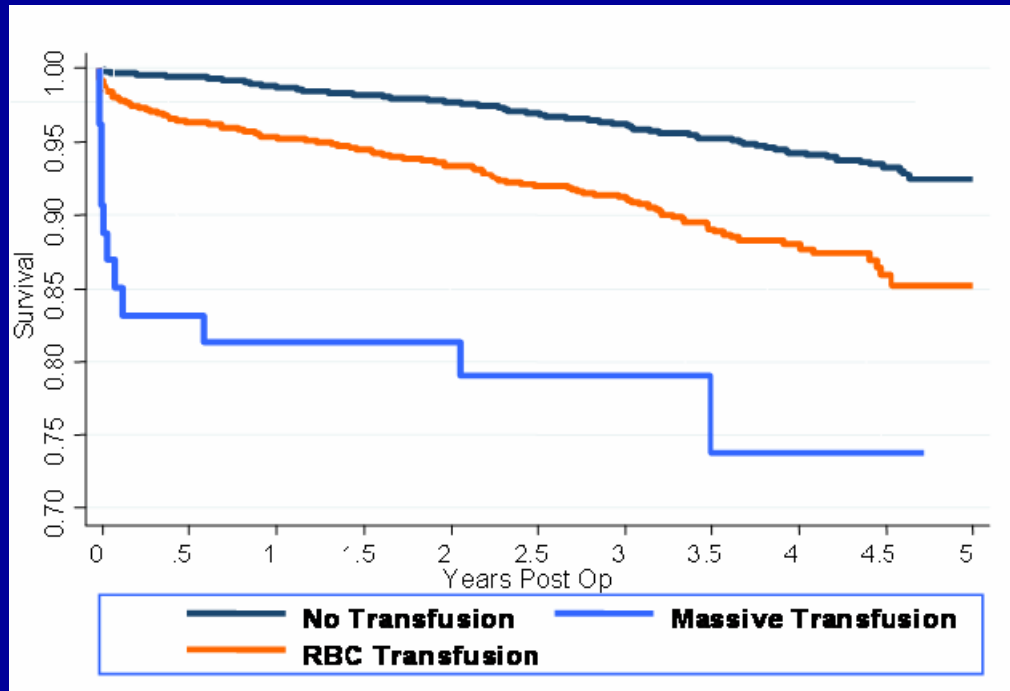
i) Ab mediated

ii) 2 event ★★ ★

Scientific evidence:

Case reports → *In-vitro* → *Ex-vivo* → *In-vivo*

questions from TRALI



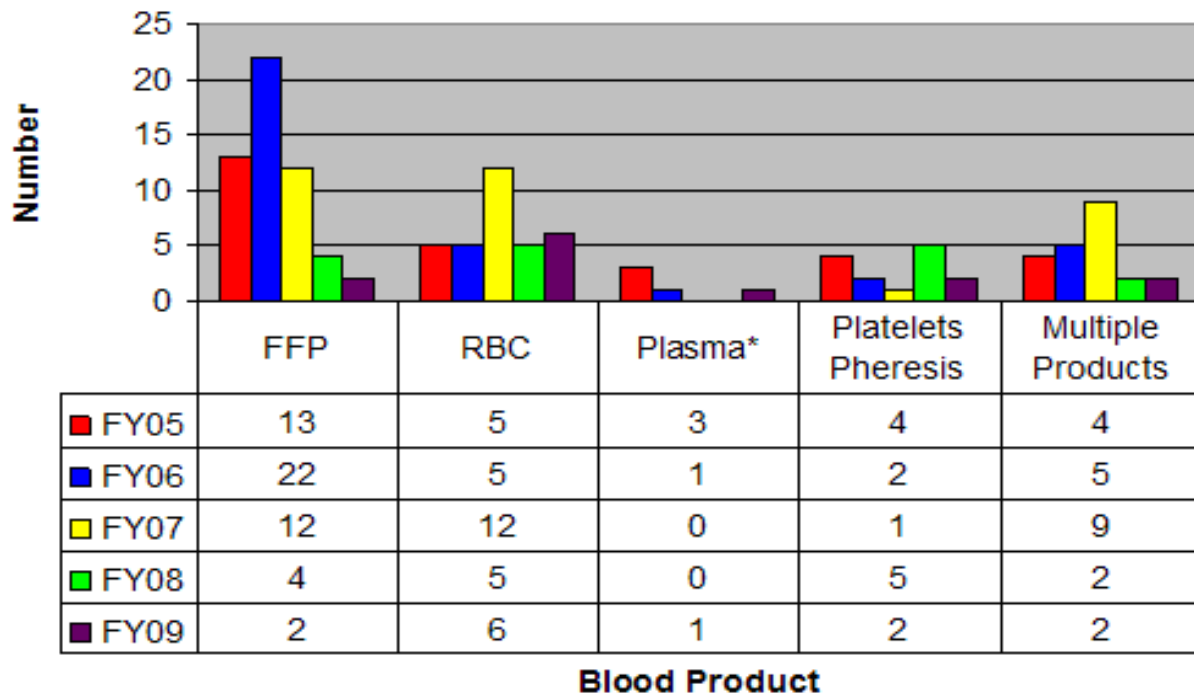
Balu B et al Long term survival after cardiac surgery (2010 Manuscript in press)

questions from TRALI

BLOOD PRODUCTS

i) Leukocyte Ab in plasma

- Associated or implicated
- Why do some Ab cause TRALI & other Ab do not?



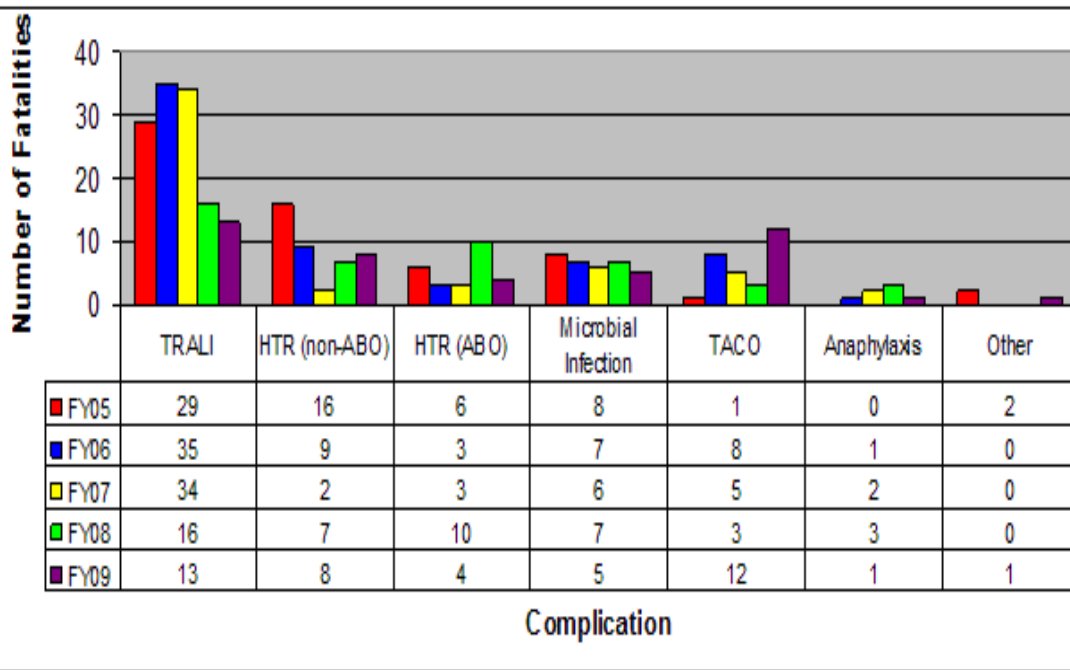


Figure 1: Transfusion-Related Fatalities by Complication, FY2005 through FY2009

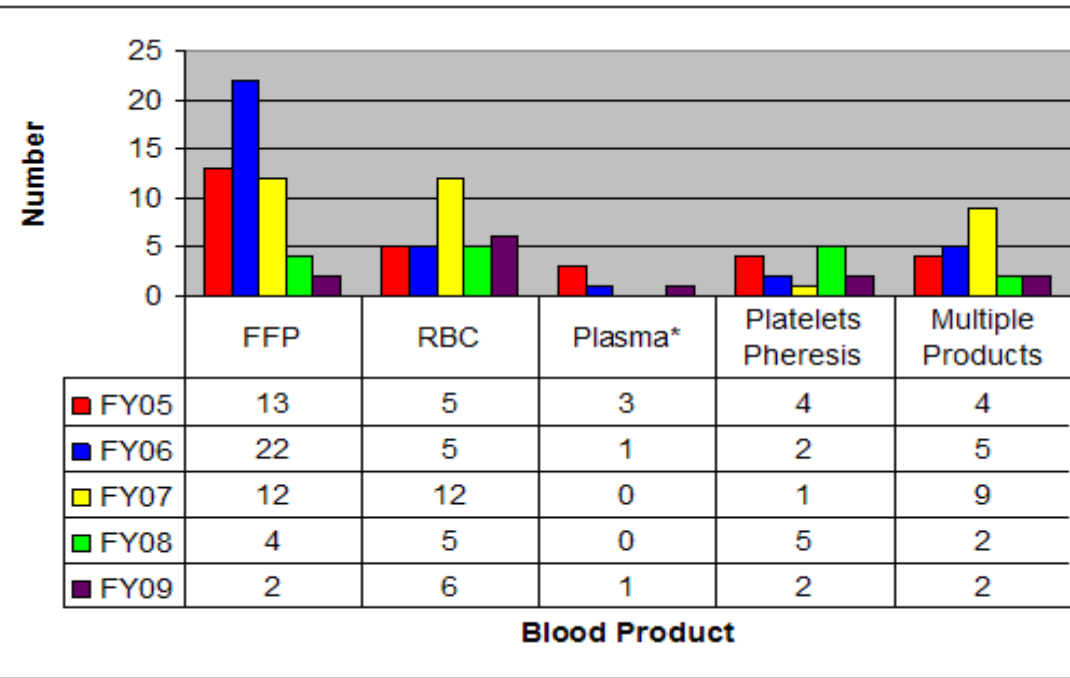


Figure 2: Reports of TRALI by Implicated Blood Product, FY2005 through FY2008