Red blood cell alloimmunization and delayed hemolytic transfusion reactions in patients with sickle cell disease

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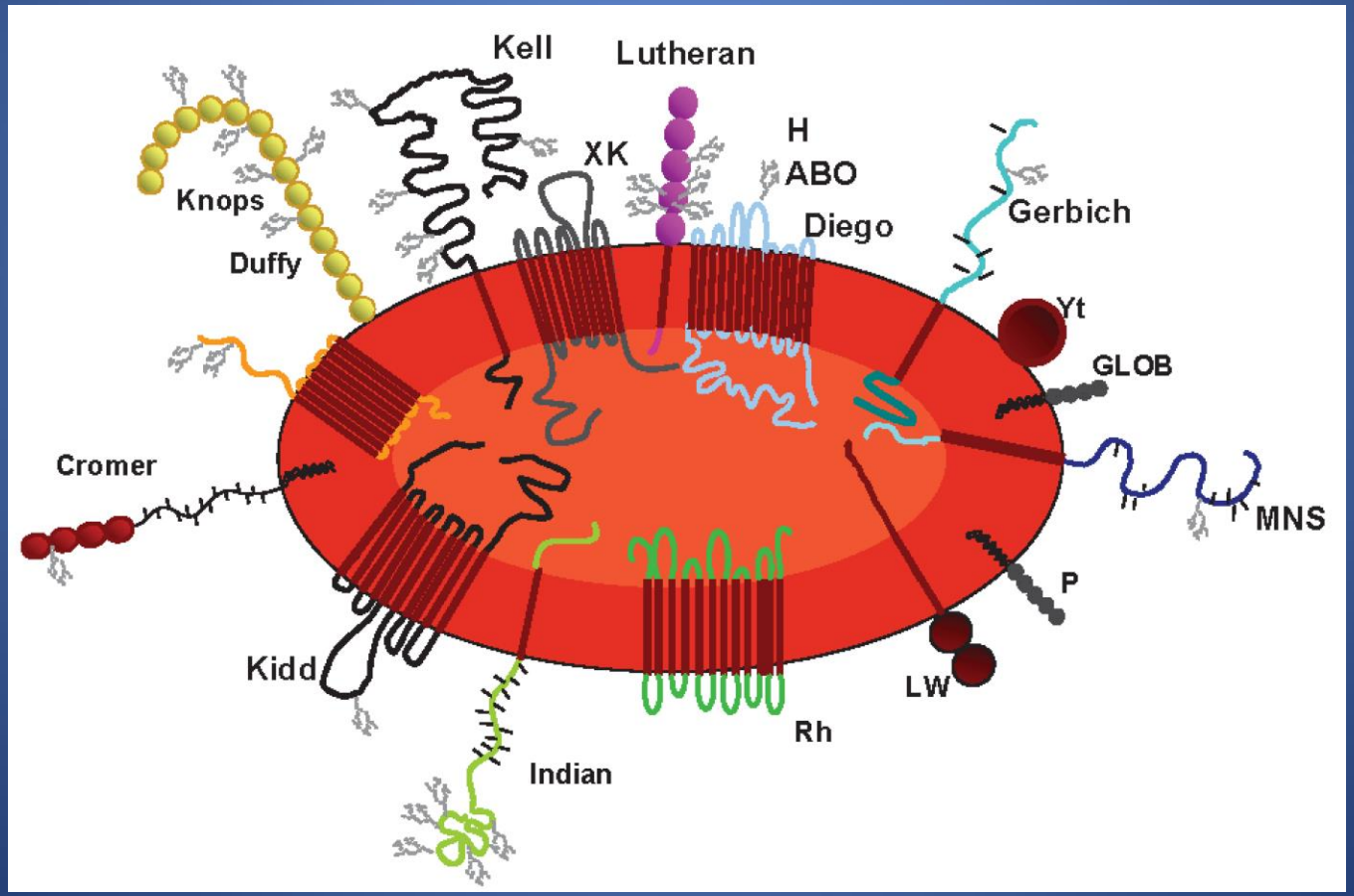
December 17, 2018

RBC Alloimmunization

- Occurs after exposure to non-self blood group antigens, through RBC transfusion, IV drug use, or pregnancy



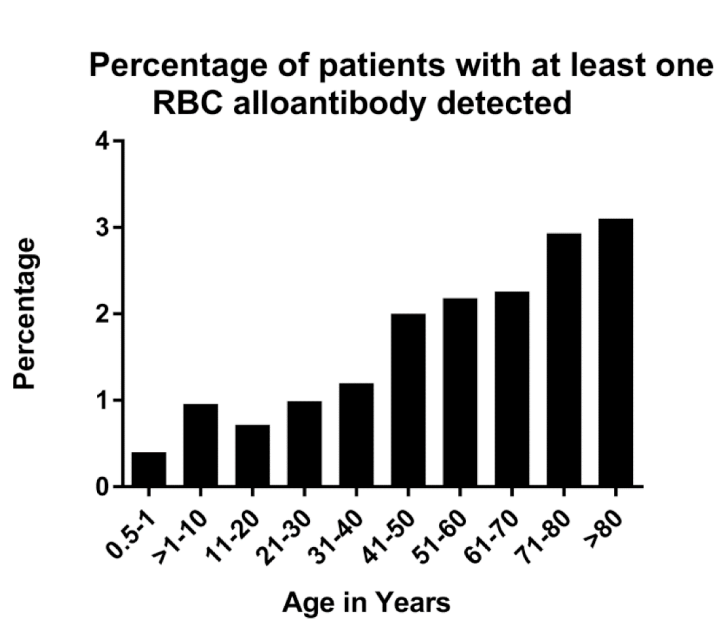
Adapted from E. Sjöberg Webster, reproduced by Tormey et al, Blood 2018 in preparation

RBC Alloimmunization

- Increases the risk of immediate as well as delayed hemolytic transfusion reactions
- May lead to lengthy and costly blood product delays
- Increases the risk of hemolytic disease of the newborn

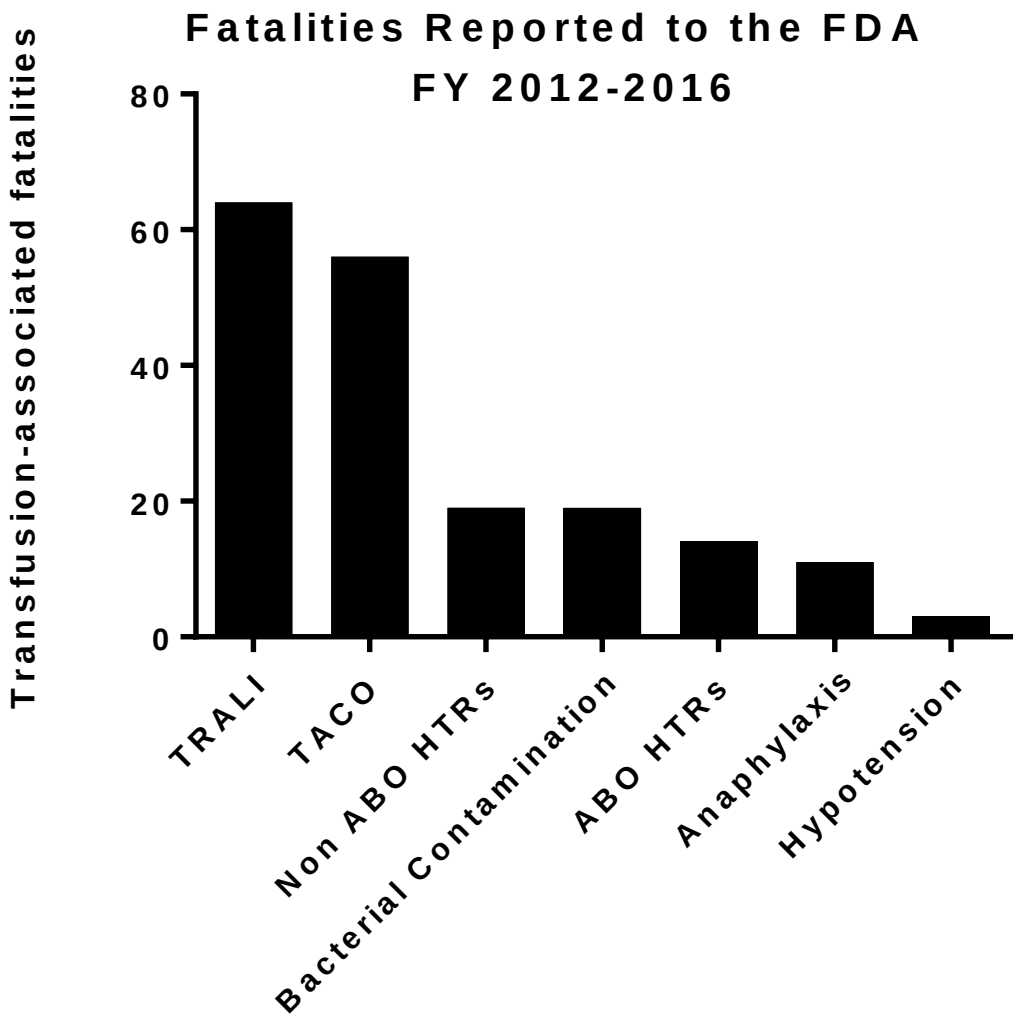
RBC Alloimmunization

- Occurs in approximately 3-5% of "general" transfused adults



REDS-III Recipient Database, with 6,597 alloimmunized patients

Karafin et al, BJH 2018



Antibodies associated with fatalities: anti-Jk^{a}, -Jk^{b}, -K, -E, -c, -C, -Fy^{a}, -Fy^{b}, -S, -Co^{b}, -M, and others (including 2 reactions with hyperhemolysis)

http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ReportaProblem/TransfusionDonationFatalities/default.htm

Dangers of Delayed Hemolytic Transfusion Reactions (DHTRs)

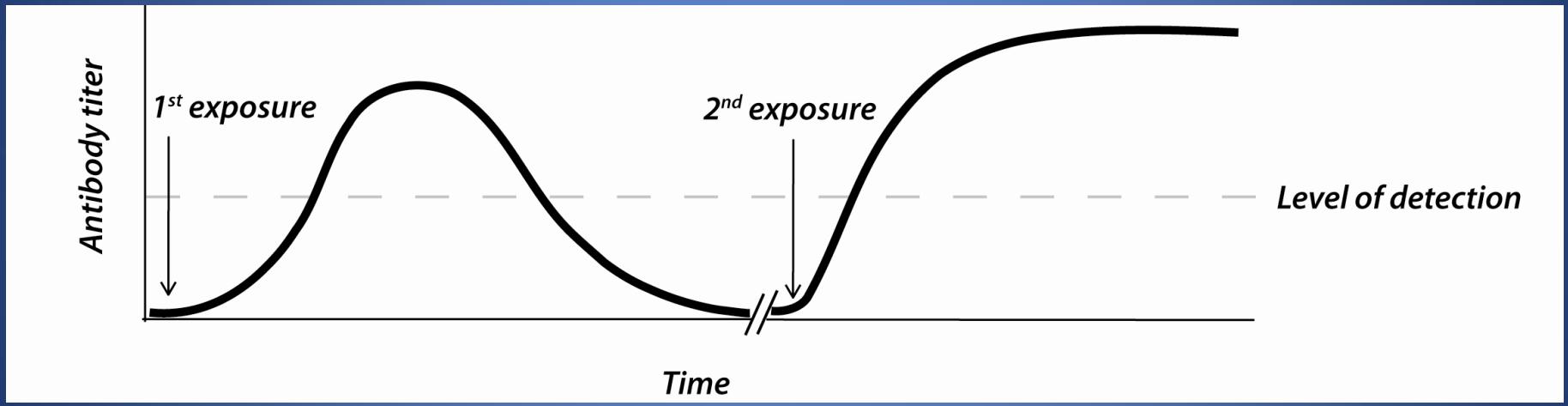
- Bystander hemolysis or hyperhemolysis, an under-reported transfusion complication, is a cause of morbidity and mortality in patients with sickle cell disease
- Poorly understood
- US-wide research registry is in the process of being developed

RBC Alloantibodies and Morbidity

- Data from the UK Serious Hazards of Transfusion (SHOT) report provide insight into both *morbidity* and mortality associated with non-ABO alloantibodies
- For DHTRs occurring between 2006-14:
  - ~60% associated with mild-moderate morbidity
  - ~10% associated with severe morbidity

http://www.shotuk.org/home/

More Than 70% of RBC Antibodies Fall Below the Level of Blood Bank Detection at Some Point ("Evanescence")



Thus, the prevalence of RBC alloimmunization is significantly underestimated

Tormey et al, Blood 2018 in preparation

Evanescence Rates by Antibody Specificity

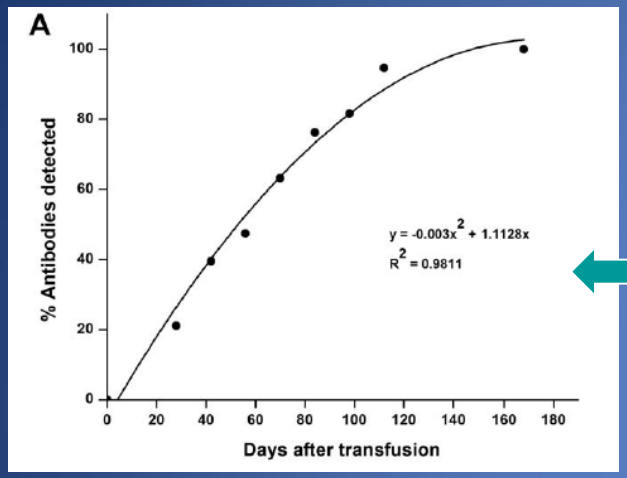
Evanescence Rate In General Patients (highest to lowest)	Evanescence Rate In SCD (highest to lowest)[22,23]
Lu^a (65%; 11/17)*	Js^a (80%; 12/15)*
C^w (61%; 19/31)*	Fy^b (78%, 7/9)
Jk^b (54%; 7/13)	S (66%, 14/22)
Le^b (52%; 13/25)	Jk^b (58%; 11/19)
P_1 (50%; 9/18)	Le^a (54%; 14/26)
Jk^a (49%; 30/61)	Fy^a (51%; 18/35)
Le^a (47.5%; 19/40)	C (47%; 27/57)
E (38%; 134/353)	Go^a (43%; 3/7)*
K (32%; 117/366)	E (41%; 37/90)
M (30%; 12/40)	K (41%; 23/56)
S (30%; 8/27)	Le^b (40%; 4/10)
c (27%; 23/84)	V (39%; 7/18)*
C (19%; 21/109)	M (38%; 3/8)
Fy^a (17%; 16/94)	D (36%; 10/28)
D (12%; 32/262)	c (0%; 0/5)

Siddon et al, Current Opinion Hematol 2018

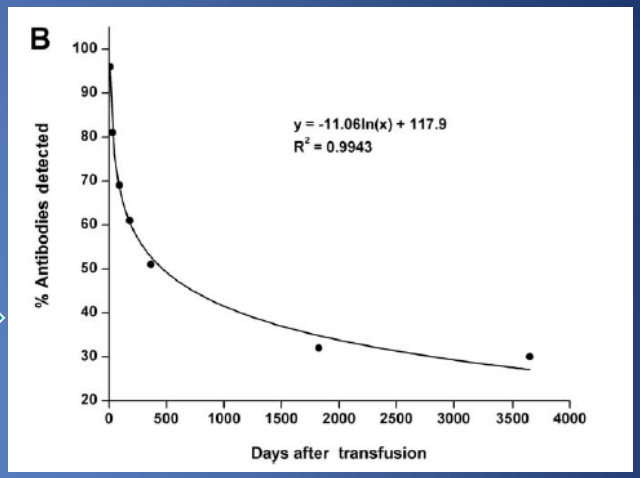
RBC Alloantibodies: Challenges in Detection

- What is a major reason for not detecting blood group alloantibodies?
  - Evanescence
- If we do detect antibodies, why aren't we preventing the complications of alloimmunization?
  - Patients may seek treatment at different hospitals
- What are our actual opportunities to detect non-ABO blood group antibodies?
  - Missed alloimmunization

How Many Antibodies Are We Detecting with Random Testing?



Based on established kinetics of antibody induction and evanescence



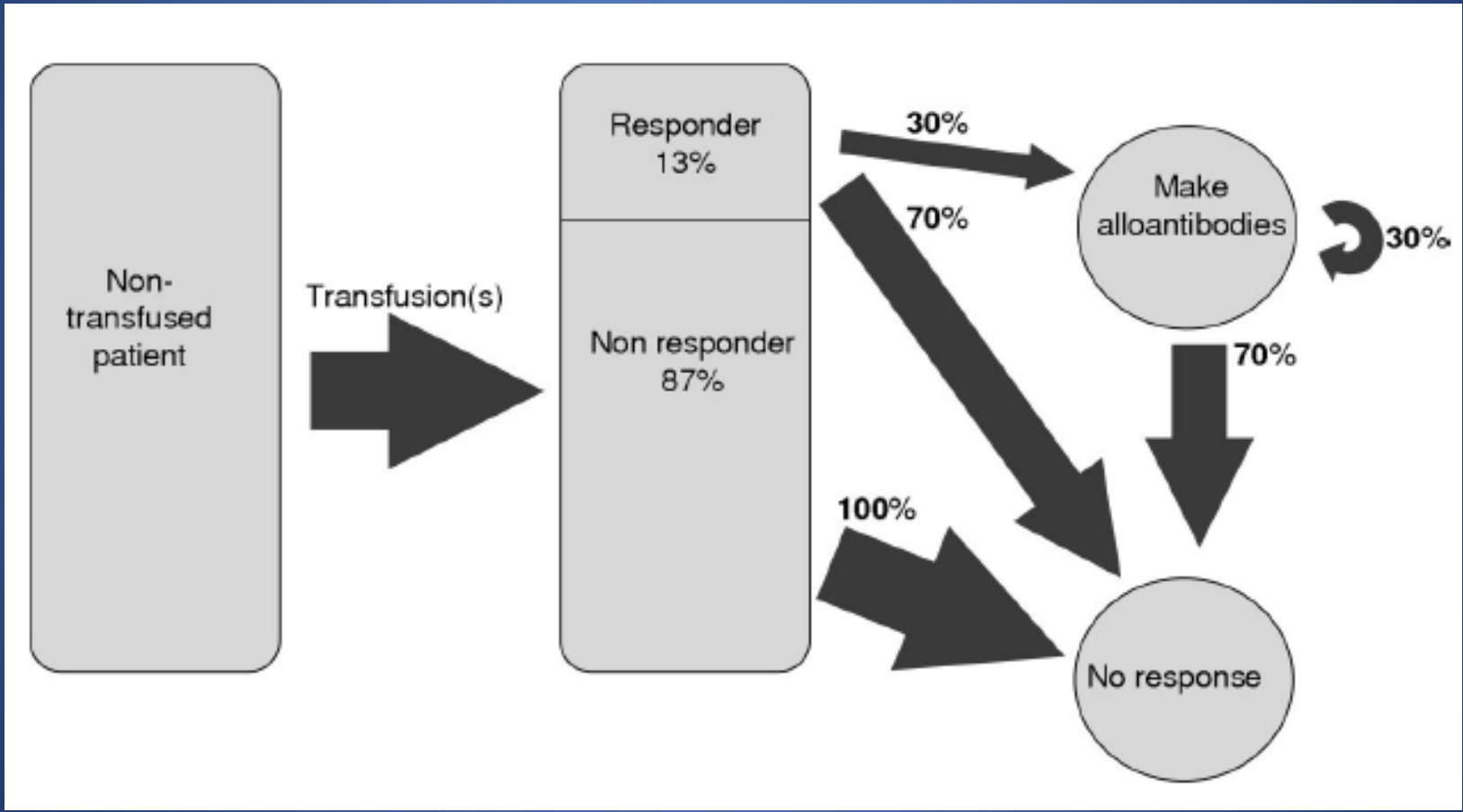
$$FADR = \frac{[D_{F/U\ 0\text{-}29}][T_{F/U\ 0\text{-}29}] + [D_{F/U\ 30\text{-}112}][T_{F/U\ 30\text{-}112}] + [D_{F/U>112}][T_{F/U>112}] + [D_{F/U\ 30\text{-}112\ \&\ >112}][T_{F/U\ 30\text{-}112\ \&\ >112}]}{T_{Tot}}$$

And with some fancy mathematics based on follow-up testing data…

It is estimated that *only about 30-32%* of transfusion-induced antibodies are likely detected by routine, non-systematic type and screen testing

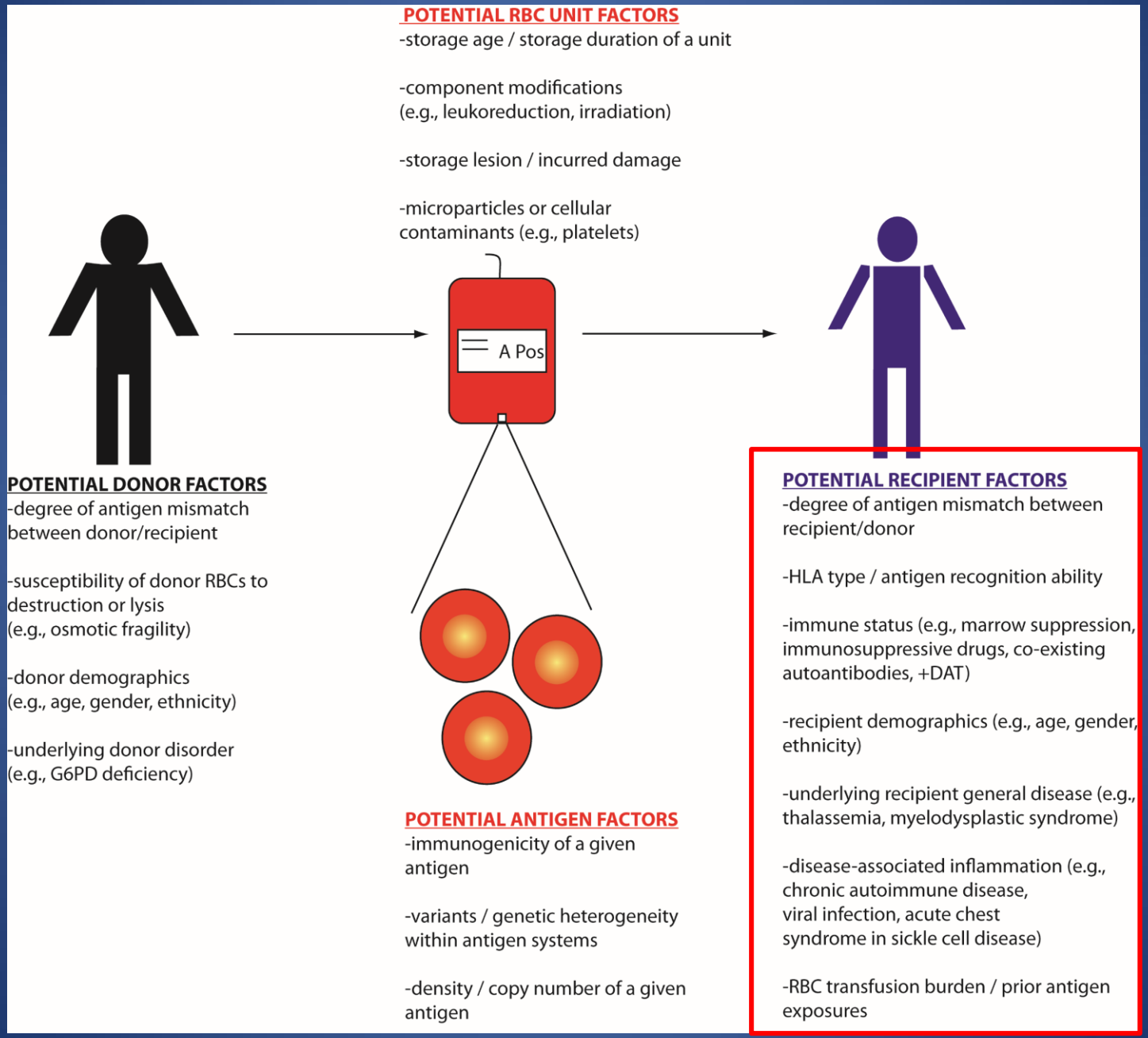
Stack G, Tormey CA. Transfusion 2016

Responders/Non-Responders



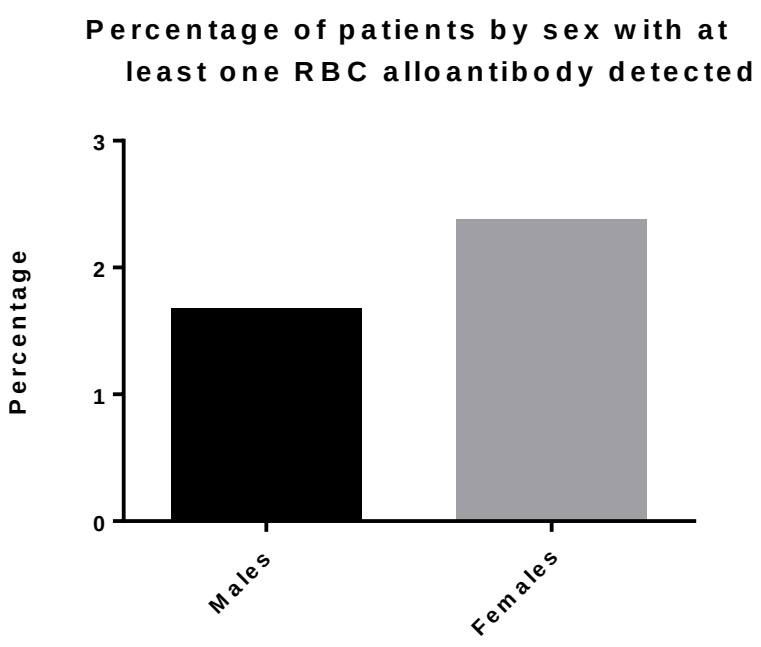
Higgins and Sloan, Blood 2008

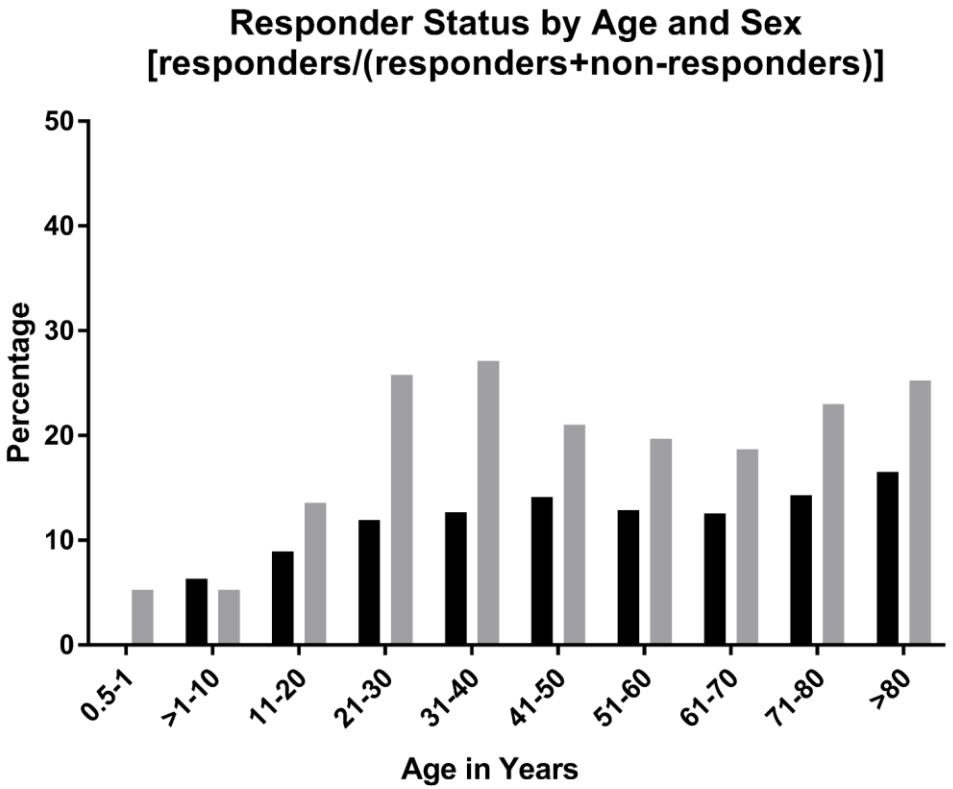
Factors Potentially Contributing to Alloantibody Responses:



Tormey et al, Blood 2018 in preparation

REDS-III Recipient Database: Female Patients Were More Likely than Males to be Alloimmunized At Any Point During the 4 Year Study Duration

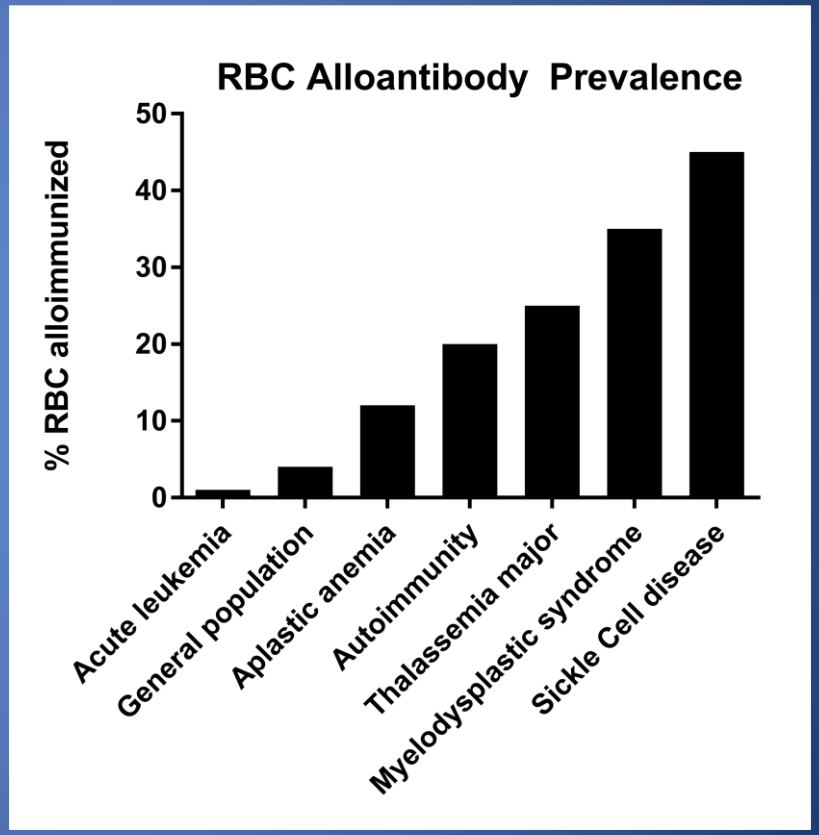




Karafin et al, BJH 2018

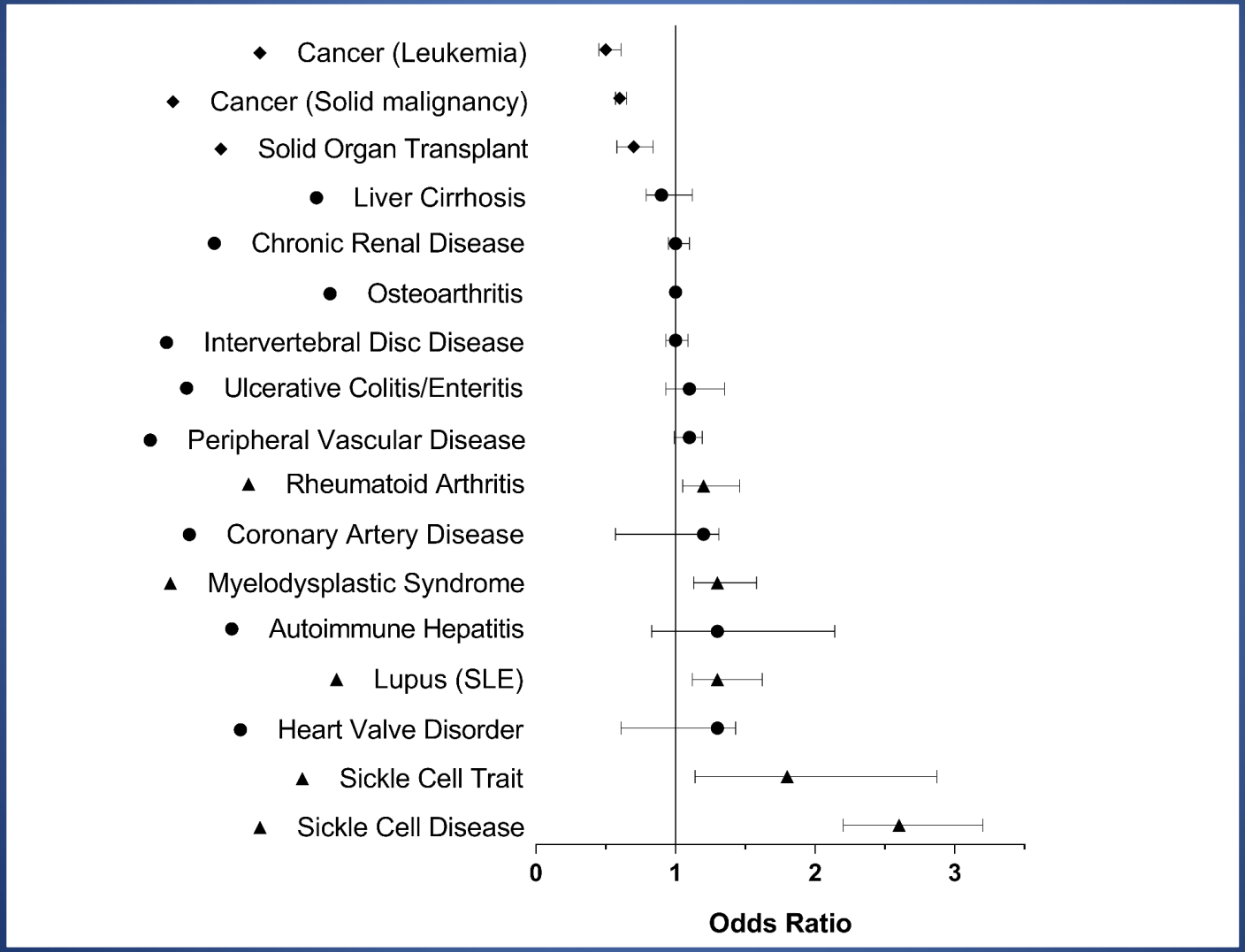
Disease Status Impacts RBC Alloimmunization

Population or disease state	Reported alloimmunization rate (%)
General adult patients	
Retrospective analysis	1-3
Prospective analysis	8-10
Hemoglobin disorders	
Sickle cell disease	19-43
Thalassemia major	5-45
Inflammatory disorders	
Autoimmune disorders, general	16
Inflammatory bowel diseases	8-9
Lymphoid disorders	
Acute lymphoid leukemia	<1
Hodgkin lymphoma	<1
Non-Hodgkin lymphoma	2-3
Myeloid disorders	
Acute myeloid leukemia	3-16
Myelodysplastic syndromes (includes myelodysplastic/myeloproliferative disorders)	15-59
Solid tumors, nonhematopoietic	1-10
Transplantation	
Hematopoietic progenitor cell	1-4
Liver transplant	4-23
Other sites or multiple organ transplantation	1-10



Hendrickson and Tormey, ASH Education Book 2016 and Blood 2018, in preparation

REDS-III Recipient Database: The odds ratio of being a "responder" as compared to a "non-responder" in the presence of a particular diagnosis

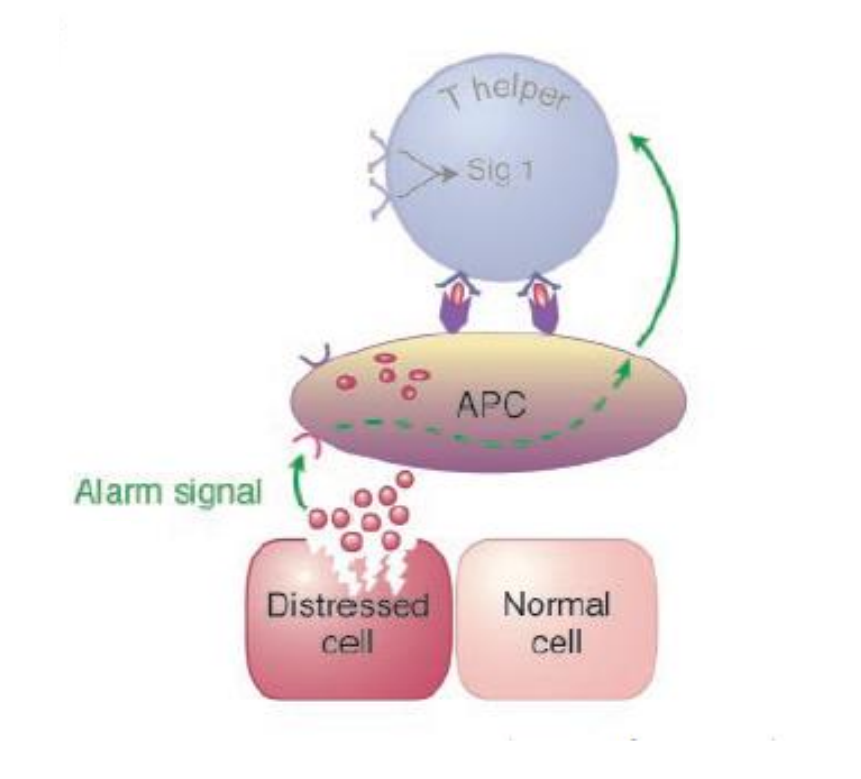


Karafin et al, BJH 2018

The Unanswered Question: Why Do So Many Patients with SCD Form Alloantibodies?

- More RBC exposure than the average transfused individual
  - RBC exposure during times of illness/inflammation may be unavoidable
- Baseline inflammation with free heme and leukocytosis and thrombocytosis, among others
- *RH* genetic diversity

Matzinger's "Danger" Theory



Matzinger, Science 2002

Human Data: Inflammation and RBC Alloimmunization

Does a febrile reaction to platelets predispose recipients to red blood cell alloimmunization?

Yazer et al, Transfusion 2009

High Risk of Transfusion-induced Alloimmunization of Patients with Inflammatory Bowel Disease

Papay et al, Am J Medicine 2012

Red Blood Cell Alloimmunization Is Influenced By Recipient Inflammatory State At Time Of Transfusion In Patients With Sickle Cell Disease

Fasano et al, BJH 2015

Human Data: Inflammation and RBC Alloimmunization

Chronic inflammatory autoimmune disorders are a risk factor for red blood cell alloimmunization

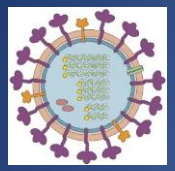
Ryder et al, BJH 2015

bjh research paper

Red cell alloimmunisation in patients with different types of infections

Evers et al, BJH 2016

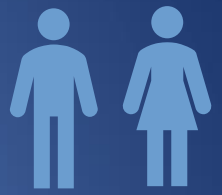
Viral Inflammation Increases Alloimmunization



bjh research paper

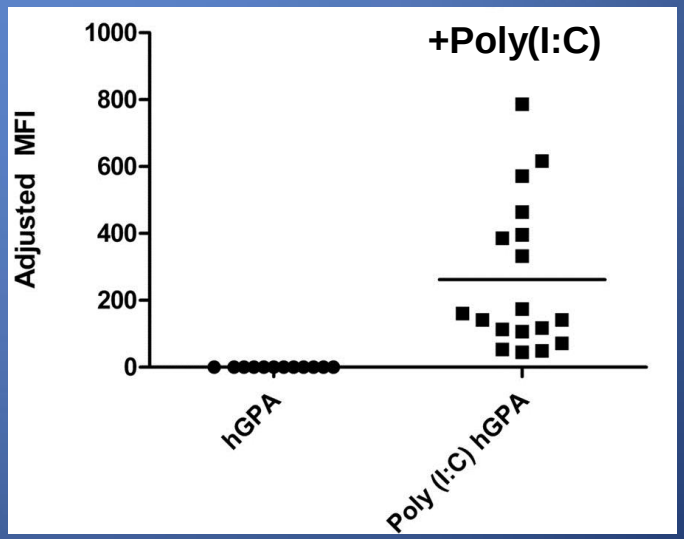
Red cell alloimmunisation in patients with different types of infections

Evers et al, Br J Haematol 2016



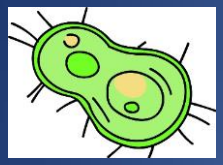
- **Disseminated Viral Infection**: Non-significant ↑ relative risk of RBC alloimmunization
  - RR = 2.41

- **Poly(I:C) ~ viral dsRNA:**
  ↑ alloimmunization



Smith et al, Blood 2012

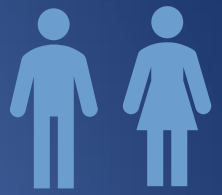
All Inflammation is Not the Same: Gram Negative Bacteremia Decreases Alloimmunization



bjh research paper

Red cell alloimmunisation in patients with different types of infections

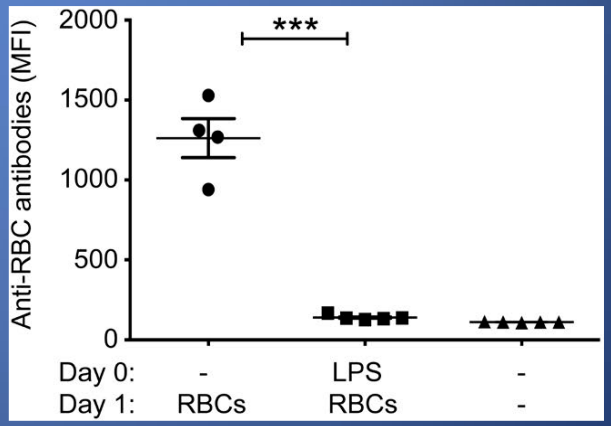
Evers et al, Br J Haematol 2016



- **Gram-negative bacteremia**: ↓ Risk of alloimmunization
  - RR = 0.58

- **LPS treatment :** ↓ alloimmunization

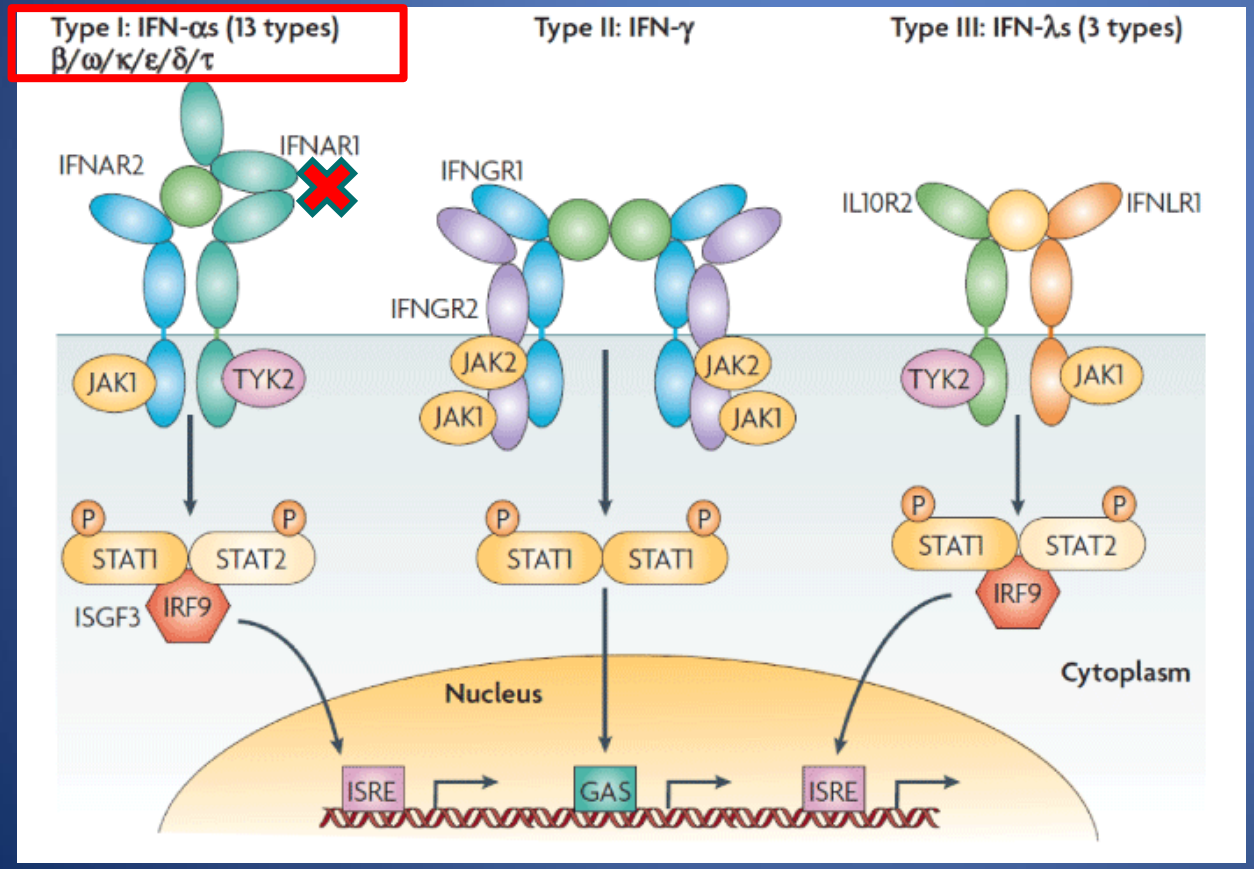
Anti-RBC IgG



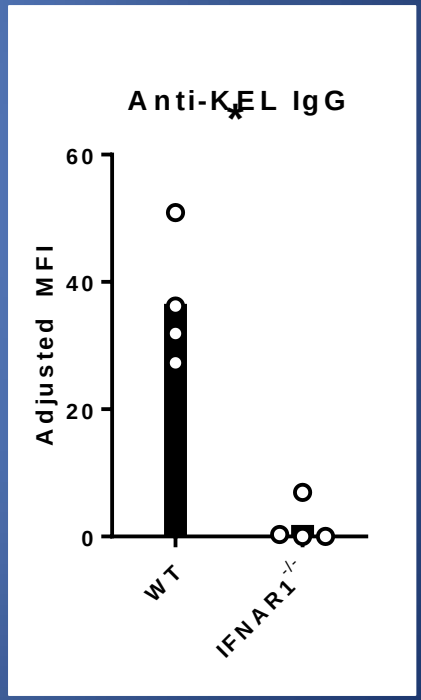
Calabro et al, J. Exp. Med 2016

IFNα/β Receptor Signaling is Required for RBC Alloimmunization in an Animal Model

Poly(I:C) = dsRNA, mimics RNA viral infections
- Induces **Type 1 Interferons** (IFNα/β)

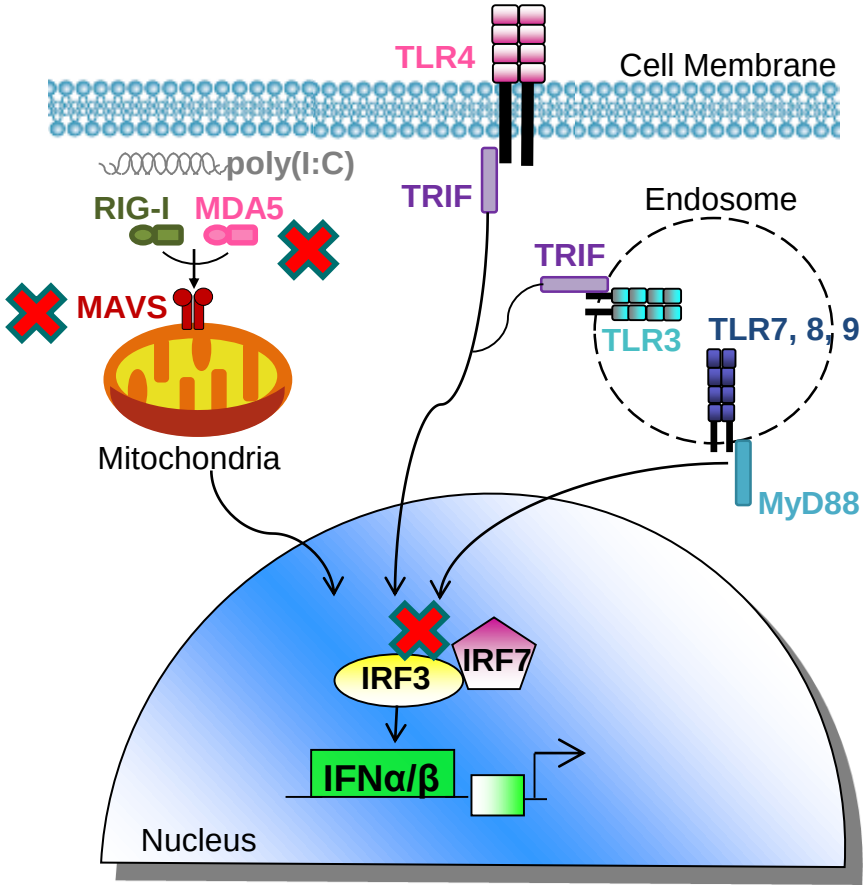


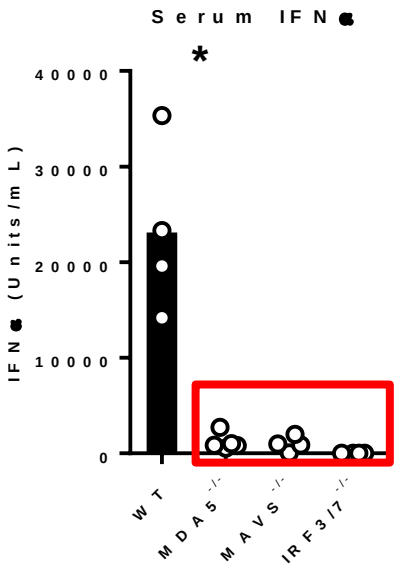
Wang et al. Arch Biotechnol Biomed, 2017



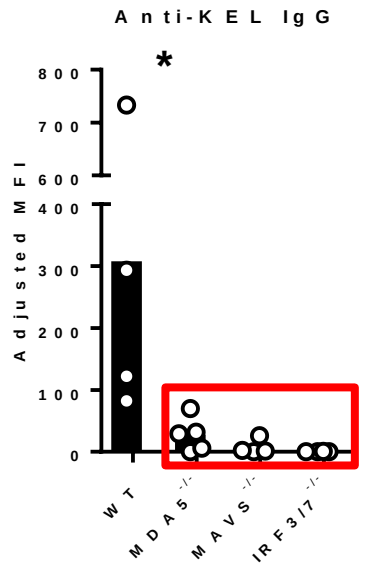
Gibb et al, JI 2017

Blockade of the MAVS or IRF 3/7 Pathways Mitigate the Effect of Poly (I:C) on Alloimmunization





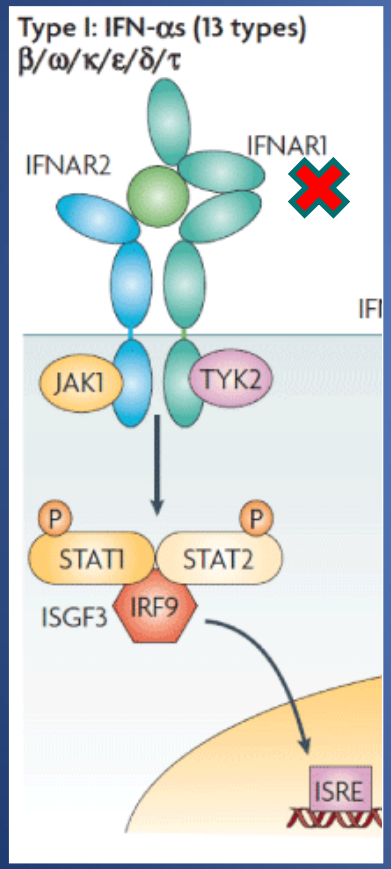
+Poly(I:C)



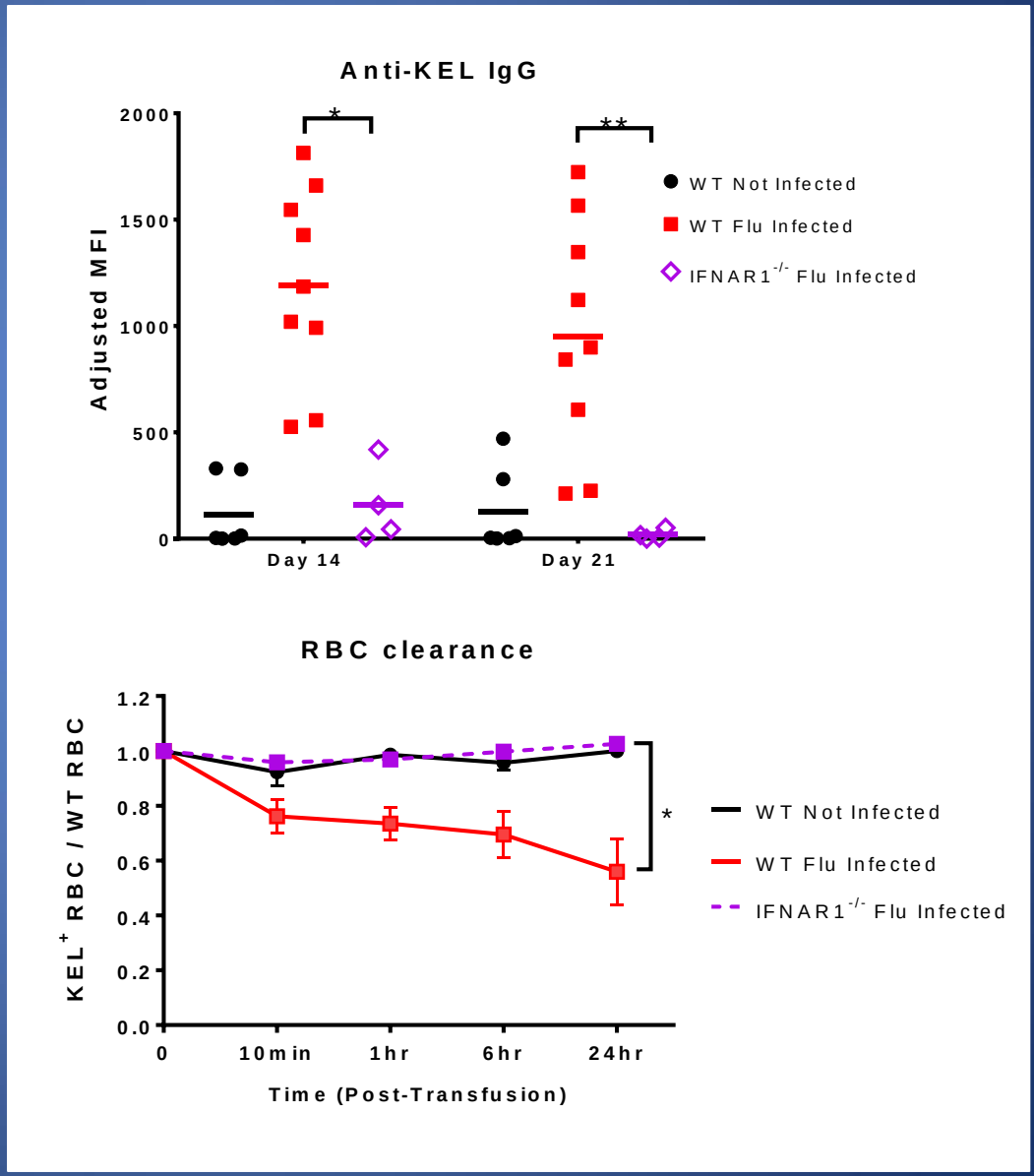
+Poly(I:C)

Gibb et al, JI 2017

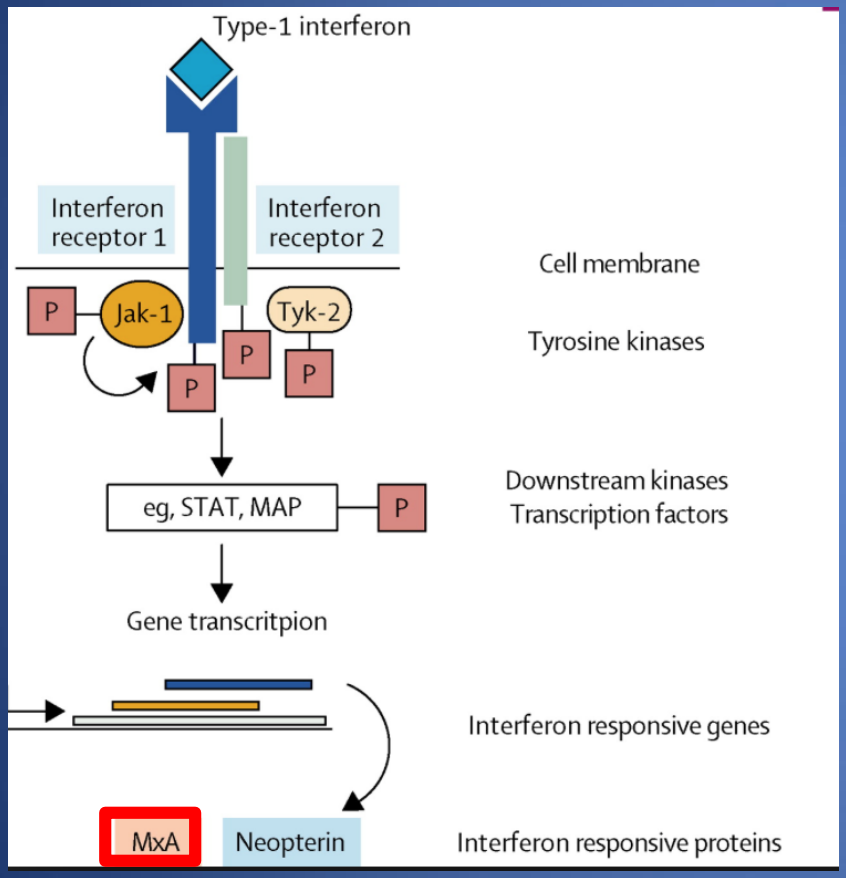
Recipient Flu Infection Increases Alloimmunization in a Type 1 IFN Dependent Manner

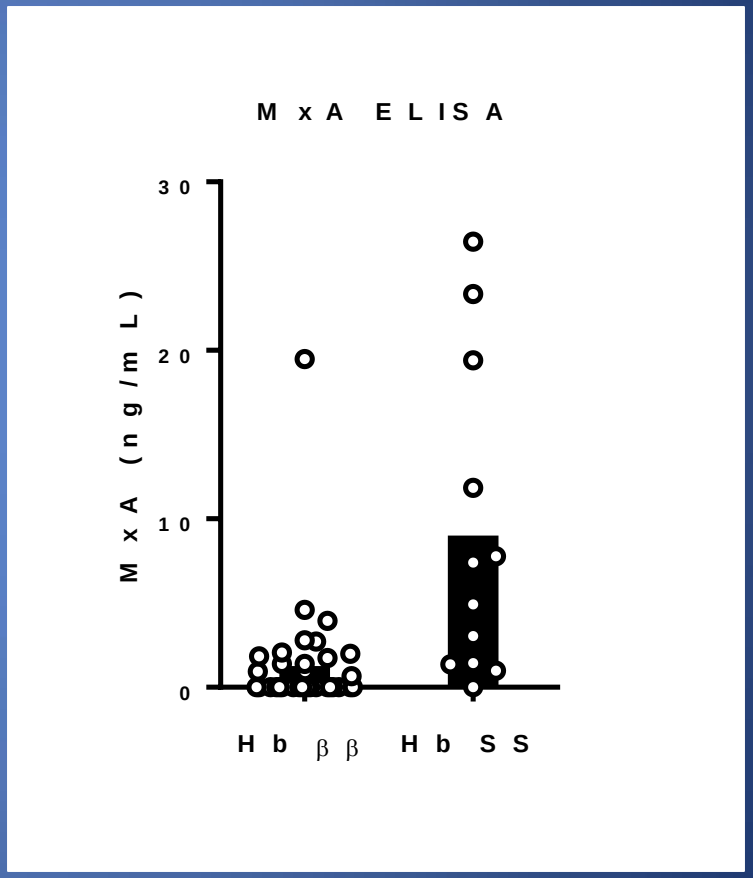


Wang et al, Arch Biotechnol Biomed, 2017.



Could Patients with SCD Have High Type 1 Interferon Levels?





Random blood sampling, preliminary data

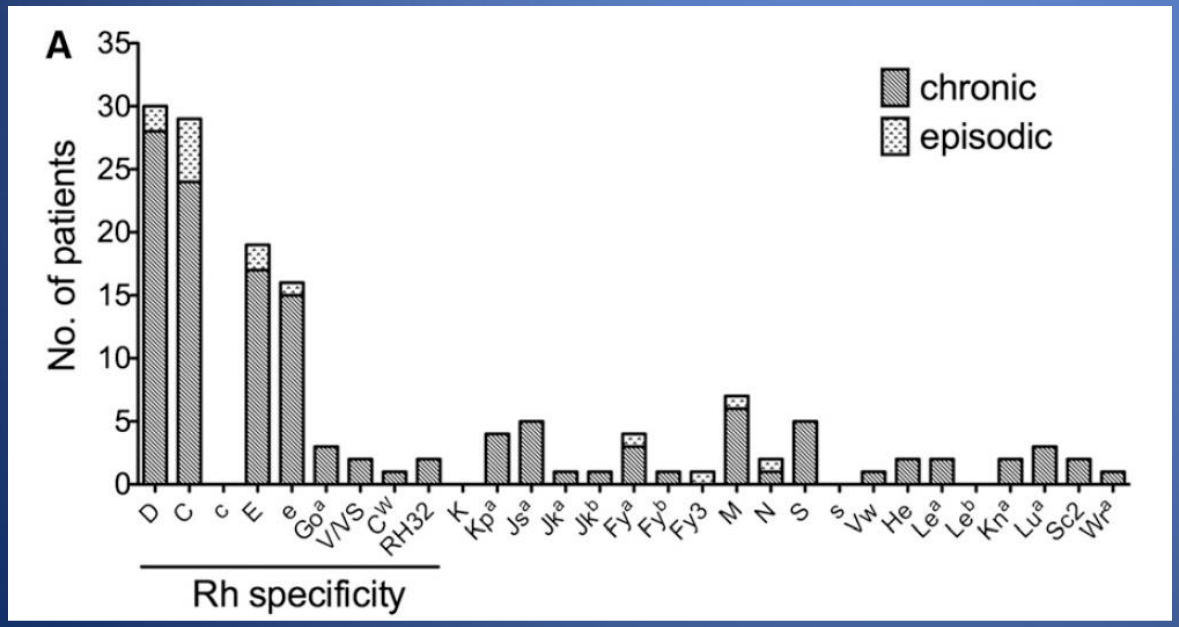
The RBC Autoantibody/RBC Alloantibody Association

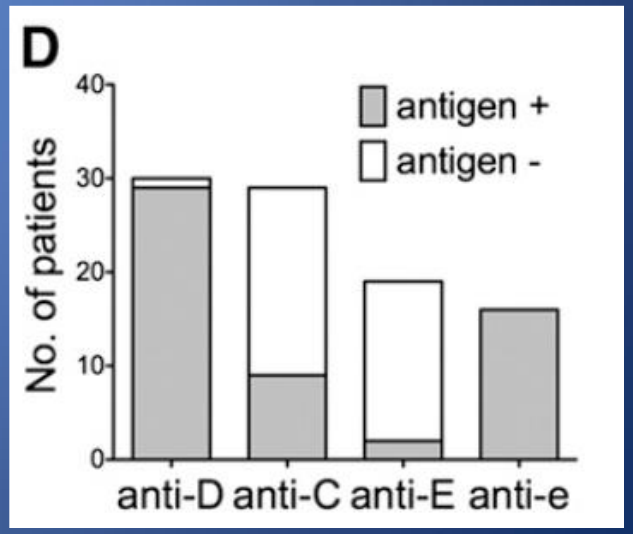
- In MDS patients, 65% with alloantibodies also had autoantibodies (Singhal et al, Haematologica 2017)
- In children with SCD, 69% with alloantibodies also had autoantibodies (Nickel et al, AJH 2015)
- In thalassemia patients, 50% with alloantibodies also had autoantibodies (Dhawan et al, ASTS 2014)

Is there a type 1 IFN connection?

The RBC Autoantibody/RBC Alloantibody Association

- Some previously identified autoantibodies are likely alloantibodies associated with Rh variant antigens
- Autoantibodies are also found, however, in diseases associated with allommunization



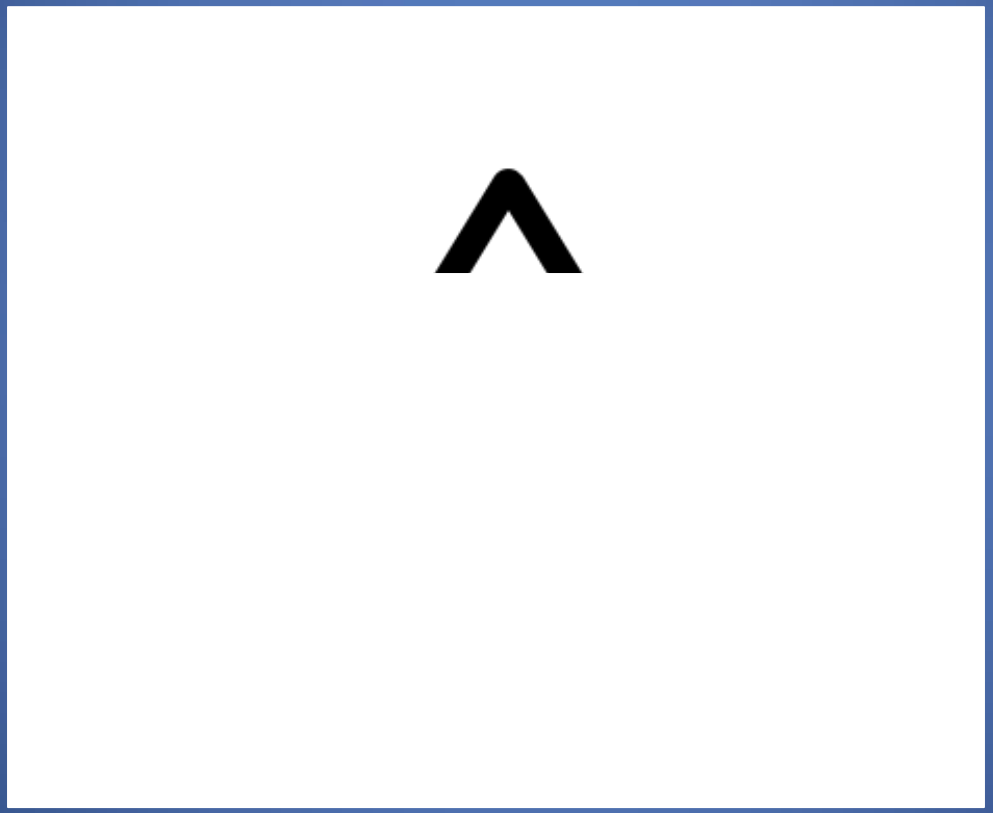


Chou et al, Blood 2013

Could some "antibody negative" DHTRs be due to antibodies (such as those in the Dombrock family) that are difficult to detect using traditional blood bank methodology?

Could some "antibody negative" DHTRs be due to alloantibodies characterized as autoantibodies?

RBC Alloimmunization in Patients with SCD is a Bigger Problem . . .



RBC Alloimmunization in Patients with SCD is a Bigger Problem . . . Than Meets the Eye

Thank You