



Working mechanism Rh immunoprophylaxis

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For Life.



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Introduction

Rh immunoprophylaxis

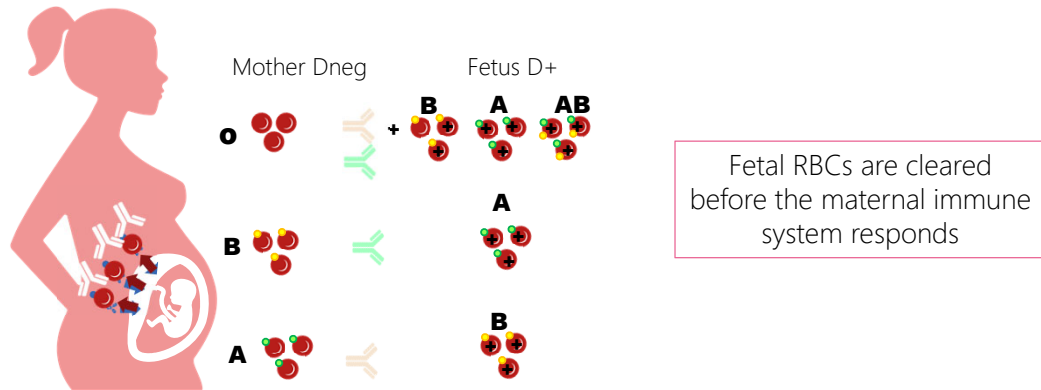
One of the most successful immunotherapies
Combined postnatal and antenatal prophylaxis : only 0.3% failures
Koelewijn et al. Transfusion 2008

However:
Working mechanism is still not fully elucidated



Original observation

ABO incompatibility decreases risk of anti-D immunization



Is it that simple, is it only RBC clearance?? Unfortunately : Probably NOT

- Trials in volunteers with different anti-D monoclonal antibodies :
not as protective as polyclonal Rhlg
some enhanced immune response

Kumpel et al. Vox Sang 2007

Contreras M, et al, Glob. libr. women's med.,2023 DOI 10.3843/GLOWM.418843

- Failure of prophylaxis
No increased frequency of women with FcRIII polymorphisms with lower affinity

Stegmann et al. Blood 2017



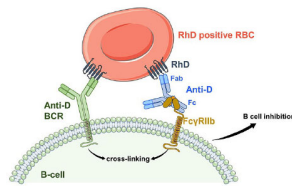
Alternative explanations

- Epitope masking/steric hindrance



NO (no saturation needed)

- FcR1Ib mediated inhibition of B



- Antigen loss

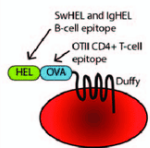


*Kumpel et al. Vox Sang 2007
 Brinc&Lazarus, Curr Opin Hematol. 2009
 Contreras M et al, 2023 Glob. libr. women's med.,*



Antibody Mediated Immune Suppression AMIS

Mouse models



HOD-model (fusion protein with B cell epitope(HEL), T cel epitope (Ova) and transmembrane domain (Duffy)



KEL-model (mouse transgenic for human KEL (at different densities))

IMPORTANT observation:

Anti-RBC alloantibodies

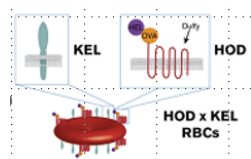
- Inhibition of antibody response
- Enhancement of antibody response



Lessons learned from murine models

Antigen (CAVE: Different mechanisms for different antigens?)

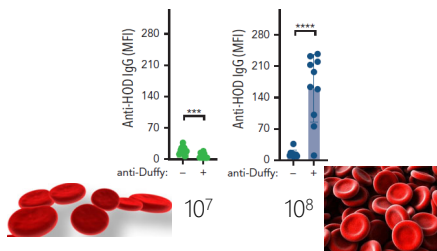
Inhibition is antigen specific



Anti-K inhibits anti-K
Anti-Fy inhibits anti-HEL/Fy

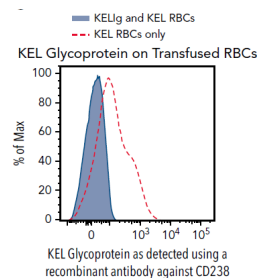
Maier et al BloodAdv 2018

RBC dose can be important



Jajoski et al Blood 2023

Antibodies induce antigen modulation



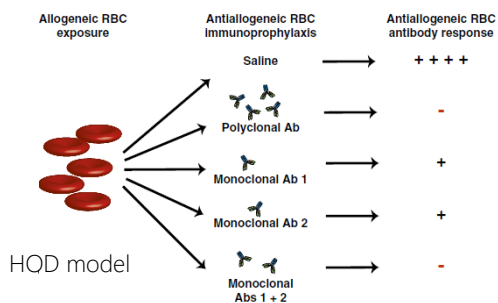
Liu J et al Blood 2016



Lessons learned from murine models

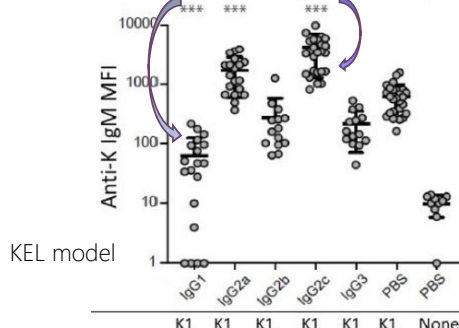
Antibodies (CAVE: Different mechanisms for different antigens?)

Blends of anti-HEL bodies > single



Bernardo et al Blood 2016

Dependent on anti-K subclass inhibition or enhancement

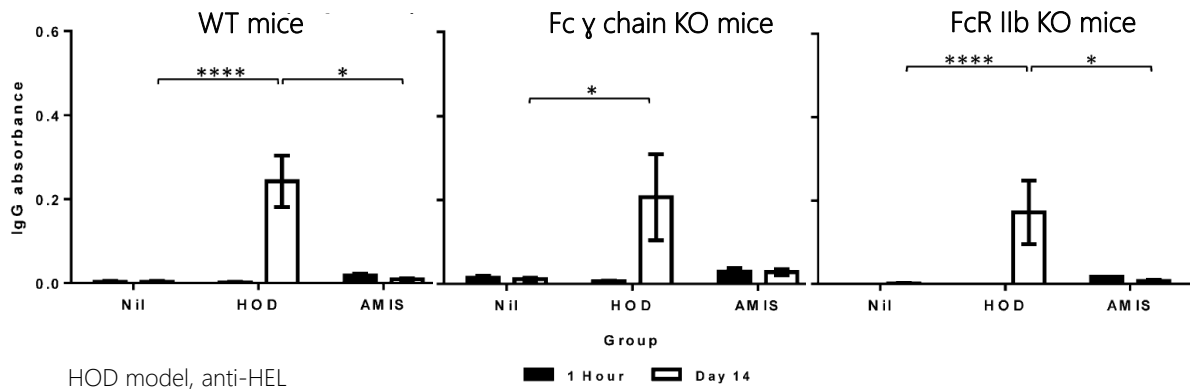


Shinde et al Front Immunol 2020
Gruber et al. Blood Adv 2020



Lessons learned from murine models

AMIS also in mice deficient for activating and inhibitory Fc receptors

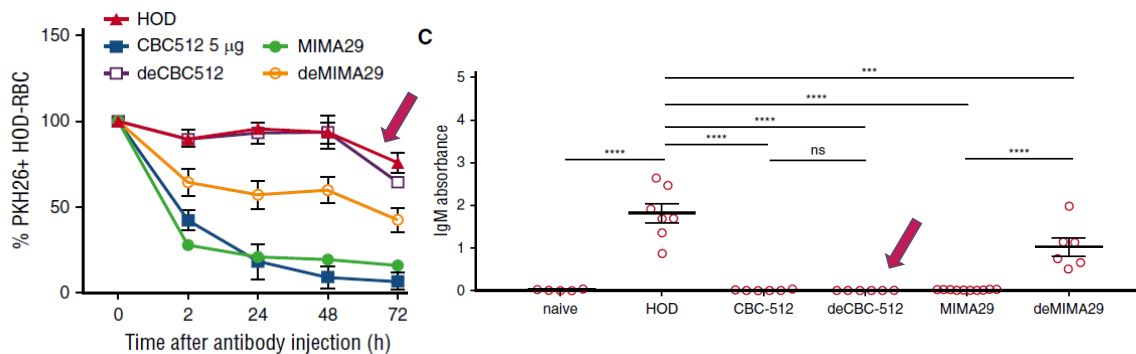


Bernardo et al. JI 2015



Lessons learned from murine models

Clearance of RBCs is NOT always related to AMIS



Deglycosylated (PNGaseF treated) anti-Fy (CBC512) does NOT mediate RBC clearance, but still complete AMIS

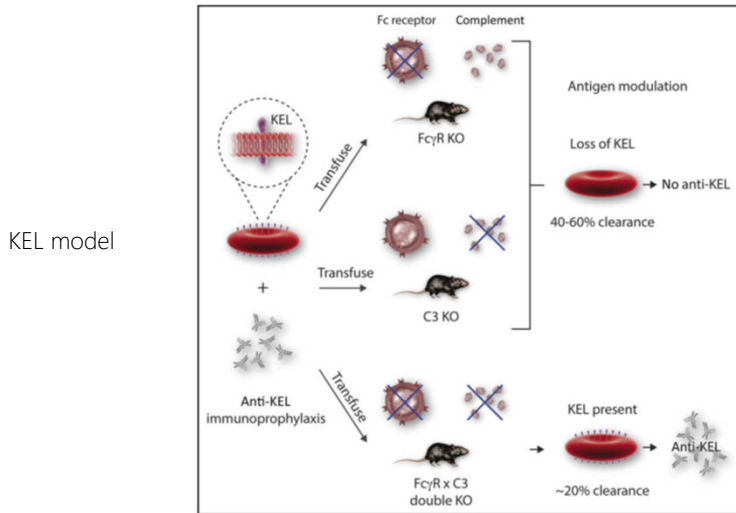
Yu H et al. JI 2014

Majoram et al. Blood 2016

Jajoski et al. Blood 2023

Lessons learned from murine models

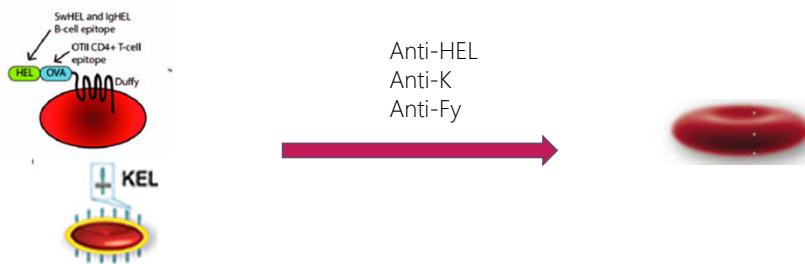
Both FcγR and C3 have to be absent to abolish AMIS



Liu et al. Blood 2016

Lessons learned from murine models

Antigen modulation is related to AMIS

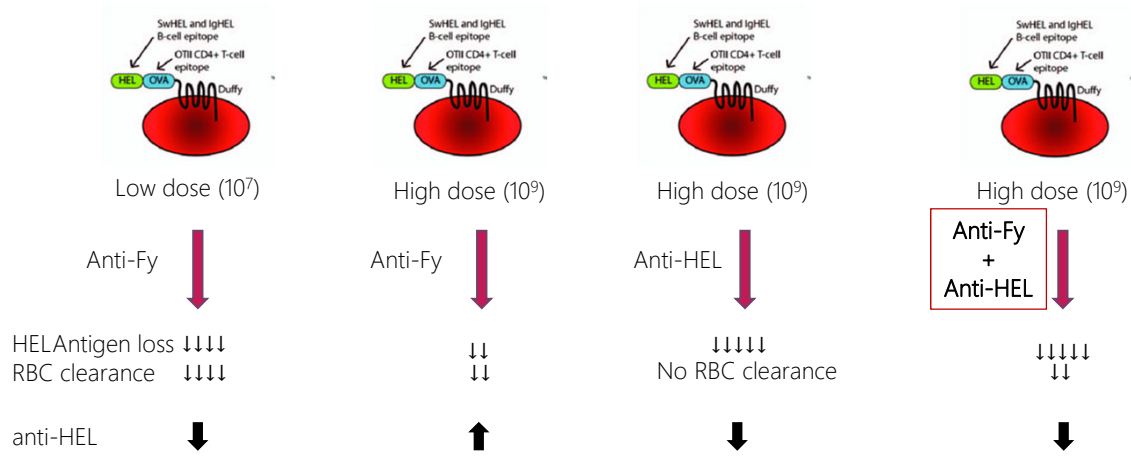


Only antibodies inducing in-vivo antigen loss induce AMIS

Liu et al. Blood 2016
Maier et al Blood Adv 2018
Cruz-Leal JI 2018
Mener A Transfusion 2019
Reviewed in: Cruz-Leal Transfusion 2021



anti-HEL induced antigen loss reverses anti-Fy induced enhancement to inhibition of antibody response



Jajovski et al. Blood Sept 2023

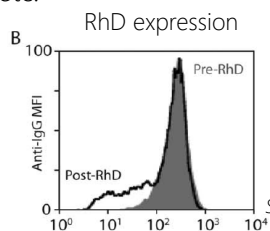


Conclusion (Cave: Mice are not men)

Recent results of animal models suggest that antigen modulation is needed for immunoprophylaxis

Many remaining questions:

- Antigen specific? (anti-D Ig can induce antigen loss in vivo)
- Role of Fcγ-receptors ?
- Role of complement ? (anti-D Ig do not bind complement)
- Role of T cells?
- etc. etc.



Sullivan et al. Transfusion 2018



THANK YOU