

# IVIg alternatives

Alan H. Lazarus, PhD

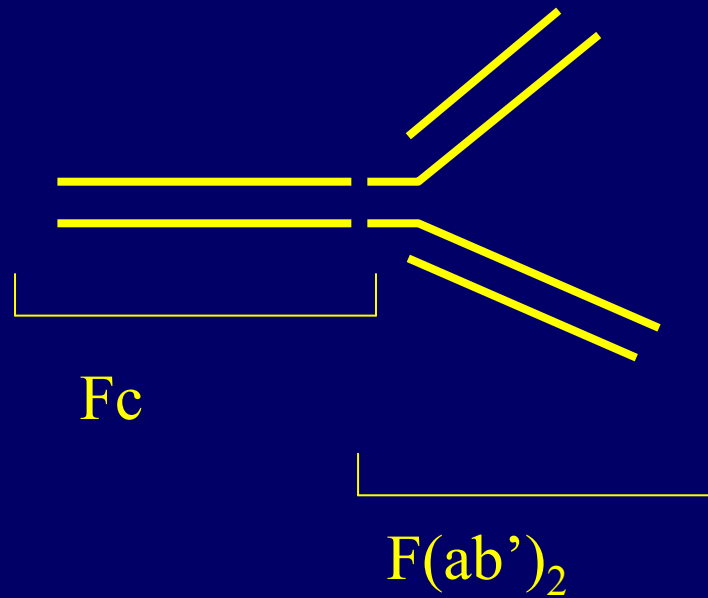
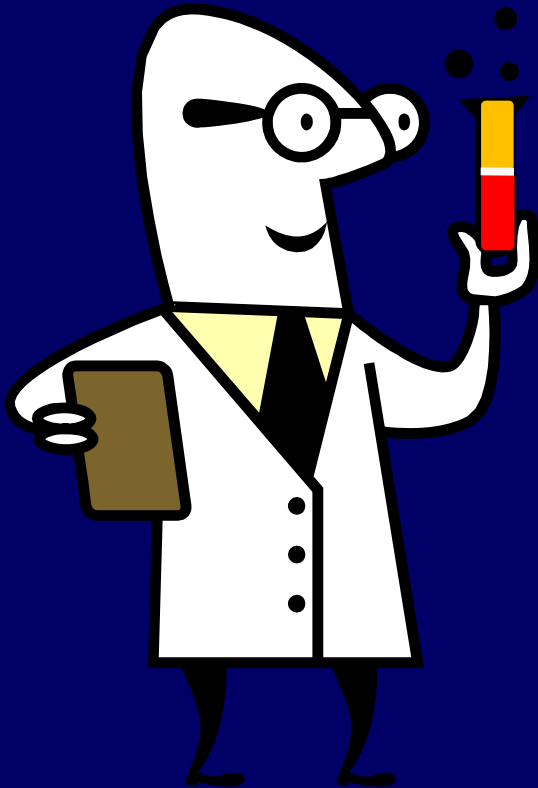
Canadian Blood Services  
St. Michael's Hospital  
University of Toronto



CANADIAN BLOOD SERVICES  
SOCIÉTÉ CANADIENNE DU SANG

# Intravenous Immunoglobulin

IVIg is IgG



# Intravenous Immunoglobulin (IVIg)

- Originally used as a replacement product for those deficient in IgG.
- In 1981 Dr. Paul Imbach reported that IVIG can rapidly reverse thrombocytopenia in an autoimmune disease to platelets (childhood ITP).

# Diseases where IVIg may be indicated

PID

B cell CLL

ITP

Kawasaki disease

BMT

Pediatric HIV

CIDP

Guillain-Barre syndrome

Myasthenia gravis

Eaton-Lambert syndrome

post-transfusion purpura

infection in m. myeloma

necrotizing fasciitis

genital HSV

toxic epidermal necrolysis

OCD post PANDAS

*(obsessive-compulsive disorders post pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections)*

How does this stuff work?



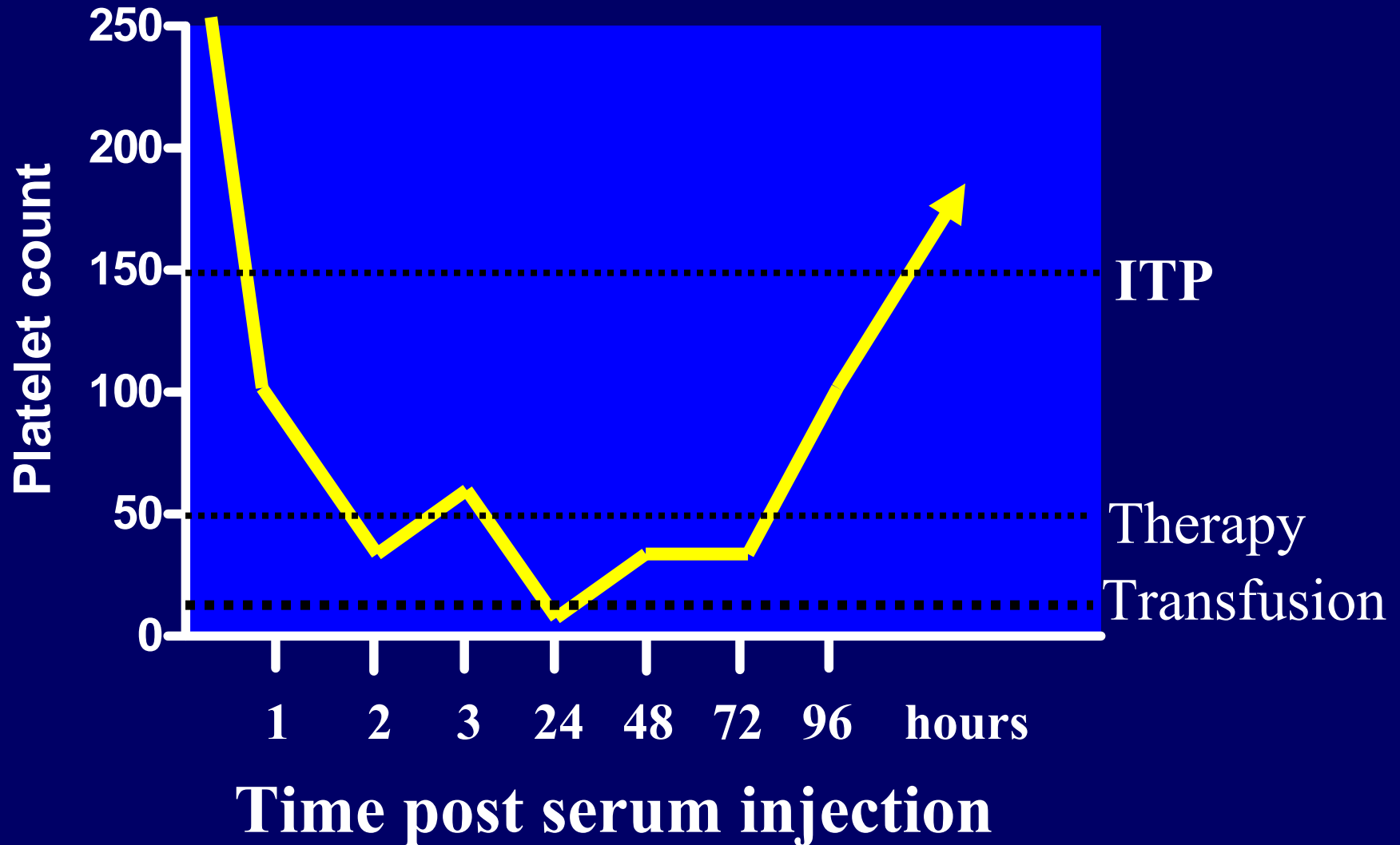
# ITP

Idiopathic (immune) thrombocytopenic purpura

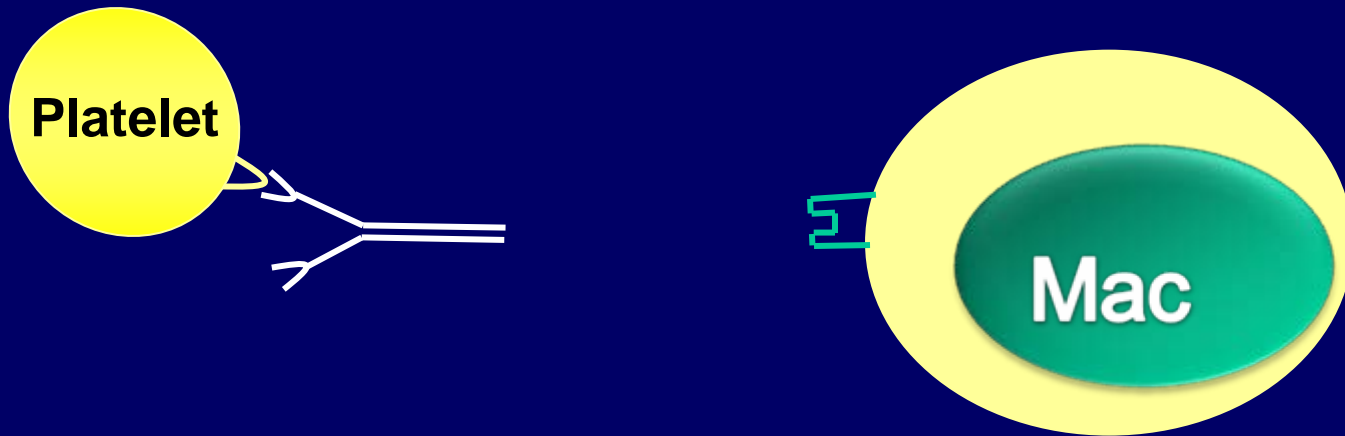
1st demonstrated by Harrington 1951

Injected himself with serum from a patient and saw a decrease in his own platelet count....

# The Harrington experiment-1951



# Immune thrombocytopenic purpura (ITP)



**How does IVIg rapidly increase platelet counts in immune thrombocytopenia?**

# Theories of IVIg action

Anti-idiotypic antibodies

Blockade of Fc receptors on macrophages

Inhibitory Fc $\gamma$ RIIb signalling

Induces changes in cytokine production.

Inhibits complement activation

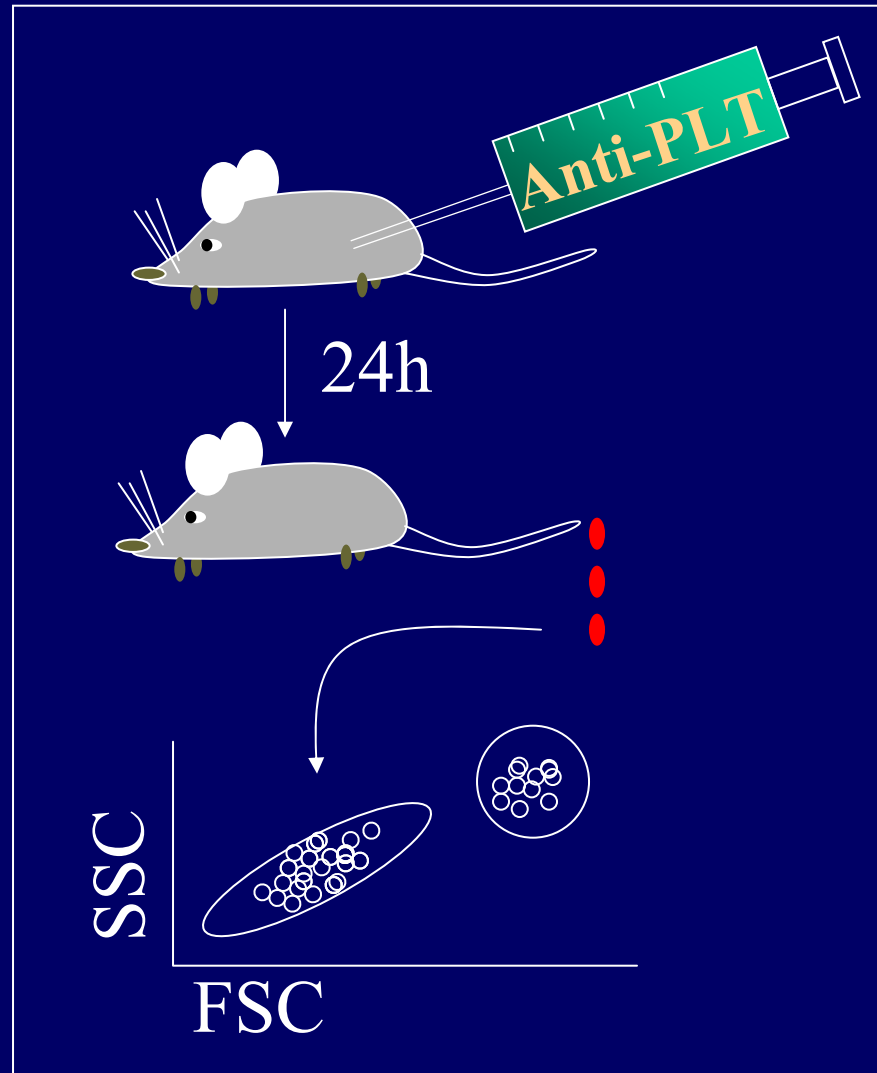
Accelerates clearance of pathogenic antibody-FcRn.

Modulate B and T cell function

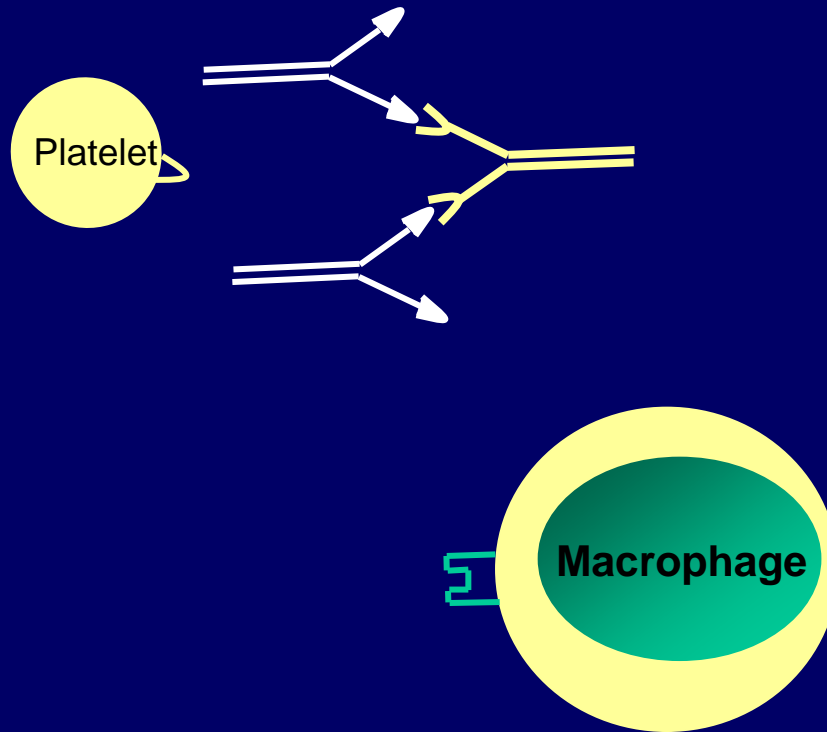
Inhibition of B cells via Fc $\gamma$ RII feedback regulation.

Apoptosis

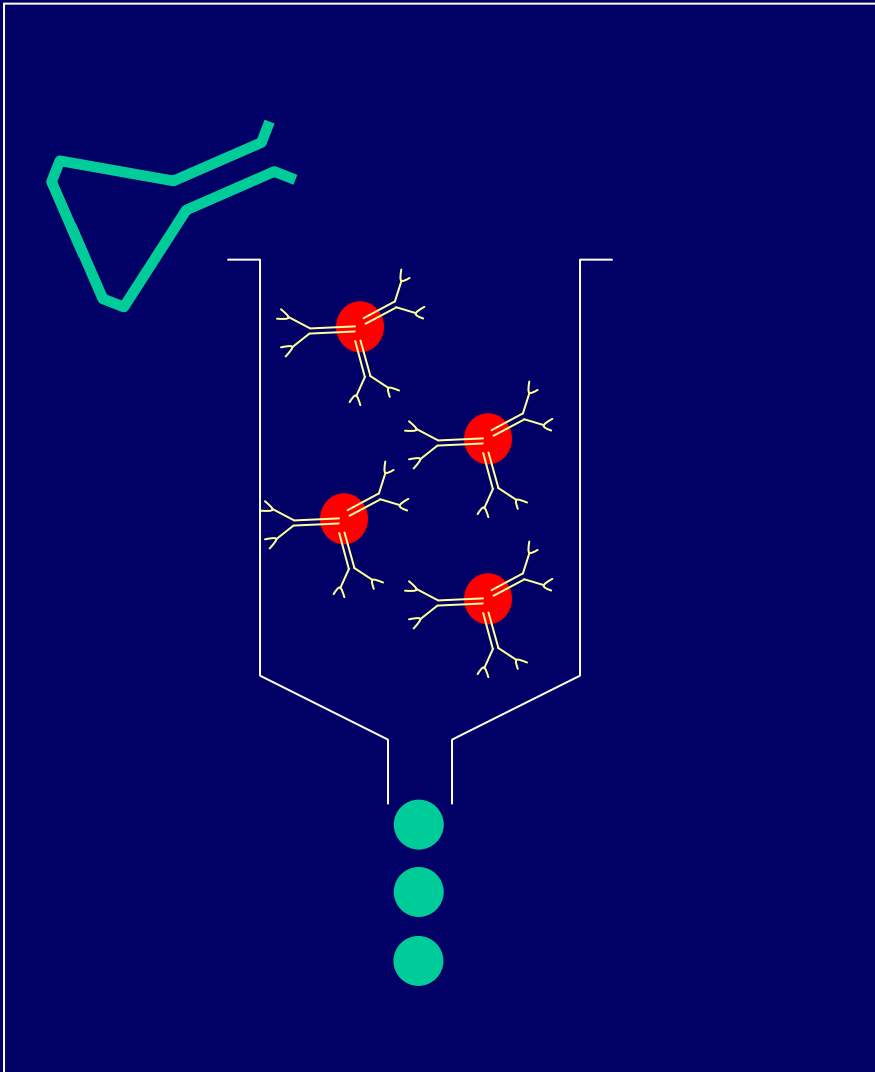
# A murine model of Passive Immune Thrombocytopenia



# Theory: Anti-idiotypic antibodies



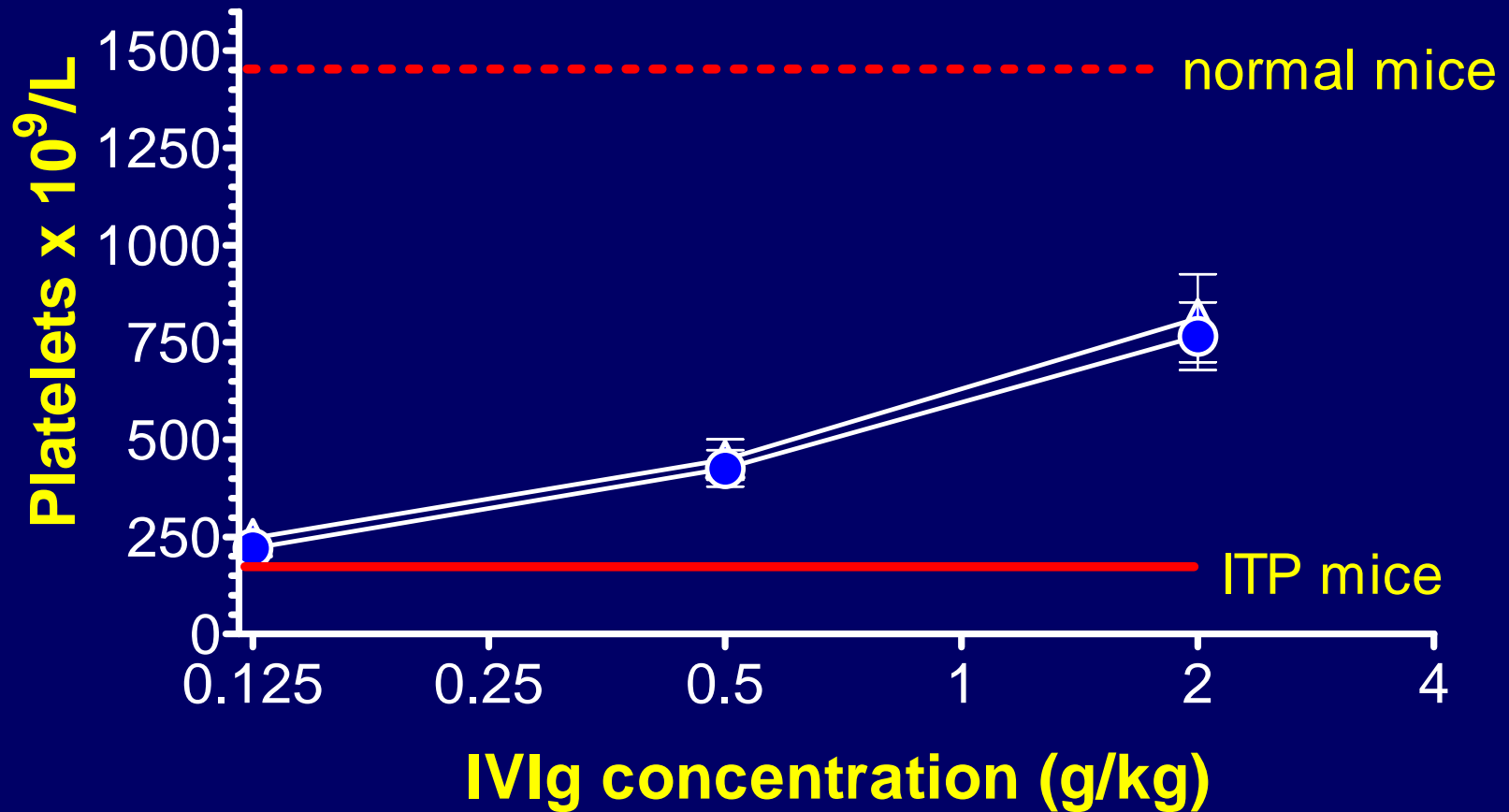
# Anti-Idiotypic depletion of IVIG



- IVIG was incubated with IgG-Sepharose
- Product assessed for anti-idiotypes by ELISA

(Crow et al, BJH 115:679, 2001)

# Anti-idiotype-depleted IVIG ameliorates immune thrombocytopenia



# Theories of IVIg action

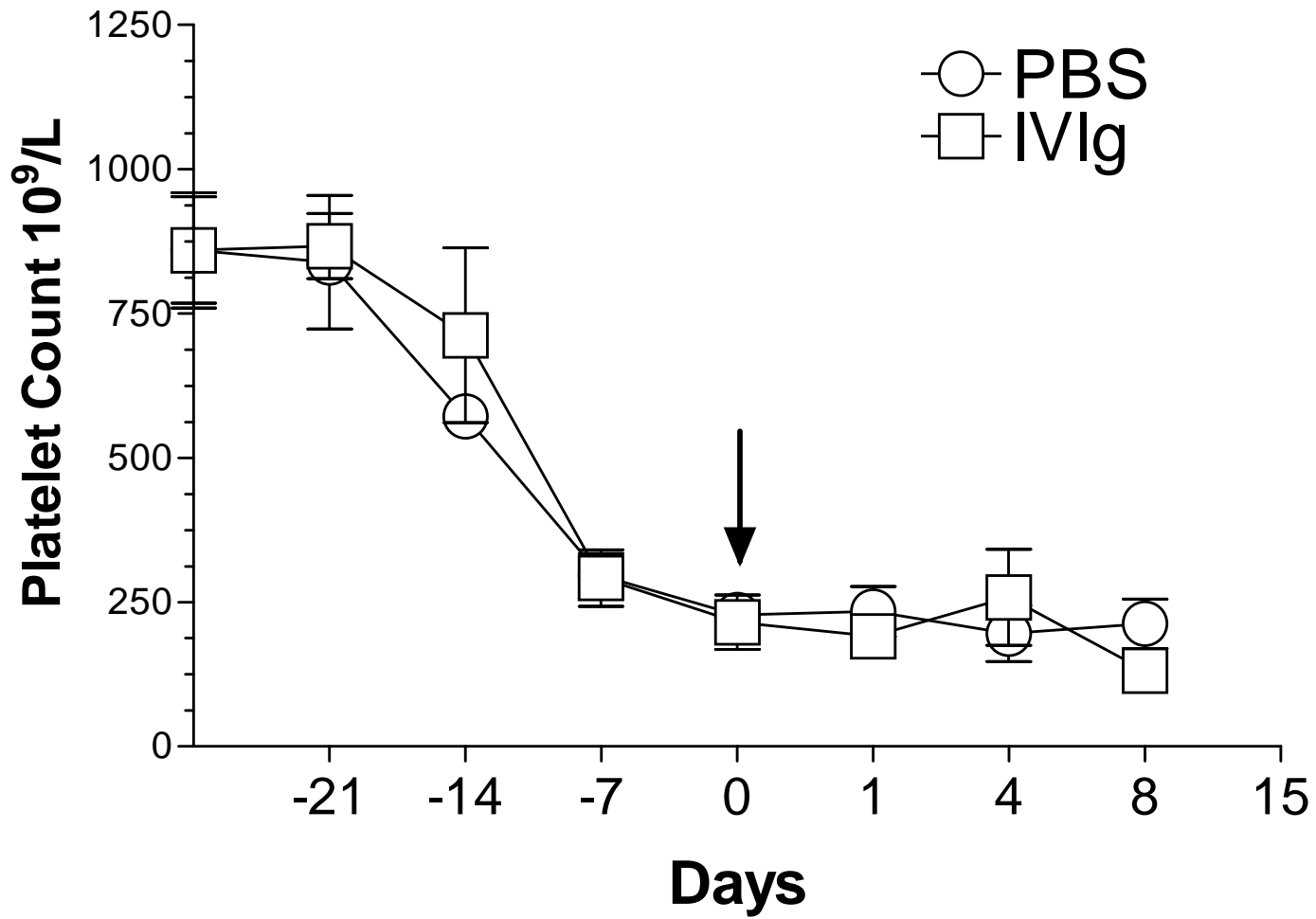
- ✗ Anti-idiotypic antibodies
- ✗ Blockade of Fc receptors on macrophages
- ? Inhibitory Fc $\gamma$ RIIb signaling ✗
- ✗ Induces changes in cytokine production
- ✗ Inhibits complement activation
- ✗ Accelerates clearance of pathogenic antibody-FcRn
- ✗ Modulate B and T cell function
- ✗ Inhibition of B cells via Fc $\gamma$ RII feedback regulation
- ✗ Apoptosis

**So we thought about all of our negative  
results....**

## *Observation*

**IVIg did not work well in diseases  
where pre-existing immune  
complexes were present**

SLE-ITP mice



## *Hypothesis*

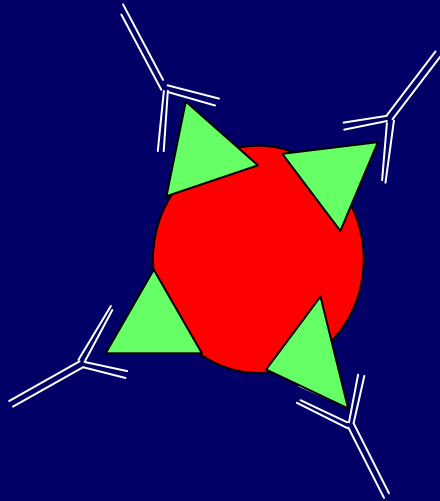
**Antibodies which bind to a (soluble) antigen will ameliorate ITP.**

## *IVIg vs anti-D*

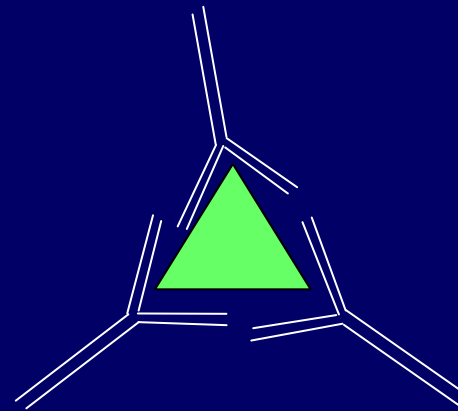
**Anti-D also can ameliorate ITP in D+ individuals; are the mechanisms the same?**

# Experimental Design

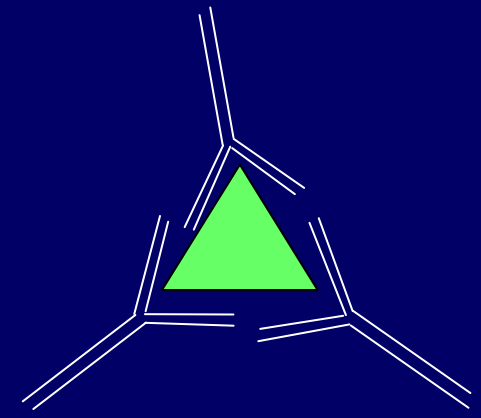
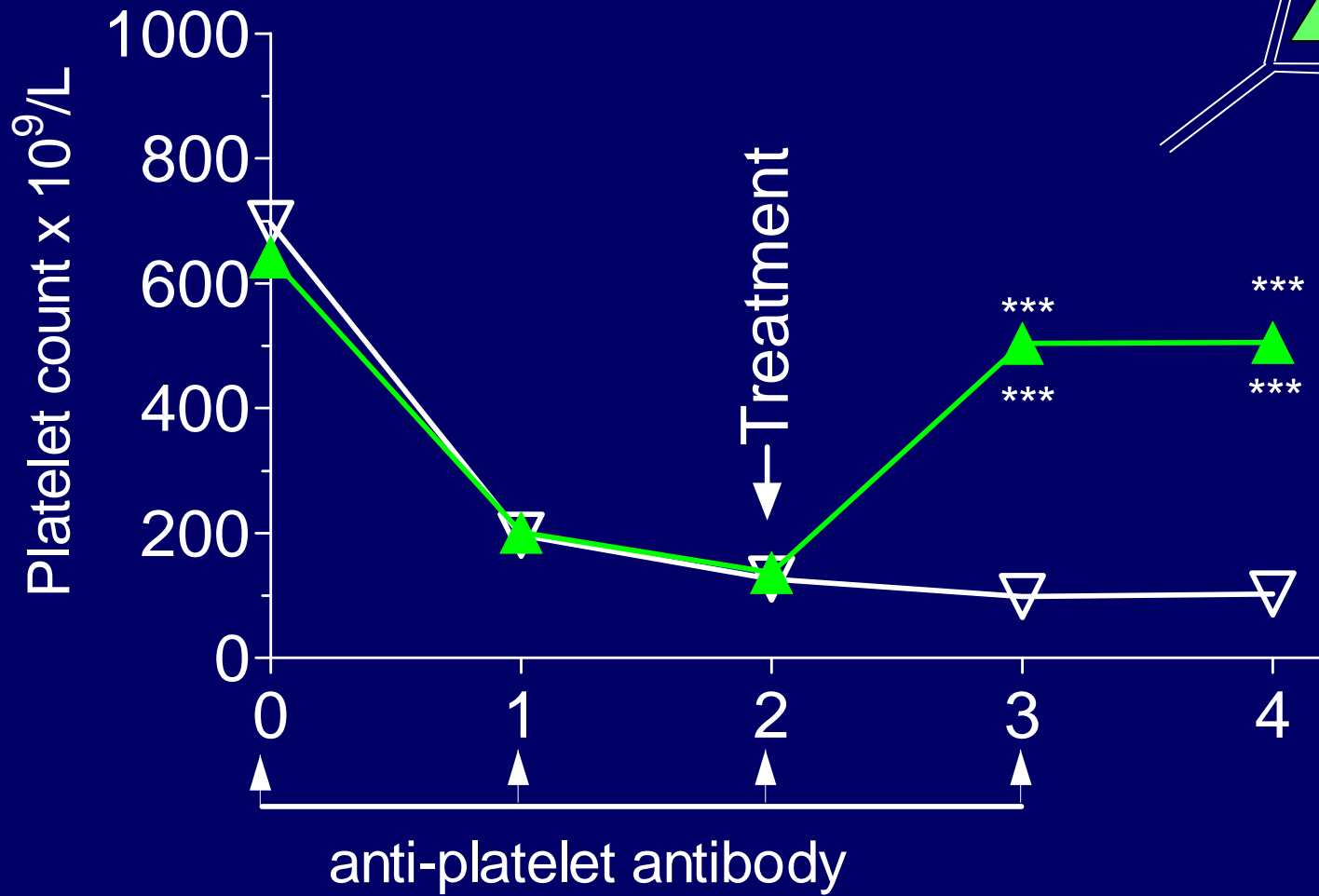
Insoluble:  
(anti-D like)

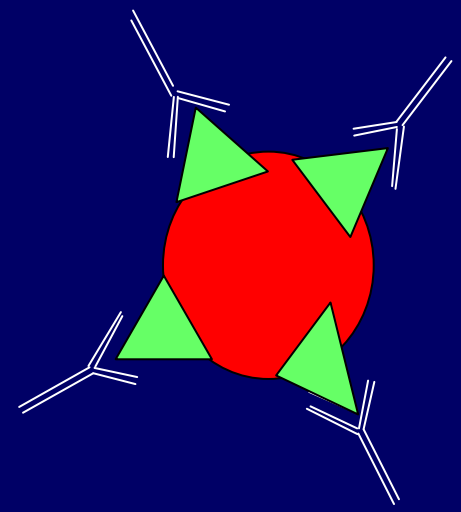
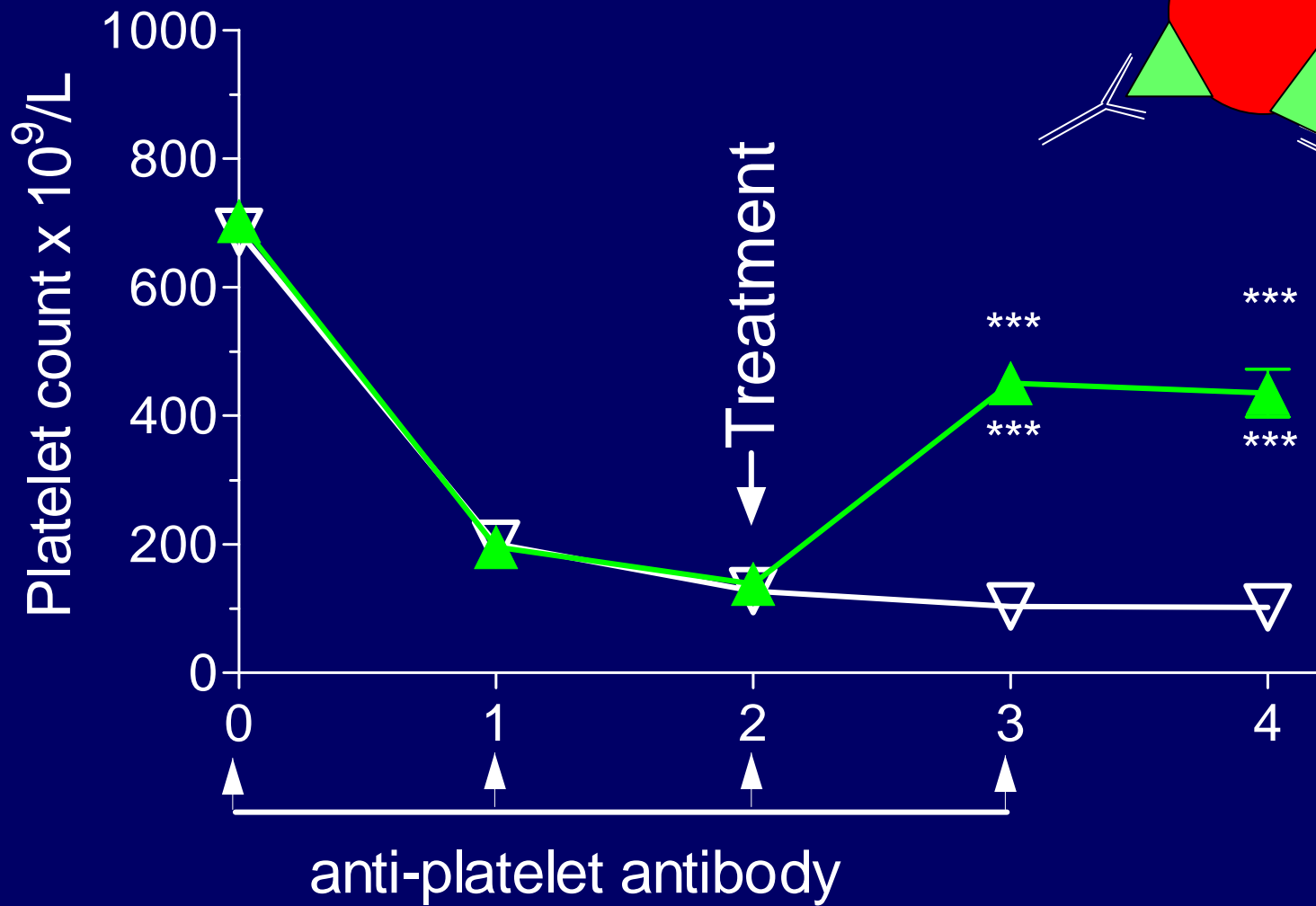


Soluble:

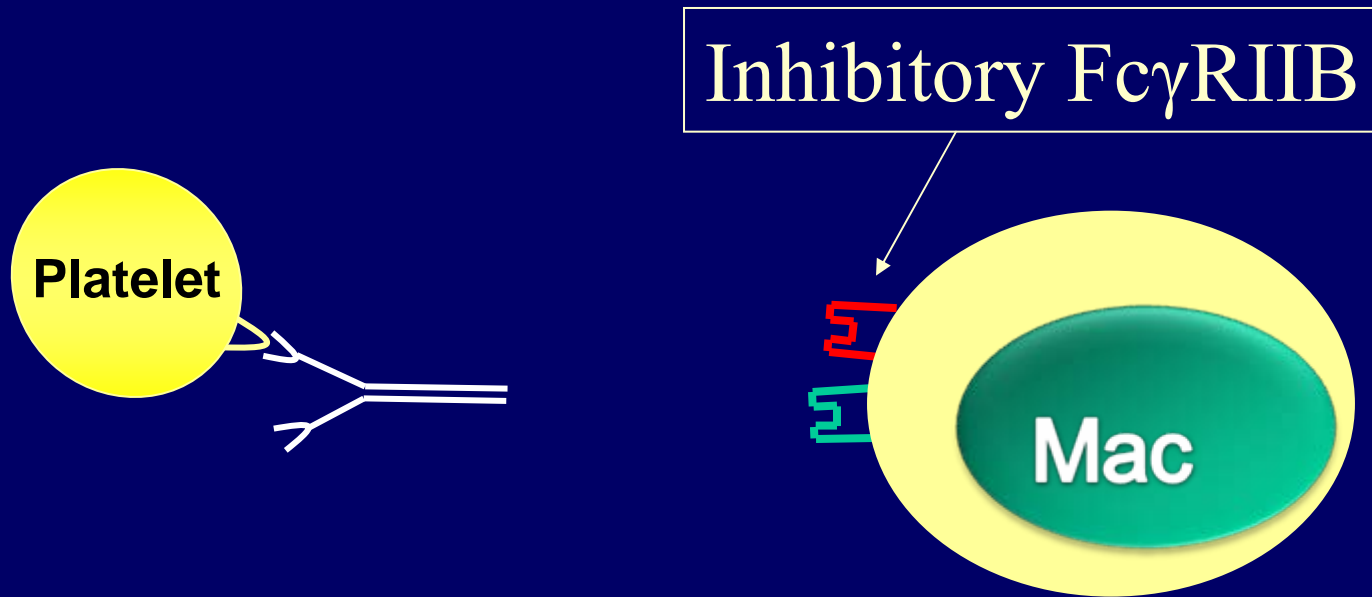


OVA

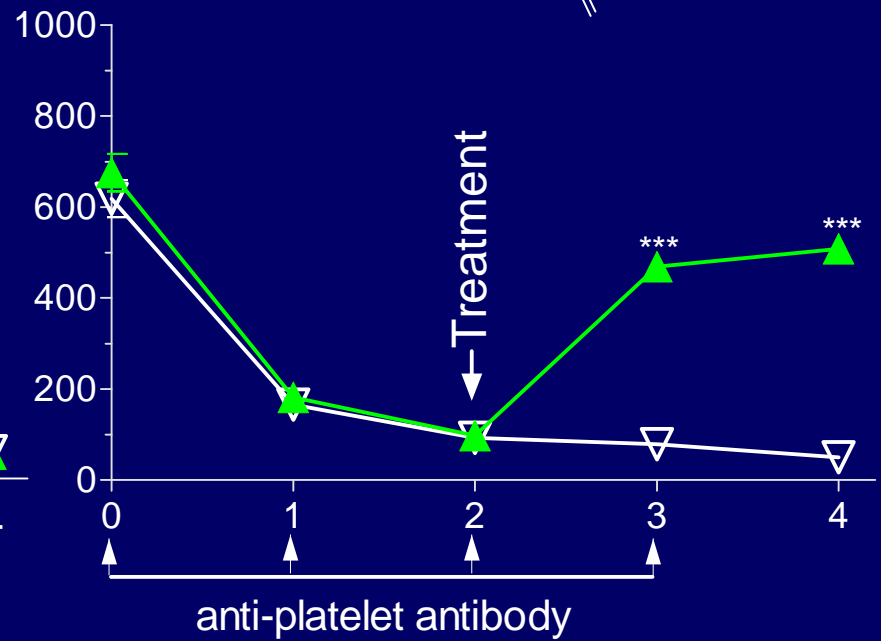
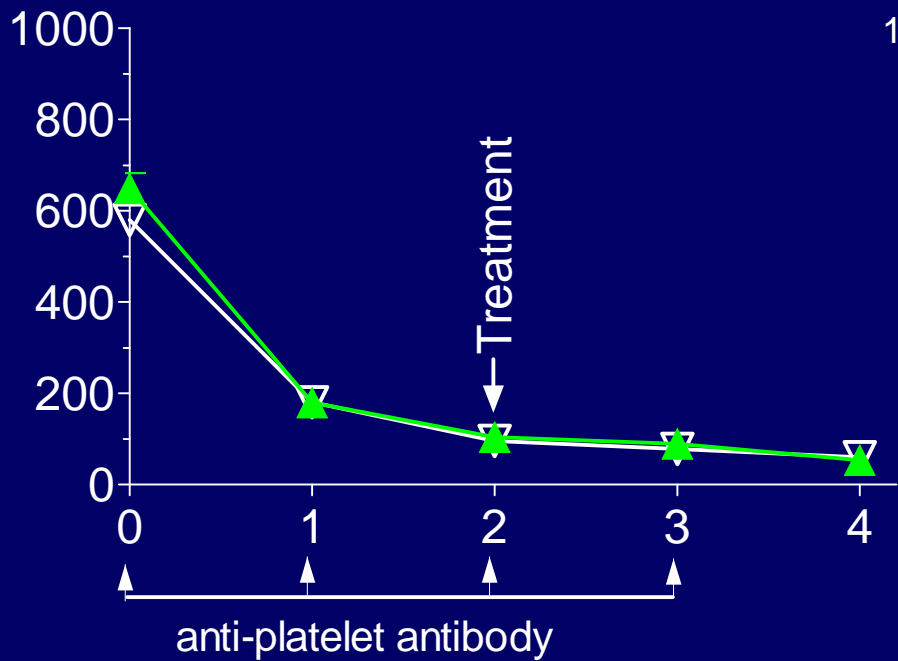
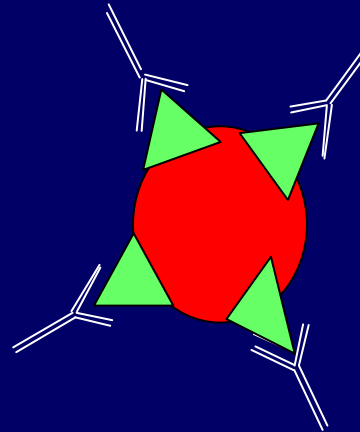
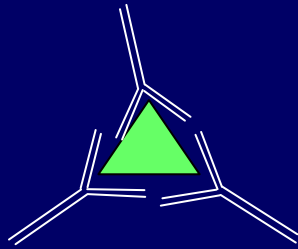




# Immune thrombocytopenic purpura (ITP)



# FcγRIIB<sup>-/-</sup> mice



**Antibodies to RBC  
which work in  
mouse ITP**

**Antibodies to soluble  
antigens which  
work in mouse ITP**

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**IgG-OVA-RBC**  
**GPA-associated protein**  
**Mouse heat stable Ag**

**IgG-OVA**  
**anti-albumin**  
**anti-transferrin**

# Effect of anti-Albumin on inflammatory arthritis

**Normal**



**Arthritis**



**sIC Treated**

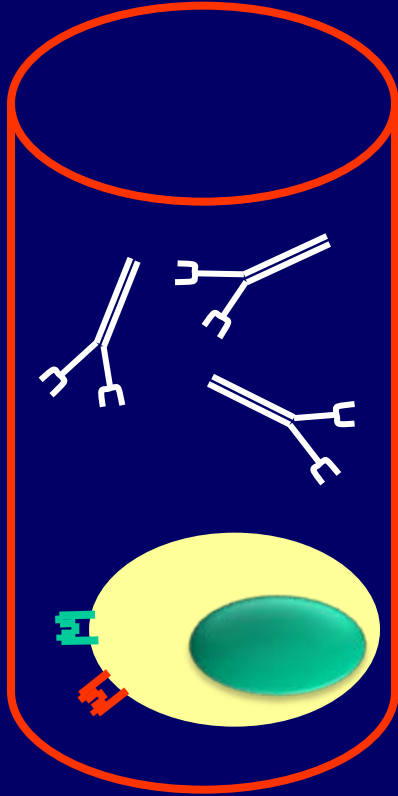


Siragam et al, J Clin Invest 115:155, 2005

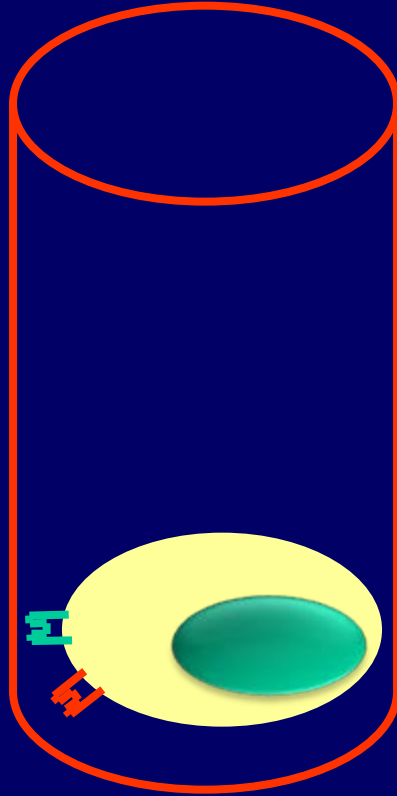
**So how does IVIg work?**

**Could IVIg effects be adoptively transferred with cells?**

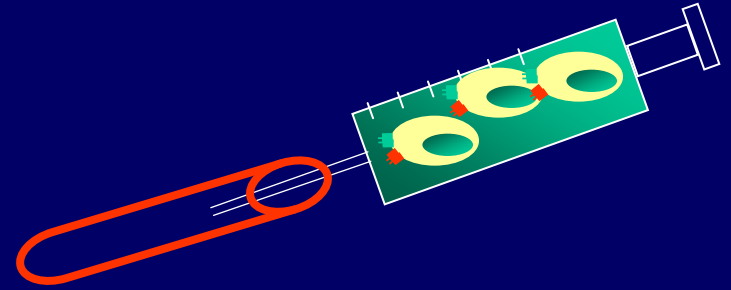
Mix



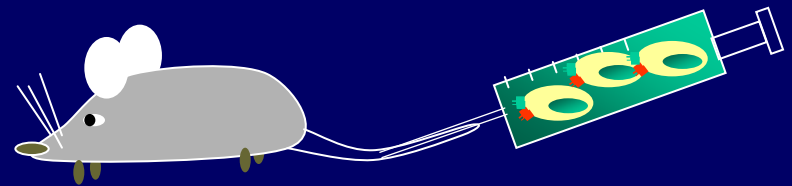
Wash



Load

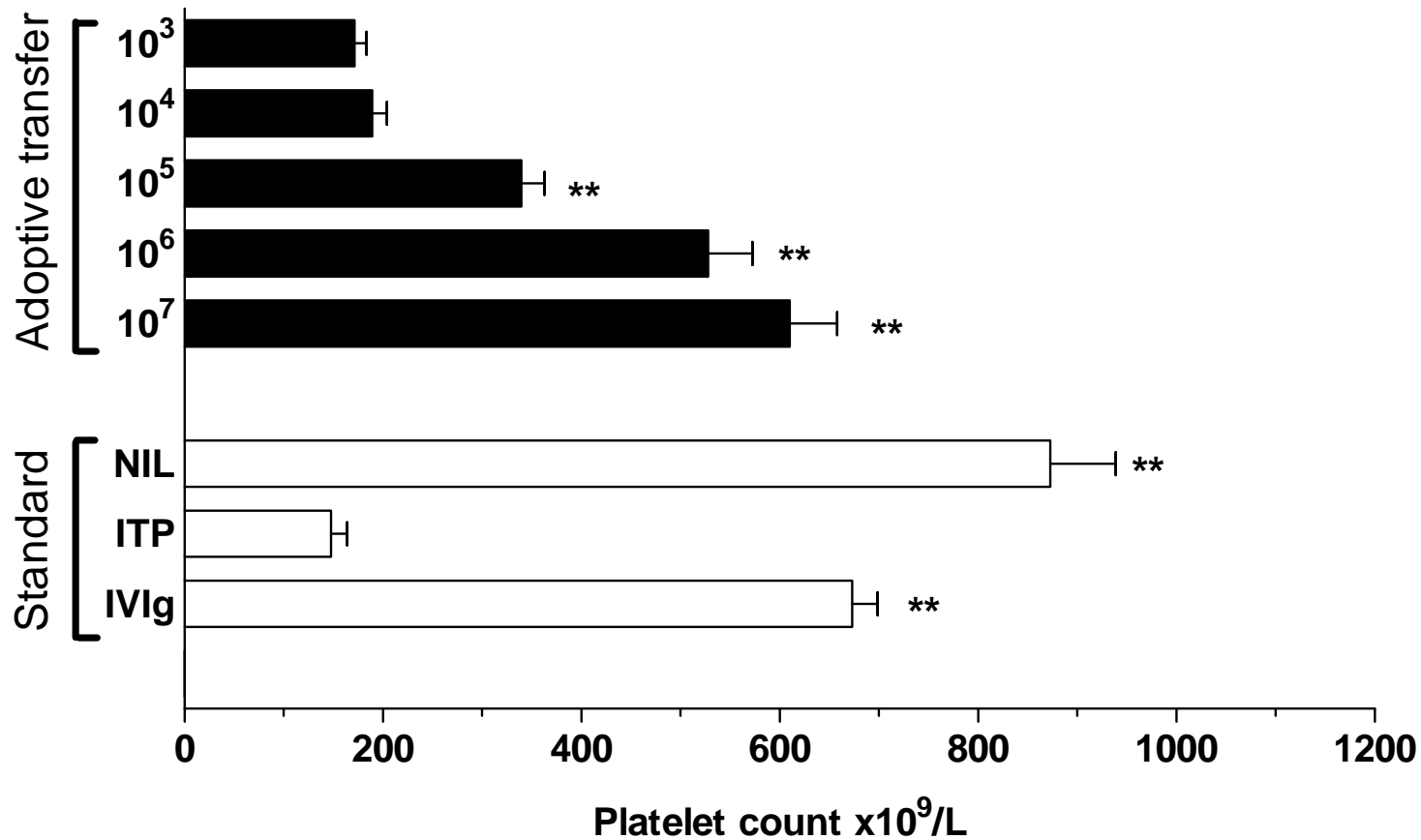


Inject

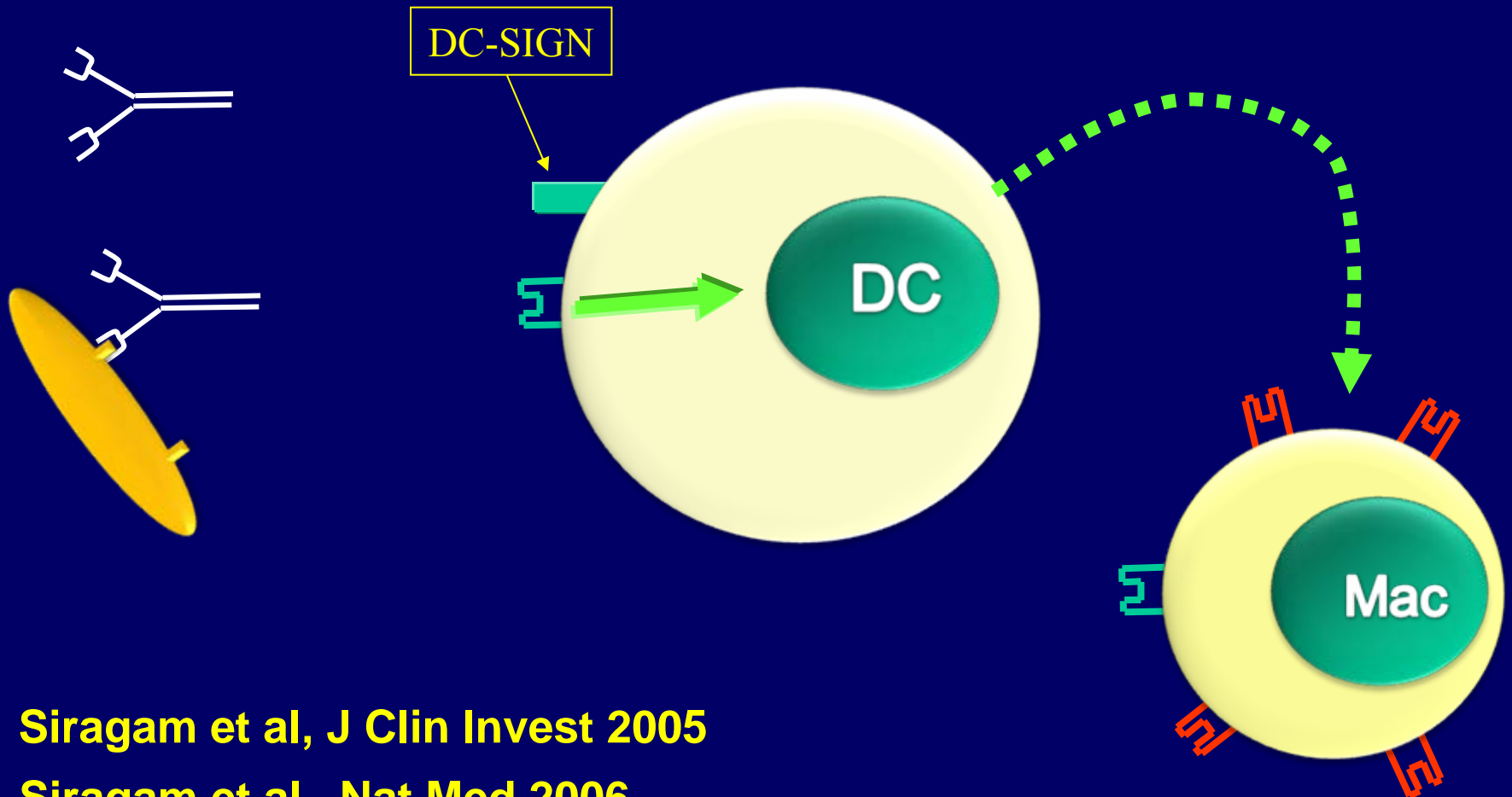


Amelioration of ITP?

# Adoptive transfer of IVIg effects with leukocytes



# Proposed model of IVIg action in murine ITP



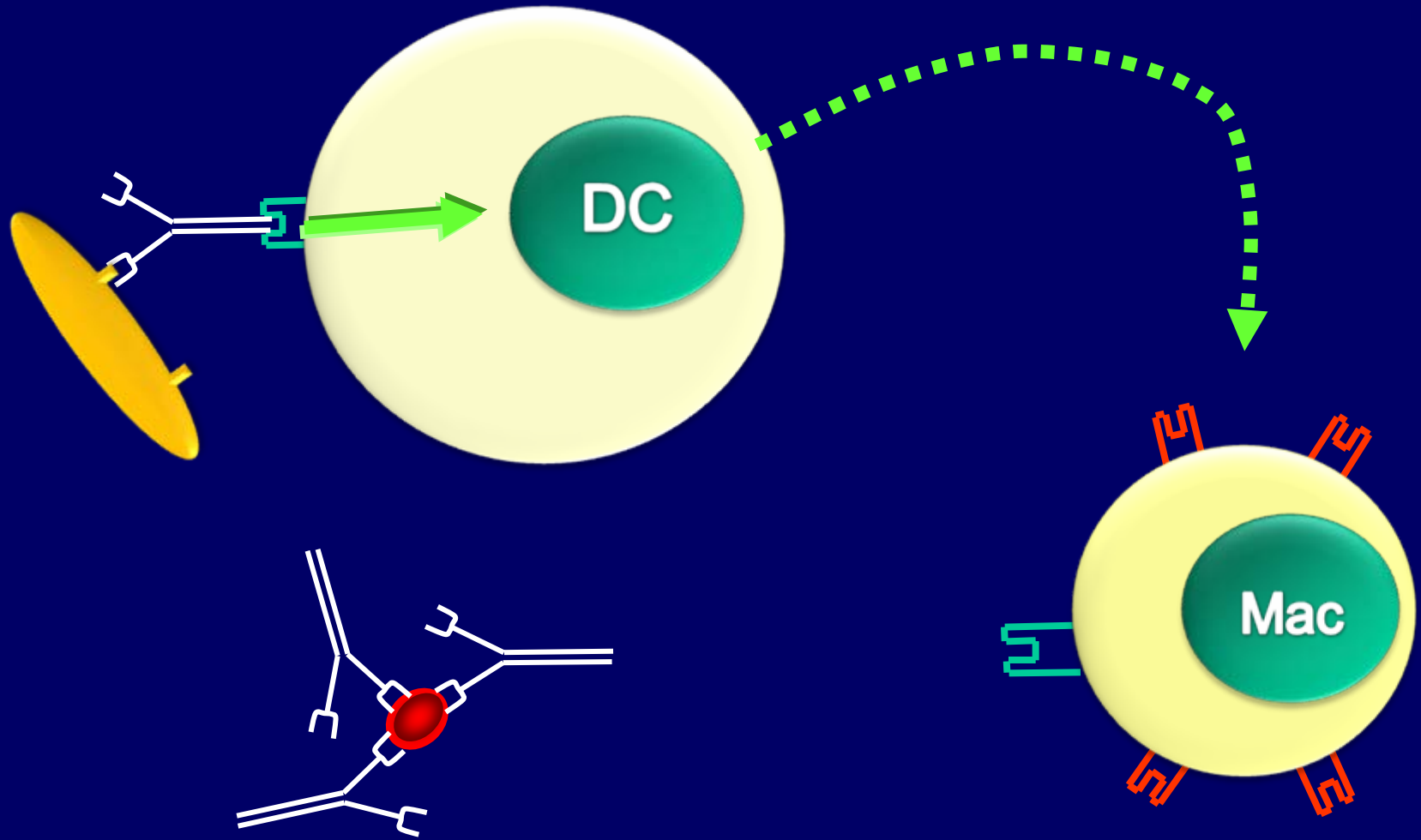
Siragam et al, J Clin Invest 2005

Siragam et al, Nat Med 2006

Anthony et al, PNAS 2008

Samuelsson et al, Science 2001

**Does anti-D ameliorate ITP via the same mechanism as IVIg?**

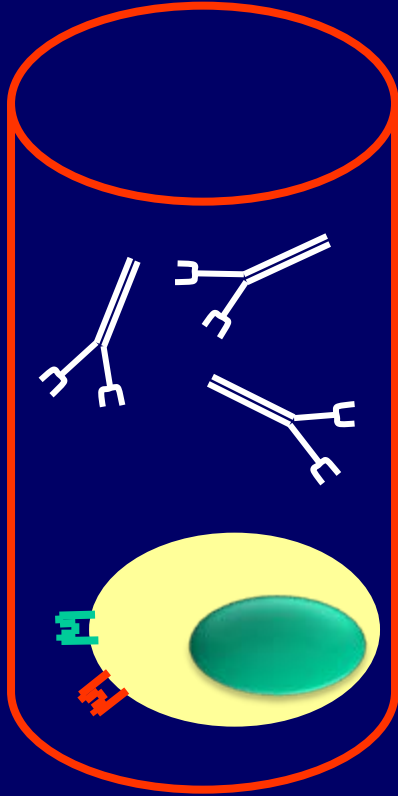


**Song et al, Blood 2005**

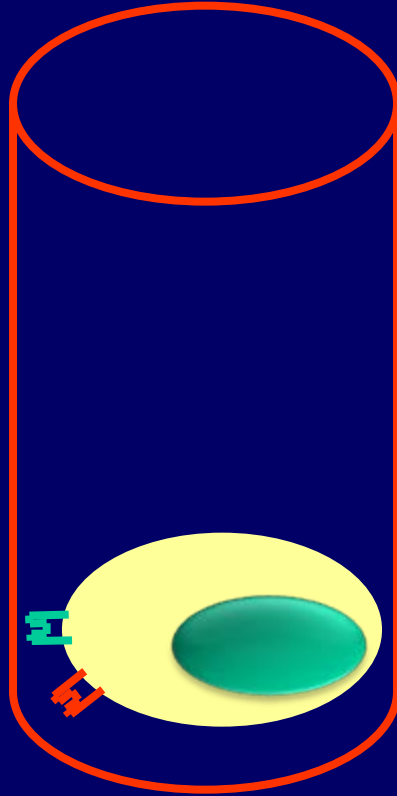
# Conclusions

- Monoclonal and polyclonal antibodies to cell-associated or soluble antigens can inhibit mITP
- Antibodies to a soluble antigen require the presence of Fc $\gamma$ RIIB, similar to IVIg
  - IVIg and anti-D likely work via a different mechanism
- IVIg ameliorates (murine) ITP by engaging activating Fc $\gamma$  receptors on dendritic cells

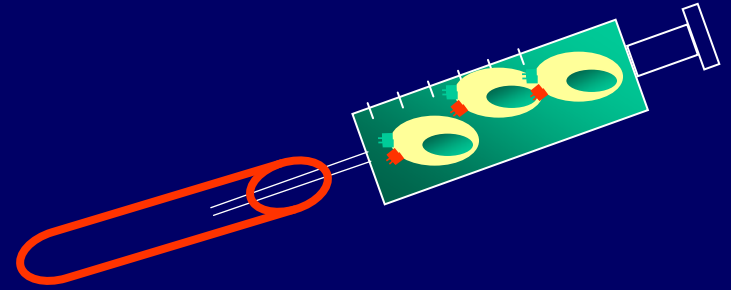
Mix



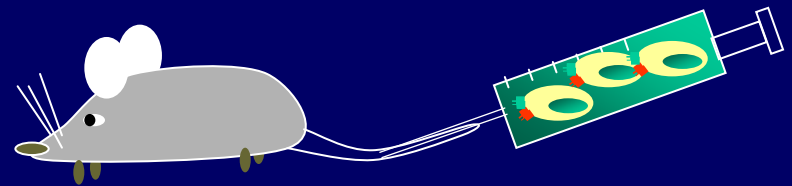
Wash



Load



Inject



Amelioration of ITP?

## Cellular therapy for autoimmune disease?

**Based upon our mouse data,  
we would need the leukocyte or DC fraction  
from 300 mls of human blood.**

### Simplest strategy (Developing Countries):



Hopefully, the patients will get better!



# Acknowledgements

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