CANADIAN BLOOD SERVICES, 5th ANNUAL INTERNATIONAL SYMPOSIUM ON
TRANSFUSION IMMUNOLOGY:MACROPHAGE FUNCTION AND IMMUNE CYTOPENIAS

University of Toronto, Reichmann Family Lecture Hall, Saturday, September 8, 2007.

Pathophysiology of the Immune Thrombocytopenias

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Toronto Platelet Immunology Group,

Toronto, Ontario, Canada.


ABSOLUT
Don

This talk is posted on:

www.angelfire.com/ut/johnsnotes/index.html

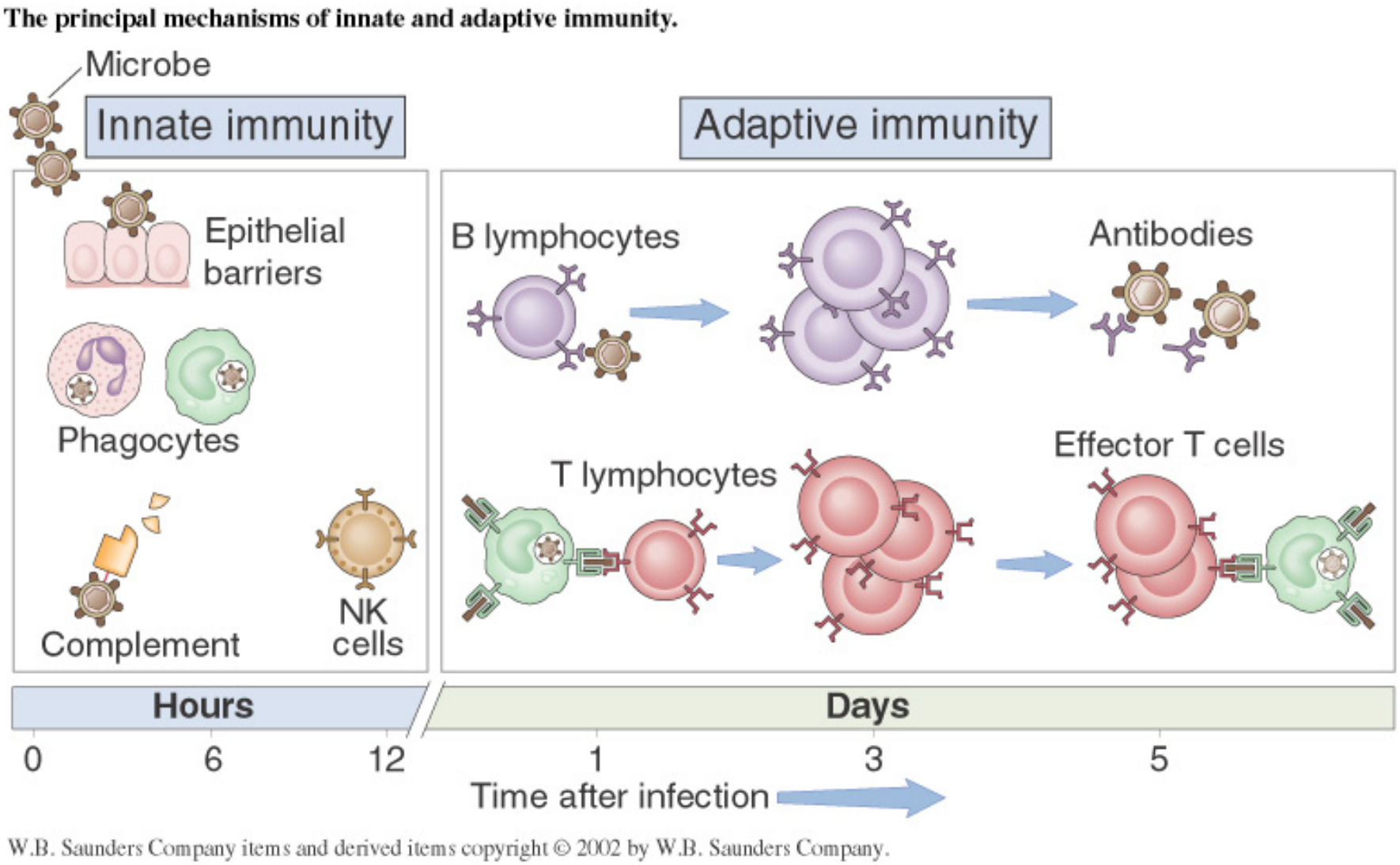
Outline of talk:

1. Crash course on immunity, T cells, autoimmunity and platelets.

Reviews of the Literature since 2004.

1. Pathophysiology of immune thrombocytopenia (ITP).
2. Pathophysiology of alloimmune thrombocytopenia (NAITP).
3. Pathophysiology of heparin induced thrombocytopenia (HIT).
4. Pathophysiology of autoimmune neutropenia.
5. Pathophysiology of platelet MHC alloimmunity.
6. Pathophysiology of septic lung injury.

The Immune System:



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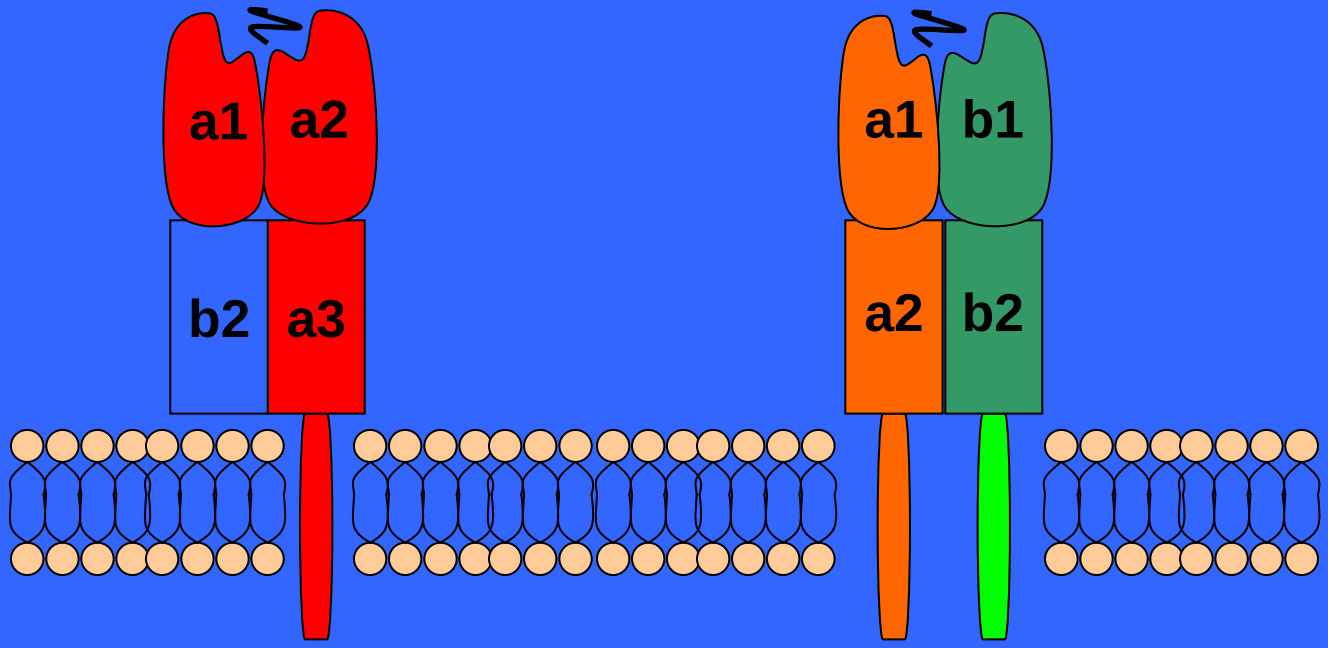
T cell Recognition:

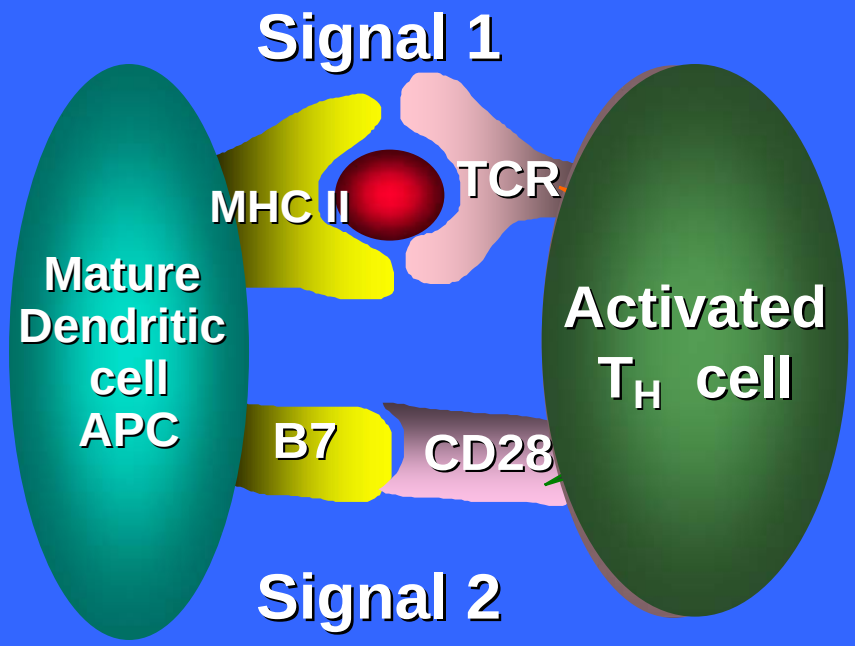
- Binds 8-10mers
- Expressed on most nucleated cells and platelets
- Presents endogenous proteins to CD8+ T cells

- Binds 13-25mers
- Expressed on APCs, Macs, B cells, activated T cells
- Presents exogenous proteins to CD4+ T cells



Class I Class II

T cell Activation:



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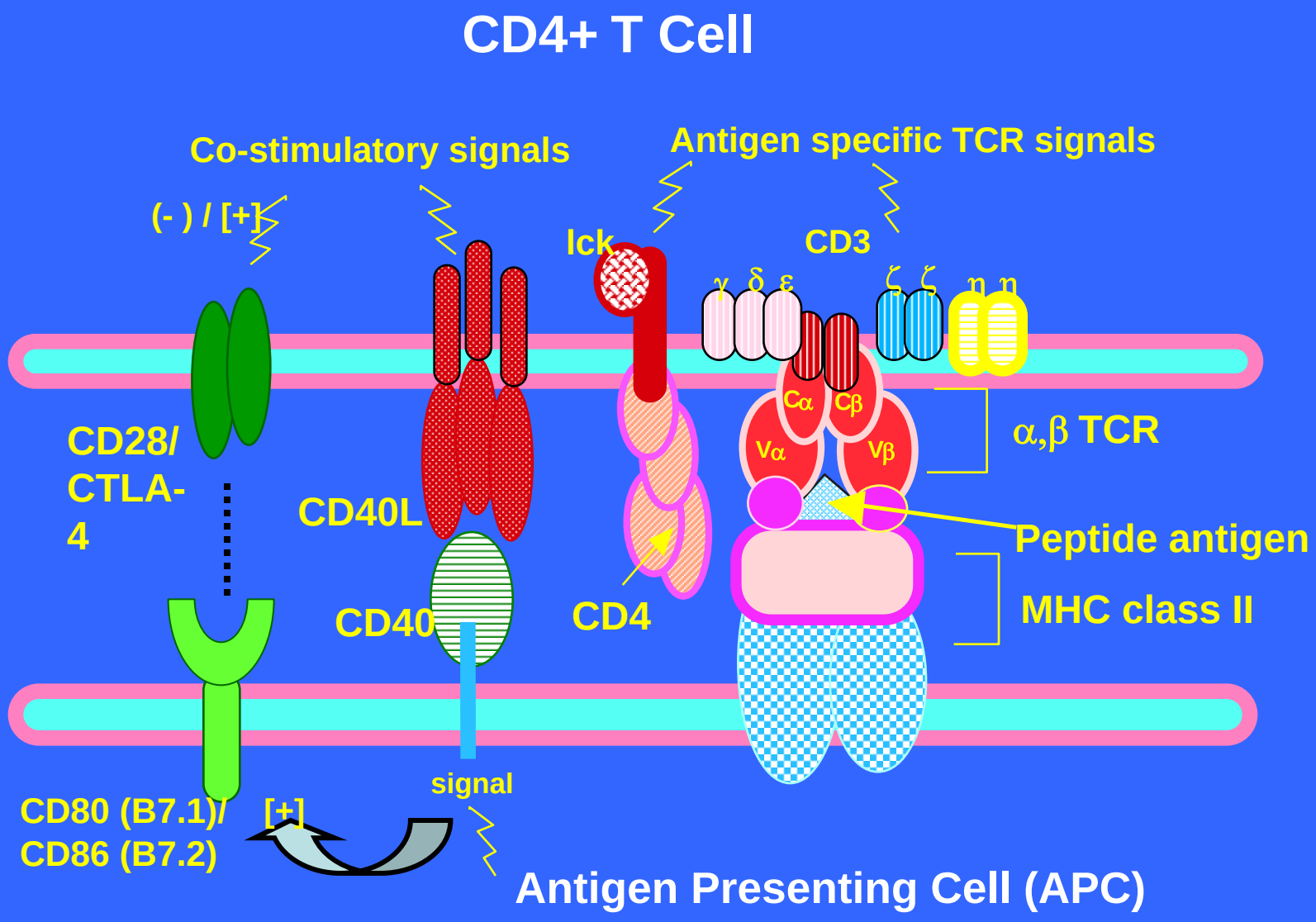
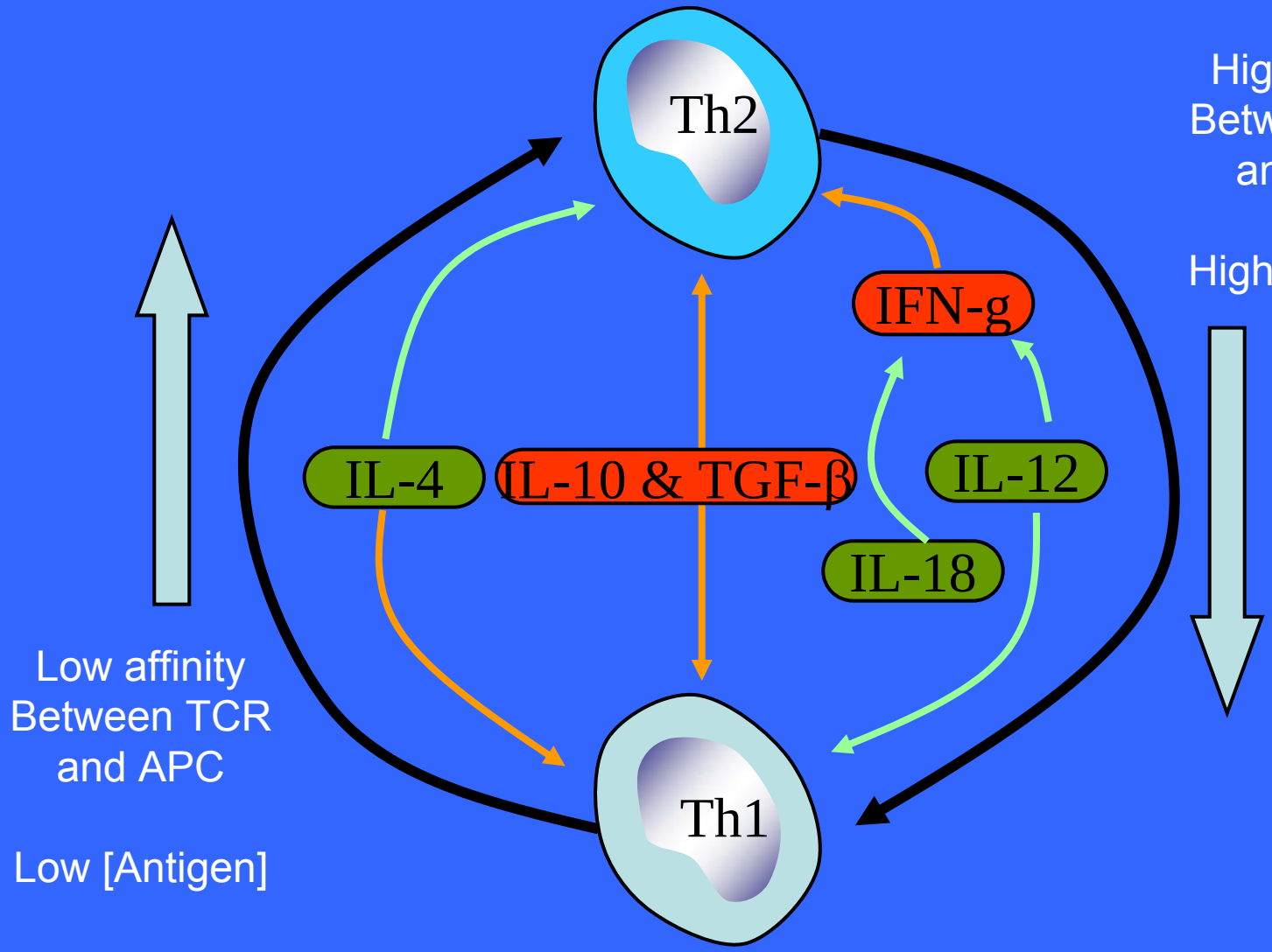
T cell activation is regulated by signals derived from the TCR /CD3/CD4 complex and the CD40L and CD28/CTLA-4 co-stimulatory molecules:



Cytokine Regulation via Th1/Th2 Balance:



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Regulatory T cells

Th1 T cells and Th2 T cells can downregulate each other by the cytokines produced. IFNγ and IL-12 downregulate Th2 cells while IL-10 inhibits Th1 cells.

T regulatory cells (Tregs) CD4+CD25+Fox3+ mediate suppression by cell-cell contact and cytokines (IL-10 and TGF).

Regulatory T cell deficiencies may result in autoimmune diseases or allergic responses.

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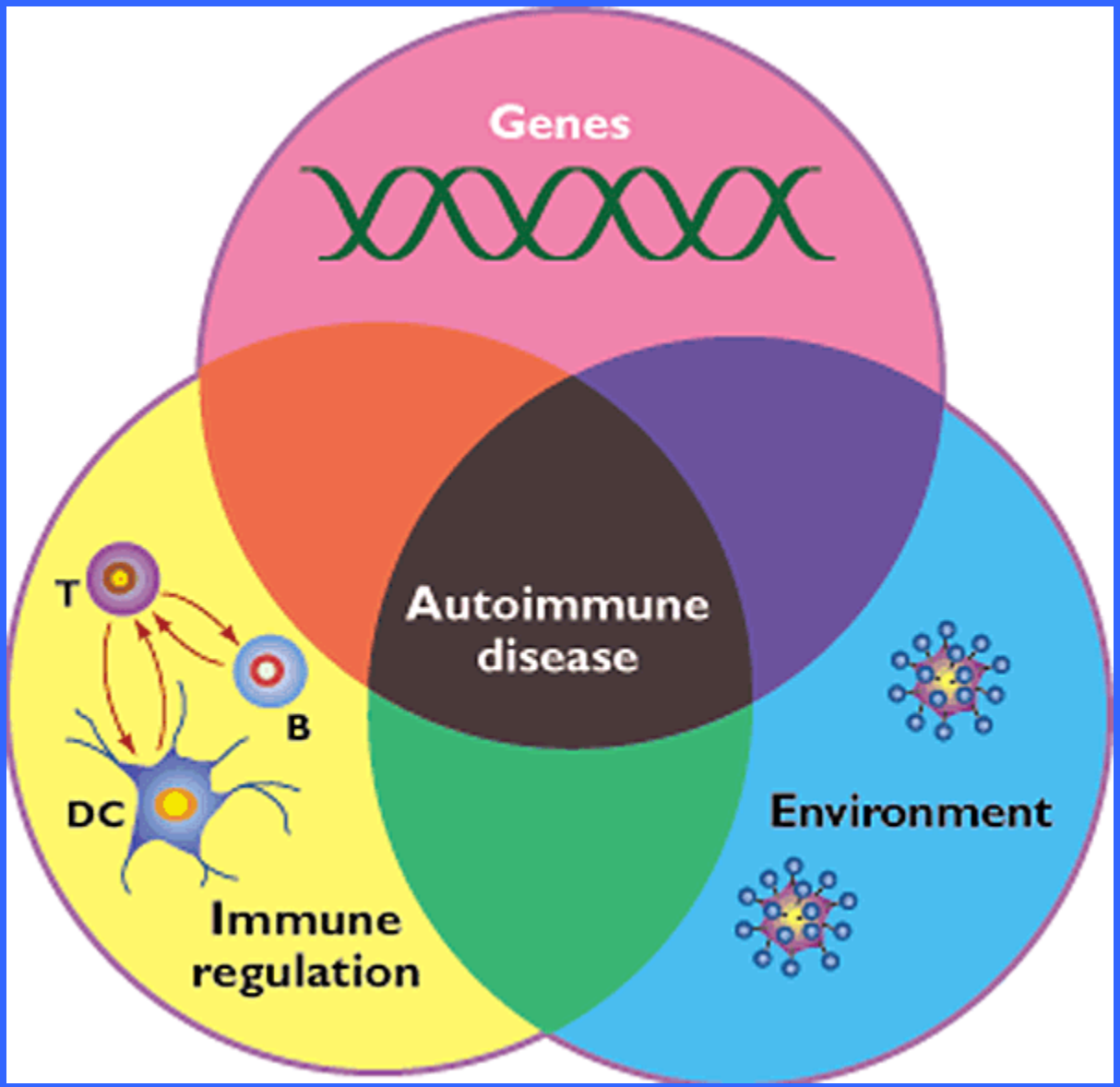
Autoimmunity:

- Immune reactivity against self.
- Generally classed into systemic (e.g. SLE, RA,GVHD) and organ-specific (e.g. MS, IDDM, IBD, ITP etc.).

Venn Diagram: Requirements for the Development of Autoimmune Disease



Nature Immunology, 2001

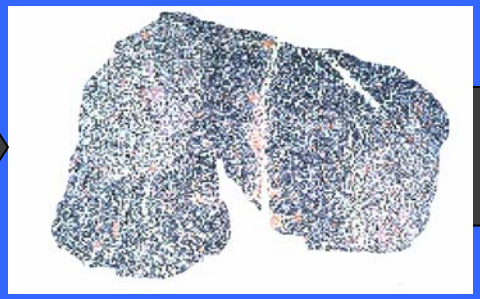
Organ specific (sp) Autoimmunity:

- **Deficiency of central and/or peripheral tolerance induction mechanisms**
  - **failure to eliminate or deactivate self reactive lymphocytes.**

T Cell Development: and potential for autoimmunity:

T cell precursors

Thymus



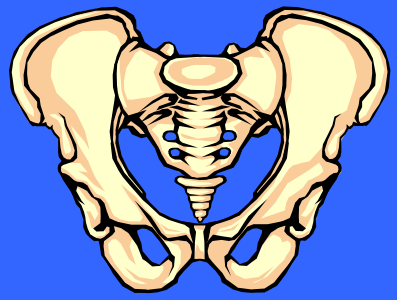
Central Tolerance

Abnormal release of autoreactive T cells

Selected T cells

Peripheral Tolerance

-anergy/deletion/ suppression



Bone marrow

Molecular mimicry

Abnormal antigen expression

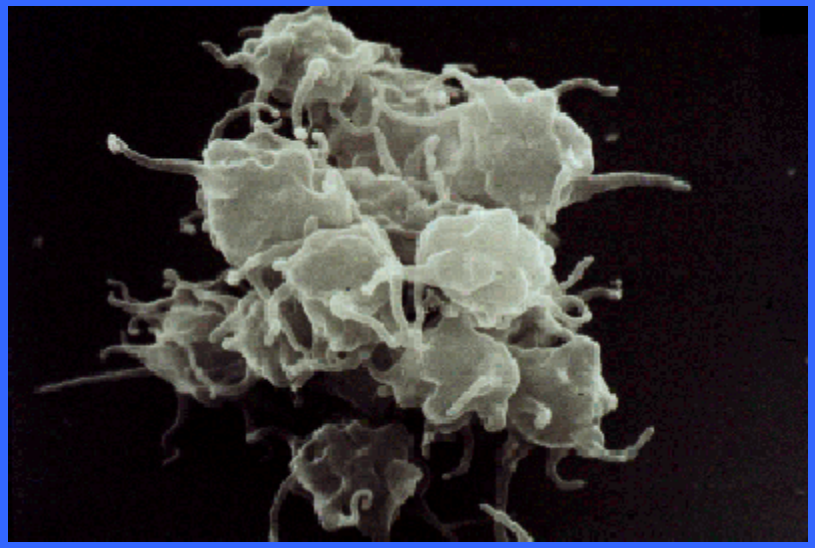
T helper 1/T helper 2 imbalance

Cytokine Milieu

Costimulation/activation faults

A crash course on platelets:

Resting



Activated

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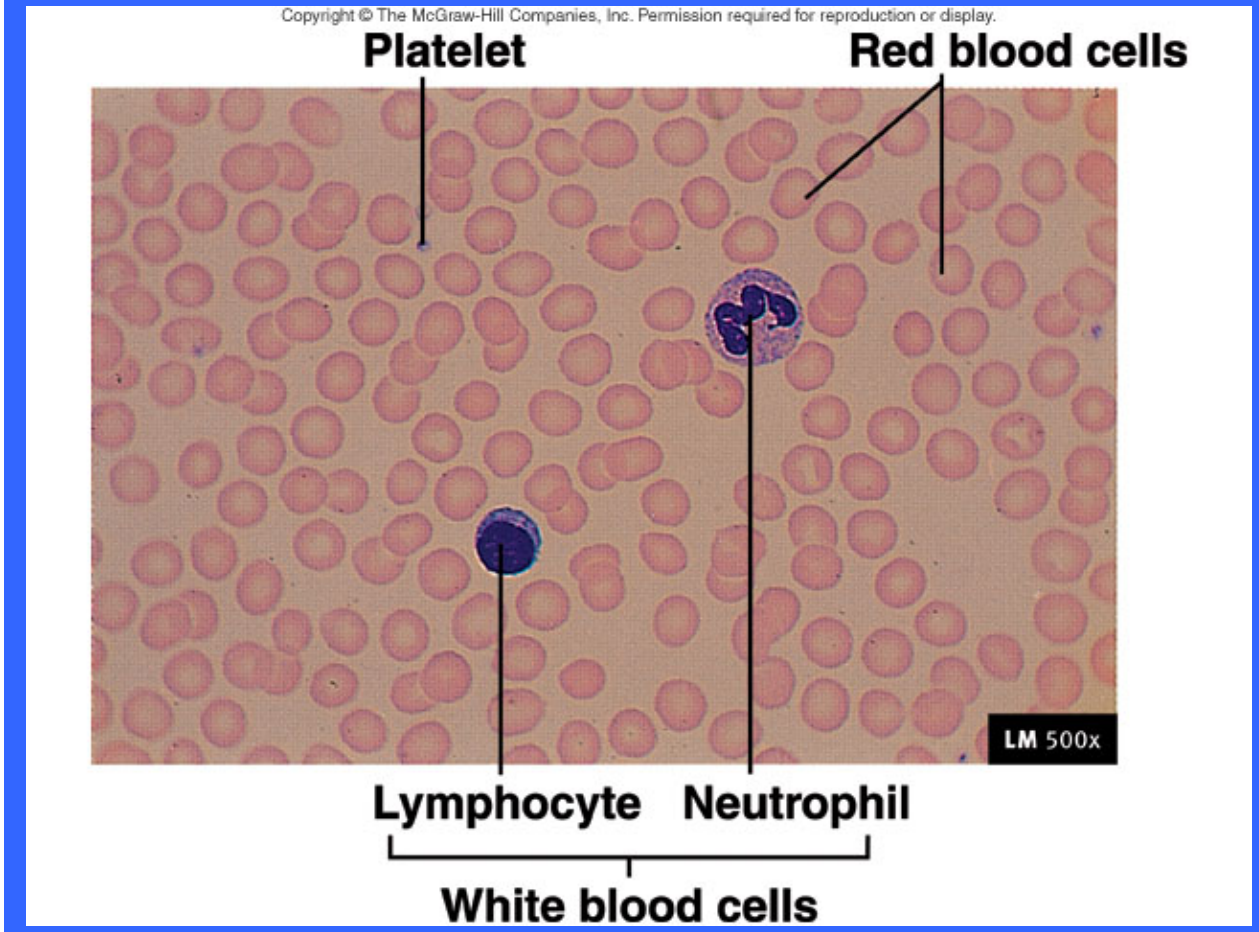
Platelets:



- Anucleated cell fragments pinched off from megakaryocytes in bone marrow
- Important in preventing blood loss
  - Platelet plug
  - Promote formation and contraction of clots

Normal range: 150-400x10^9/L

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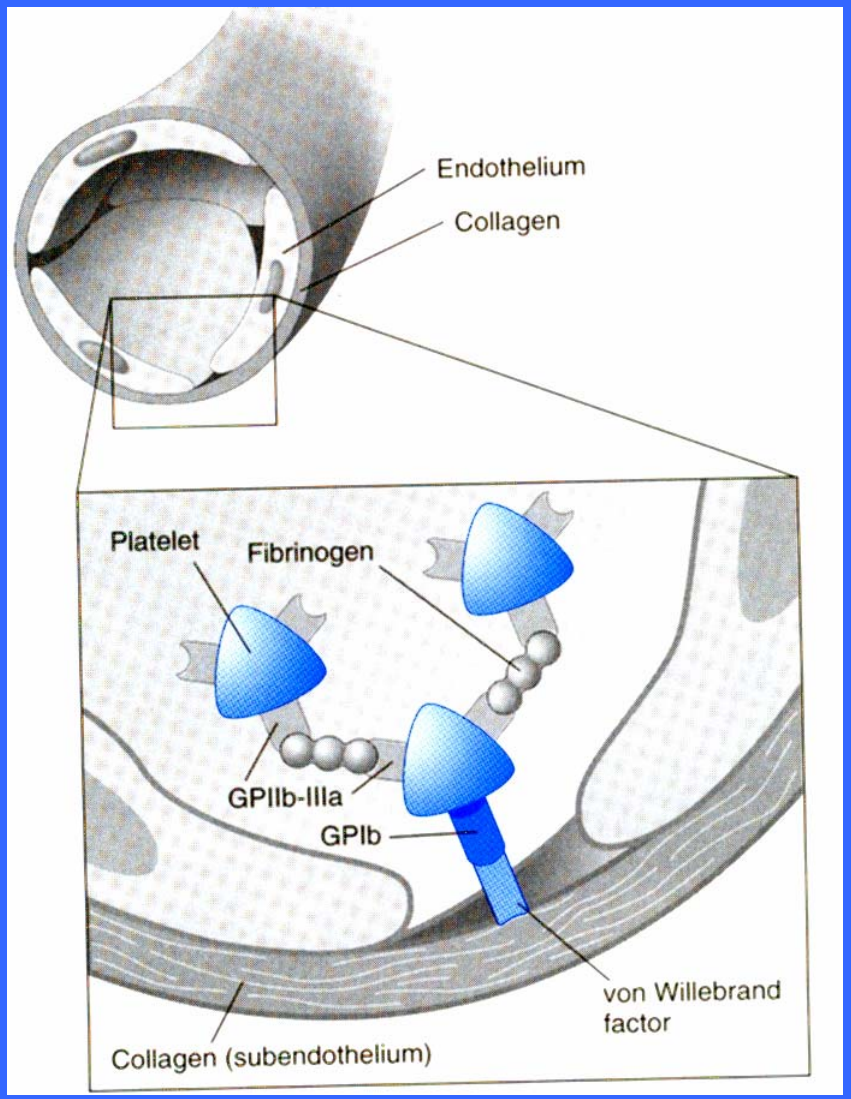
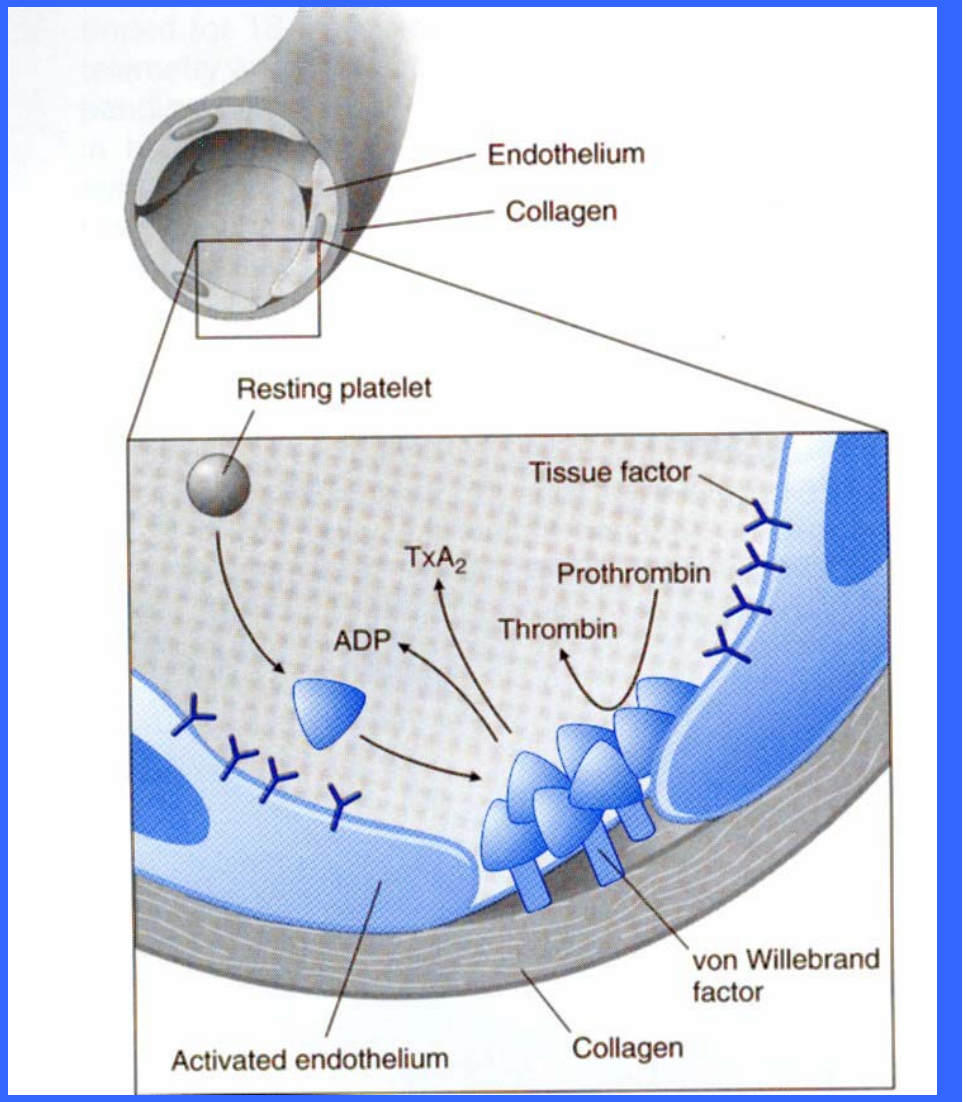
Platelet adhesion and aggregation



Platelet activation



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How platelets interact with innate immune mechanisms

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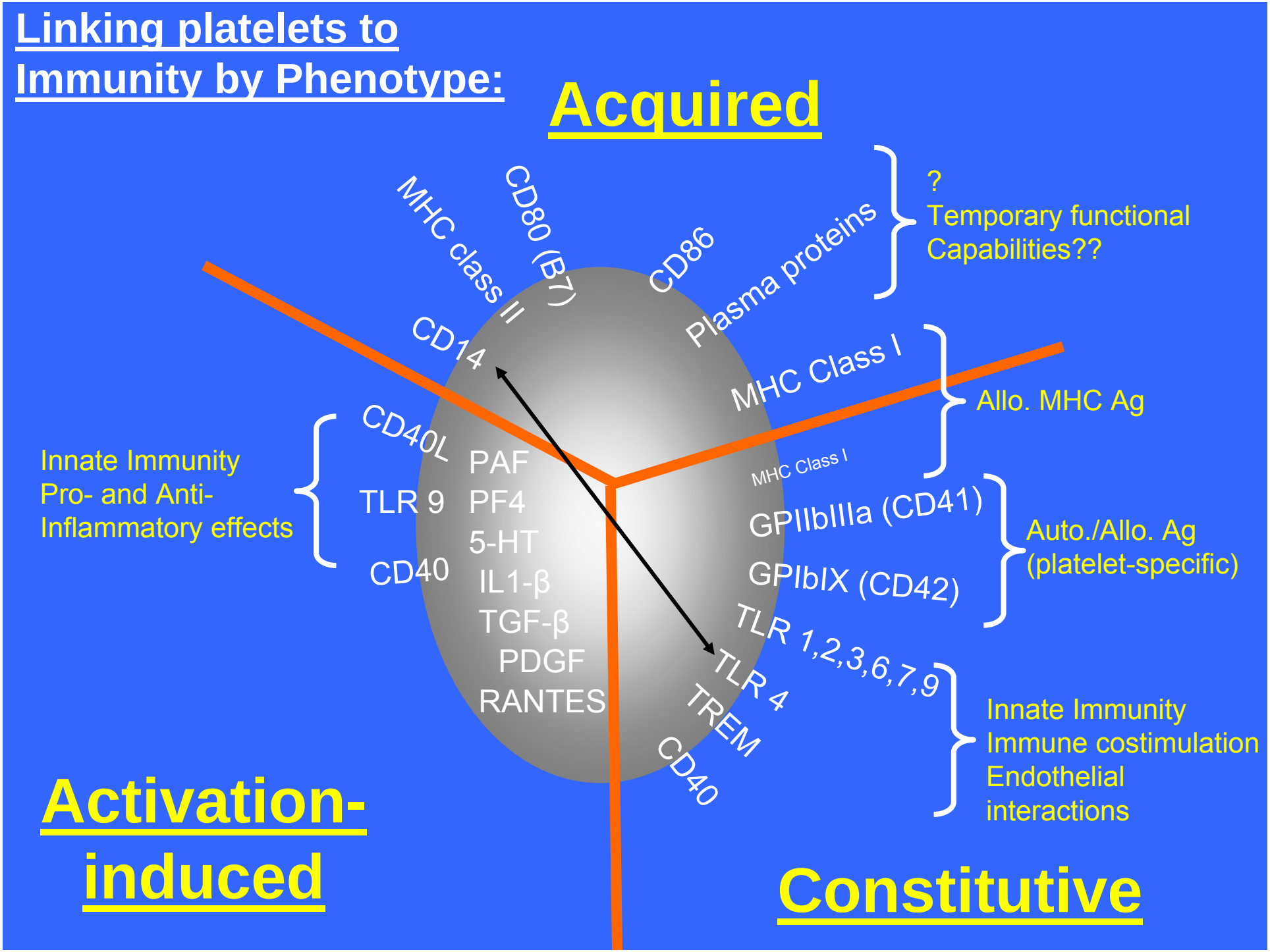
Linking platelets to Immunity by Phenotype:



Platelets and CD40/CD40L (132 papers since 1998):

CD40 ligand on activated platelets triggers an inflammatory reaction of endothelial cells

Nature, 1998

Volker Henn*†, Joseph R. Slupsky†‡, Michael Gräfe§, Ioannis Anagnostopoulos‖, Reinhold Förster¶, Gert Müller-Berghaus‡ & Richard A. Kroczek*

* *Molecular Immunology, Robert Koch-Institute, 13353 Berlin, Germany*
‡ *Haemostasis Research Unit, Max-Planck-Institut für Physiologische und Klinische Forschung, Kerckhoff-Klinik, 61231 Bad Nauheim, Germany*
§ *Deutsches Herzzentrum, Augustenburger Platz 1, 13353 Berlin, Germany*
‖ *Institute of Pathology, Klinikum Benjamin Franklin, Freie Universität Berlin, Germany*
¶ *Max-Delbrück-Center for Molecular Medicine, 13122 Berlin, Germany*
† *These authors contributed equally to this work.*

Enhanced Levels of Soluble and Membrane-Bound CD40 Ligand in Patients With Unstable Angina

Possible Reflection of T Lymphocyte and Platelet Involvement in the Pathogenesis of Acute Coronary Syndromes

Pål Aukrust, MD, PhD; Fredrik Müller, MD, PhD; Thor Ueland, BS; Trude Berget, MD; Elinor Aaser, MD; Anne Brunsvig, BS; Nils Olav Solum, PhD; Kolbjørn Forfang, MD, PhD; Stig S. Frøland, MD, PhD; Lars Gullestad, MD, PhD

Circulation, 1999

Role of Platelet P-Selectin and CD40 Ligand in the Induction of Monocytic Tissue Factor Expression

Eva Lindmark, Taavo Tenno, Agneta Siegbahn

Arteriosclerosis Thromb Vas Biol, 2000

HEMOSTASIS, THROMBOSIS, AND VASCULAR BIOLOGY

The inflammatory action of CD40 ligand (CD154) expressed on activated human platelets is temporally limited by coexpressed CD40

Blood, 2001

Volker Henn, Sabine Steinbach, Kerstin Büchner, Peter Presek, and Richard A. Kroczek

Brief report

Increased soluble and platelet-associated CD40 ligand in essential thrombocythemia and reactive thrombocytosis

Blood, 2002

Jean-François Viallard, Anne Solanilla, Bruno Gauthier, Cécile Contin, Julie Déchanet, Christophe Grosset, Jean-François Moreau, Vincent Praloran, Paquita Nurden, Jean-Luc Pellegrin, Alan T. Nurden, and Jean Ripoche

CD40 Is Constitutively Expressed on Platelets and Provides a Novel Mechanism for Platelet Activation

Circ Res, 2003

David P. Inwald, Alison McDowall, Mark J. Peters, Robin E. Callard, Nigel J. Klein

Cutting Edge: T Cells Trigger CD40-Dependent Platelet Activation and Granular RANTES Release: A Novel Pathway for Immune Response Amplification[1]

J Immunol, 2004

Silvio Danese, Carol de la Motte,† Brenda M. Rivera Reyes,* Miquel Sans,* Alan D. Levine,* and Claudio Fiocchi[2]**

Cooperation between platelet-derived CD154 and CD4$^+$ T cells for enhanced germinal center formation

J Leuk Biol, 2005

Bennett D. Elzey,* Julieann F. Grant,†,‡ Haley W. Sinn,* Bernhard Nieswandt,§ Thomas J. Waldschmidt,†,‡ and Timothy L. Ratliff*,†,¶,‖,**,††,1

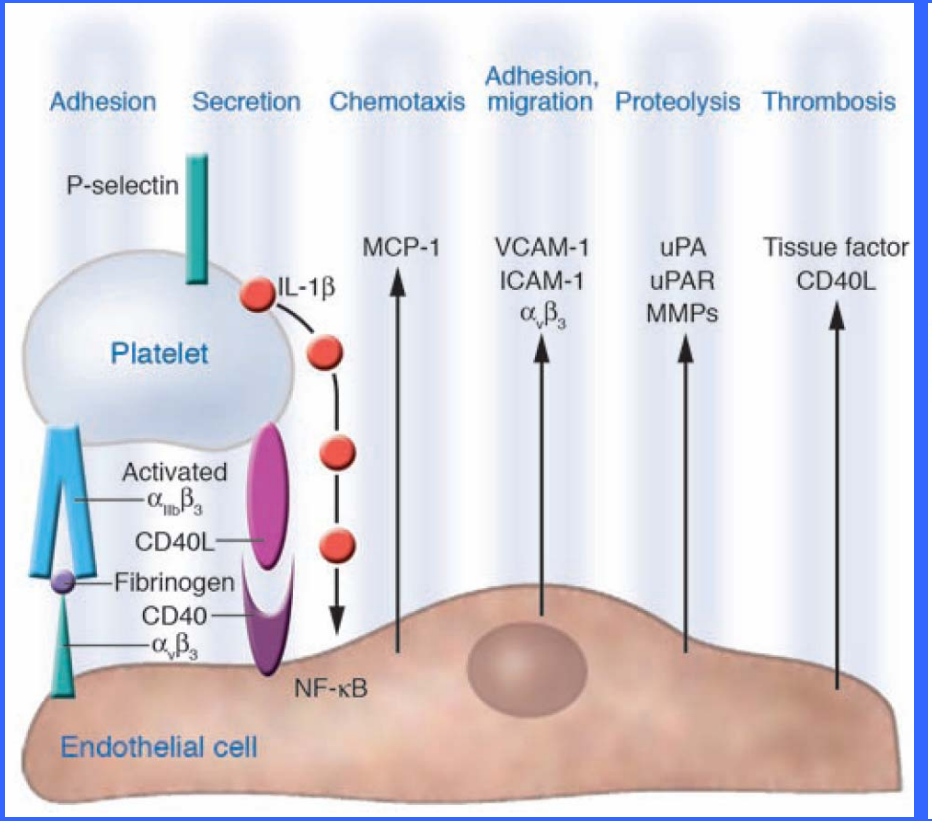
Platelet-derived or soluble CD154 induces vascularized allograft rejection independent of cell-bound CD154

J Clin Invest, 2006

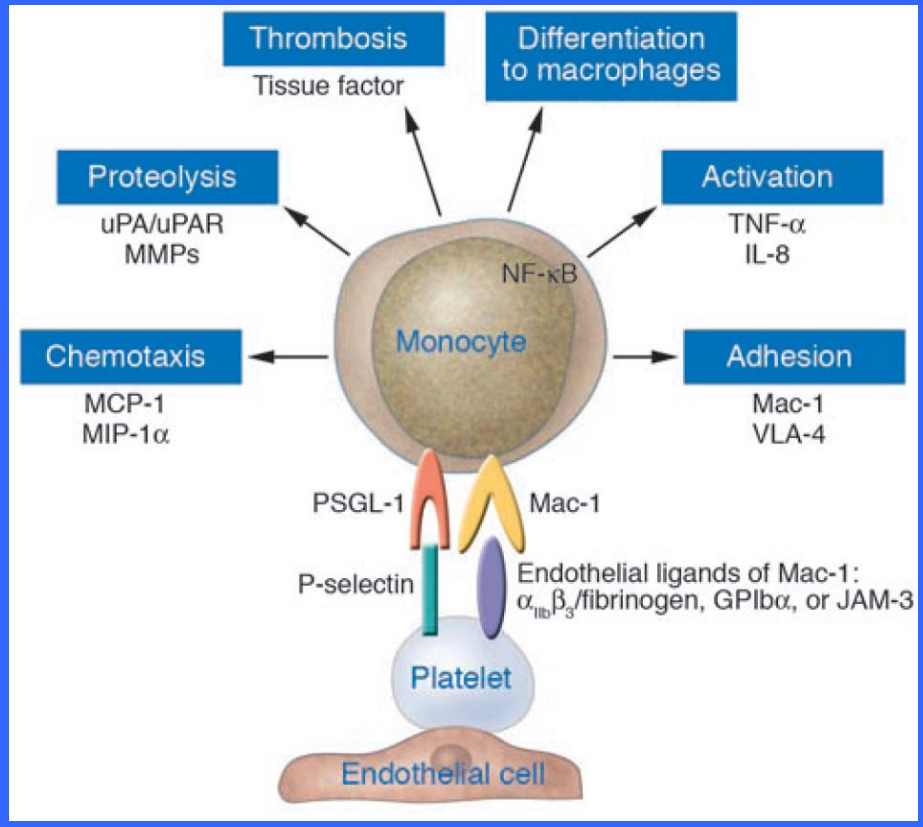
He Xu, Xiaojie Zhang, Roslyn B. Mannon, and Allan D. Kirk

Platelet can regulate innate immune mechanisms in many ways:

Direct



Indirect



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Immune thrombocytopenic purpura (ITP)

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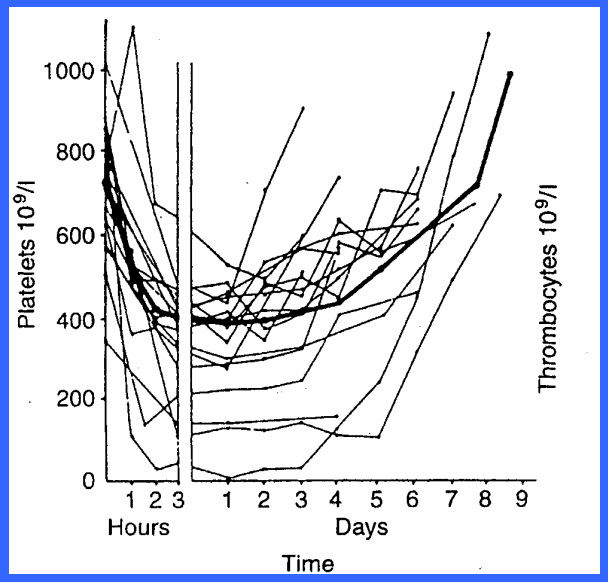
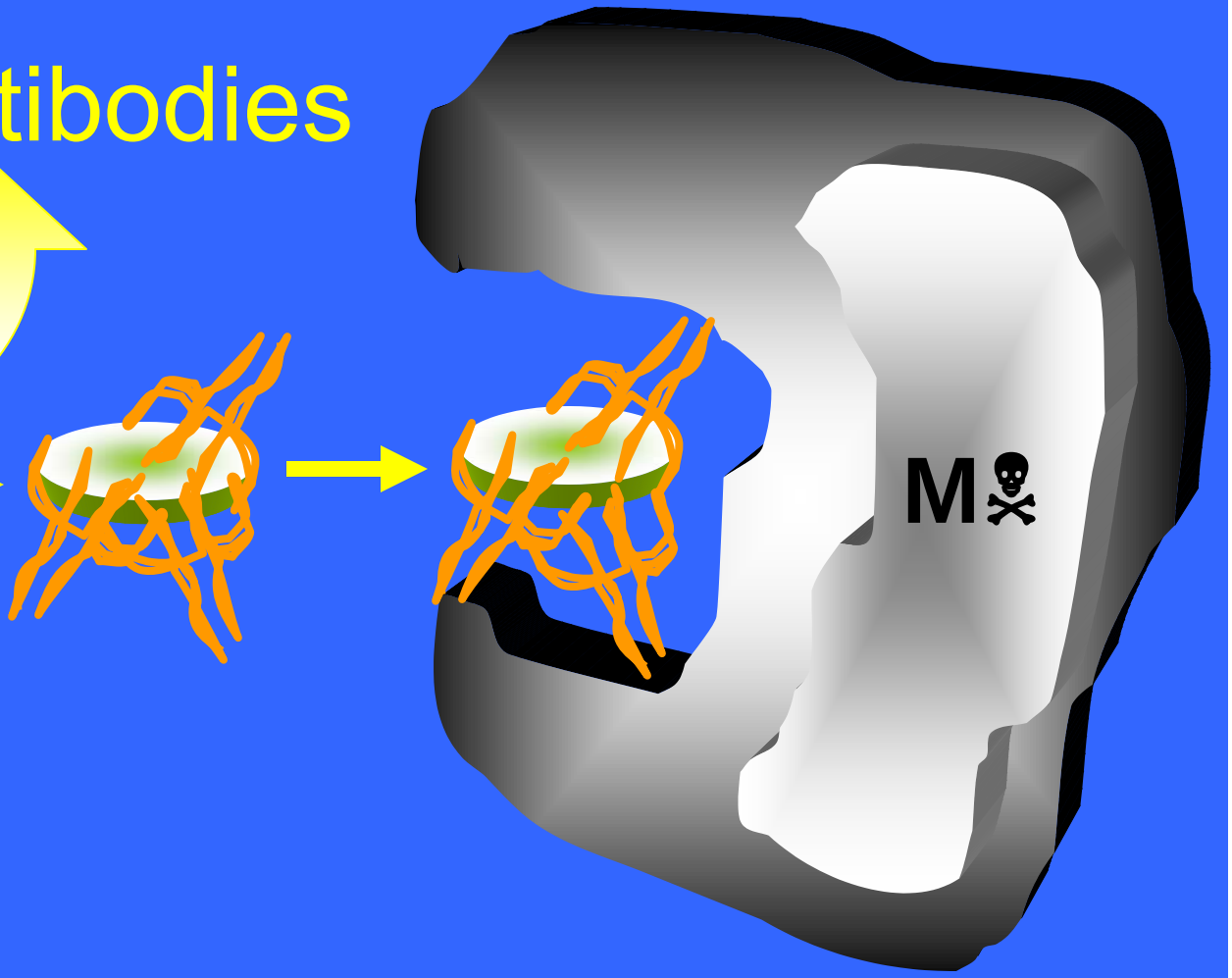
ITP, pathogenesis:

Autoantibodies

Platelet



Harrington et al, J Lab Clin Med 38:1, 1951



Increased
RES Destruction

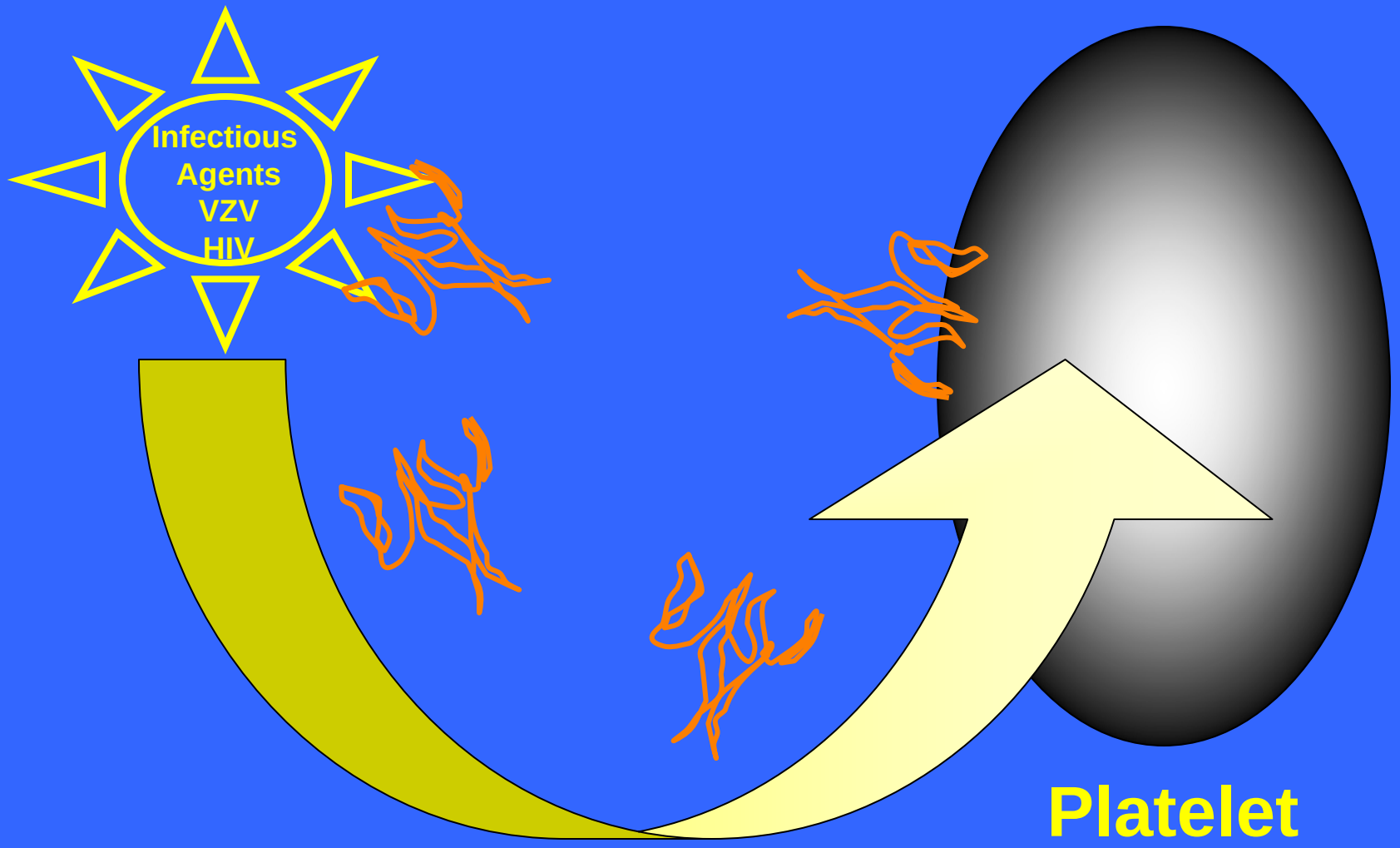
Acute ITP:

Good example of molecular mimicry.

Cross reactivity of anti-viral antibodies with normal platelet epitopes.

Wright et al Brit J Haematol 95:145,1996

Acute ITP, Molecular Mimicry:



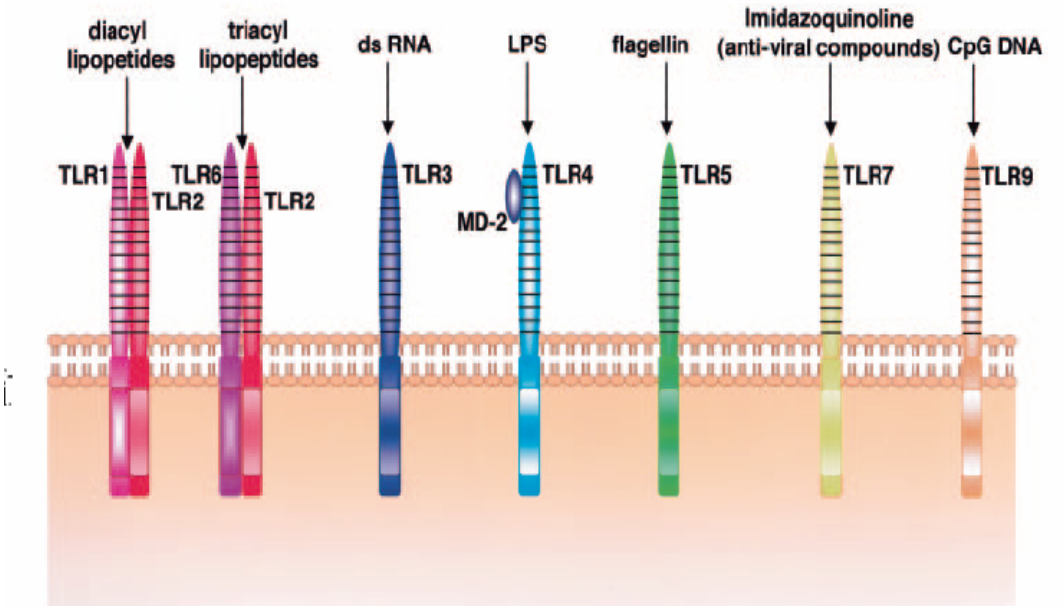
Are there other immune mechanisms where infectious agents and platelets interact and potentially affect T cells?

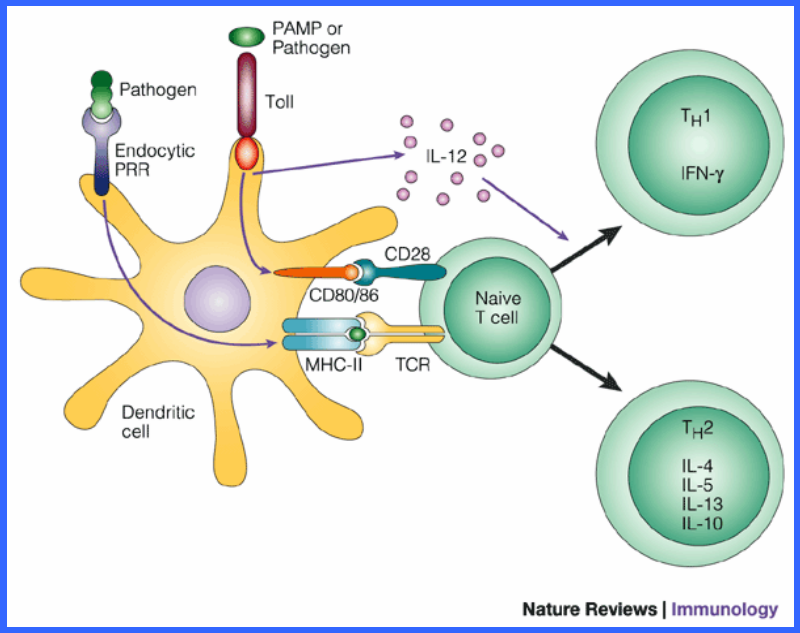
In other immune-mediated diseases, the answer is yes!

Iannacone M et al. Platelets mediate cytotoxic T lymphocyte-induced liver damage. Nat Med 11:1167, 2005

What about in acute ITP?

Toll-like receptors:





Akira J.Biol.Chem. 2003 278:38105–38108

www.angelfire.com/ut/johnsnotes/index.htm

Recent Literature: Platelet–TLR (16 papers)

- Semple et al. Platelets. 15:267,2004.
- Shiraki et al. Thromb. Res. 113:379, 2004.
- Coppinger et al. Blood. 103:2096, 2004.
- Yu et al. Int. Immunopharmacol. 5:571, 2005.
- Cognasse et al. Immunol. Cell Biol. 83:196, 2005.
- Ward et al. Thromb. Haemost. 94:831, 2005.
- Alves-Filho JC. Thromb Res. 115:537, 2005.
- Andonegui et al. Blood. 106:2417, 2005.
- Aslam et al. Blood. 107:637, 2006.
- Patrignani et al. Blood. 107:3572, 2006.
- Ståhl et al. Blood. 108:167, 2006.
- Jayachandran et al. J Appl Physiol. 102:429, 2007.
- Clarke et al. Nat Med. 13:463, 2007.
- Semple et al. Blood. 109:4803, 2007.
- Cognasse et al. Curr Immunol Rev. 3:109-115, 2007.
- Bazin et al Infect Immunity 2007, in press.

Platelets Express TLR that is Functional:

MURINE PLATELETS EXPRESS TOLL LIKE RECEPTOR 2: A POTENTIAL REGULATOR OF INNATE AND ADAPTIVE IMMUNITY

J. Semple, R. Aslam, J. Freedman ***Platelets, 2004***

St. Michael's Hospital, Toronto, ON, Canada

Regular Article

Expression of Toll-like receptors on human platelets ***Thromb Res, 2004***

Rio Shiraki[a], Nobutaka Inoue[a,*], Satoru Kawasaki[b], Asumi Takei[b], Makoto Kadotani[b], Yoshio Ohnishi[b], Junya Ejiri[a], Seiichi Kobayashi[c], Ken-ichi Hirata[a], Seinosuke Kawashima[a], Mitsuhiro Yokoyama[a]

IMMUNOBIOLOGY

Platelets express functional Toll-like receptor-4 ***Blood, 2005***

Graciela Andonegui, Steven M. Kerfoot, Kelly McNagny, Kirsten V. J. Ebbert, Kamala D. Patel, and Paul Kubes

IMMUNOBIOLOGY

Blood, 2006

Platelet Toll-like receptor expression modulates lipopolysaccharide-induced thrombocytopenia and tumor necrosis factor-α production in vivo

Rukhsana Aslam, Edwin R. Speck, Michael Kim, Andrew R. Crow, K. W. Annie Bang, Frederick P. Nestel, Heyu Ni, Alan H. Lazarus, John Freedman, and John W. Semple

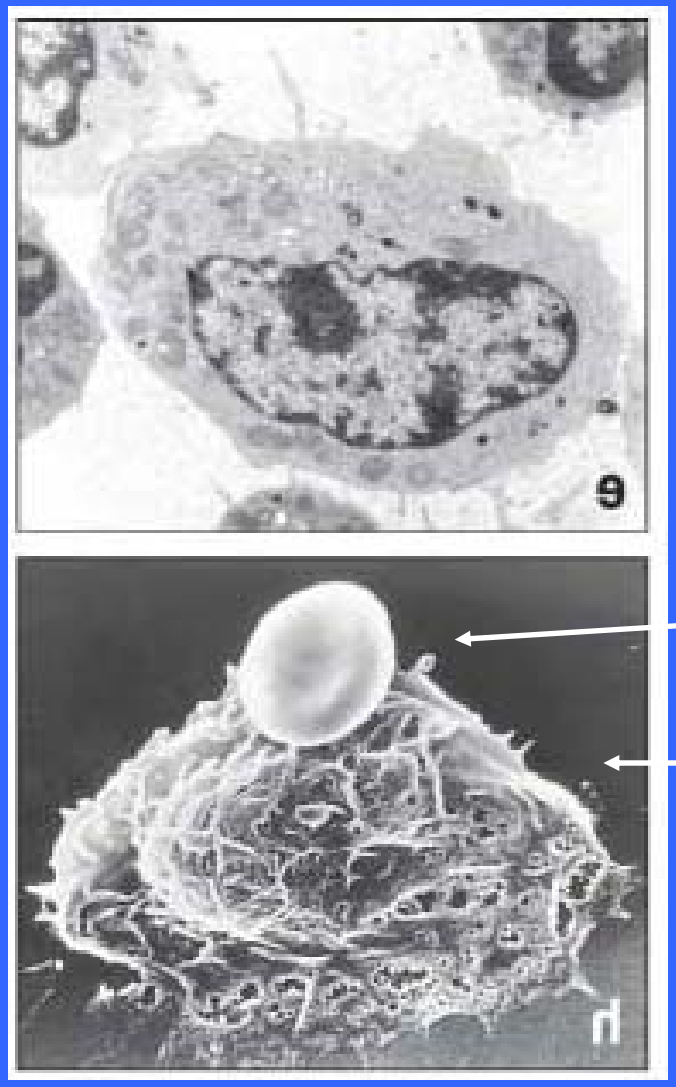
HEMOSTASIS, THROMBOSIS, AND VASCULAR BIOLOGY

Brief report ***Blood, 2007***

Platelet-bound lipopolysaccharide enhances Fc receptor–mediated phagocytosis of IgG-opsonized platelets

John W. Semple,[1-6] Rukhsana Aslam,[5,6] Michael Kim,[6] Edwin R. Speck,[5,6] and John Freedman[1,3-6]

How do platelets and LPS interact with monocytes?



RBC (couldn't find a picture with a plt and macrophage)

macrophage

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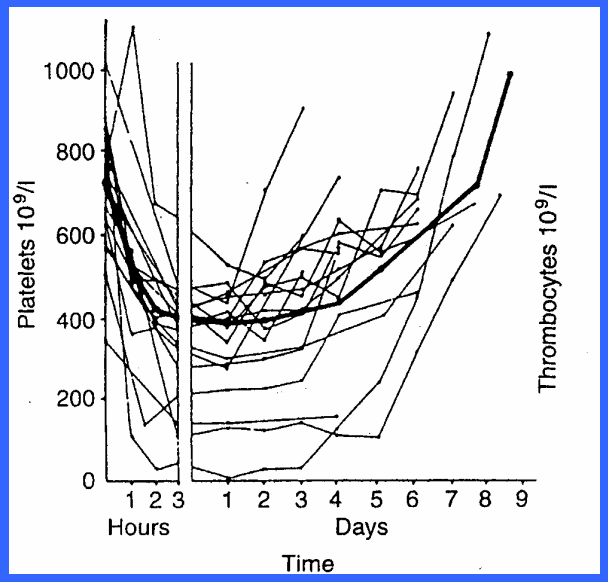
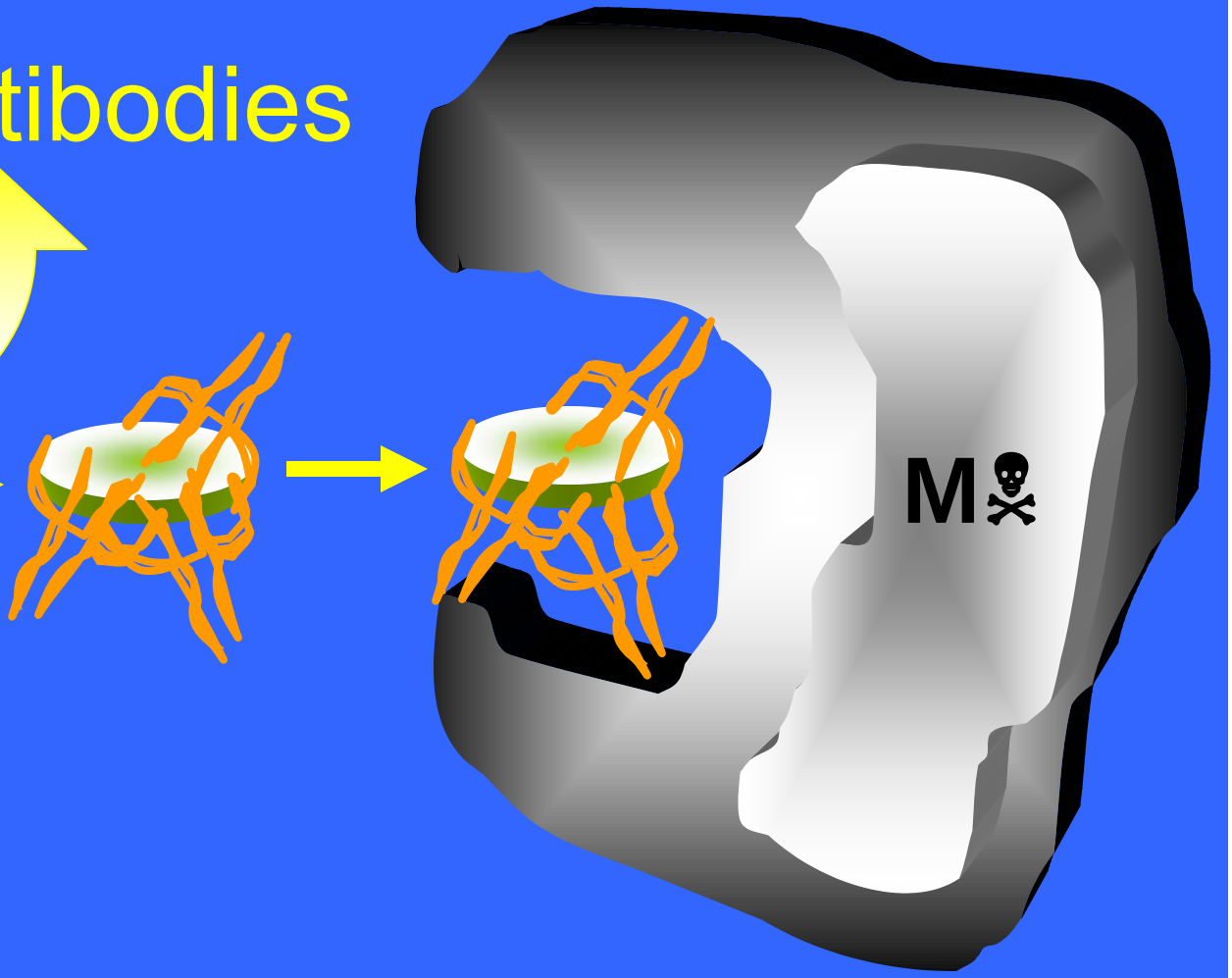
ITP, pathogenesis:

Autoantibodies

Platelet

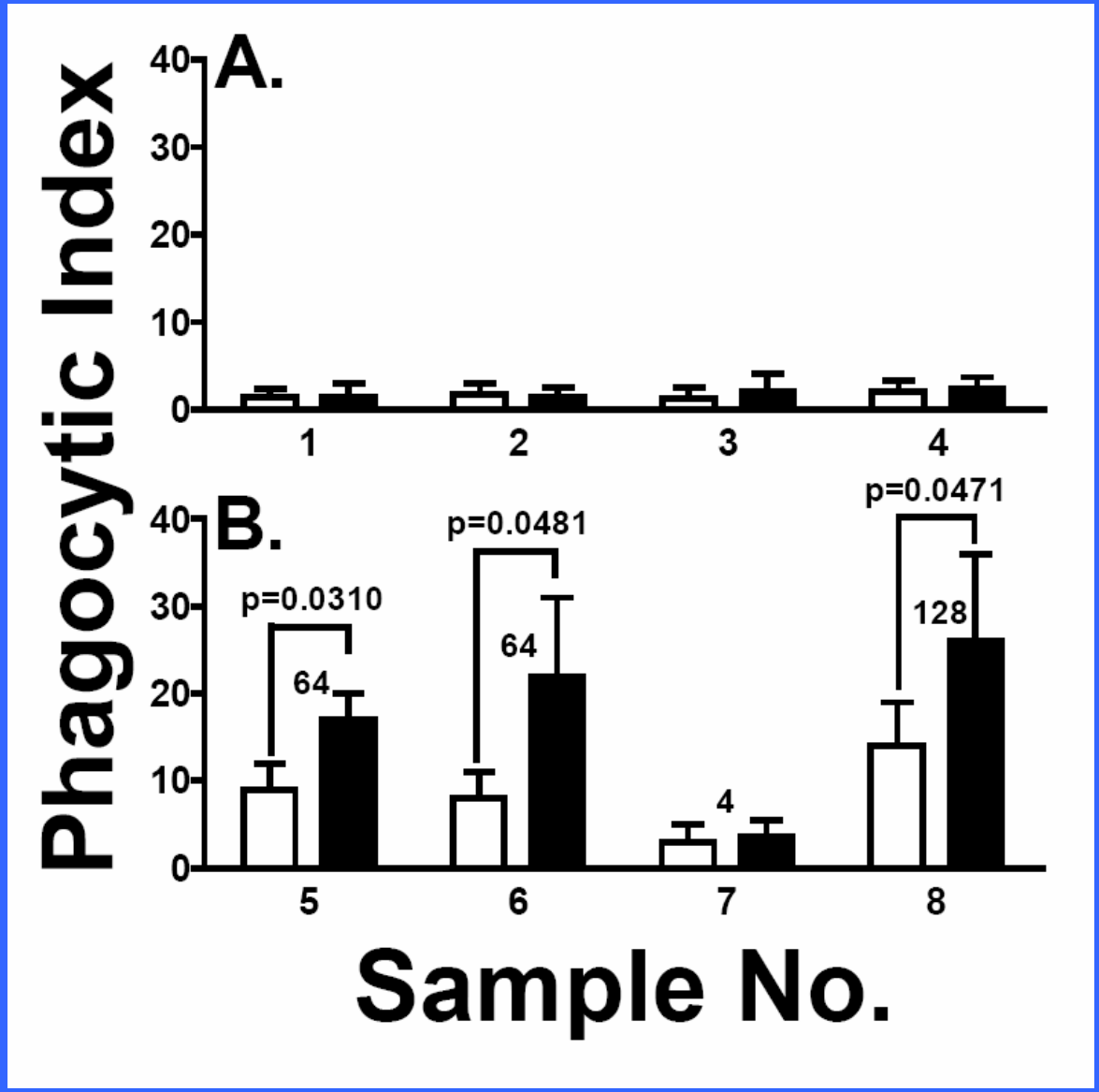


Harrington et al, J Lab Clin Med 38:1, 1951



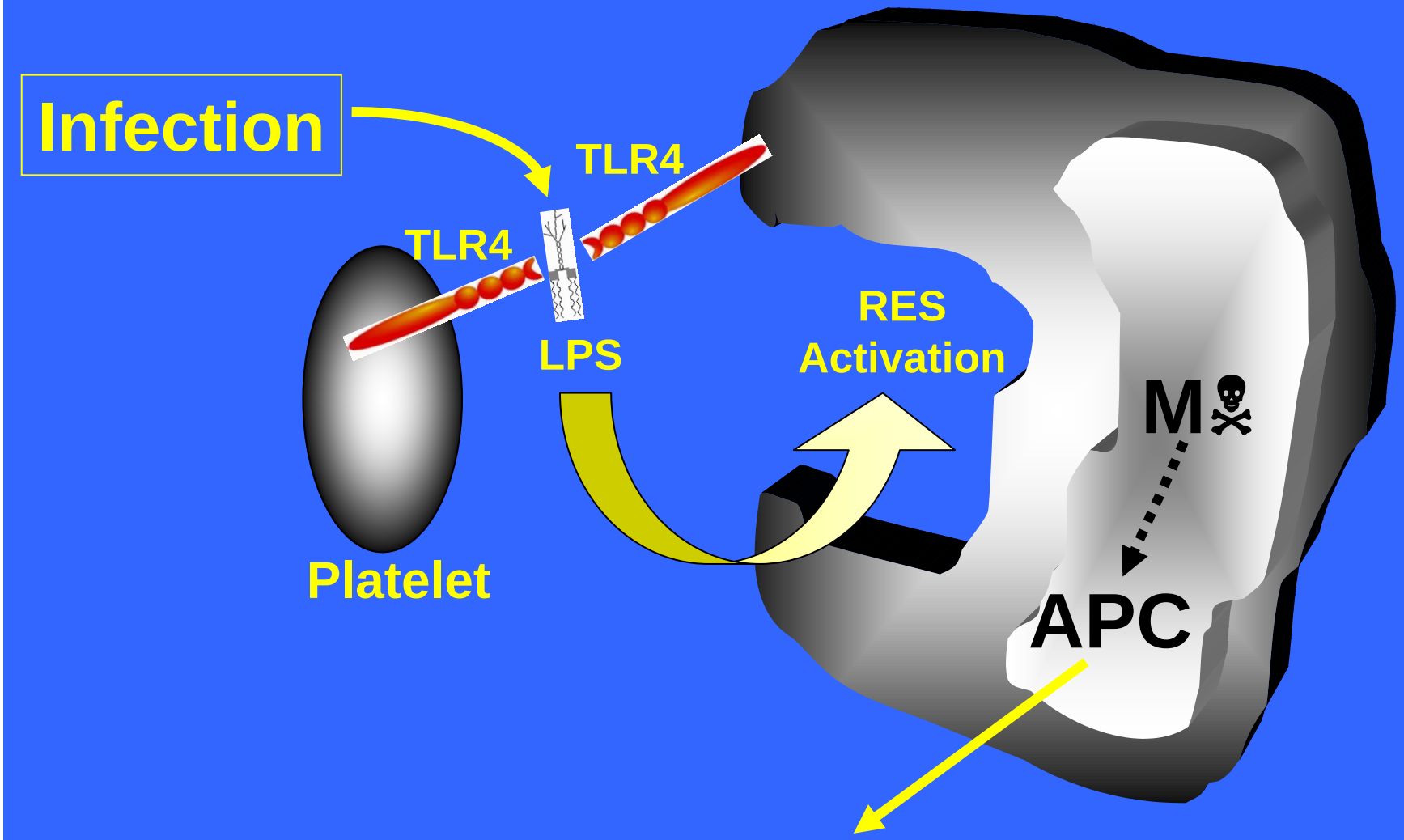
Increased
RES Destruction

Platelet-bound LPS Synergizes with autoantibodies to enhance platelet phagocytosis:



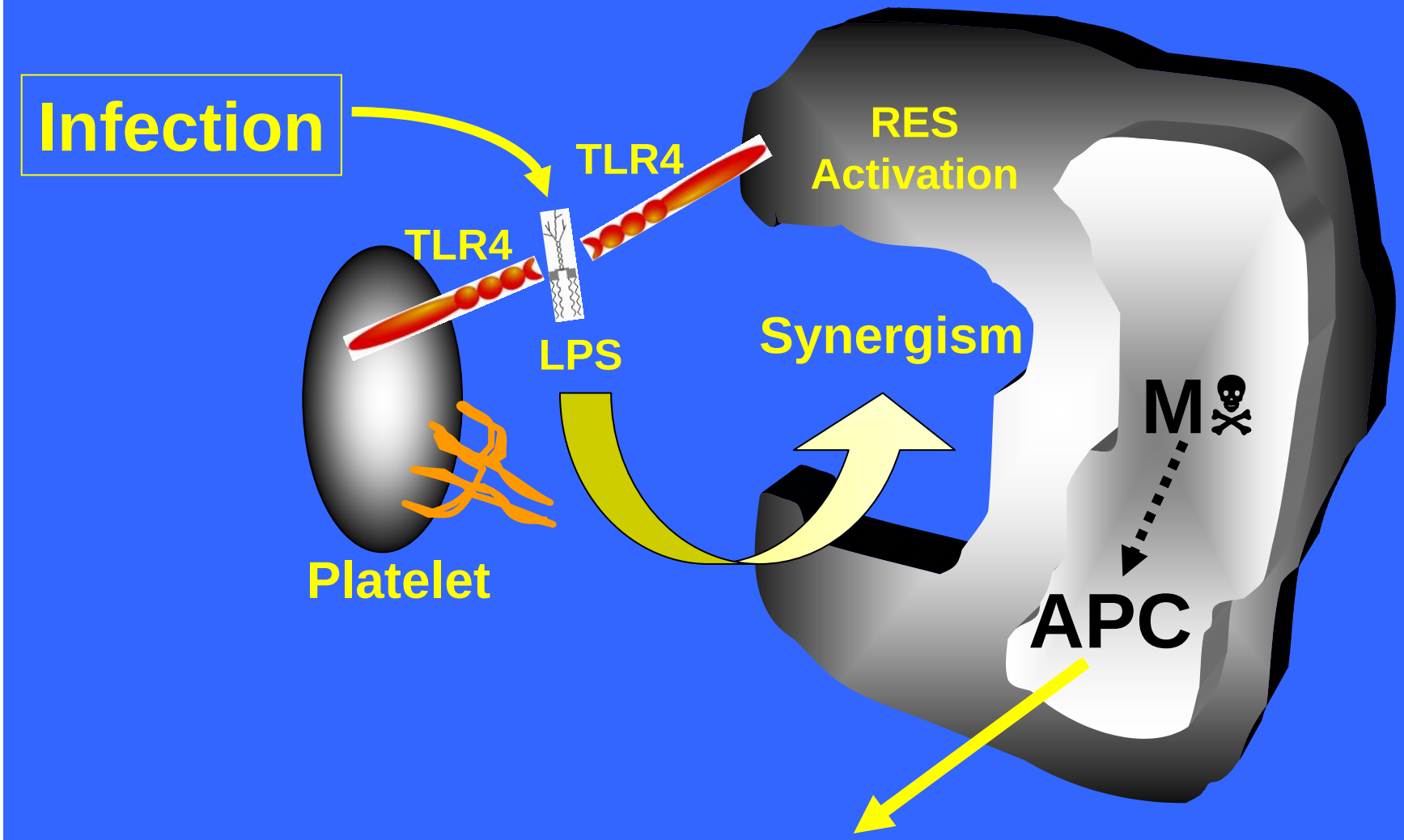
Semple et al Blood, 2007

Platelet-TLR-induced RES activation:



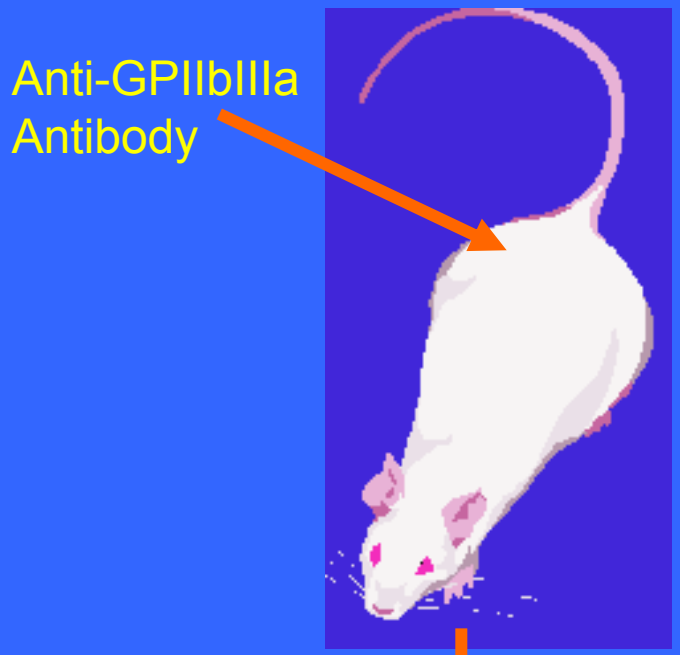
Potential for:
Altered processing/presentation to T cells:
Autoreactive T cell activation

Platelet-TLR-induced RES activation:



Enhanced Phagocytosis:
Altered processing/presentation to T cells:
Autoreactive T cell activation

Is there in vivo Proof? Perhaps Alan's mouse model:

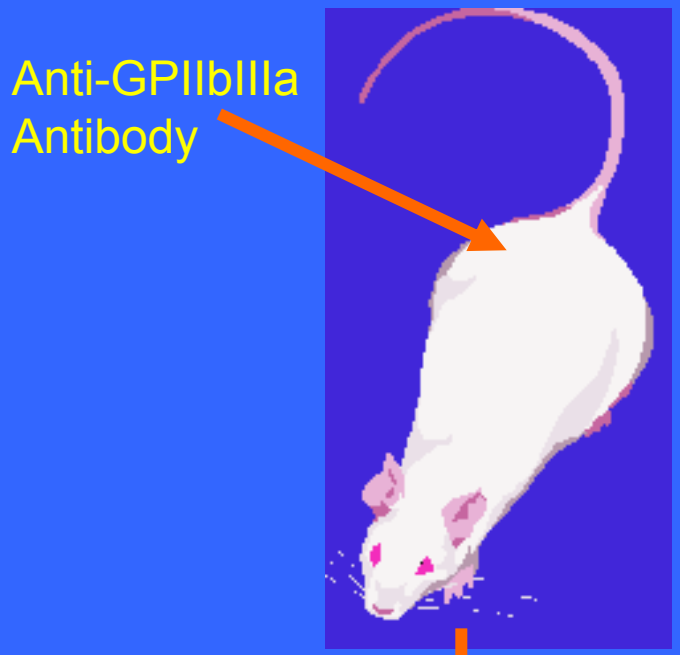


British Journal of Haematology, 2001, **115**, 679–686

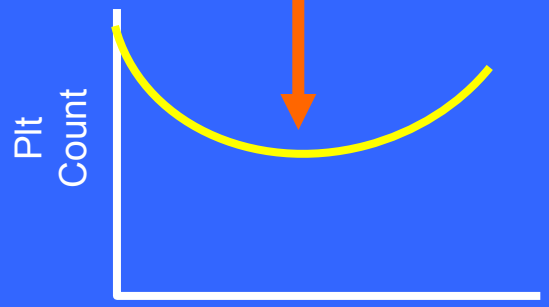
IVIg inhibits reticuloendothelial system function and ameliorates murine passive-immune thrombocytopenia independent of anti-idiotype reactivity

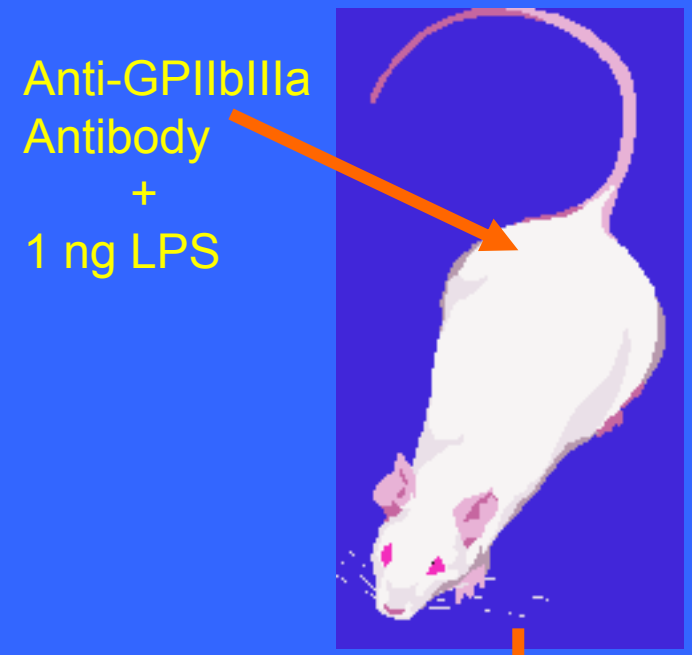
ANDREW R. CROW,[1,2] SENG SONG,[1] JOHN W. SEMPLE,[1] JOHN FREEDMAN[1,2] AND ALAN H. LAZARUS[1,2]

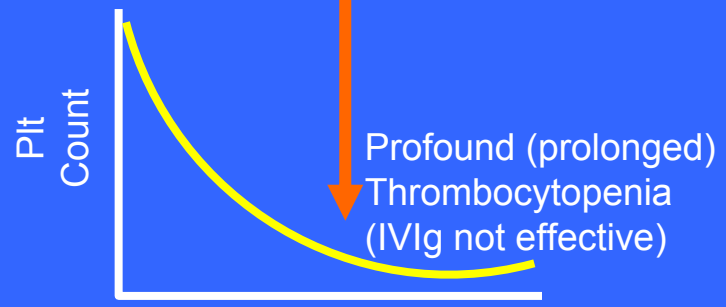
In vivo Proof (Bazin et al Infect Immunity 2007):



1 day



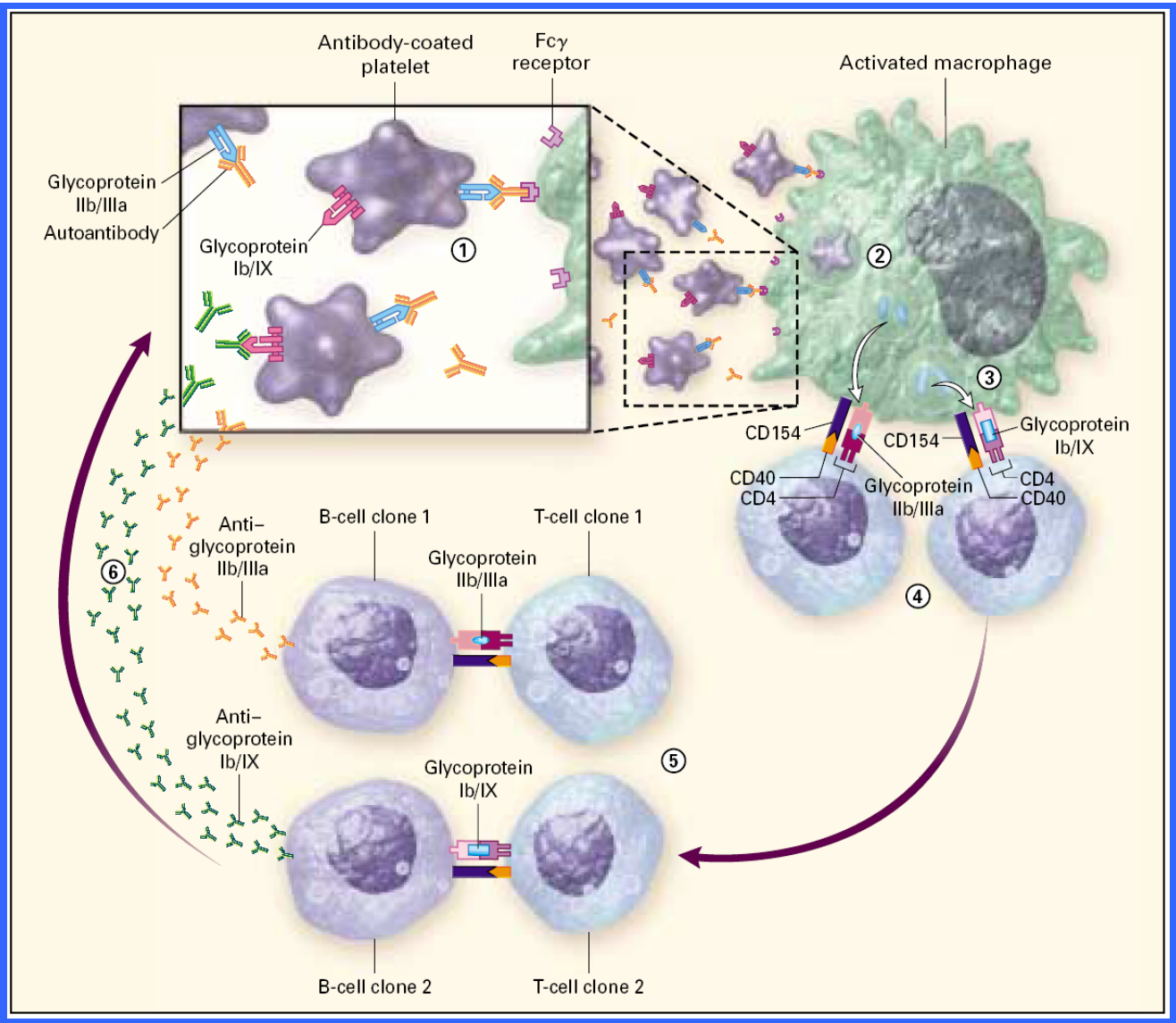




These results suggest that infectious agents in combination with anti-platelet antibodies can significantly affect platelet destruction in vivo.

They may explain why thrombocytopenia worsens in some patients with ITP during infections (adding LPS) and, alternatively, resolves in other patients with ITP who are treated with bacterial eradication therapy e.g. H. pylori (removing LPS).

Pathophysiology of Chronic ITP:



Cines DB, Blanchette VS. N Engl J Med. 2002;346:995-1008.

History of T cell involvement in ITP:

Enhanced MIF production (1970's) (3)

↓

PBMC blastogenesis against platelets (1970 -1980's) (17)

↓

PBMC IL-2 production against platelets (1991) (10)

↓

Anti-platelet T cells clones (1993) (10)

↓

Th1 cytokine bias during active disease (1996) (15)

↓

HLA association (Japanese) (1998) (3)

↓

GPIIIA peptide mapping (1998) (9)

↓

Fas/FasL abnormalities (2000) (6)

↓

Cell-mediated cytotoxicity against platelets (2003) (3)

↓

Depressed CD4+CD25+Fox3+ T regulatory cells (2003) (7)

↓

Genomics: IFN-upregulated genes in ITP (2007) (1)

Recent Literature: T cells and ITP

1. Ling Y et al. Circulating dendritic cells subsets and CD4+Foxp3+ regulatory T cells in adult patients with chronic ITP before and after treatment with high-dose dexamethasome. Eur J Haematol, Published online: 10-Aug-2007 doi: 10.1111/j.1600-0609.2007.00917.x
2. Sukati H et al. Mapping helper T-cell epitopes on platelet membrane glycoprotein IIIa in chronic autoimmune thrombocytopenic purpura. Blood, 109:4528, 2007.
3. Liu B et al. Abnormality of CD4+CD25+ regulatory T cells in idiopathic thrombocytopenic purpura. Eur J Haematol. 78(2):139-143, 2007.
4. Chen X et al. Interferon-γ +874A/T and interleukin-4 intron3 VNTR gene polymorphisms in Chinese patients with idiopathic thrombocytopenic purpura. Eur J Haematol. 79(3):191-197, 2007 .
5. Li N.et al. Platelet-lymphocyte conjugation differs between lymphocyte subpopulations. J Thromb Haemostasis. 4(4):874-81, 2006
6. Liu F et al. Effect of protein kinase C on T lymphocyte proliferation and apoptosis in acute idiopathic thrombocytopenic purpura. Acta Haematologica. 116(3):173-80, 2006.
   Ishiyama M et al. Clonally expanded T-cells in the peripheral blood of patients with idiopathic Thrombocytopenic purpura and Helicobacter pylori infection. *Int J Hematol. 83(2):147-51, 2006.*
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9. Takedatsu H et al. Determination of thrombopoietin-derived peptides recognized by both cellular and humoral immunities in healthy donors and patients with thrombocytopenia. *Stem Cells. 23(7):975-82, 2005.*
10. Wu C et al. Effect of protein kinase C on proliferation and apoptosis of T lymphocytes in idiopathic thrombocytopenic purpura children. *Cell Mol Immunol. 2(3):197-203, 2005.*
11. Olsson B et al. Disturbed apoptosis of T-cells in patients with active idiopathic thrombocytopenic purpura. *Thromb Haemostasis. 93(1):139-44, 2005*

Mapping T cell epitopes in ITP:

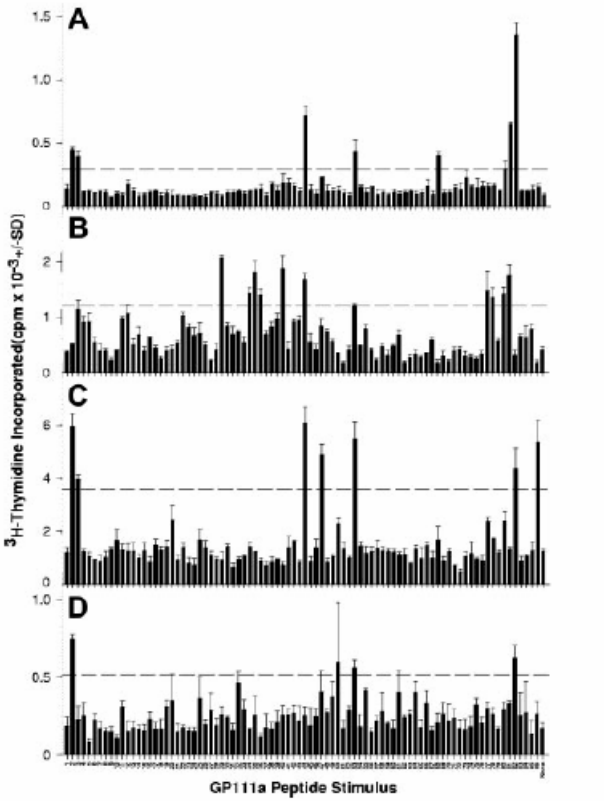
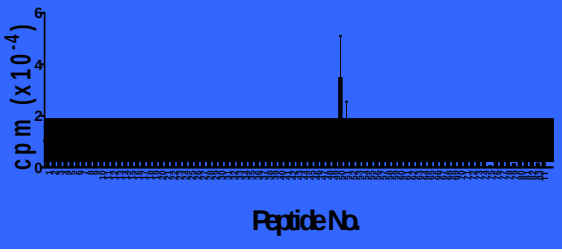


Figure 1. PBMCs from patients with AITP proliferate in response to peptides from the sequence of GPIIIa. PBMCs were isolated from representative patients AITP1 (A), AITP8 (B), AITP10 (C), and AITP20 (D) tested for the ability to proliferate against the panel of 86 peptides spanning the GPIIIa molecule. The dashed horizontal line denotes the level of proliferation taken as representing a significant positive response (SI > 3).

Peripheral blood of 4 adults with chronic ITP.

Sukati H et al. Blood, 109:4528, 2007.



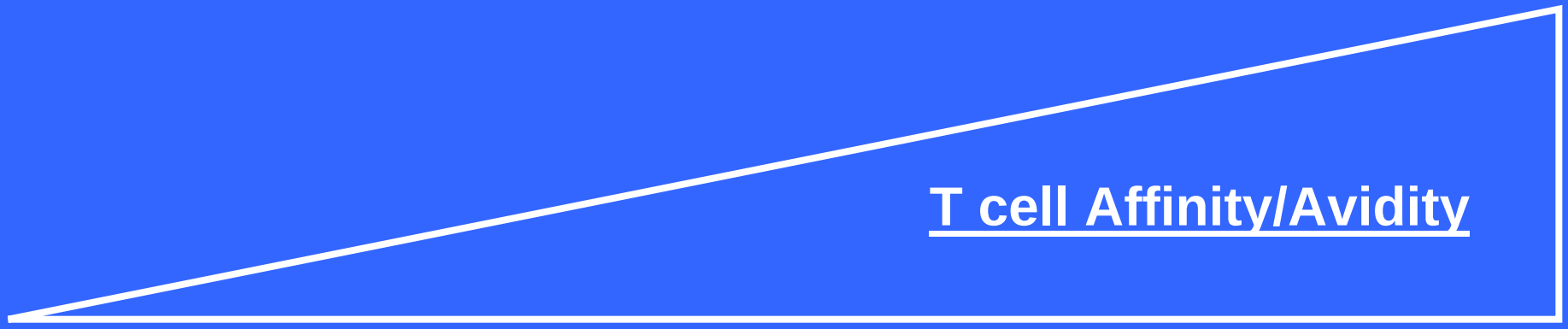
Spleen cells from 4/7 children with chronic ITP.

Semple et al. Blood, 98:441a,2001.

These results suggest that the T cell anti-GPIIIa reactivity patterns are different in children and adults with chronic ITP.

Thus, peptide therapies can be developed but need to be tailored to the particular disorder.

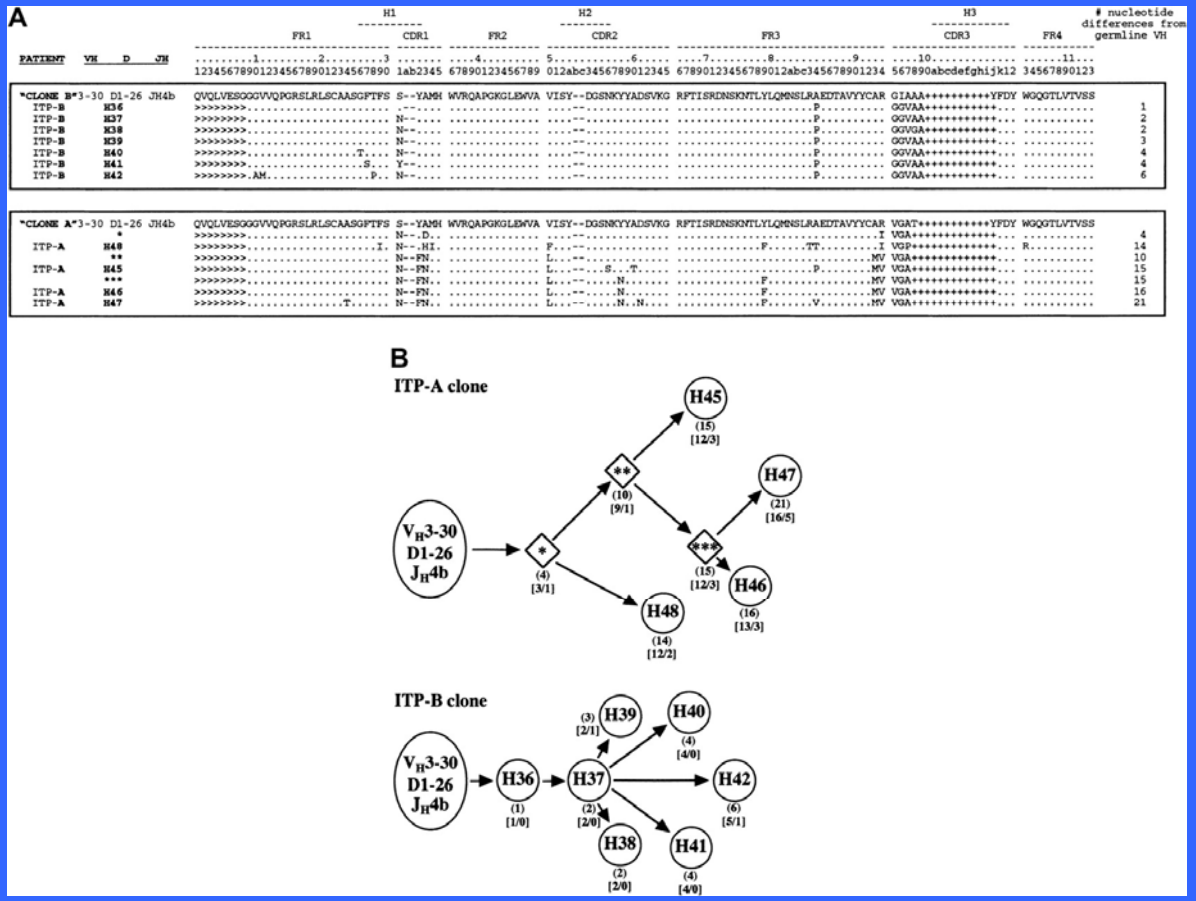
A cellular immunologist (reductionist) view of haematology and all the IgG antibodies that everyone is talking about.



Naïve/Auto	Allo (HPA1a) (point mutations)	Allo (Rh) (polymorphic)	Xeno (DPTT, MHC)	Allo (MHC)

If there is an IgG antibody,
there is a T cell.
If there is somatic mutation,
there is a T cell.

What can B cells tell us about T cells in ITP?:

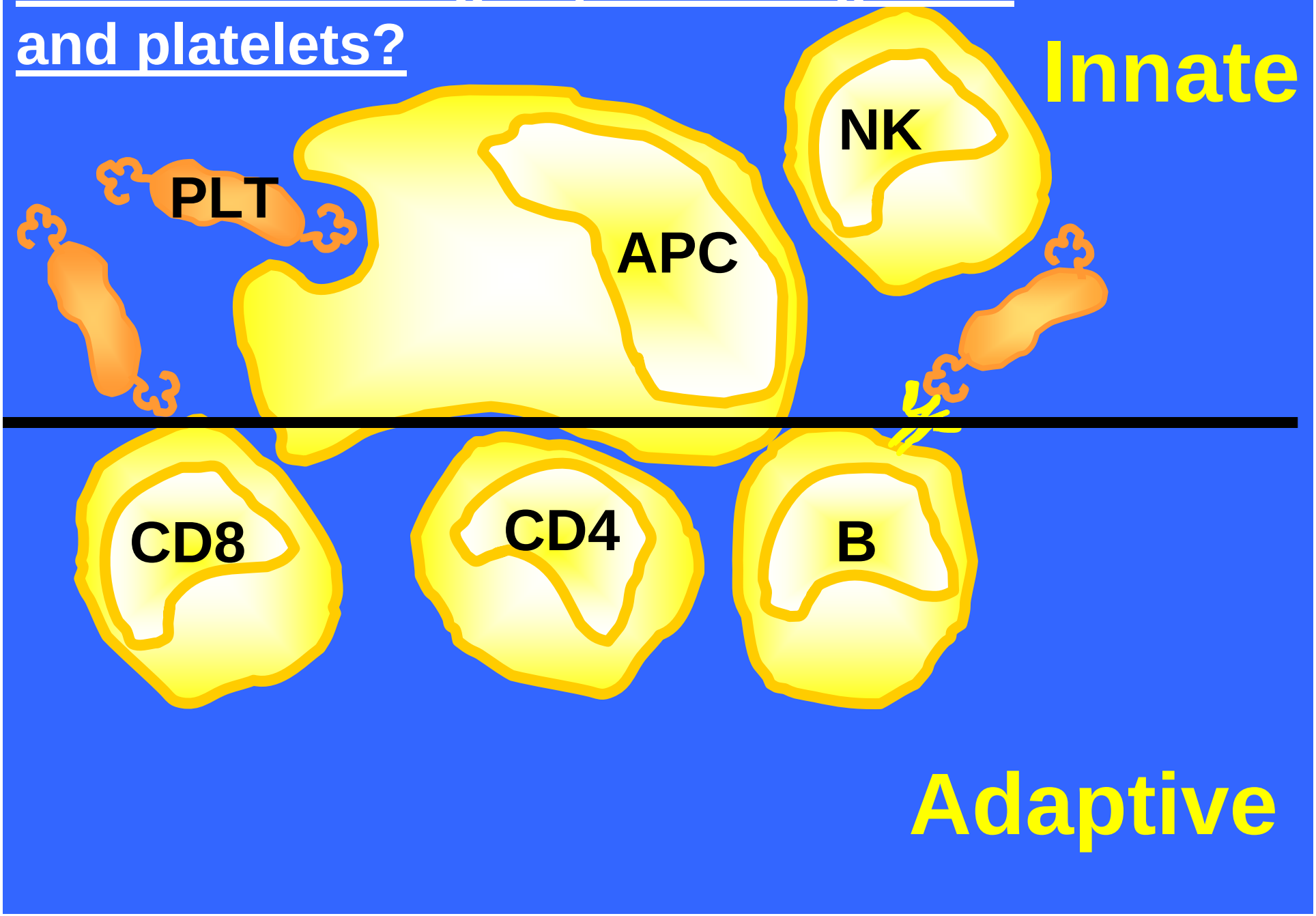


Antibody proof that chronic ITP is A T cell initiated disease.

Roark JH et al. analysis of autoantibodies in idiopathic thrombocytopenic purpura reveals evidence of clonal expansion and somatic mutation. Blood. 100(4):1388-98, 2002.

Hamidpour M et al. The isolation and characterization of anti-platelet antibodies. Eur J Haematol. 76(4):331-8, 2006.

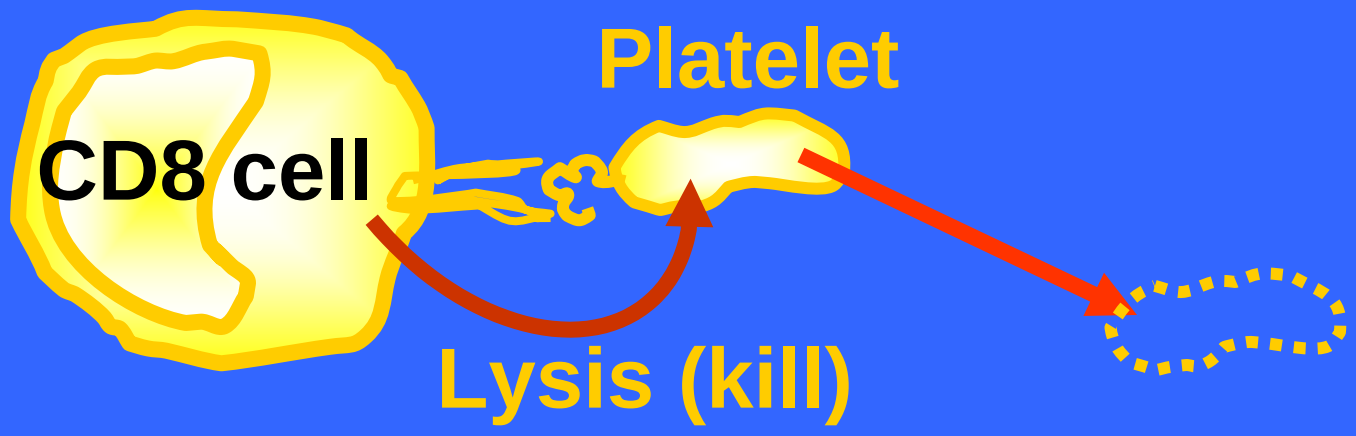
What about antigen presenting cells and platelets?



Recent Literature: Platelets/APC/NK(T) cells and ITP (Innate)

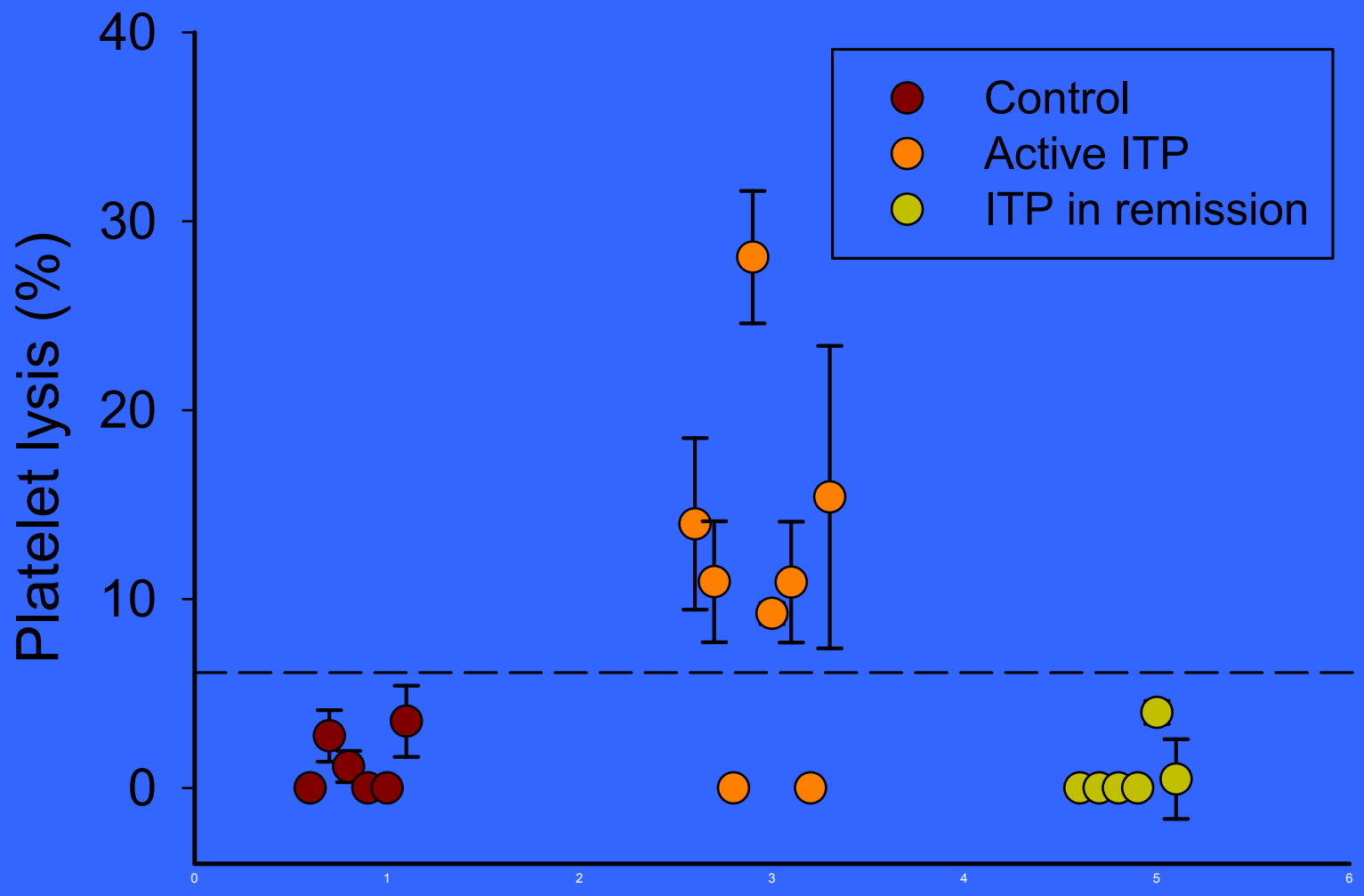
1. Catani L et al. Dendritic cells of immune thrombocytopenic purpura (ITP) show increased capacity to present apoptotic platelets to T lymphocytes. Exp Hematol. 34(7):879-87, 2006.
2. Johansson U et al. The role of natural killer T (NKT) cells in immune thrombocytopenia: is strong in vitro NKT cell activity related to the development of remission?. Brit J Haematol. 129(4):564-5, 2005.
3. Palumbo JS et al. Platelets and fibrin(ogen) increase metastatic potential by impeding natural killer cell-mediated elimination of tumor cells. Blood. 105:178-85, 2005.
4. Kissel et al Human platelets target dendritic cell differentiation and production of proinflammatory cytokines. Transfusion. 46(5):818-824, 2006.
5. Hopkins LM et al. MHC class I-associated peptides identified from normal platelets and from individuals with idiopathic thrombocytopenic purpura. Human Immunol. 66(8):874-83, 2005.
6. Solanilla A et al. Platelet-associated CD154 in immune thrombocytopenic purpura. Blood. 105(1):215-8, 2005.
7. Elzy BD et al. The emerging role of platelets in adaptive immunity. Cell Immunol, 238:1-9, 2005.
8. Gawaz M et al, Platelets in inflammation and atherogenesis. J. Clin. Invest. **115**:3378–3384 (2005).
9. Elzey BD et al. Cooperation between platelet-derived CD154 and CD4+ T cells for enhanced germinal center formation. J Leuk Biol. 78(1):80-4, 2005.
10. Hagihara M et al. Platelets, after exposure to a high shear stress, induce IL-10-producing, mature dendritic cells in vitro. J Immunol. 172(9):5297-303, 2004.
11. Czapigaa M et al, Platelets deliver costimulatory signals to antigen-presenting cells: A potential bridge between injury and immune activation Exp Hematol. 32:135–139, 2004.
12. Danese S et al. T Cells Trigger CD40-Dependent Platelet Activation and Granular RANTES Release: A Novel Pathway for Immune Response Amplification. J Immunol. 172: 2011–2015, 2004.
13. Weyrich AS et al, Platelets: signaling cells in the immune continuum. Trends in Immunol. 25:489-495, 2004.

T cell-mediated platelet destruction in ITP:



Olsson et al Nat Med 2003.
Zhang F et al. Eur J Haematol 76(5):427-31, 2006

Suggests that a novel therapeutic targeting cell mediated immunity may benefit some ITP patients.



Olsson et al. Nature Med., 2003

MAIN CONCLUSION (early):

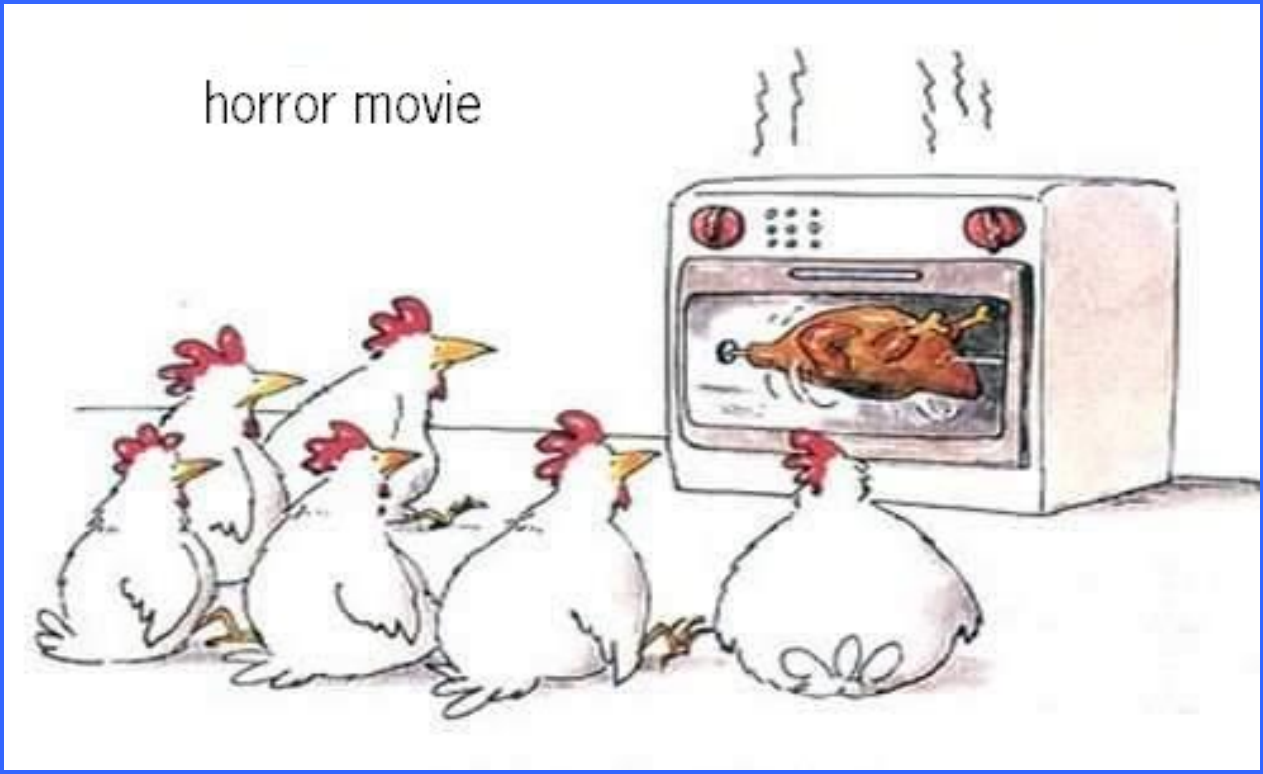
1. ITP is associated with many different T cell abnormalities and these defects are not only responsible for IgG anti-platelet autoantibody production but in some cases (40%), the direct destruction of platelets.

2. The T cell abnormalities in ITP also appear to be related to or perhaps caused by a variety of innate immune events and cells e.g. infections, macrophages/dendritic cells (antigen presenting cells) and/or the platelets themselves.

3. Based on the recent literature, it appears that ITP may be aggrevated because CD4+ regulatory T cell disturbances and more research is required to better understand these events

4. This will allow the development of peptide antigen-specific immunotherapies.

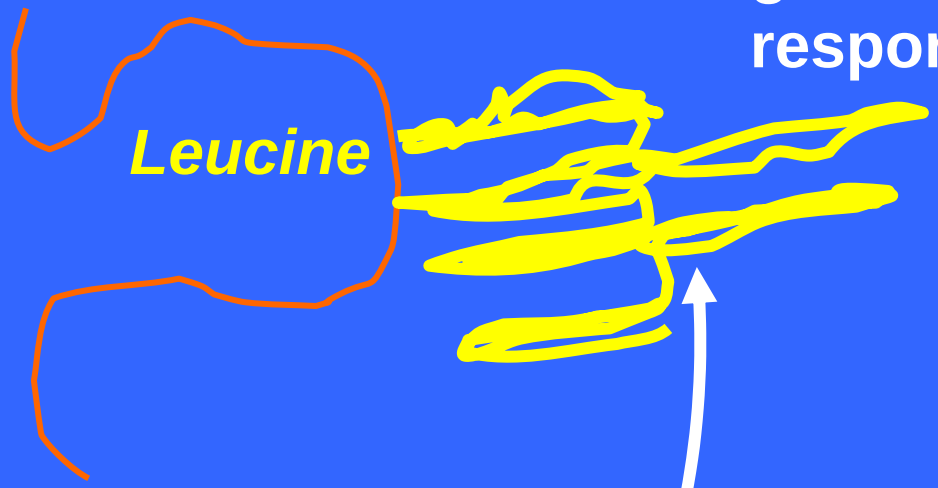
Neonatal Alloimmune thrombocytopenia (NAIT)



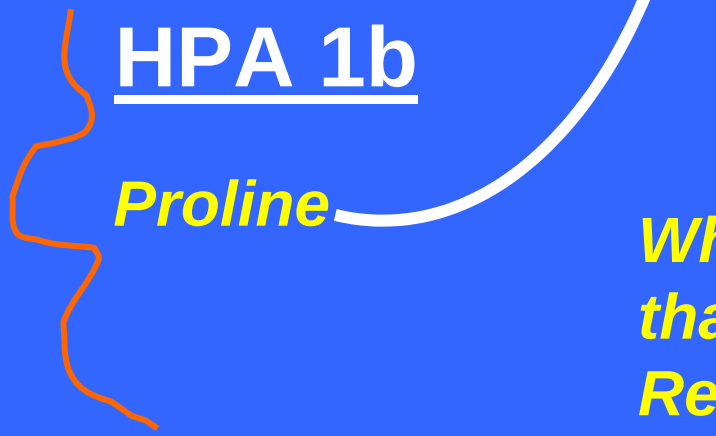
NAITP:

HPA 1a

IgG anti-HPA 1a antibody response



HPA 1b



What are the T cell epitopes that are responsible for this Response?

Sorry, some history:

Maslanka K et al. Identification of T cells that respond in a primary bulk culture to a peptide derived from a platelet glycoprotein implicated in neonatal alloimmune thrombocytopenia. *J Clin Invest. 98(8):1802-8, 1996.*

Suggested that a T cell epitope for anti-HPA 1a antibody production may actually be part of the antibody epitope (e.g. around the leucine residue).

Literature:

1. Sukati H et al. Characterization of the alloreactive helper T-cell response to the platelet membrane glycoprotein IIIa (integrin-beta3) in human platelet antigen-1a alloimmunized human platelet antigen-1b1b women. Transfusion. *45(7):1165-77, 2005.*

2. Jackson DJ et al. Reactivity of T cells from women with antibodies to the human platelet antigen (HPA)-1a to peptides encompassing the HPA-1 polymorphism. *Clin Exp Immunol. 142(1):92-102, 2005.*

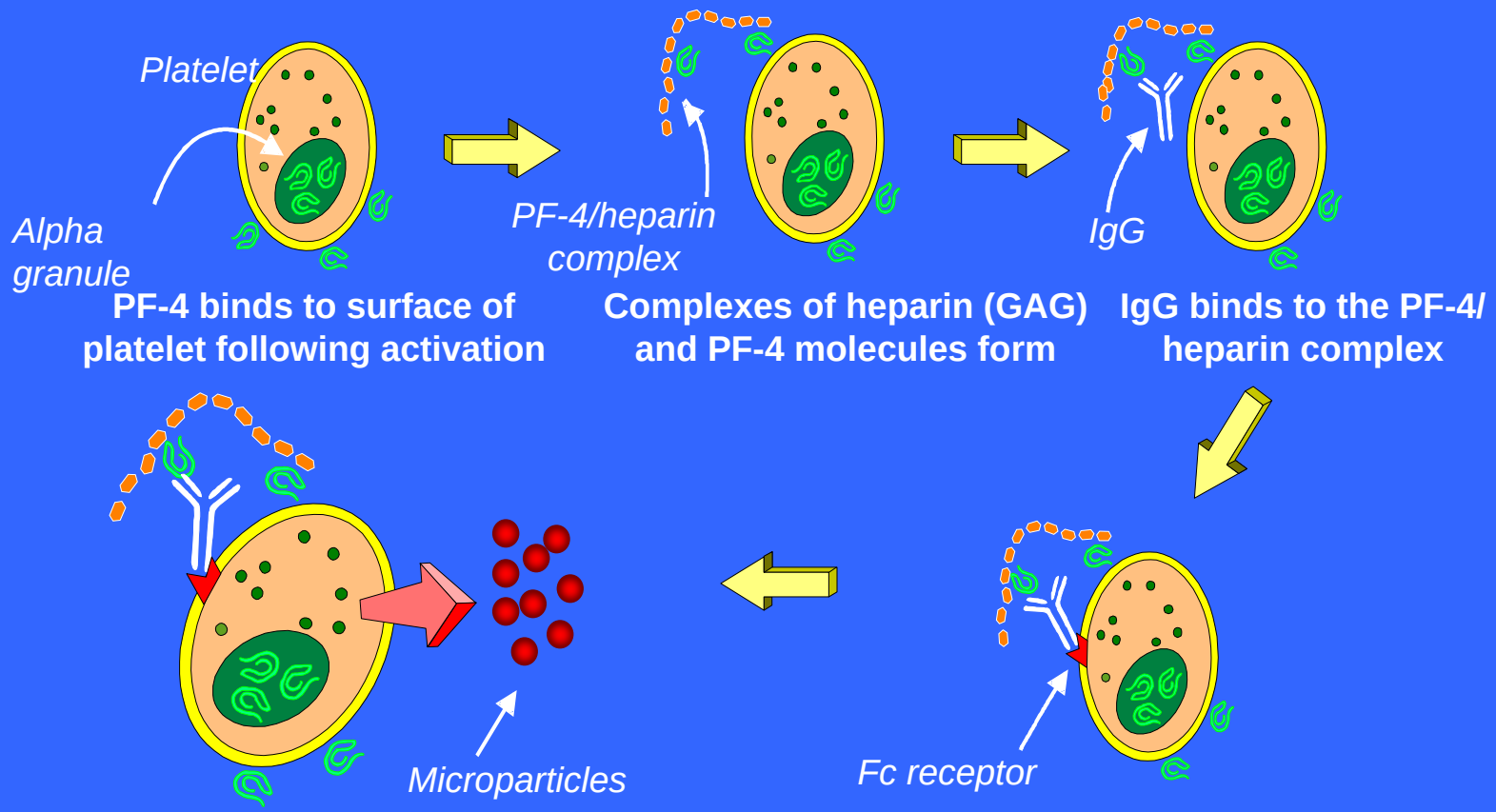
TRANSFUSION MEDICINE

Blood 107:2976, 2006

A novel murine model of fetal and neonatal alloimmune thrombocytopenia: response to intravenous IgG therapy

Heyu Ni, Pingguo Chen, Christopher M. Spring, Ebrahim Sayeh, John W. Semple, Alan H. Lazarus, Richard O. Hynes, and John Freedman

Heparin-induced thrombocytopenia (HIT):



PF-4 binds to surface of platelet following activation

Complexes of heparin (GAG) and PF-4 molecules form

IgG binds to the PF-4/ heparin complex

IgG/PF-4/heparin complex activates via the Fc receptor

Fc stimulation leads to the generation of procoagulant-rich microparticles

www.angelfire.com/ut/johnsnotes/index.htm

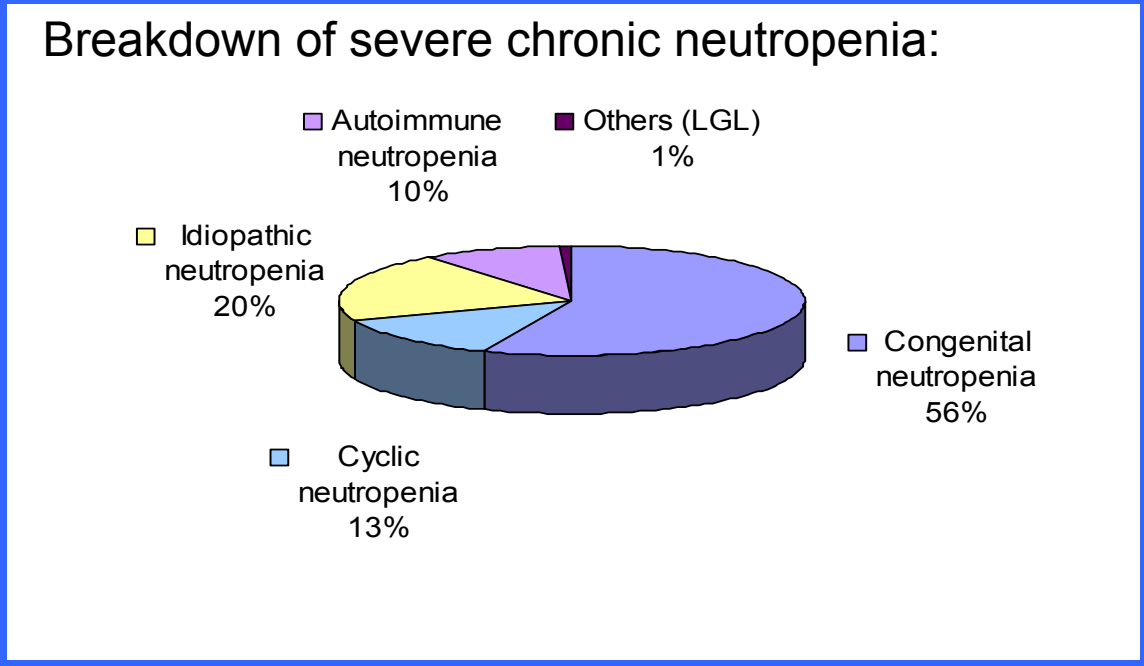
Literature:

1. Suvarna S et al. PF4/heparin complexes are T cell-dependent antigens. Blood. 106(3):929-31, 2005.

2. Ji SL et al. Inhibitory effect of heparin-derived oligosaccharides on secretion of interleukin-4 and interleukin-5 from human peripheral blood T lymphocytes. World J Gastroenterol. 10(23):3490-4, 2004 .

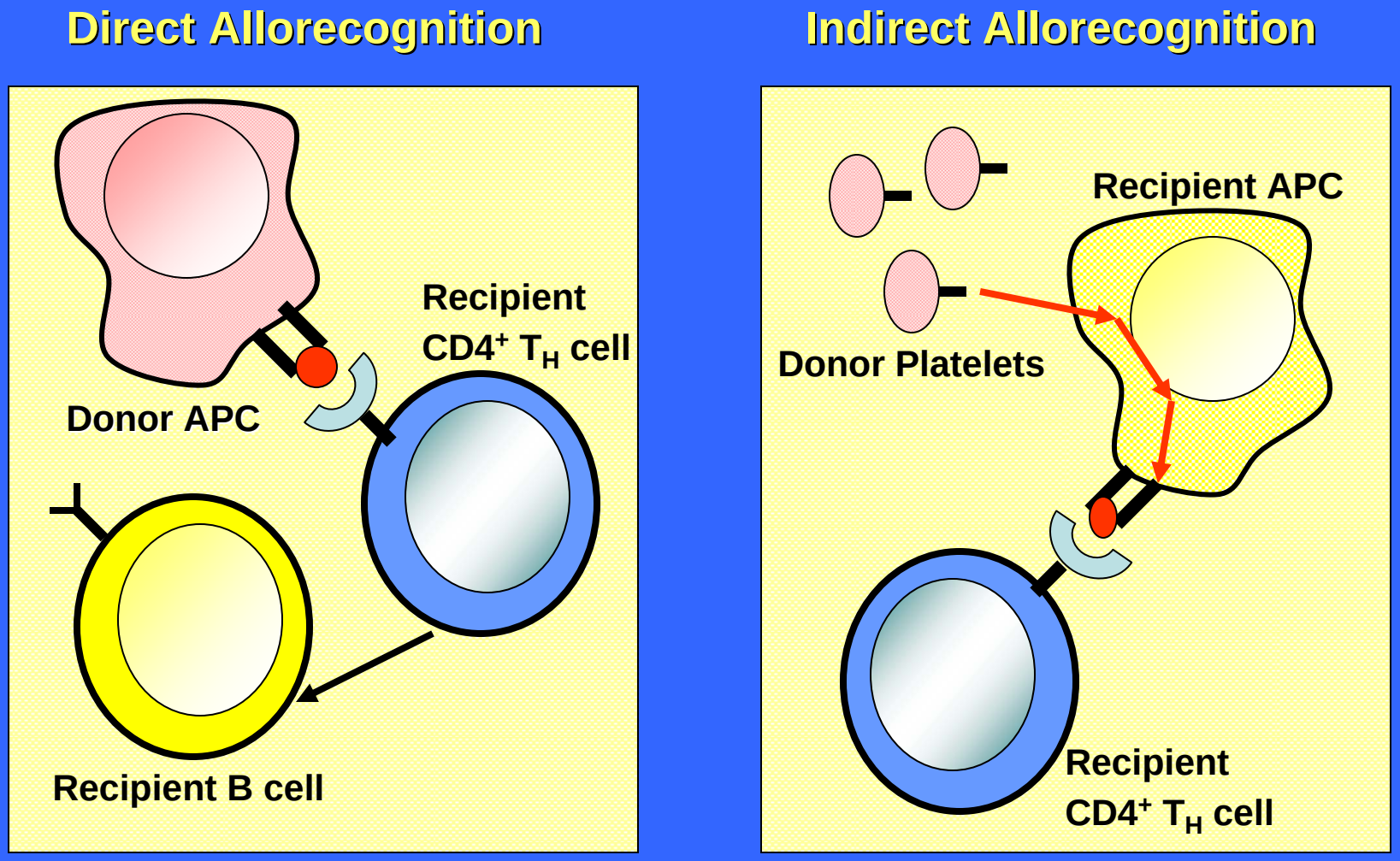
3. Bacsi S et al. Complexes of heparin and platelet factor 4 specifically stimulate T cells from patients with heparin-induced thrombocytopenia/thrombosis. Blood. 94(1):208-15, 1999.

Literature: T cells in autoimmune neutropenia



Papadaki HA et al. Activated T-lymphocytes with myelosuppressive properties in patients with chronic idiopathic neutropenia. Brit J Haematol. 128(6):863-76, 2005

Platelet MHC alloimmunization:



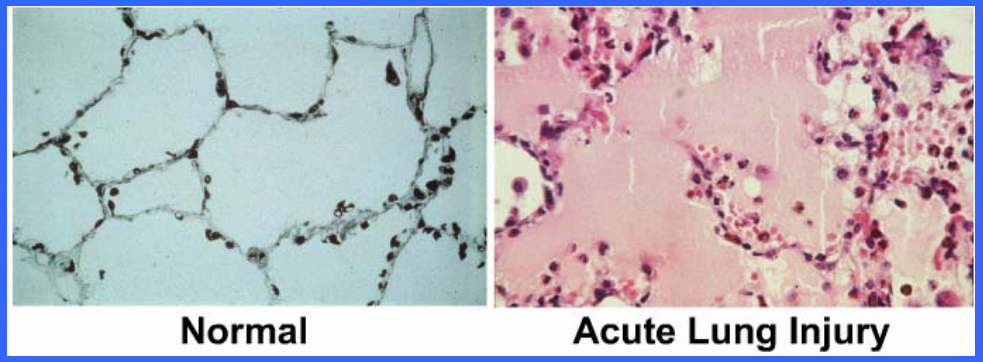
Literature:

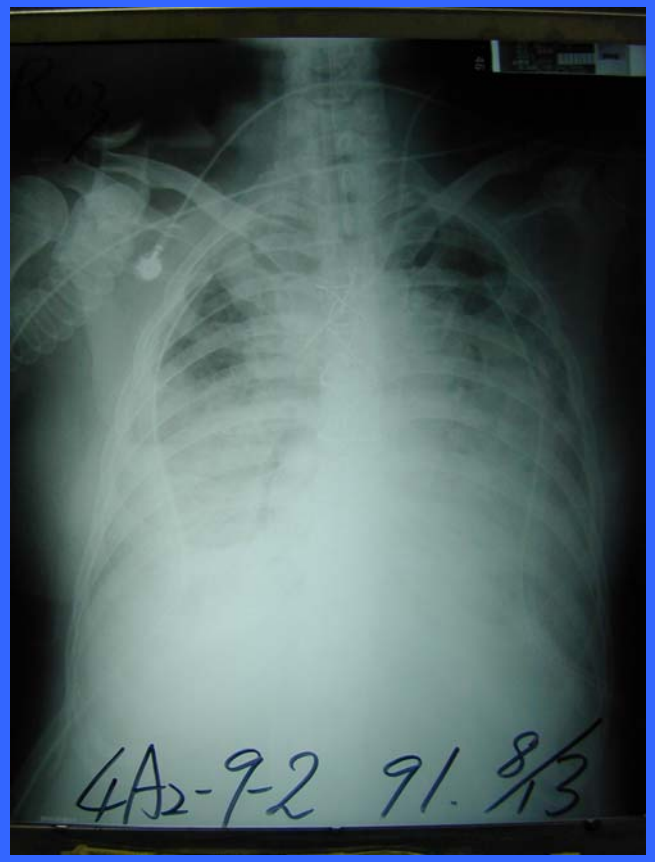
1. Slichter S et al. Evaluation of different methods of leukoreduction of donor platelets to prevent alloimmune platelet refractoriness and induce tolerance in a canine transfusion model. Blood, 105: 847-854, 2005.

2. Sayeh E et al. Immune responsiveness against allogeneic platelet transfusions is determined by the recipient's major histocompatibility complex class II phenotype. Transfusion. 44(11):1572-8, 2004.

3. Sayeh E et al. IgG antiplatelet immunity is dependent on an early innate natural killer cell-derived interferon-gamma response that is regulated by CD8+ T cells. Blood. 103(7):2705-9, 2004.

Septic lung injury and perhaps TRALI:





Yasmin S et al. Soluble CD40 ligand accumulates in stored blood components, primes neutrophils through CD40, and is a potential cofactor in the development of transfusion-related acute lung injury. Blood published 13 June 2006, 10.1182/blood-2006-04-017251

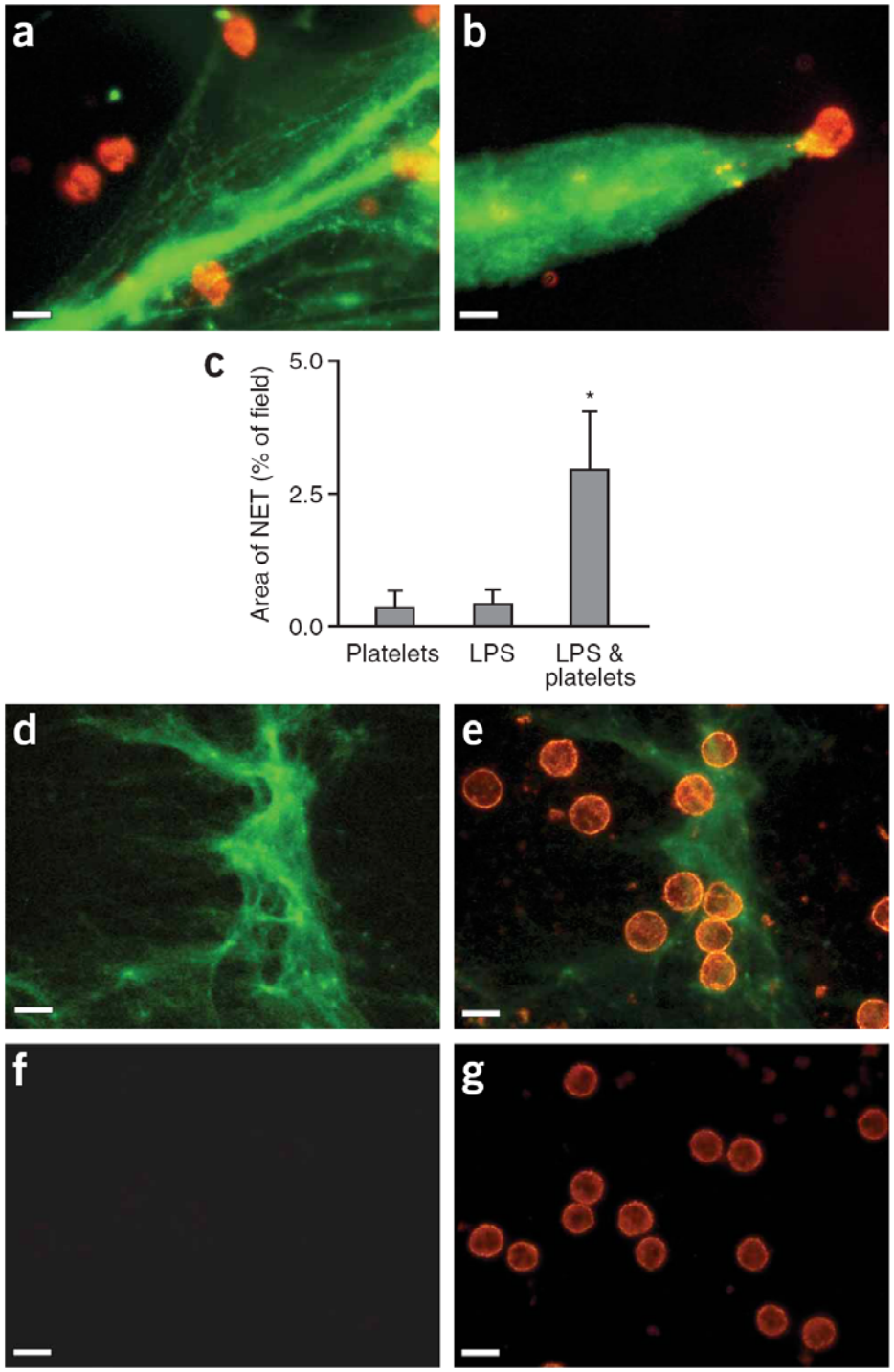
Yet another function of platelet TLR4 expression:

nature medicine

VOLUME 13 (4): 463, APRIL 2007.

Platelet TLR4 activates neutrophil extracellular traps to ensnare bacteria in septic blood

Stephen R Clark[1,6], Adrienne C Ma[1,6], Samantha A Tavener[1], Braedon McDonald[1], Zahra Goodarzi[1], Margaret M Kelly[1,2], Kamala D Patel[1,3], Subhadeep Chakrabarti[1,3], Erin McAvoy[1], Gary D Sinclair[2,3], Elizabeth M Keys[2], Emma Allen-Vercoe[4], Rebekah DeVinney[4], Christopher J Doig[5], Francis H Y Green[2] & Paul Kubes[1]


a
b
c
Area of NET (% of field)
5.0
2.5
0.0
*
Platelets
LPS
LPS &
platelets
d
e
f
g

Netting bacteria in sepsis

Constantin Urban & Arturo Zychlinsky

Platelets act as intermediaries in the pathogenesis of sepsis—sensing bacteria and signaling neutrophils to release fibrous traps that remove bacteria from the bloodstream. This response may also contribute to tissue injury (pages 463–469).

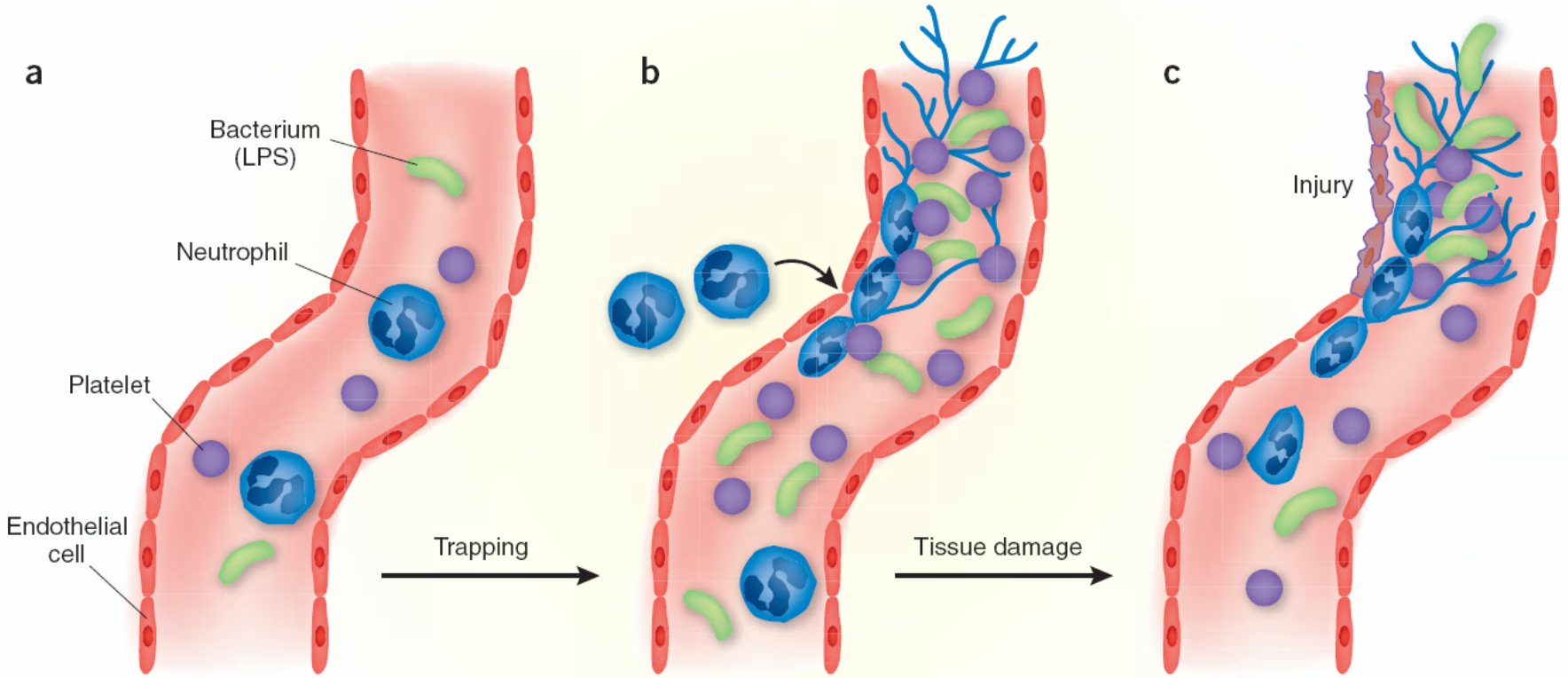


Figure 1 Platelets activate neutrophils in sepsis. (**a**) At low levels of LPS, platelets and neutrophils are in circulation. (**b**) When LPS levels increase, LPS binds to TLR4 on platelets. Platelets, in turn, activate adherent neutrophils to from NETs. More neutrophils are recruited to the blood stream. (**c**) The release of NETs results in bacterial trapping, but also in tissue damage.

Things to think about:

The immune thrombocytopenias are caused by platelets initially being recognized by the innate immune system. These recognition events are critical to whether adaptive autoimmuneprocesses e.g. anti-platelet autoantibodies will be stimulated.

Platelets express a variety of pro- and anti-inflammatory molecules that links them with the innate immune system.

Some of the pro-inflammatory molecules expressed on platelets e.g. TLR4, at least, enable the cells to very quickly bind infectious agents and present them to the innate immune system.

Thus, platelets perhaps have a critical role in mediating their own immunological fate within a host.

Questions?

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