Update on the Pathophysiology and Therapy of Immune Thrombocytopenia (ITP)

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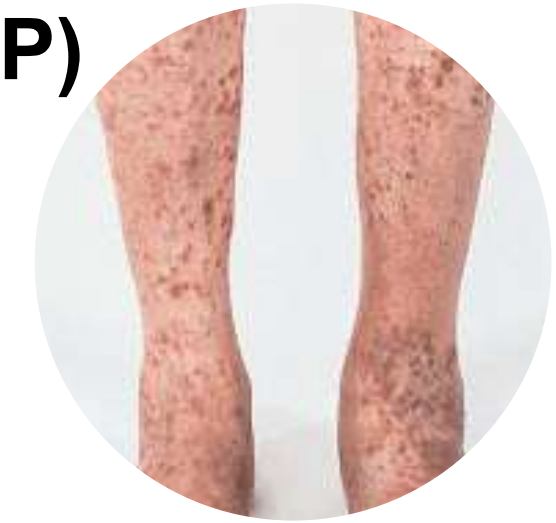
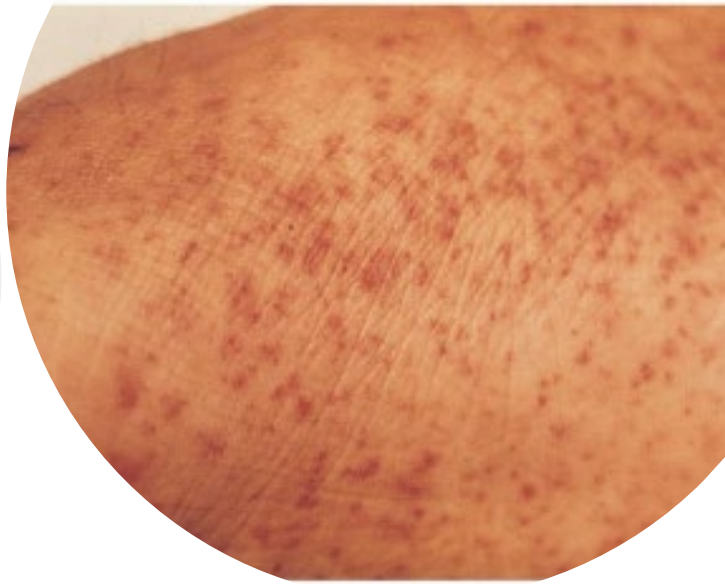
John W. Semple Disclosures:

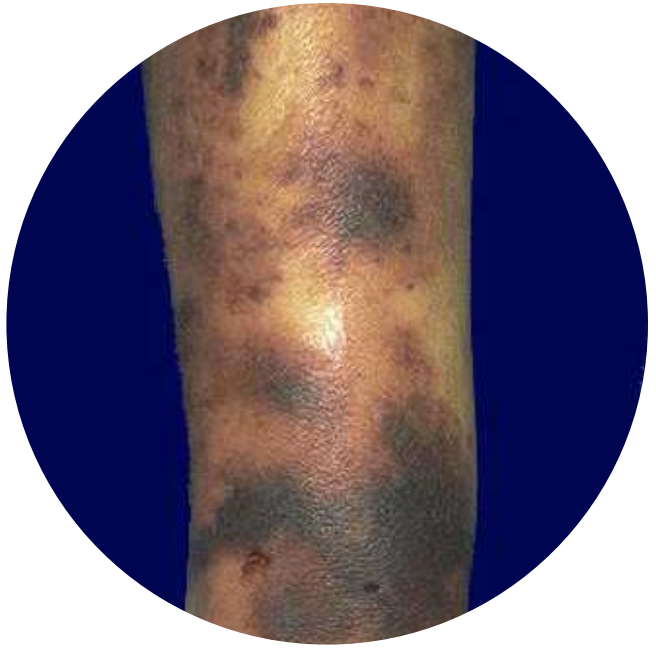
- **Amgen:** Honouraria, Ad boards
- **Argenx:** Honouraria, Ad boards
- **CellPhire Therapuetics:** Grants
- **Ionis:** Grants
- **Novartis:** Grants, Honouraria, Ad boards
- **Platelet BioGenesis:** Grants
- **SOBI:** Honouraria
- **Takeda:** Honouraria, Ad borads
- **UCB:** Honouraria, Ad boards

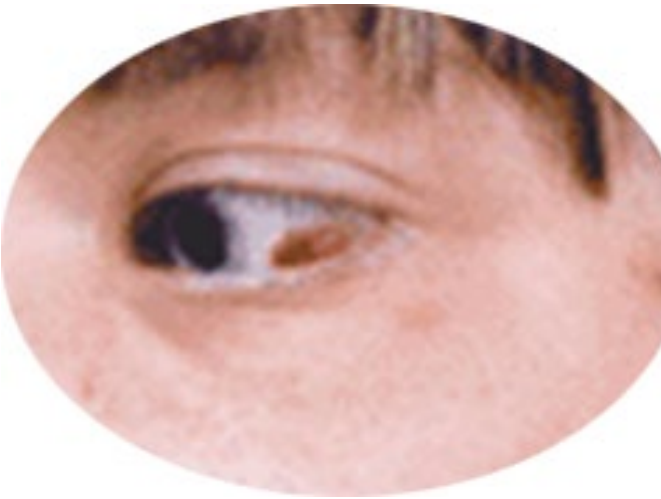
Immune Thrombocytopenia (ITP)

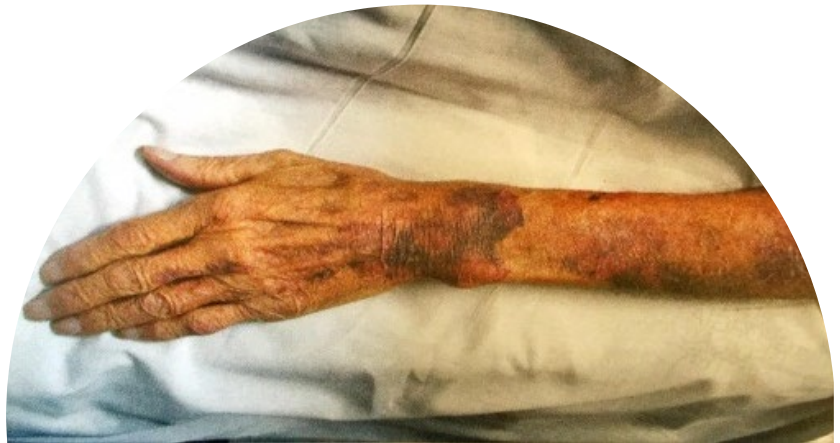
- Autoimmune bleeding disorder
- Incidence 3-16/100,000
  Prevalence 35-60/100,000
- Newly diagnosed (< 3 months), persistent (3-12 months), chronic (>12 months)
- Therapeutic options include: corticosteroids, intravenous immunoglobulin (IVIg), anti-D, thrombopoietin receptor agonists (TPO-RAs), Rituxan, Fostamatinib etc…..











Rodeghiero et al. Blood, 2009.
Wintrobe's Clinical Hematology, 13th edition. 2014.
Hematology: Clinical Principles and Applications, 4th edition. © 2012 Elsevier Inc.

Immune ThrombocytoPenia (ITP):

Platelet count: $<100x10^9/L$

Newly Diagnosed ITP: Within 3 months from diagnosis.

Persistent ITP: Between 3 to 12 months from diagnosis. Includes patients not reaching spontaneous remission or not maintaining complete response off therapy.

Chronic ITP: > 12 month duration. Organ specific autoimmune disease. Presence of GPIIIa-reactive T cells. Th0/Th1 skewing. Cytokine abnormalities.

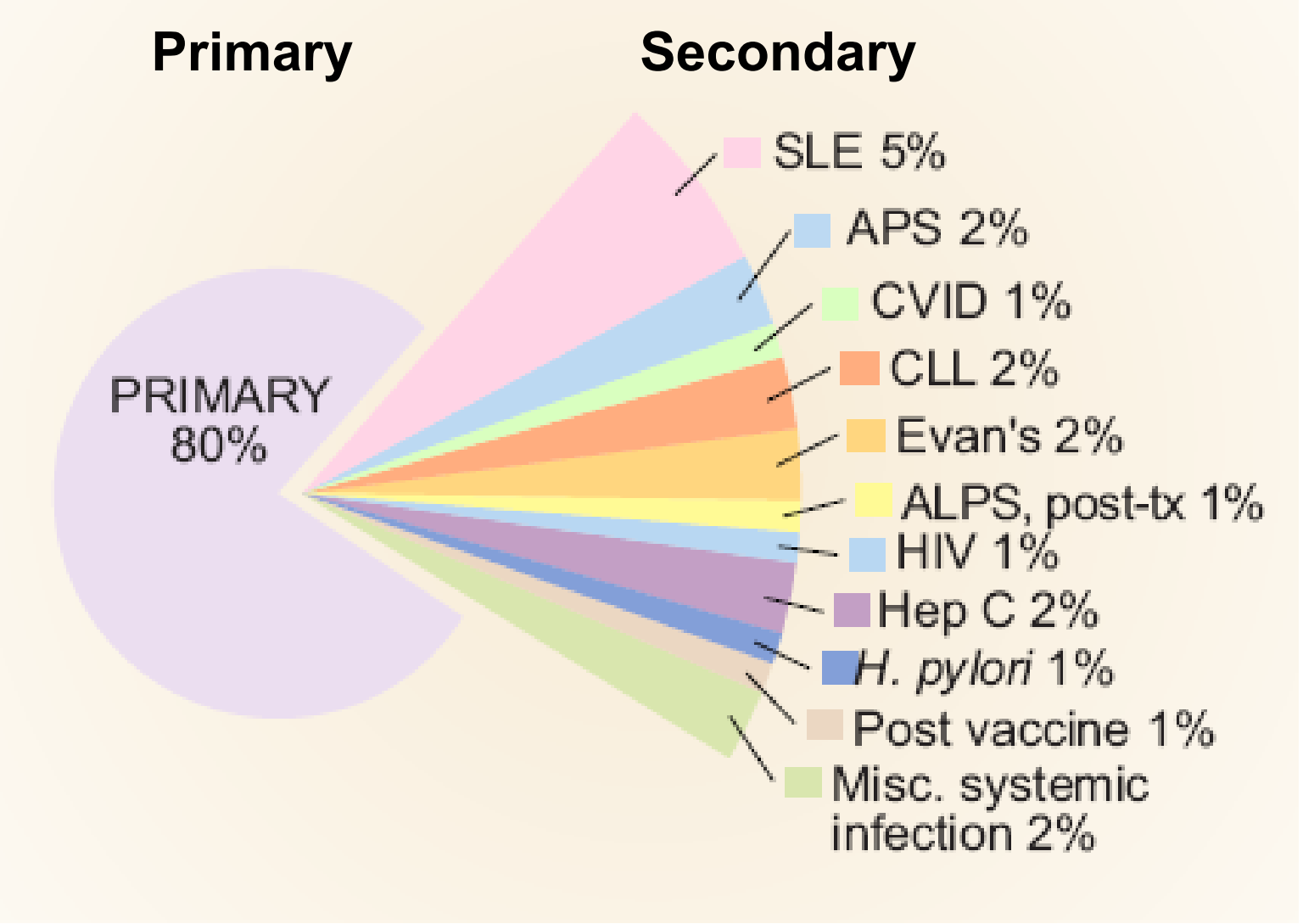
Severe ITP: Presence of bleeding symptoms at presentation sufficient to mandate treatment or occurrence of new bleeding symptoms requiring additional therapeutic intervention with a different drug or dose.

Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group

Francesco Rodeghiero,[1] Roberto Stasi,[2] Terry Gernsheimer,[3] Marc Michel,[4] Drew Provan,[5] Donald M. Arnold,[6] James B. Bussel,[7] Douglas B. Cines,[8] Beng H. Chong,[9] Nichola Cooper,[10] Bertrand Godeau,[4] Klaus Lechner,[11] Maria Gabriella Mazzucconi,[12] Robert McMillan,[13] Miguel A. Sanz,[14] Paul Imbach,[15] Victor Blanchette,[16] Thomas Kühne,[15] Marco Ruggeri,[1] and James N. George[17]

Blood 2009;113:2386-2393.

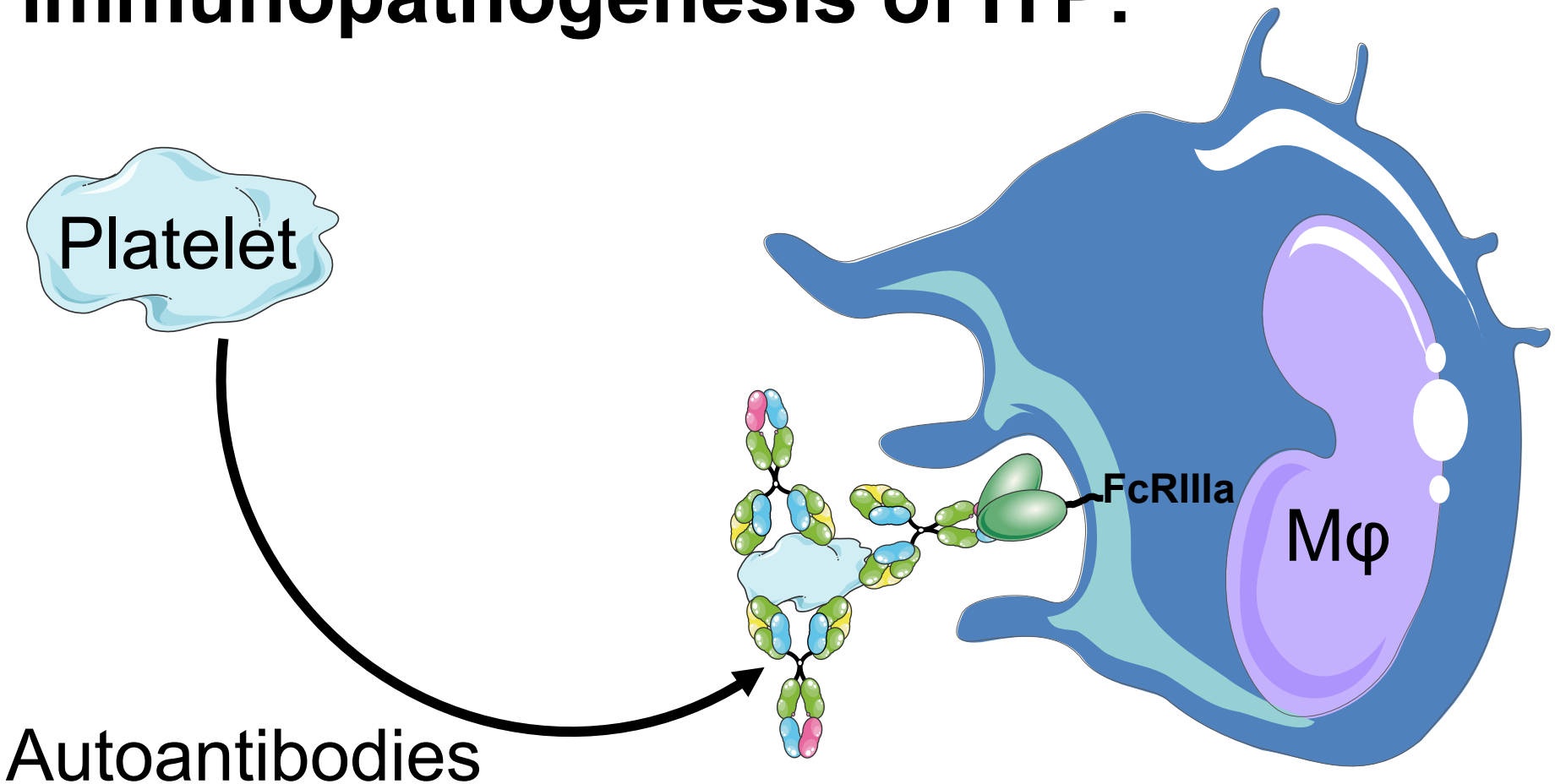
Not all ITP is Primary ITP



The ITP syndrome: pathogenic and clinical diversity (Blood. 2009;113:6511-6521)

Douglas B. Cines,[1,2] James B. Bussel,[3] Howard A. Liebman,[4] and Eline T. Luning Prak[1]

Classic immunopathogenesis of ITP:



Autoantibodies

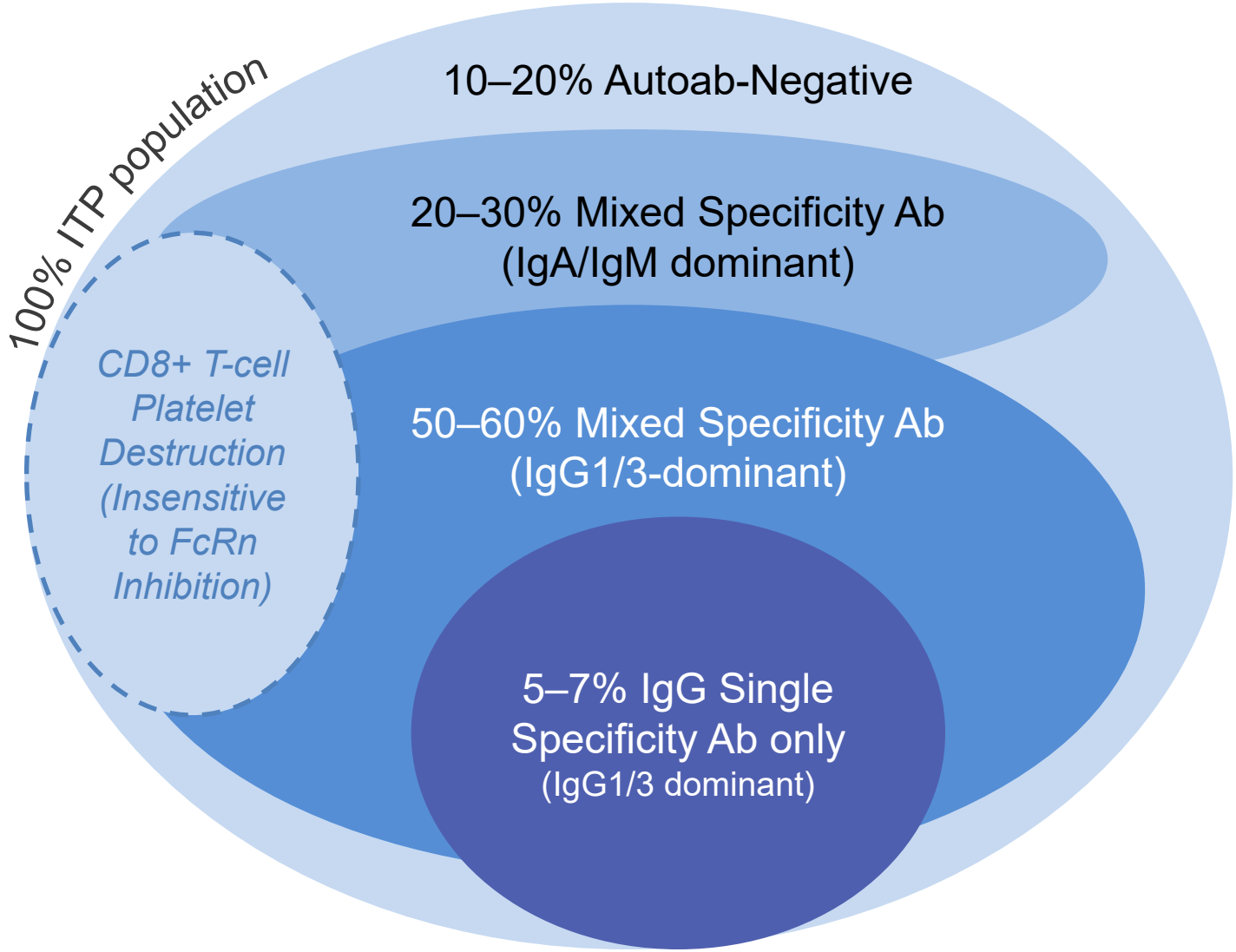
- Anti-GPIIbIIIa
- Anti-GPIb/IX
- Anti-GPV

FcR-mediated platelet phagocytosis (Spleen)

CD: cluster of differentiation; Fc, fragment crystallizable; FcR: Fc receptor; GP, glycoprotein; IgG: immunoglobulin G; Mφ: macrophage; RES: reticuloendothelial system.

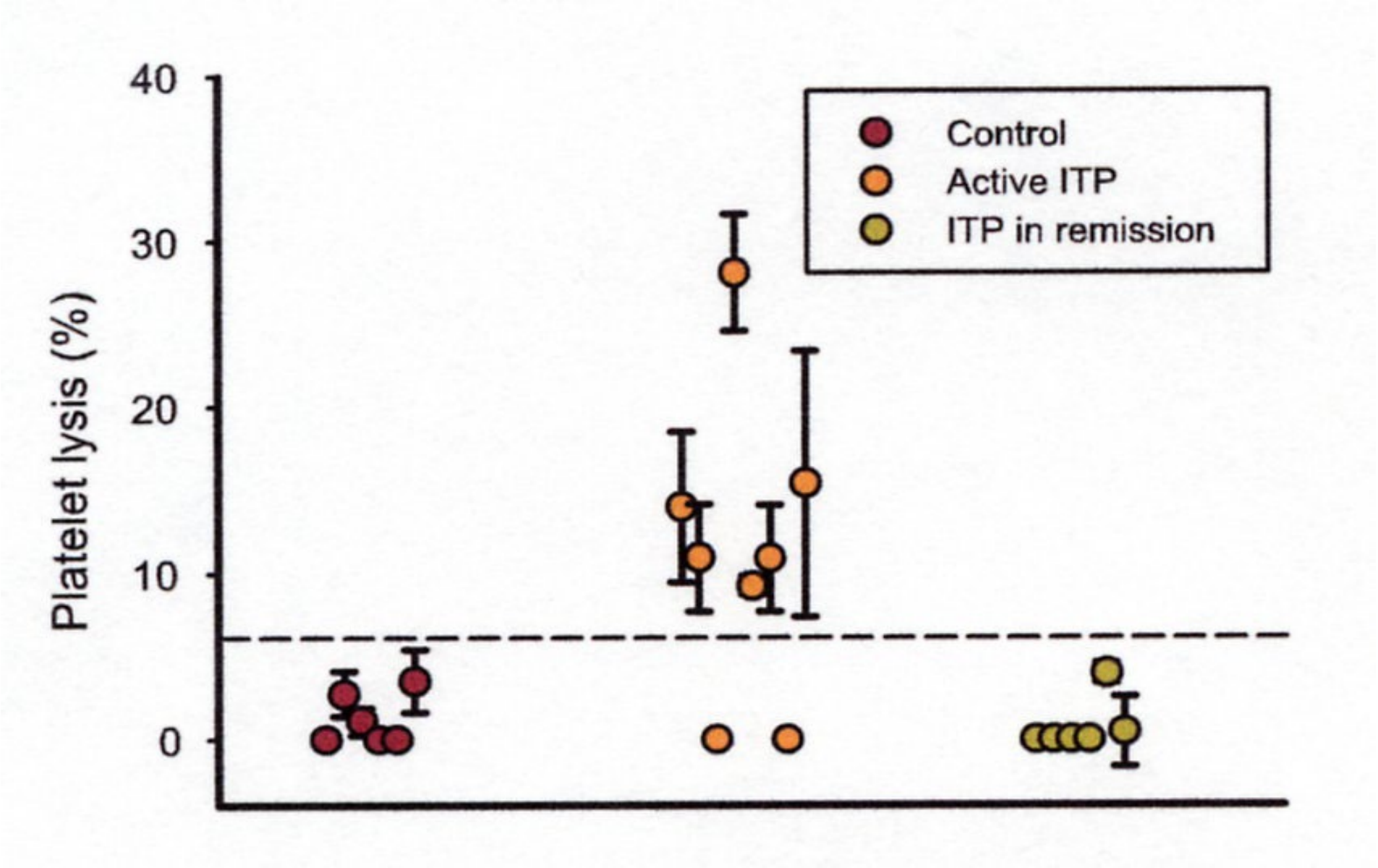
Semple JW, unpublished.

The autoantibody ‘footprint’ in immune thrombocytopenia:



1 .Chan H et al. Br J Haematol 2003;122:818–24; 2. He R et al. Blood 1994;83:1024-32; 3. McMillan R. Semin Hematol 2000;37:239-48; 4. Porcelijn L et al. Bailliere’s Clin Hematol 1998;11:331–41; 5. Stahl D et al. Eur J Haematol 2005;75:318–27; 6. Zhao C et al. Haematologica 2008;93:428; 7. Guo L et al. Blood 2006;127:735; 8. Nishioka T et al. Cytometry B Clin Cytom 2005;68:37–42; 9. Hymes K et al. Blood 1980;56:84; 10. Olsson B et al. Nat Med 2003;9:1123–4; 11. Al-Samkari H et al. Blood Adv 2020;4:9–18; 12. Porcelijn L et al. Br J Haematol 2018;182,423–6.

T-cell-mediated platelet cytotoxicity in ITP



Olsson et al Nat Med. 2003 Sep;9(9):1123-4., Zhao et al Haematologica, 2008 Sep;93(9):1428-30, Chow et al Blood 2010;115:1247-1253

ITP Autoantibodies Suppress Megakaryocyte Growth in vitro

Immune thrombocytopenic purpura (ITP) plasma and purified ITP monoclonal autoantibodies inhibit megakaryocytopoiesis in vitro

Blood. 2003;102:887-895

Mei Chang, Peggy A. Nakagawa, Shirley A. Williams, Michael R. Schwartz, Karen L. Imfeld, Jeffrey S. Buzby, and Diane J. Nugent

Suppression of in vitro megakaryocyte production by antiplatelet autoantibodies from adult patients with chronic ITP

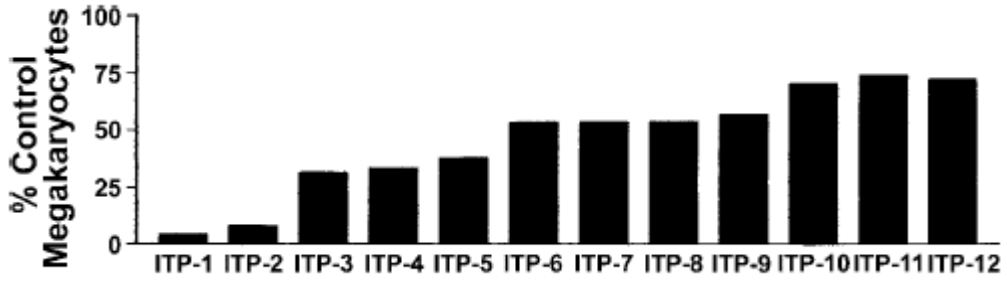
Robert McMillan, Lei Wang, Aaron Tomer, Janet Nichol, and Jeanne Pistillo

Blood. 2004;103:1364-1369

Immune thrombocytopenia: antiplatelet autoantibodies inhibit proplatelet formation by megakaryocytes and impair platelet production *in vitro*

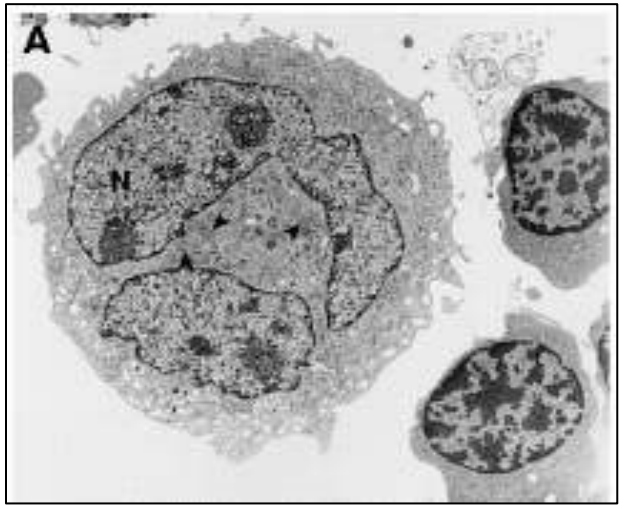
Haematologica 2015; 100(5): 623-32

Muna Iraqi,[1,2]* Jose Perdomo,[1,2]* Feng Yan,[1,2,3] Philip Y-l Choi,[1,2] and Beng H. Chong[1,2,3]

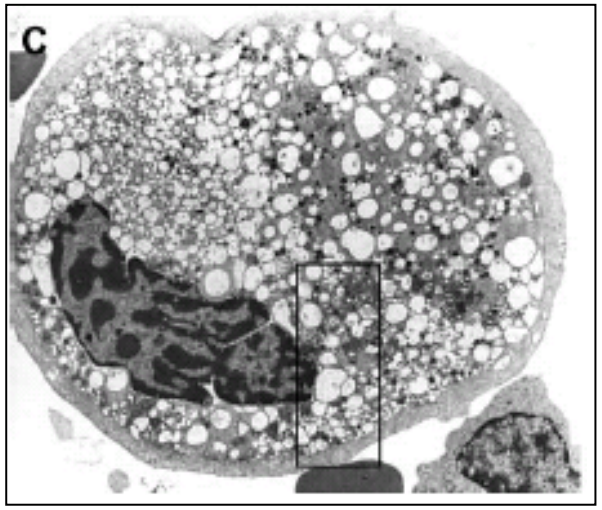


Anti-platelet antibodies and CTL induce apoptosis in megakaryocytes:

Healthy Control



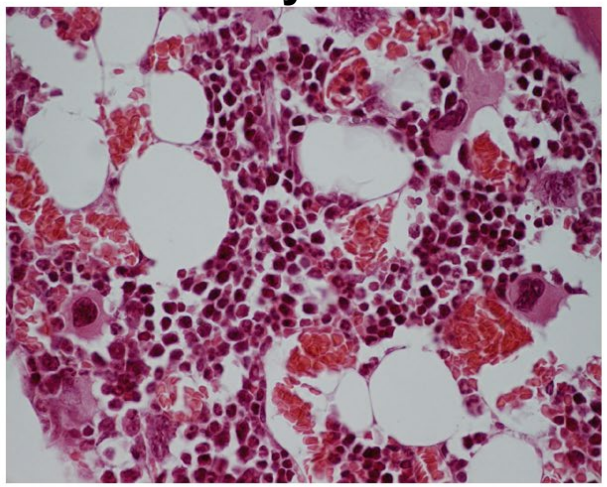
ITP



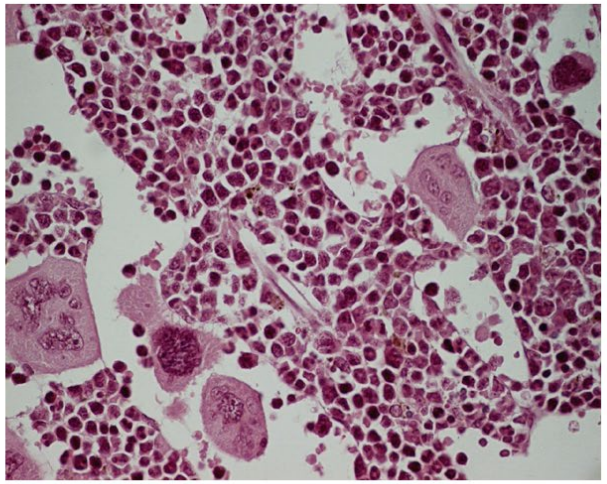
Ab-mediated ITP

Houwerzijl EJ et al. Blood 2004;103:500-506

Healthy Control



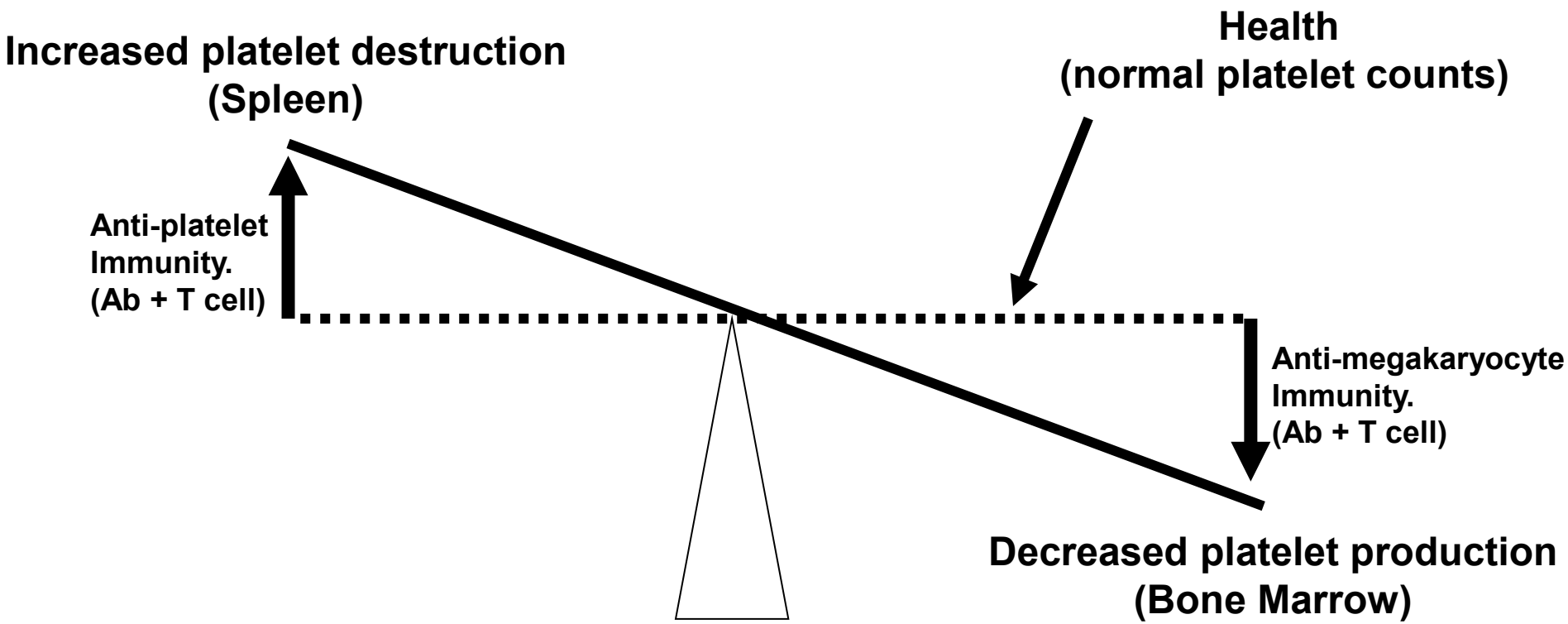
ITP



CTL-mediated ITP

Chow et al Blood 2010;115:1247-1253

Today: ITP is due to two reasons



ITP effector immunity is comprised of antibodies and T cells.

Events Leading to ITP (?).

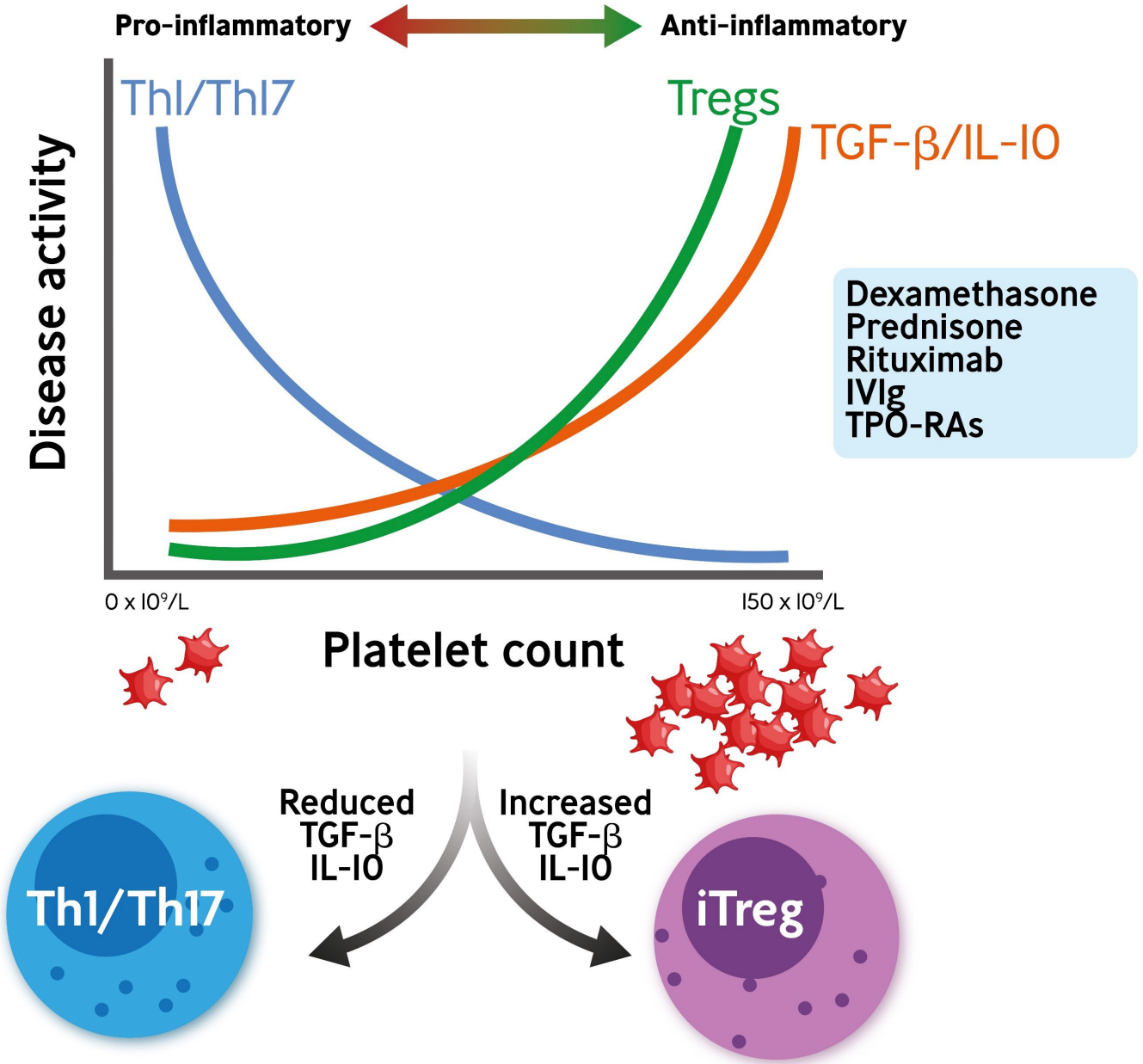
1. **Loss of immune tolerance.**
   Reduced Tregs,
   Reduced Bregs,
   Reduced MDSC etc.

2. **Enhanced autoreactive Th1/Th17 responses lead to anti-platelet autoantibody and cytotoxic T cell (CTL) production.**

3. **These events then destroy platelets in a variety of mechanisms.**
   Splenic FcR-mediated phagocytosis,
   Splenic/BM CTL-mediated plt./MK destruction,
   Peripheral complement-mediated platelet lysis,
   Peripheral antibody dependent cellular cytotoxicity (ADCC),
   Desialyation of platelet antigens and hepatic AMR-mediated destruction, etc.

Loss of Immune Tolerance: The lack of a suppressive side to ITP.

Platelet – Treg Relationships in ITP:



Semple JW et al. ISBT Science Series (2020) 15, 315–319

B regulatory cells (Bregs)

blood

2012 120: 3318-3325
Prepublished online August 2, 2012;
doi:10.1182/blood-2012-05-432575

Defective regulatory B-cell compartment in patients with immune thrombocytopenia

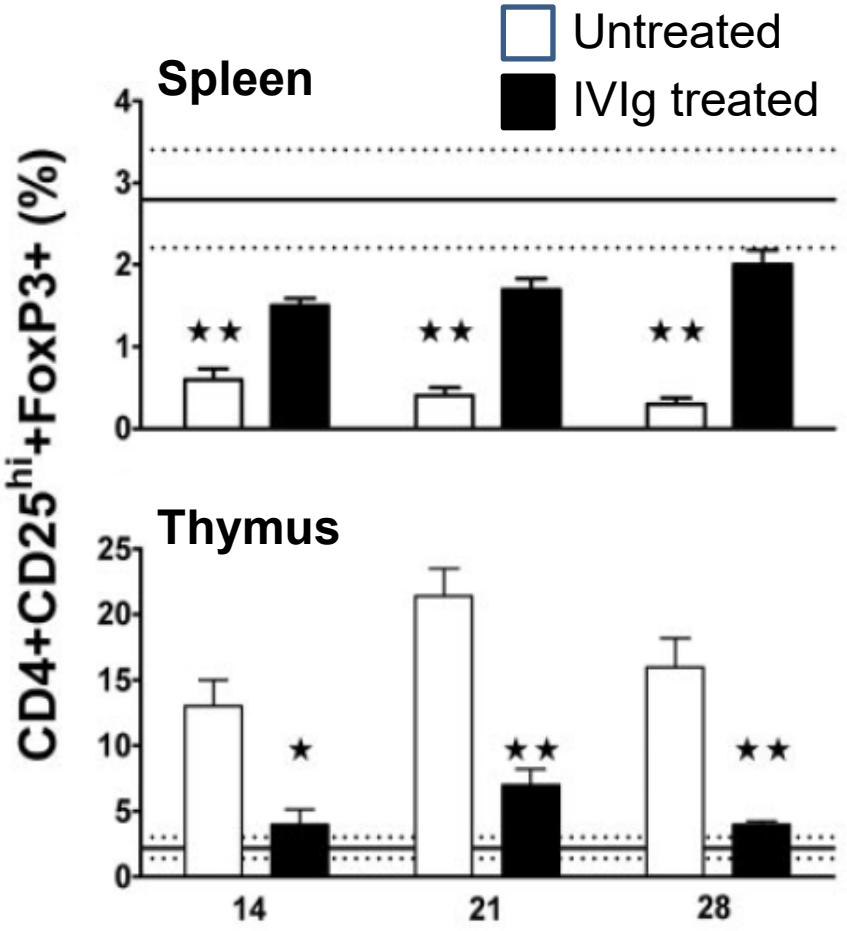
Xiaojuan Li, Hui Zhong, Weili Bao, Nayla Boulad, Jessie Evangelista, Muhammad Anis Haider, James Bussel and Karina Yazdanbakhsh

First study to show reduced phenotypic and functional levels of peripheral Bregs in patients with ITP.

- Significantly altered frequency and expression of peripheral $CD19^{+}$ $CD24^{hi}/CD38^{hi}$ Bregs
- Impaired IL-10 response in stimulated B-cells
- Decreased Breg suppressive activity and reduced dampening of monocyte activation in patients with low platelet counts

Peripheral Tregs and Bregs are not gone, but sequestered

Tregs sequestered in thymus



Bregs sequestered in spleen

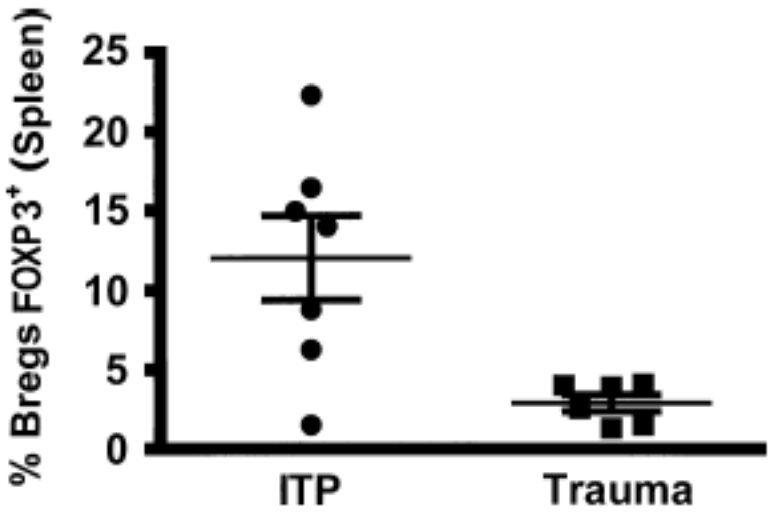


Fig 1. Percentage of $CD19^+CD24^+FOXP3^+$ B-regulatory cells in spleens removed from patients with ITP and trauma controls. ITP, immune thrombocytopenia.

Aslam R et al. Blood. 2012;120(10):2127-2132); Aslam R et al BJH 2016, 173:150;

Myeloid Derived Suppressor Cells (MDSC)

Morphologically and functionally heterogeneous population of bone marrow derived immune cells.

Potent regulators of adaptive immunity: Striking ability to inhibit T cell proliferation.

Originally described in malignancies but they are also present in inflammatory and autoimmune diseases.

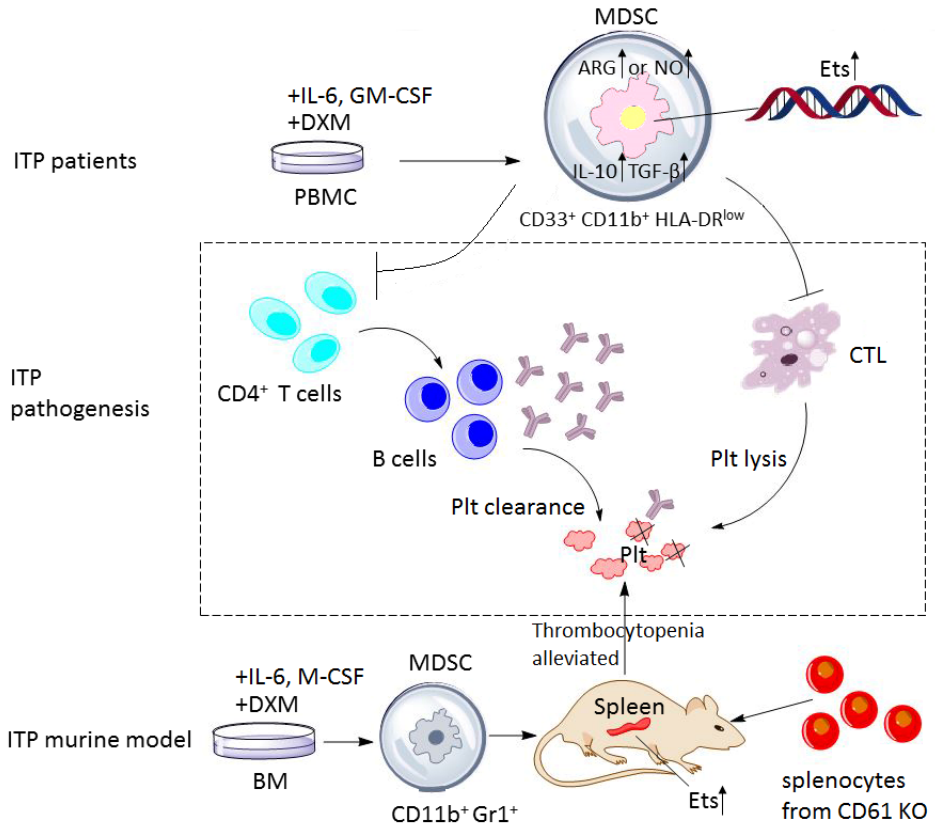
MDSC in ITP

blood

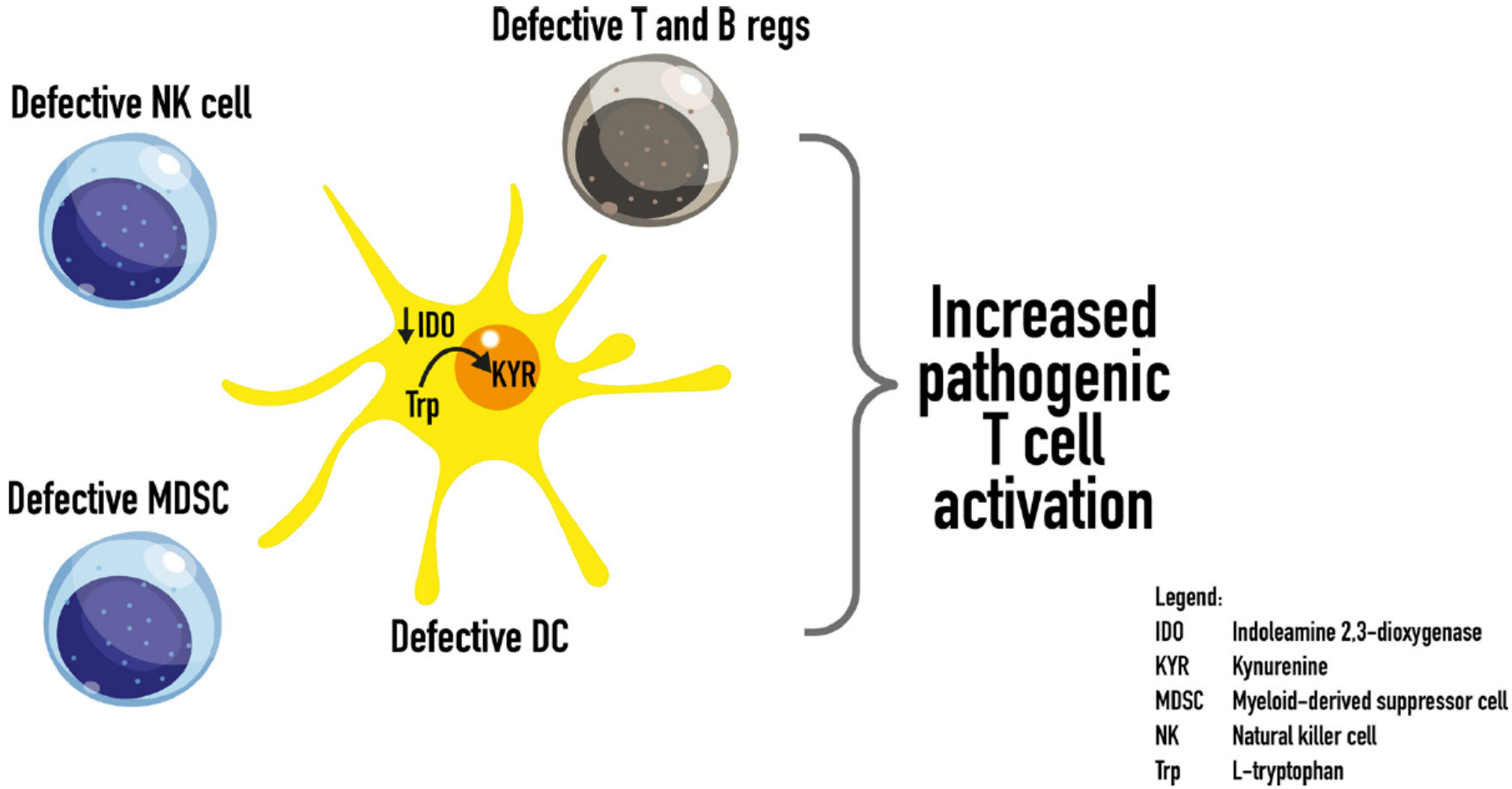
Prepublished online January 7, 2016;
doi:10.1182/blood-2015-10-674531

High-dose dexamethasone corrects impaired myeloid-derived suppressor cell function via Ets1 in immune thrombocytopenia

Yu Hou, Qi Feng, Miao Xu, Guo-sheng Li, Xue-na Liu, Zi Sheng, Hai Zhou, Ji Ma, Yu Wei, Yuan-xin Sun, Ying-yi Yu, Ji-hua Qiu, Lin-lin Shao, Xin-guang Liu, Ming Hou and Jun Peng



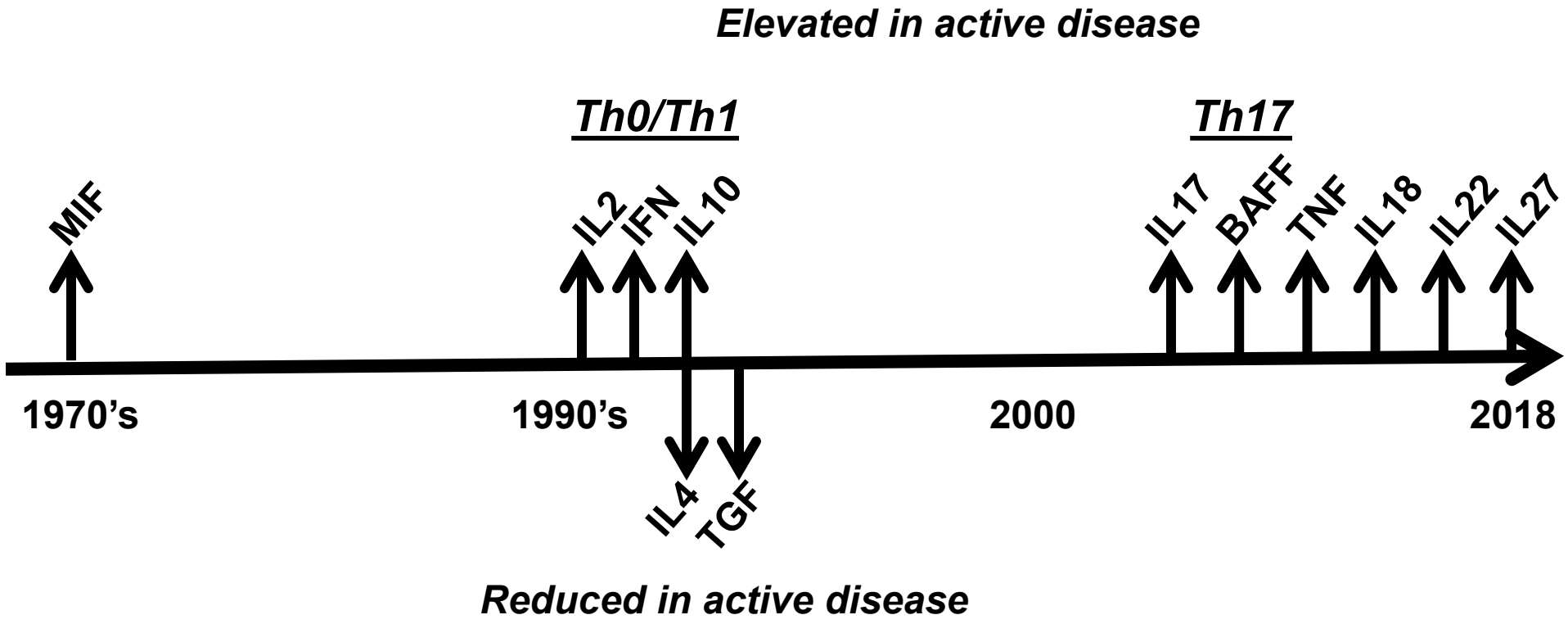
Loss of Immune tolerance leads to increased T cell activation



Provan and Semple, Lancet EBioMedicine 2022;76: 103820, https://doi.org/10.1016/j. ebiom.2022.103820

Loss of Immune tolerance leads to:
Enhanced autoreactive Th1/Th17 responses and cytotoxic T cell (CTL) production.

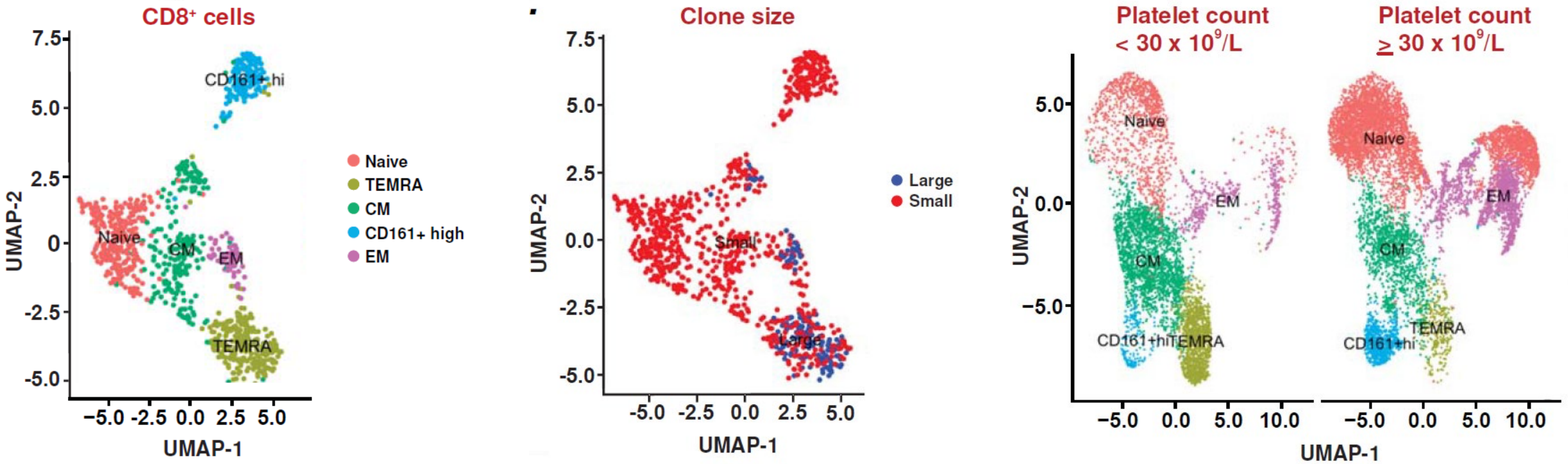
Major T cell Cytokines so far Identified in patients with ITP:



Coopamah M et al. TMR, 2013; Semple JW et al. Curr Opin Hematol, 2010, 2012; McKenzie C et al. Brit J Haematol, 2013; Zufferey A et al. JCM, 2017; Semple JW et al. Curr Opin Hematol 2020, Audia S et al. HemaSphear 2021

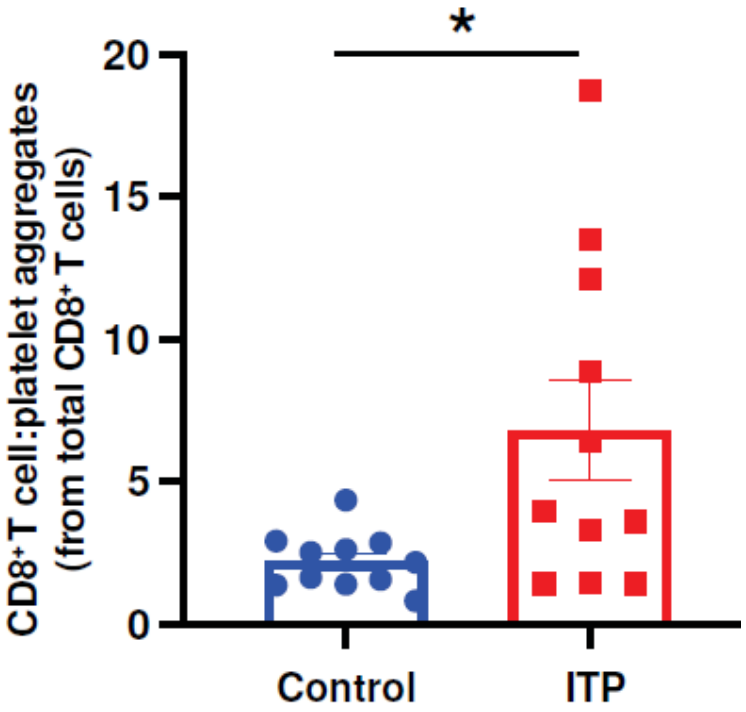
Terminally differentiated effector memory (TEMRA) CD8+ T cells in chronic ITP patients

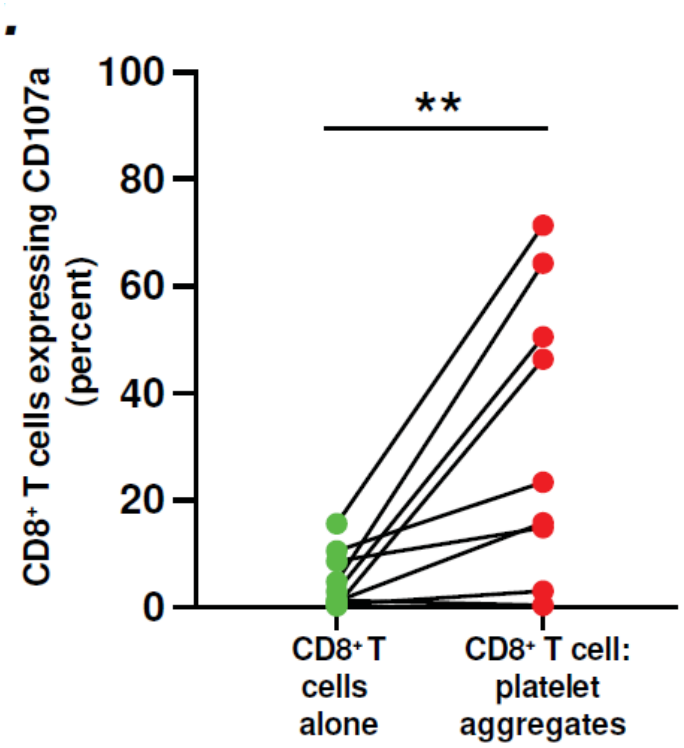
Single-cell RNA and T cell receptor sequencing

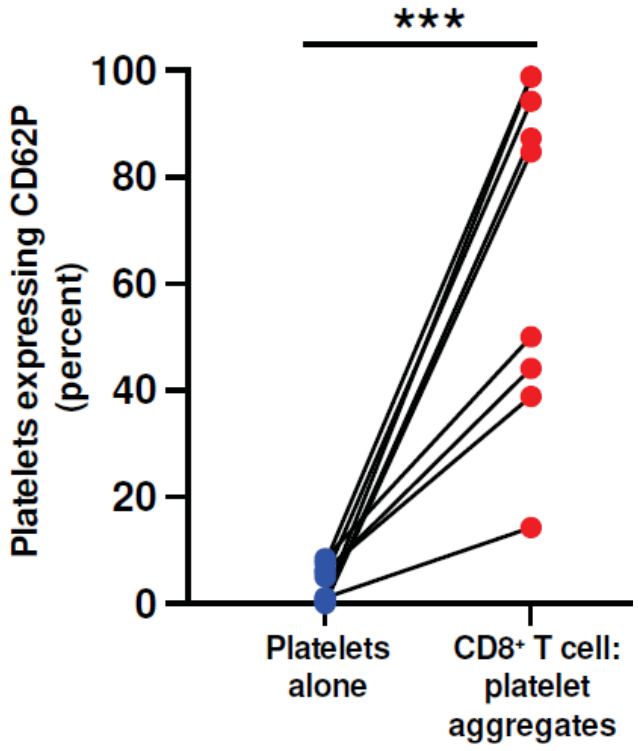


Malik et al, Blood 2023

CD8+ T cell: platelet aggregates with increased CD107a and CD62P

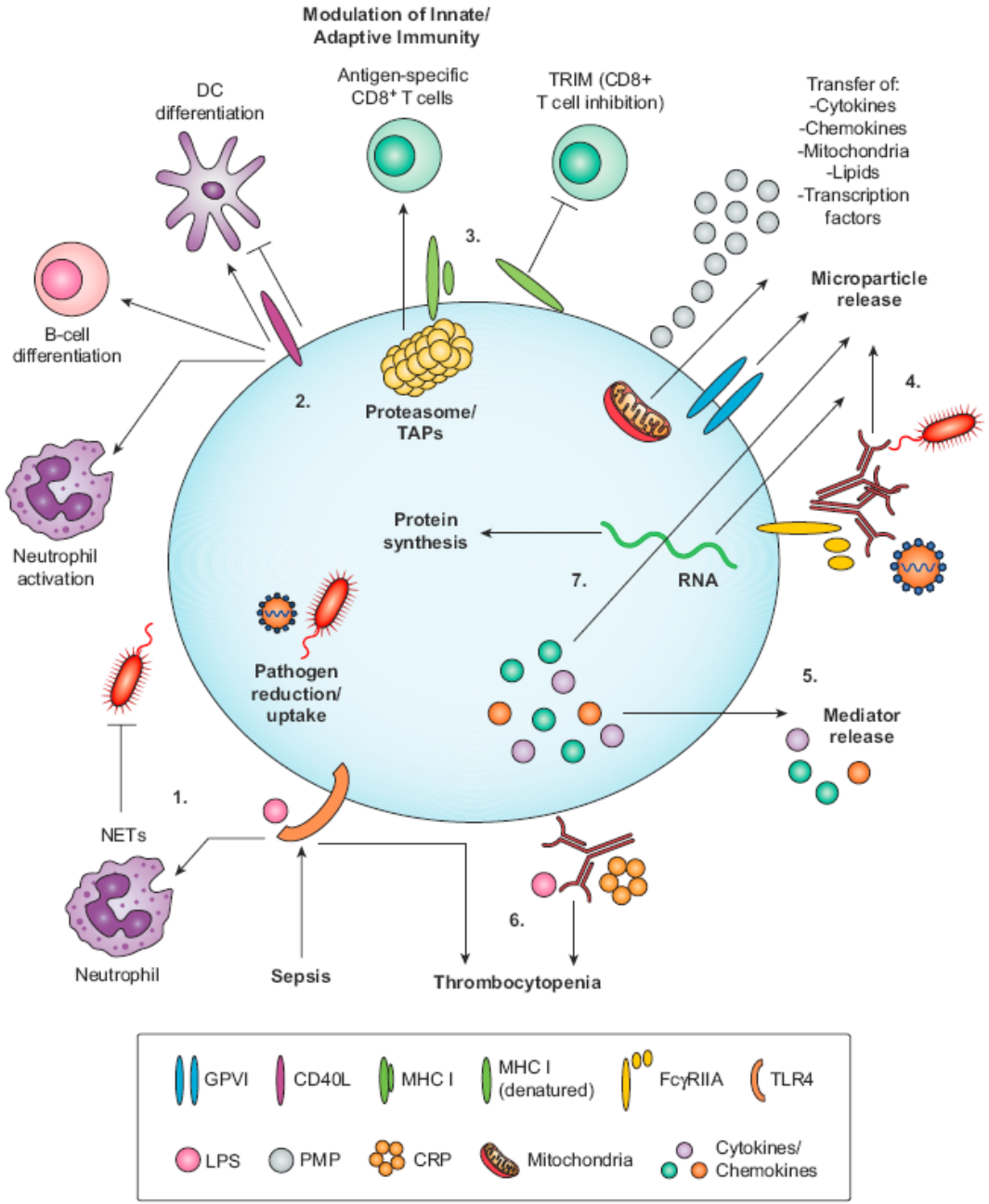






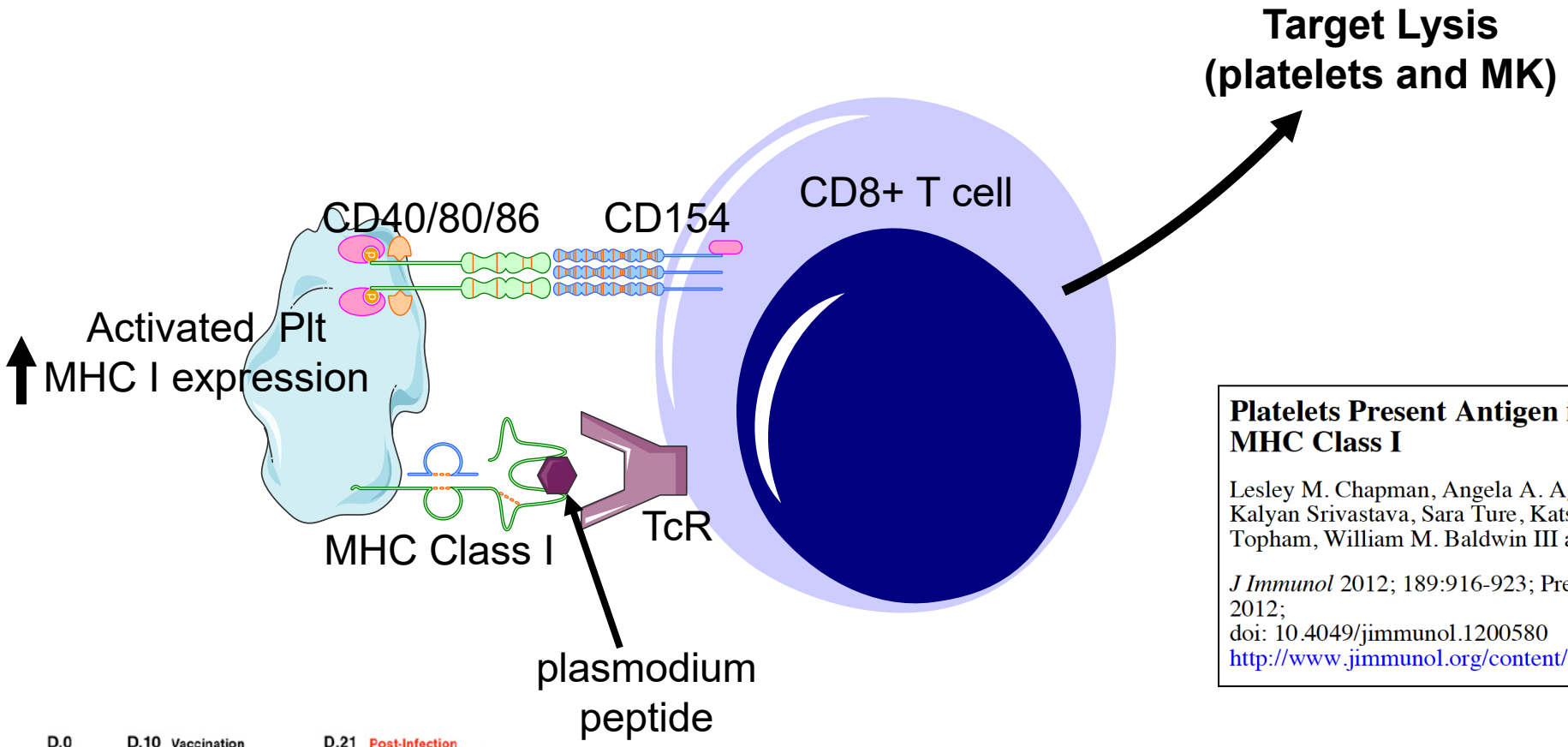
Malik et al, Blood 2023

Platelets are immune cells:



Kapur R et al. J Immunol, 2015, 194: 5579–5587

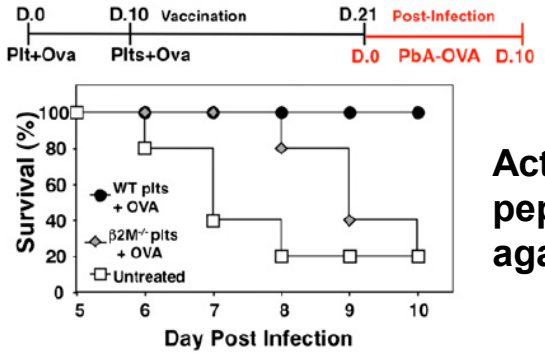
Platelets can cross present antigens to CD8+ T cells.



Platelets Present Antigen in the Context of MHC Class I

Lesley M. Chapman, Angela A. Aggrey, David J. Field, Kalyan Srivastava, Sara Ture, Katsuyuki Yui, David J. Topham, William M. Baldwin III and Craig N. Morrell

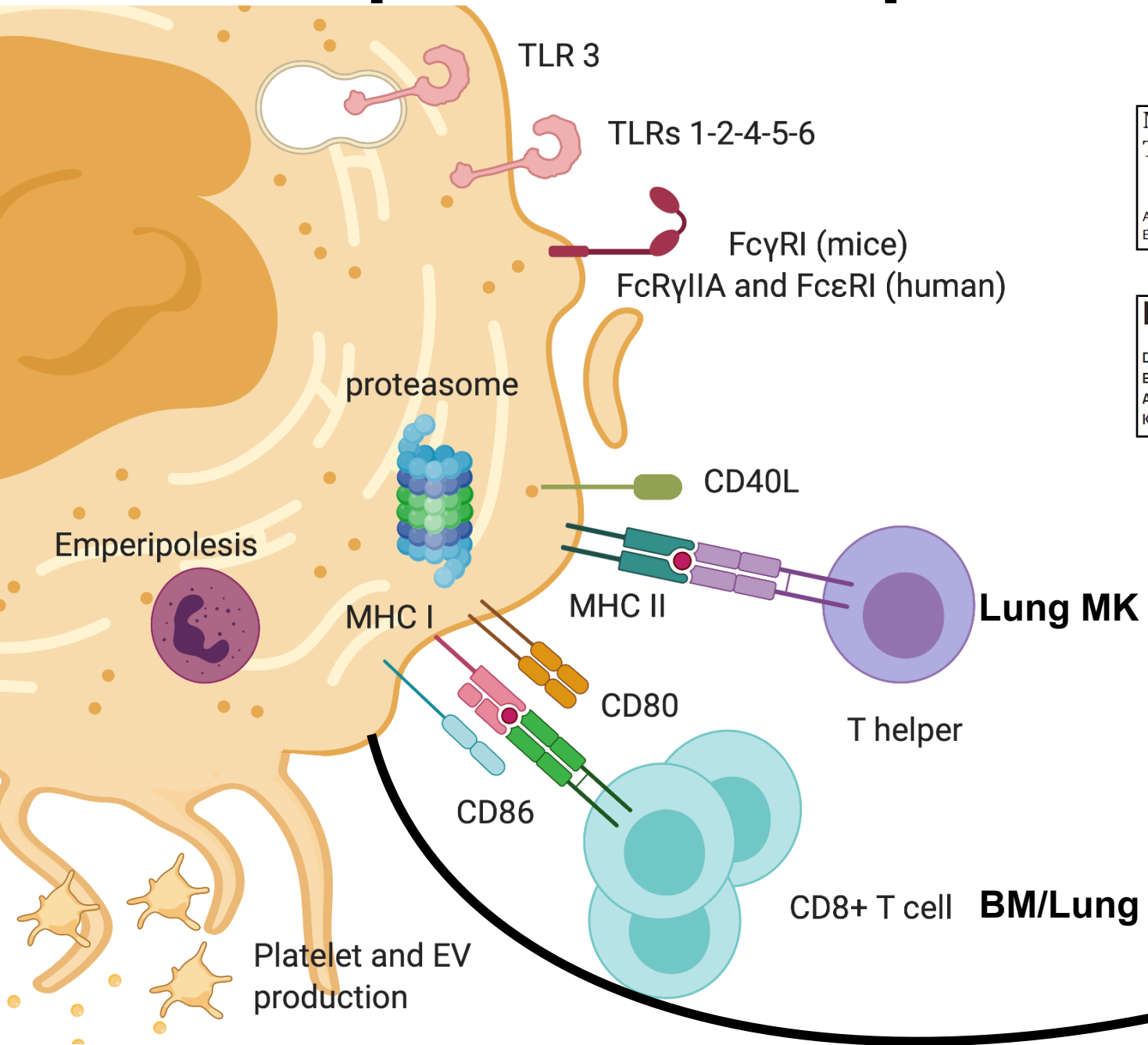
J Immunol 2012; 189:916-923; Prepublished online 15 June 2012;
doi: 10.4049/jimmunol.1200580
http://www.jimmunol.org/content/189/2/916



Activated murine MHC class I+ platelets present plasmodium peptides to CD8+ T cells and can act as a Ag delivery vehicles to protect against *P. berghei* induced fatal experimental cerebral malaria (ECM).

PbA-OVA: Plasmodium berghei ANKA-OVA

MK also process and present antigens.



Mature murine megakaryocytes present antigen-MHC class I molecules to T cells and transfer them to platelets

Blood Adv. 1(20):1773-1785, 2017.

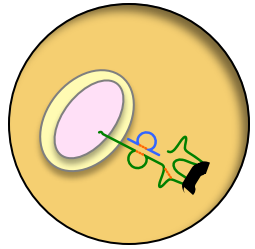
Anne Zufferey,[1] Edwin R. Speck,[1] Kellie R. Machlus,[2,3] Rukhsana Aslam,[1] Li Guo,[1] Mark J. McVey,[1,4] Michael Kim,[1] Rick Kapur,[1,5] Eric Boilard,[6] Joseph E. Italiano Jr,[2,3,7] and John W. Semple[1,5,8,9]

Lung megakaryocytes are immune modulatory cells

Daphne N. Pariser,[1,2] Zachary T. Hilt,[1] Sara K. Ture,[1] Sara K. Blick-Nitko,[1] Mark R. Looney,[3] Simon J. Cleary,[3] Estheany Roman-Pagan,[1] Jerry Saunders II,[4] Steve N. Georas,[2,5] Janelle Veazey,[2] Ferralita Madere,[2] Laura Tesoro Santos,[6] Allison Arne,[1] Nguyen P.T. Huynh,[7,8] Alison C. Livada,[1,9] Selena M. Guerrero-Martin,[10] Claire Lyons,[10] Kelly A. Metcalf-Pate,[10] Kathleen E. McGrath,[4] James Palis,[4] and Craig N. Morrell[1,2,5,9]

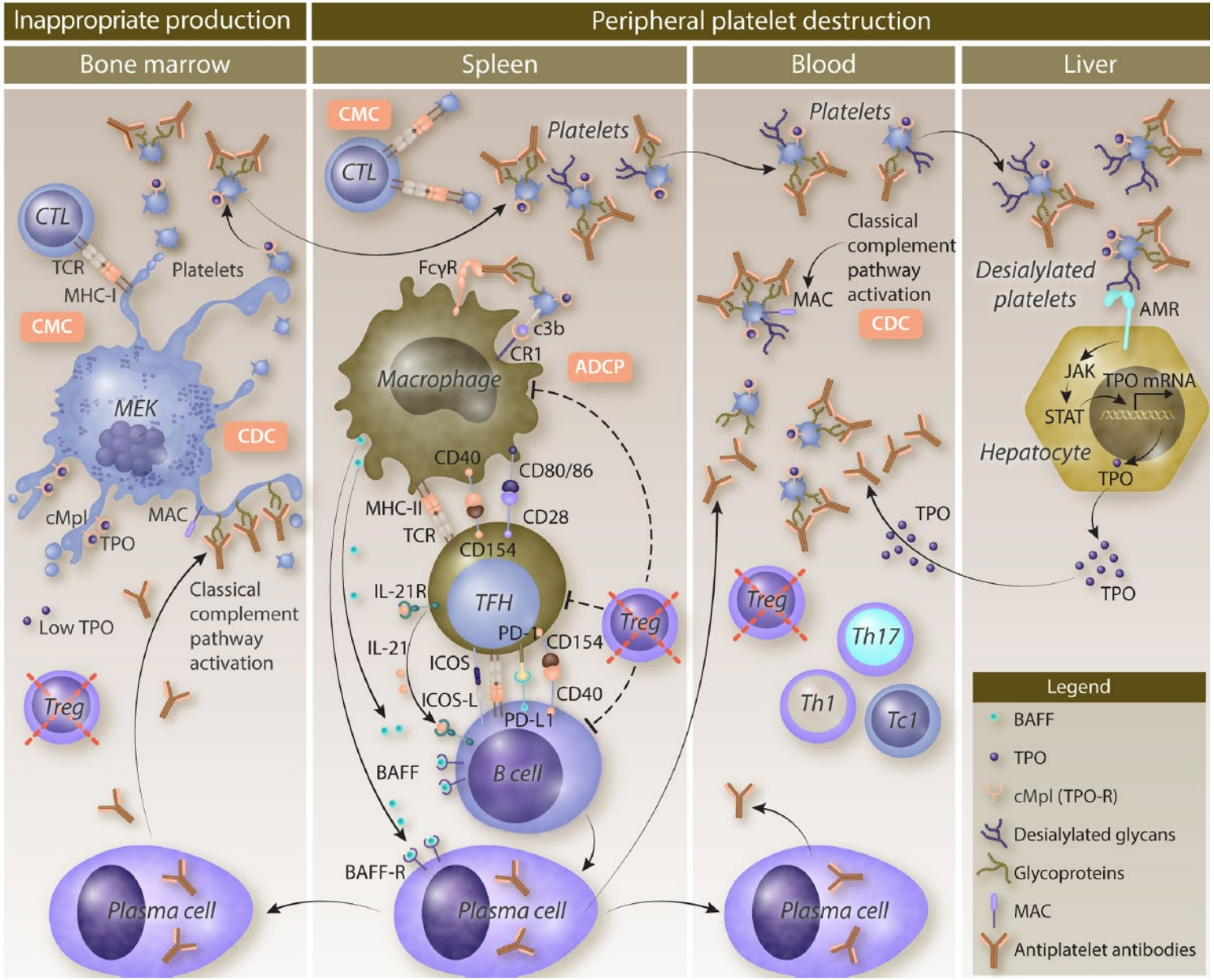
J Clin Invest. 2021;131:137377.

Shed Platelets (with MHC/peptide)



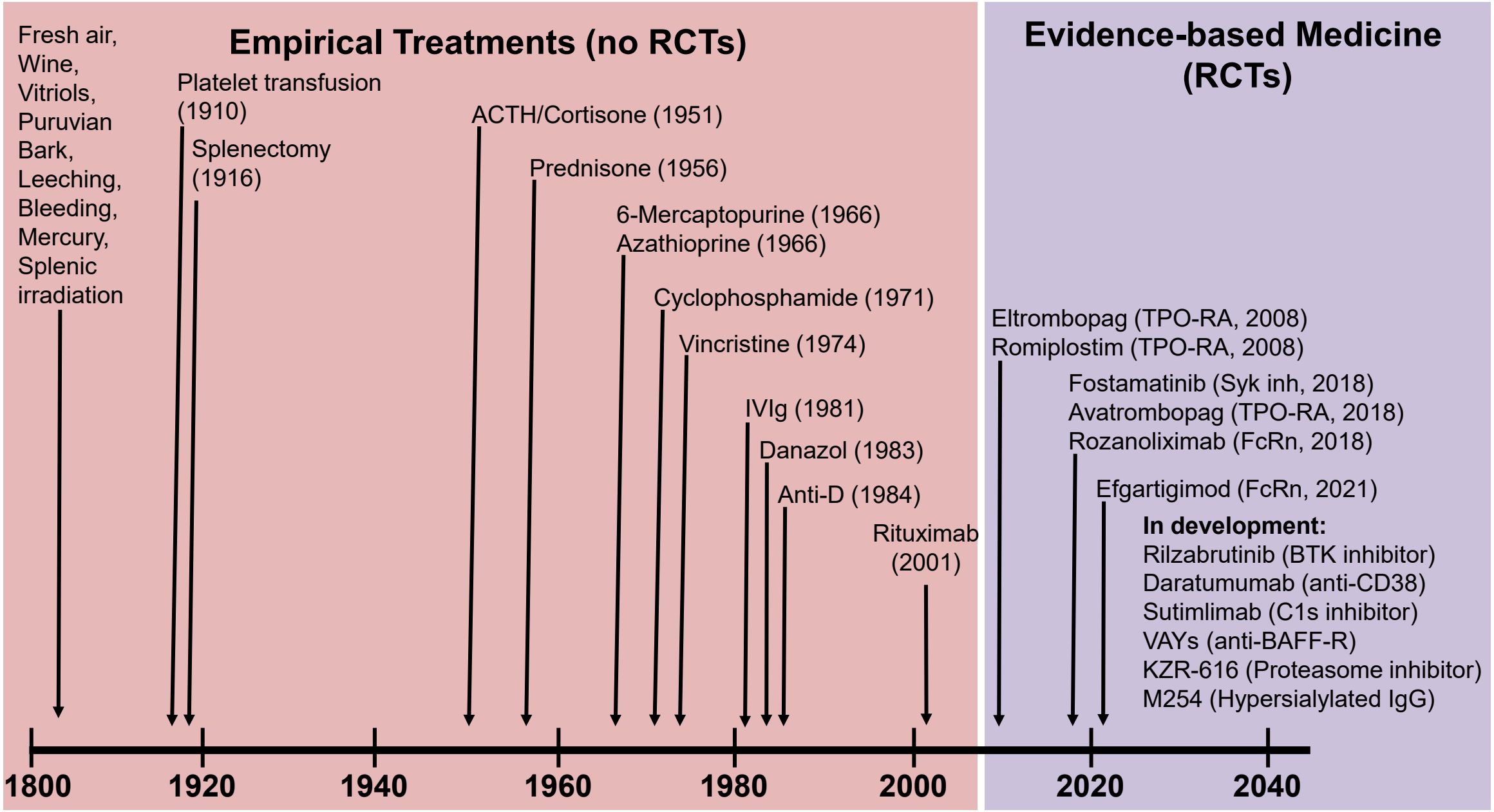
Adapted from Marcoux et al. Platelets (2020)

Sites and Mechanisms of Platelet Destruction in ITP:



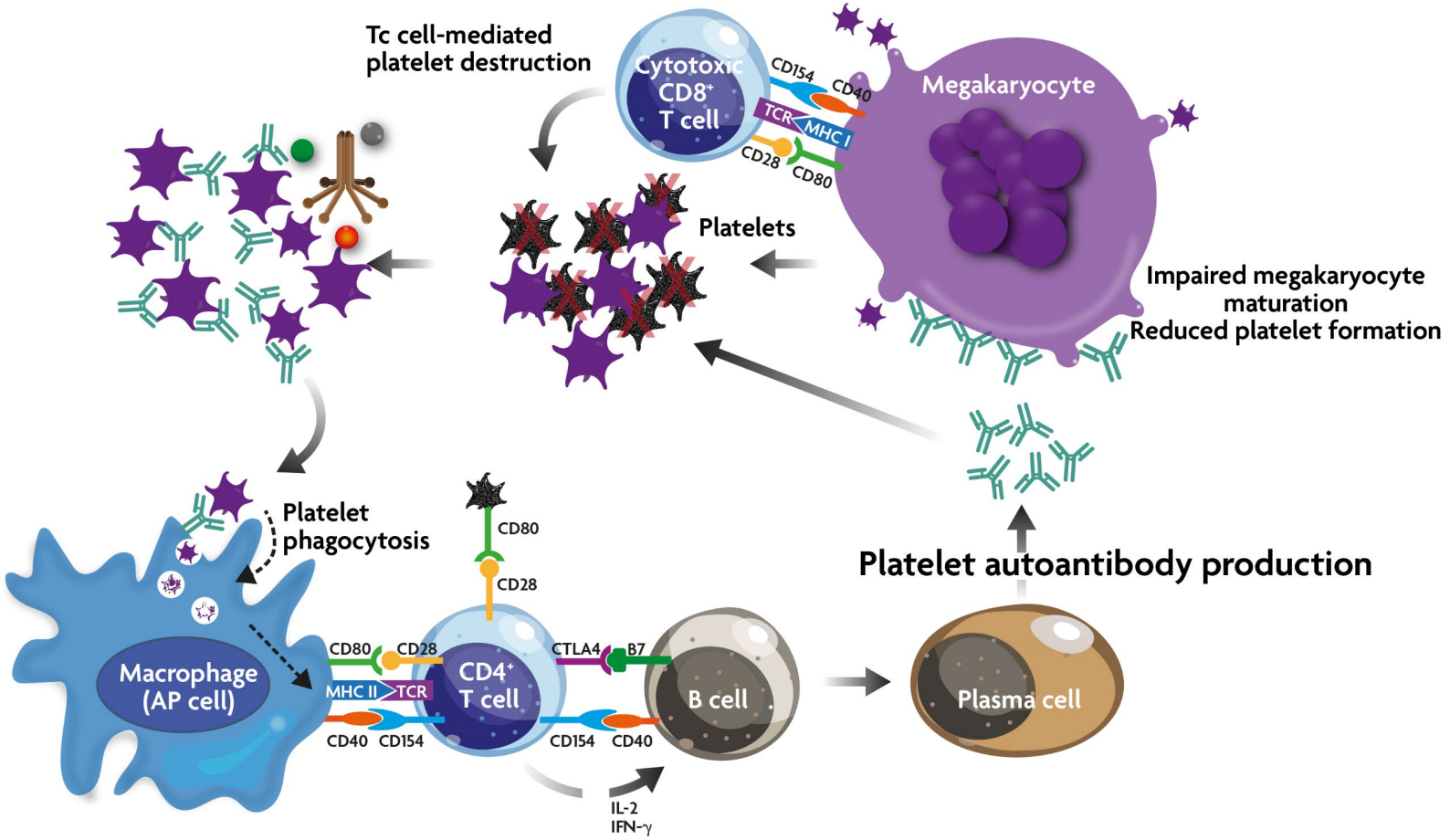
Audia S et al. HemaSphere (2021) 5:6(e574). http://dx.doi.org/10.1097/

Therapies for ITP thoughout the ages



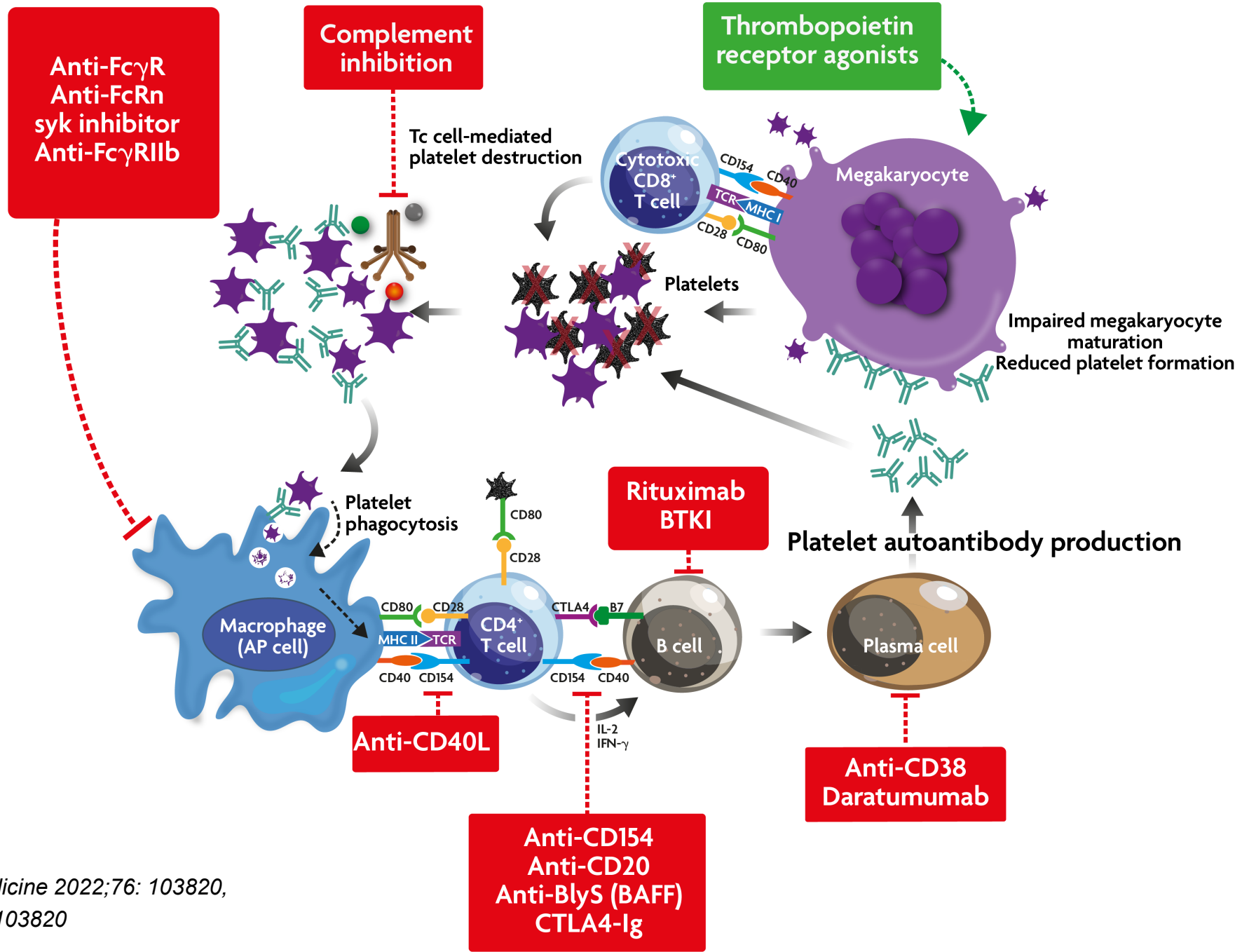
Courtesy of Drew Provan

ITP pathophysiology:



Provan and Semple, Lancet EBioMedicine 2022;76: 103820, https://doi.org/10.1016/j. ebiom.2022.103820

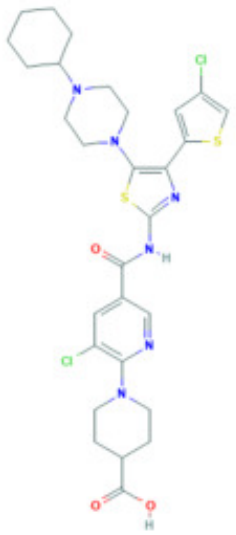
ITP Therapy:



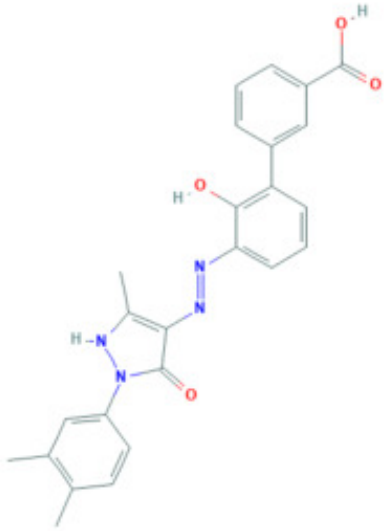
Provan and Semple, Lancet EBioMedicine 2022;76: 103820, https://doi.org/10.1016/j. ebiom.2022.103820

Thrombopoietin Receptor Agonists (TPO-RA).

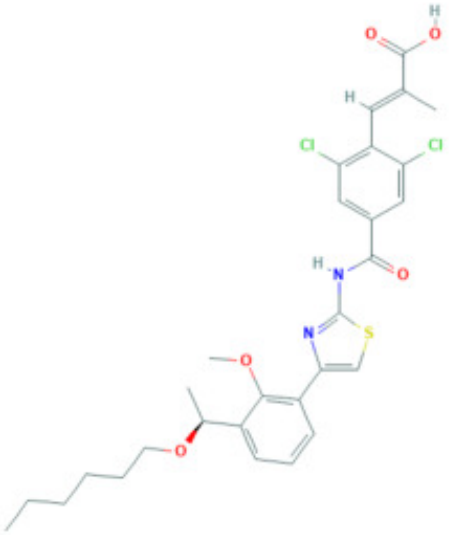
Avatrombopag (Doptelet)



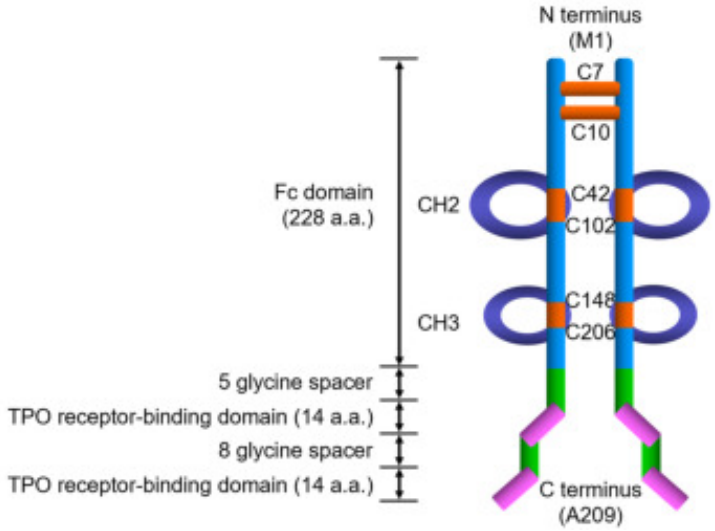
Eltrombopag (Promacta, Revolade)



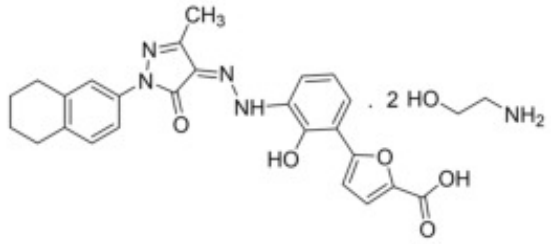
Lusutrombopag (Mulpleta, Mulpleo)



Romiplostim (Nplate)

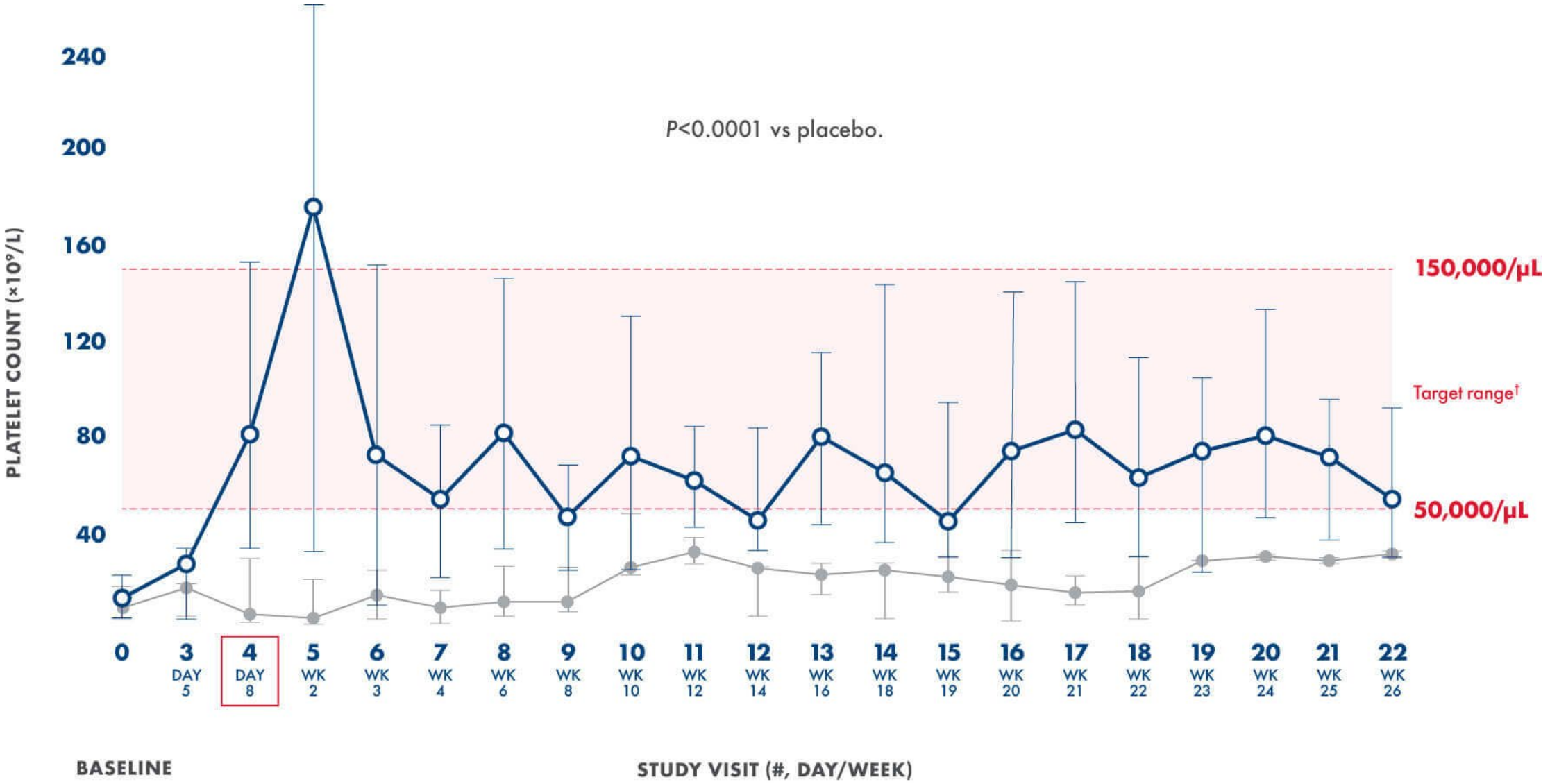


Hetrombopag (under development in China)



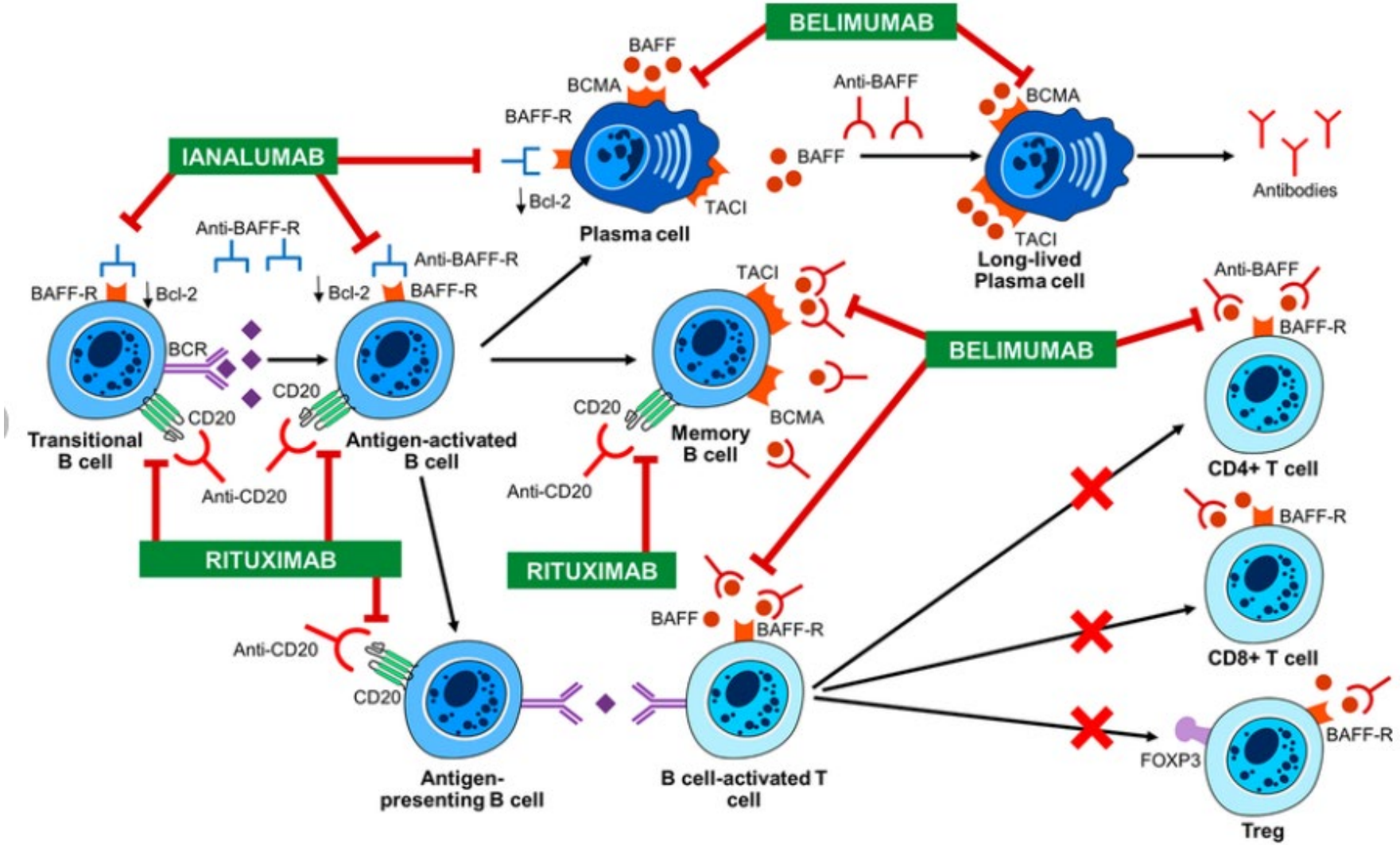
Kuter DJ. Blood Rev, 2022

Typical TPO-RA Responses (Avatrombopag)



Jurczak W et al. Br J Haematol. 2018;183(3):479-490.

B-cell activating factor (BAFF)/receptor (BAFF-R)



ianalumab (VAY736): Binds BAFF-R and inhibits function and depletes B cells by an ADCC process

Czaja AJ et al. Digest Dis Sci. 2022;67:4979–5005

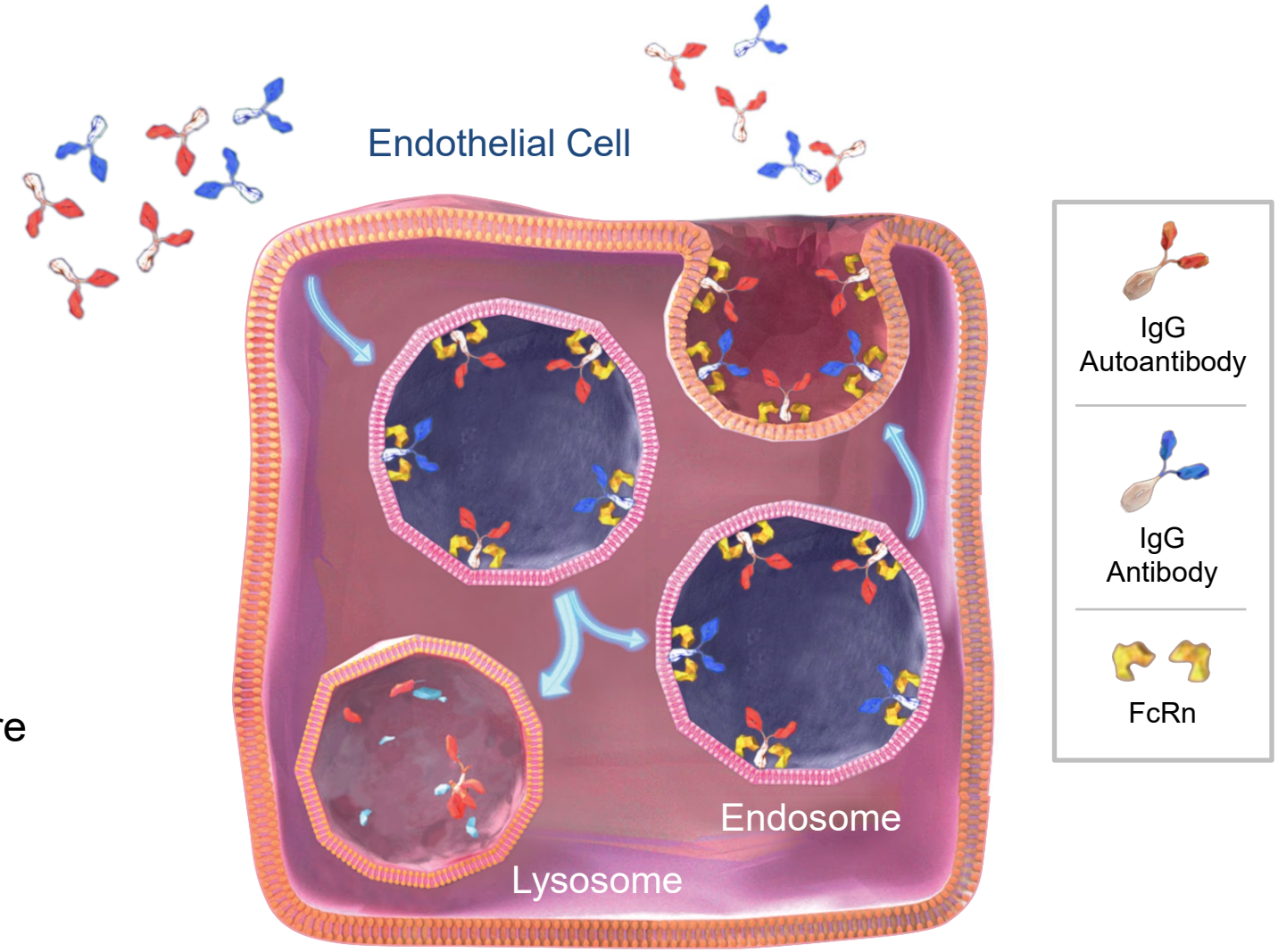
The Function of FcRn in IgG Regulation

Studies have shown:

1. Circulating antibodies are taken up into the cell via pinocytosis. Within the endosome, IgG antibodies are able to bind to FcRn[1,2]

2. Unbound IgGs enter the lysosomal degradation pathway, while the bound IgGs are rescued from degradation due to FcRn binding[1,2]

3. The IgG antibodies bound by FcRn are then released back into circulation, thereby extending their half-life[1,2]



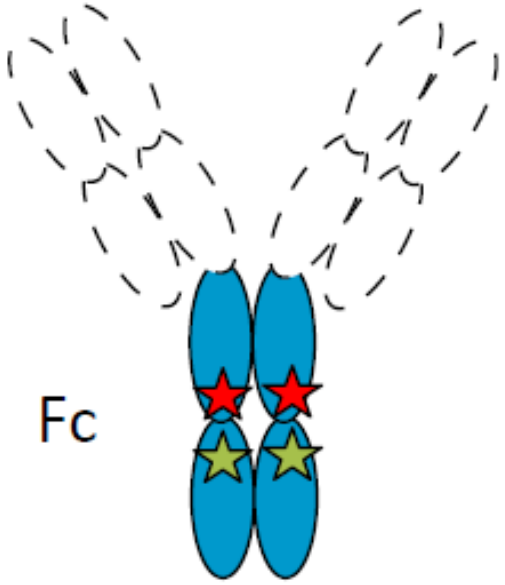
Courtesy of Francesco Zaja

FcRn, neonatal fragment crystallizable receptor; IgG, immunoglobulin G.

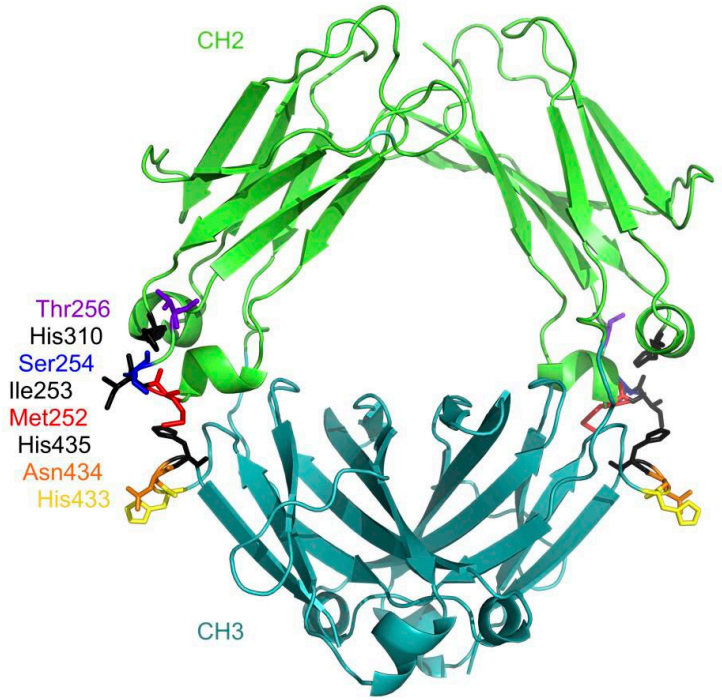
1. Sesarman A. *Cell Mol Life Sci*. 2010 Aug;67(15):2533-2550. **2.** Habib A. *Supp Neuro Review*. Published March 2020. Accessed March 1, 2021. https://www.neurologyreviews-digital.com/neurologyreviews/nord_march_2020/MobilePagedReplica.action?pm=2&folio=34#pg36.

Structure of efgartigimod (ARGX-113)

Abdegs – ‘sticky’ IgG with increased affinity for FcRn and slow ‘off-rate’ at pH 7



Antibody-Fc with ABDEG™ technology



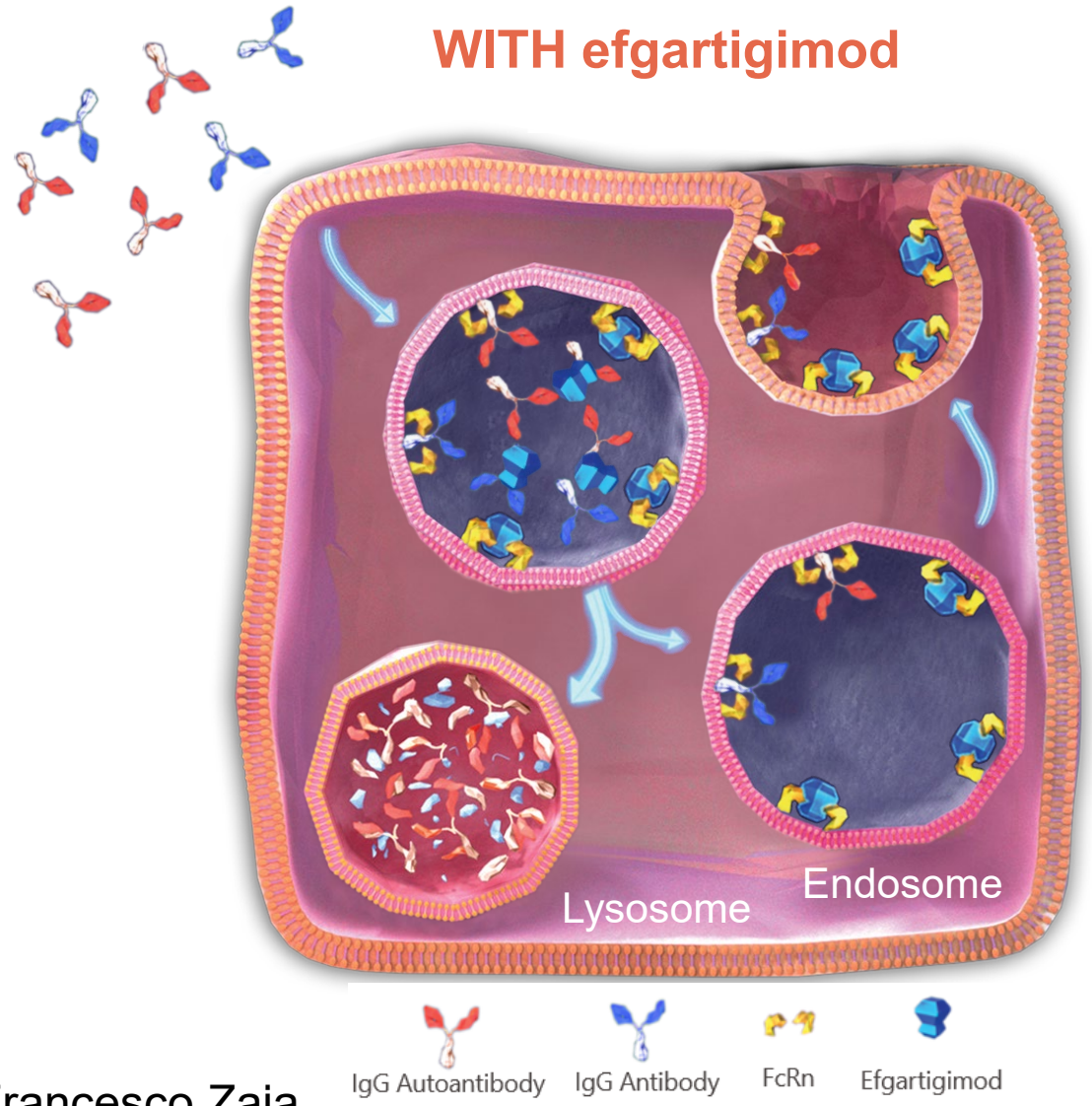
FDA Approved for Myasthenia gravis

argenx

Vaccaro C, et al. Nat Biotech 2005;23:1283–8. Ultrichts P, et al. J Clin Invest. 2018;128(10):4372–86.

Proposed Efgartigimod Mechanism of Action (MOA)

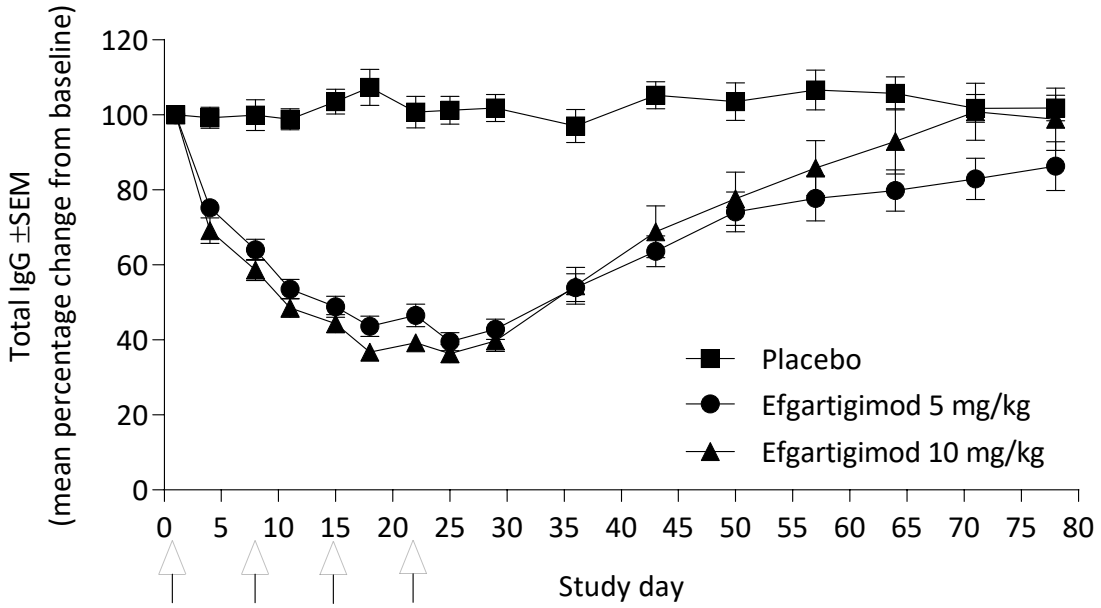
- Efgartigimod is a **human IgG1 Fc fragment**, a natural **ligand of FcRn**, engineered for **increased affinity to FcRn**[1,2]
- Binds in the same way as endogenous IgG, preserving characteristic pH-dependent binding[2]
- Has a half-life of 4.89 days[3]
- Designed to **outcompete endogenous IgG**, therefore preventing recycling and **promoting IgG lysosomal degradation**



Vaccaro C et al. Nat Biotech. 2005;23(10):1283-8
Ulrichts et al. J Clin Invest 2018; 128(10): 4372-4386
Howard JF et al. Neurology. 2019;92(23):e2661-e2673

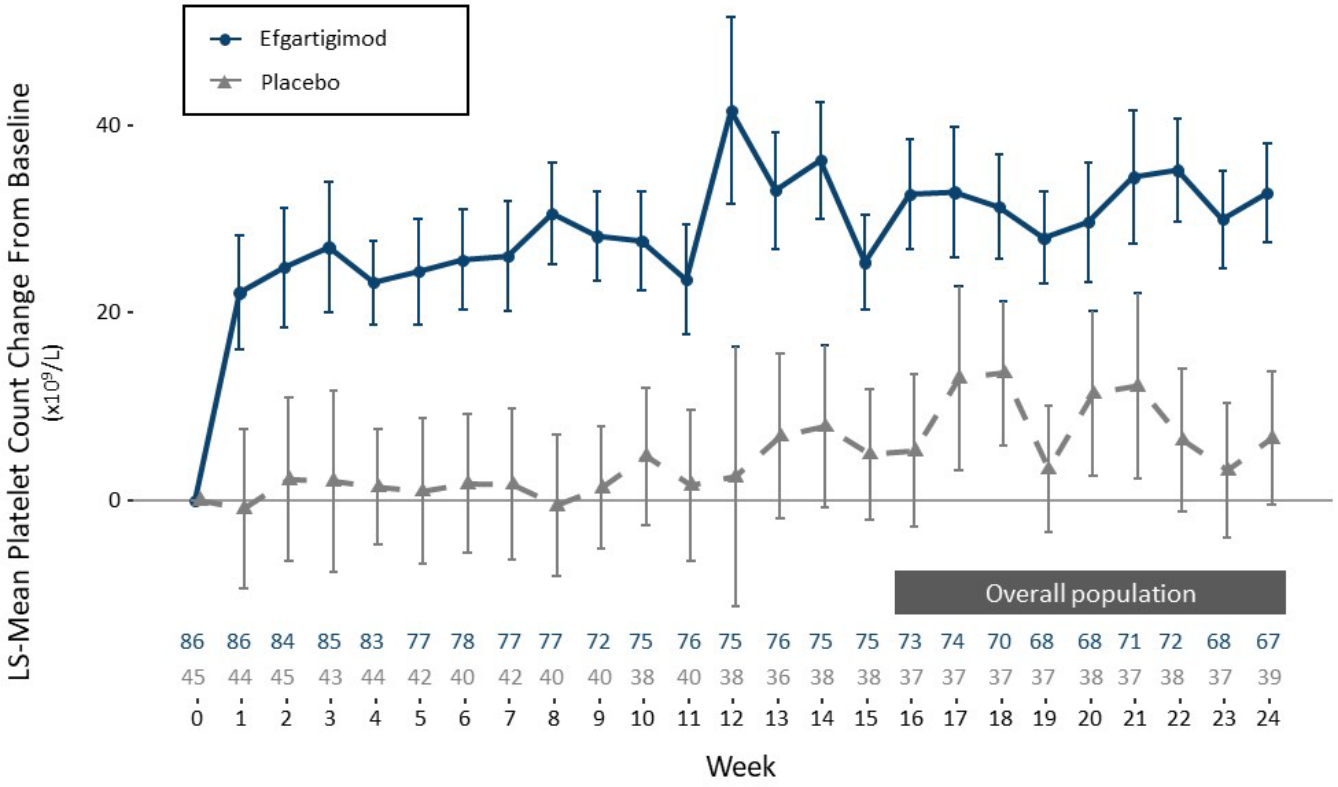
Courtesy of Francesco Zaja

Efgartigimod: ADVANCE IV Study – Platelet response



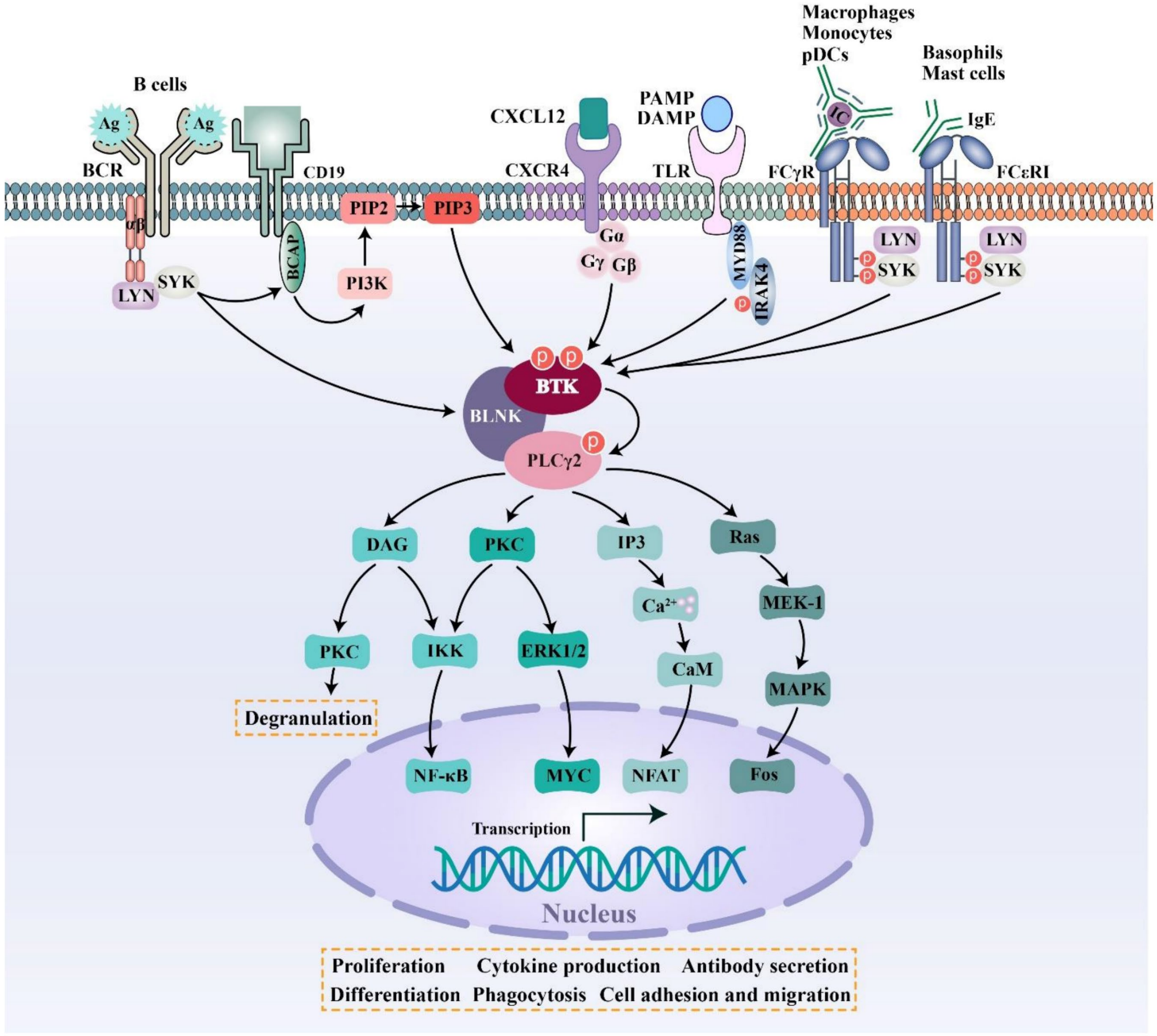
Mean percentage change from baseline (±SEM) of total IgG assessed per treatment group.

Newland A et al. Am J Hematol.2020 Feb; 95(2): 178–187.

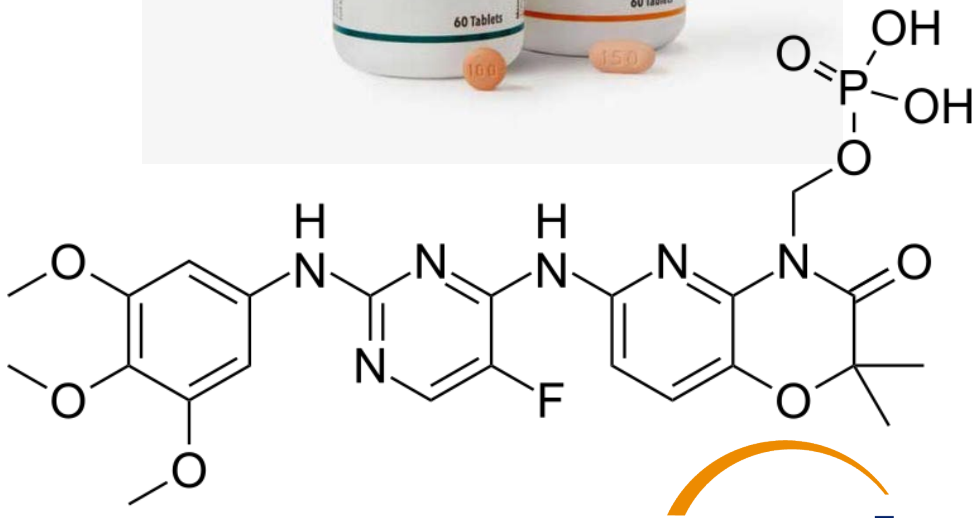


Broome CM et al. Lancet. 2023 Nov 4;402(10413):1648-1659

Spleen Tyrosine Kinase (Syk) Inhibitor



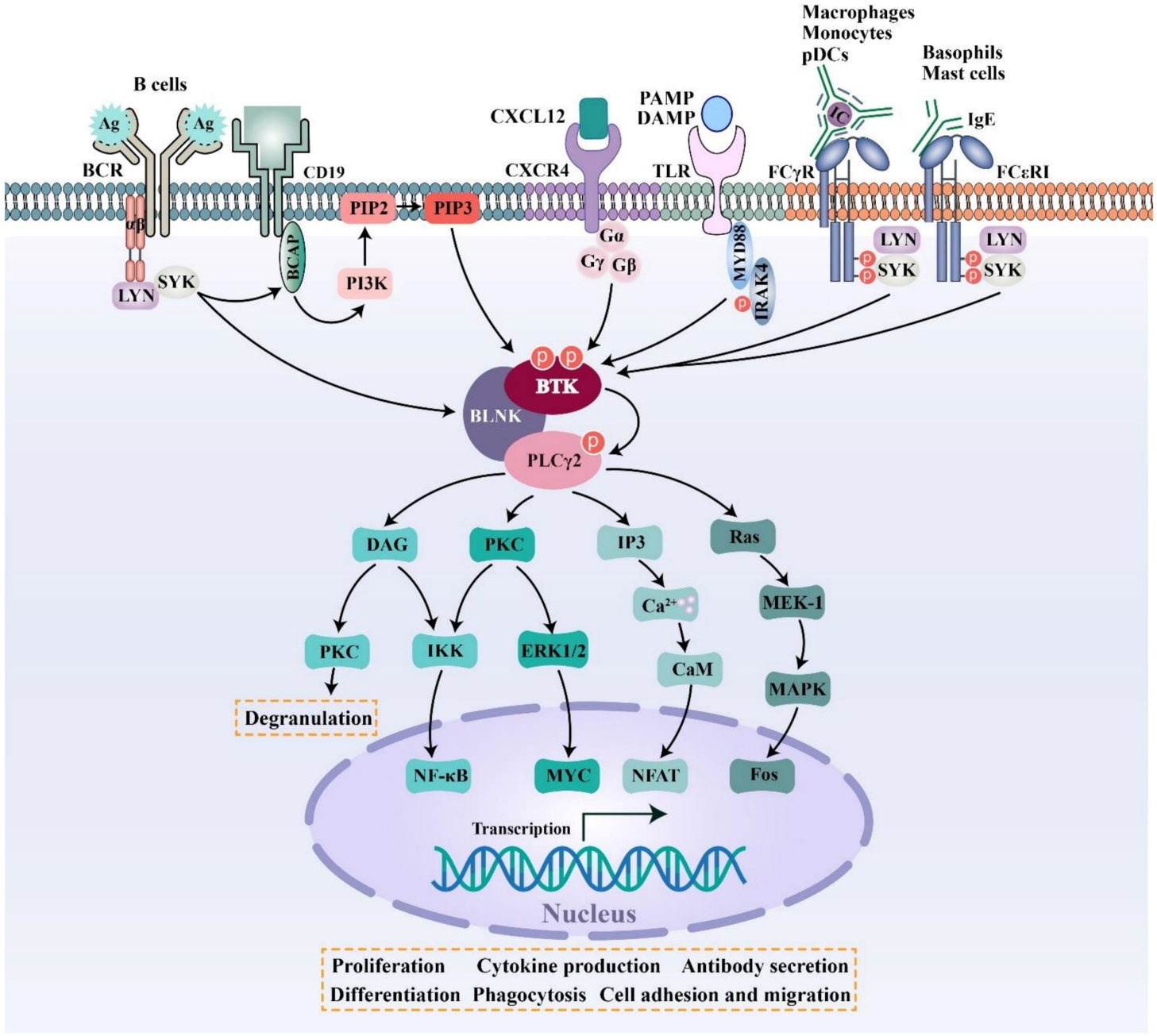
Fostamatinib (FDA Approved, 2018)

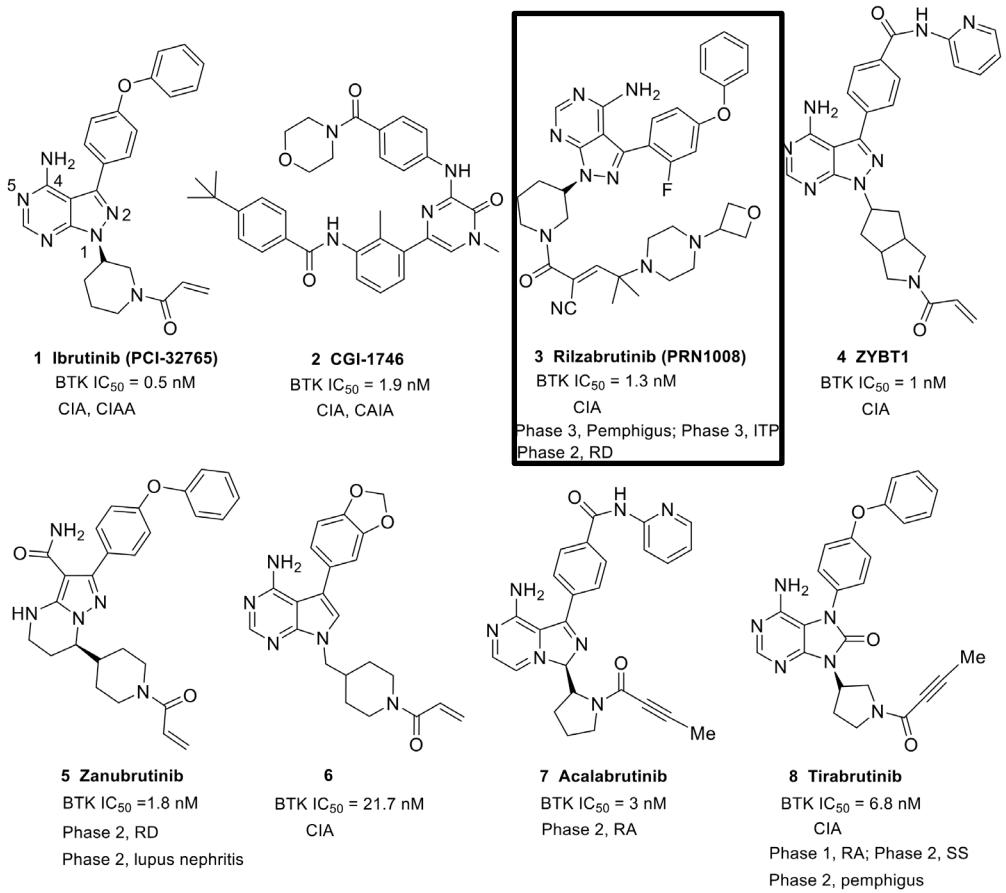


rigel®

Paik J. Drugs. 2021;81,935–943

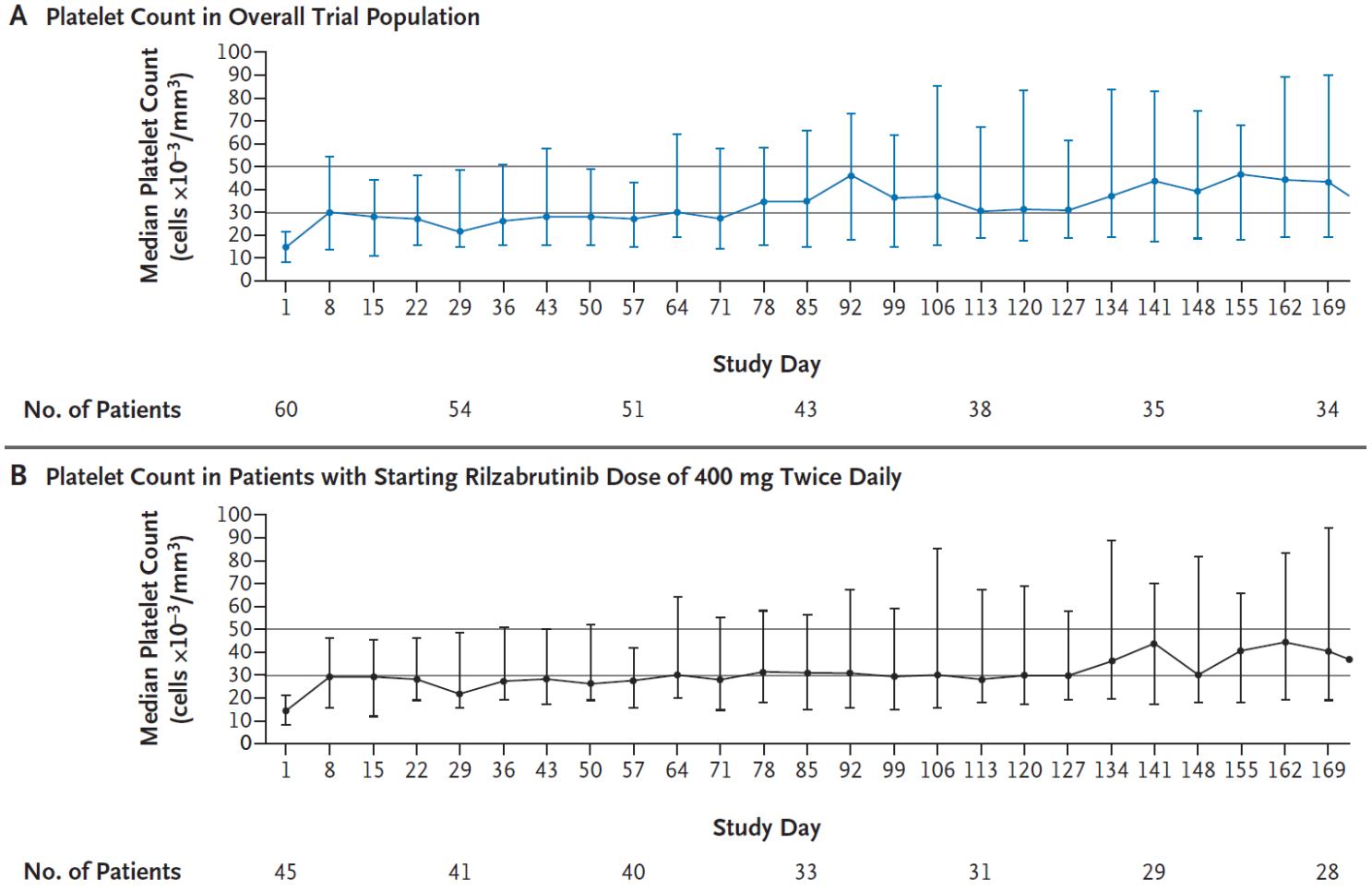
Bruton Tyrosine Kinase (BTK) Inhibitors





Zhang D et al. Molecules. 2021;26,4907.

Rilzabrutinib



Nov, 2022: Rilzabrutinib granted FDA Fast Track Designation for treatment of immune thrombocytopenia.

Rilzabrutinib was active and associated with only low-level toxic effects. The dose of 400 mg twice daily was identified as the dose for further testing. Overall, rilzabrutinib showed a rapid and durable clinical activity that improved with length of treatment.

Kuter D et al. N Engl J Med 2022; 386:1421-1431

Conclusions:

Increase peripheral platelet destruction with reduced platelet production (all due to the autoimmunity).

Antibody and/or CD8+ T-cell mediated effector functions (anti-platelet T cell immunity being predominant).

Abnormal Th1/Th17 responses due to a lack of tolerance (faulty Tregs, DC, MDSC) due to cellular trafficking within lymphoid organs are responsible for initiating/perpetuating platelet autoimmunity in ITP.

There are now and, in the future, a plethora of therapies for patients with ITP and almost all are evidenced based and predicted from the known pathophysiology.

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- Rick Kapur (Amsterdam)
- Joe Italiano (Boston)
- David Kuter (Boston)
- Ming Hou/Jun Peng (Jinan)

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