Thérapeutiques innovantes et hémopathies bénignes: HPN et Aplasie médullaire

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Marseille 30 Septembre 2013

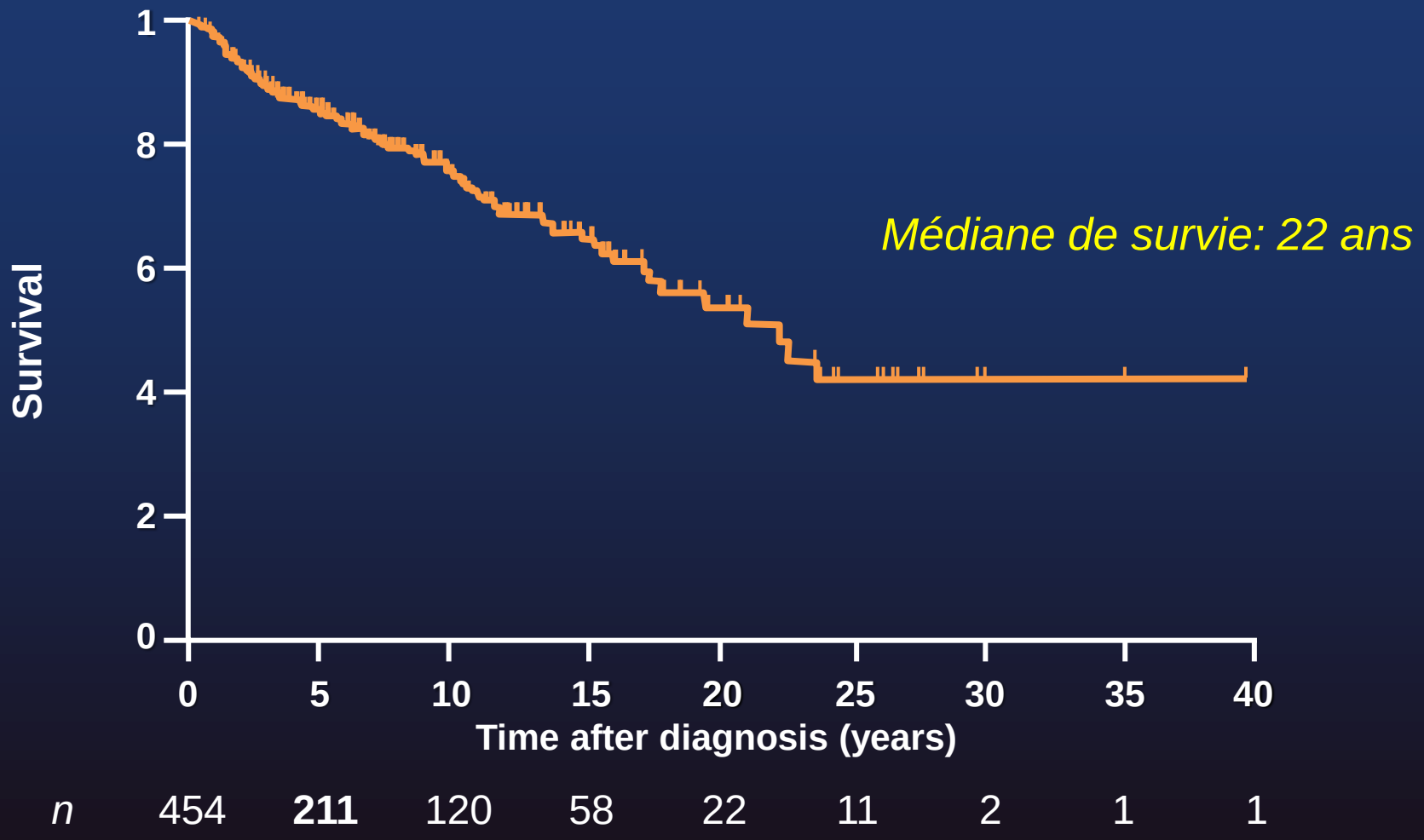
Paroxysmal Nocturnal Hemoglobinuria (PNH):

Acquired hemolytic anemia
Thrombosis
+/- aplastic anaemia

- Rare disease:
  - Prevalence: 15.9 / million[1]
- Median age early 30's[3-5]

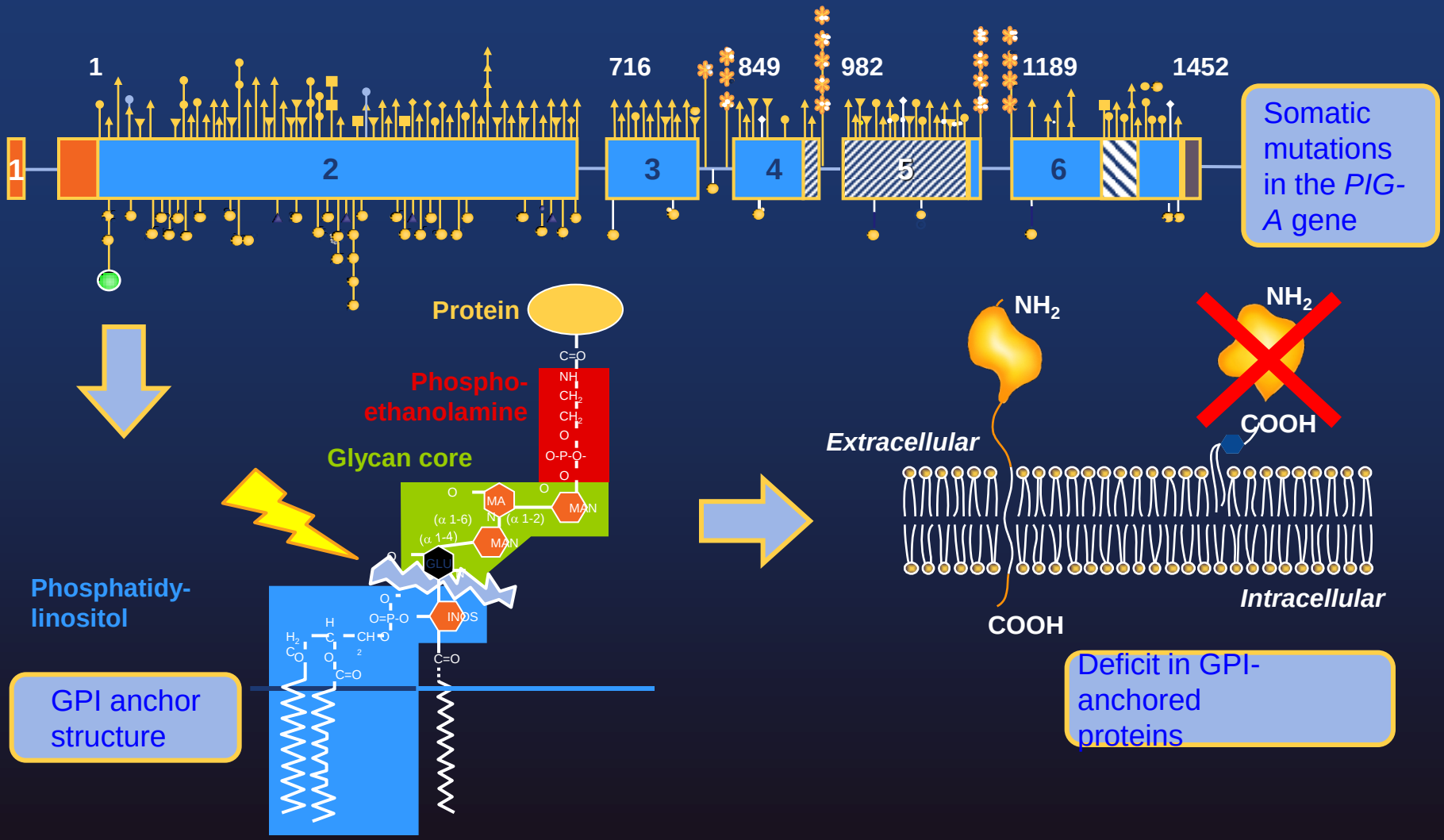
1. Hill A et al. *Blood*. 2006;108(11):290a. Abstract 985. 2. Hillmen P et al. *N Engl J Med.* 1995;333:1253-1258. 3. Nishimura JI, et al. *Medicine*. 2004;83:193-207. 4. Socié G et al. *Lancet*. 1996;348:573-577. 5. Peffault de Latour et al. Blood; 112:3099-3106.

Mortality rate in PNH: Data From French Patients



Peffault de Latour et al. Blood 2008; 112:3099-3106.

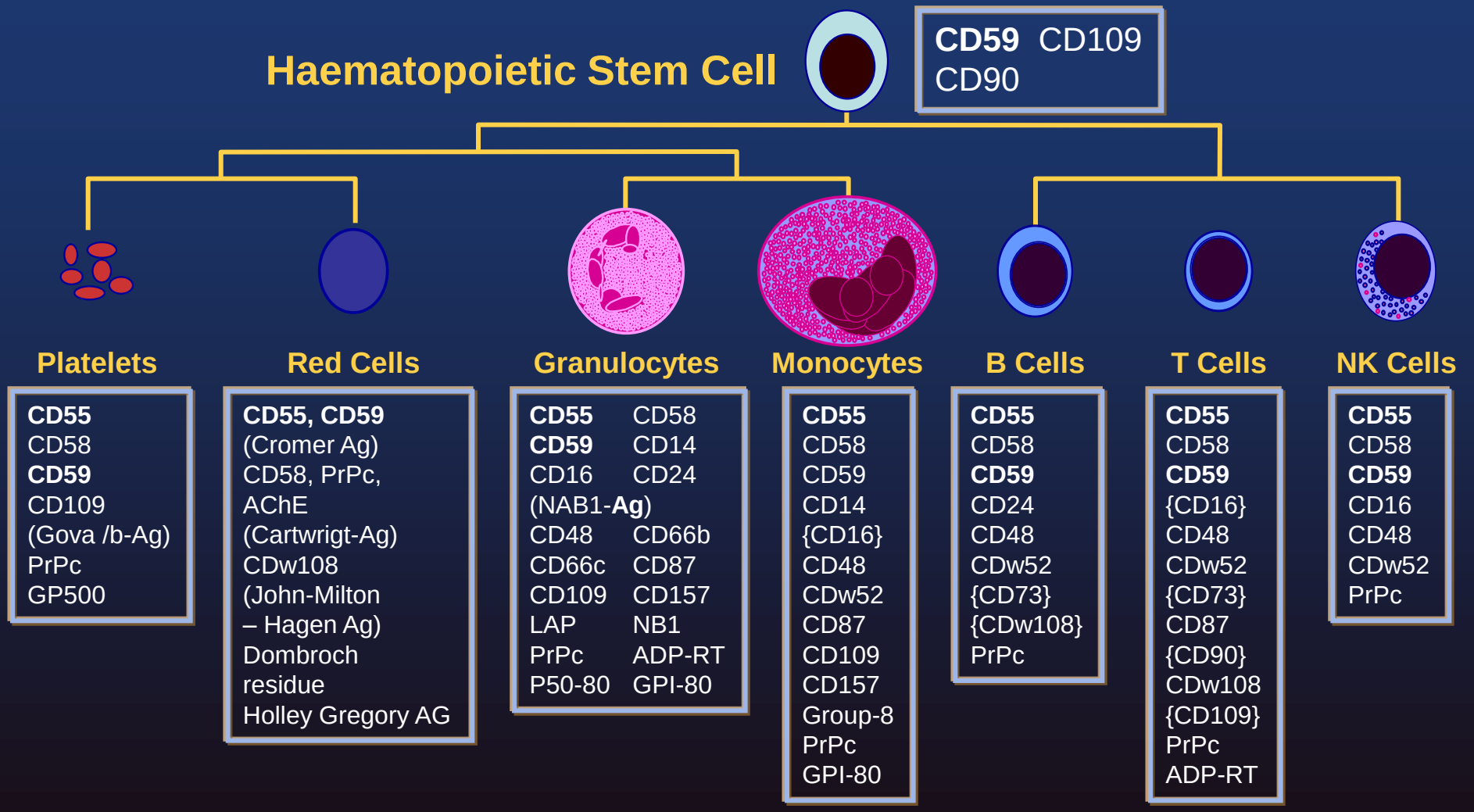
Pathophysiology



PNH, paroxysmal nocturnal haemoglobinuria;
PIG-A, phosphatidylinositol glycan class A; GPI, glycosylphosphatidylinositol

Young NS *et al*. *Hematology Am Soc Hematol Educ Program* 2000:18–38

Pathophysiology - PNH



Bessler 2003

The Defect in PNH

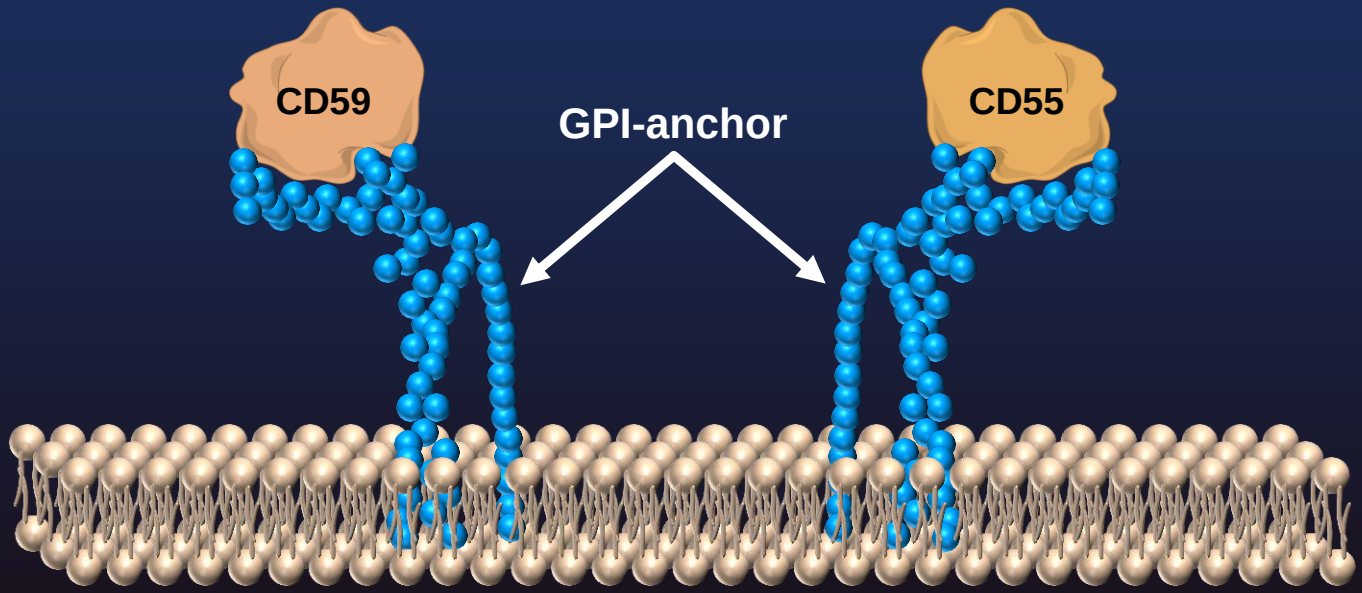
PNH is an acquired hemolytic disorder characterized by the somatic mutation of the PIG A gene

CD59

- Forms a defensive shield for RBCs from complement-mediated lysis
- Inhibits the assembly of the membrane attack complex

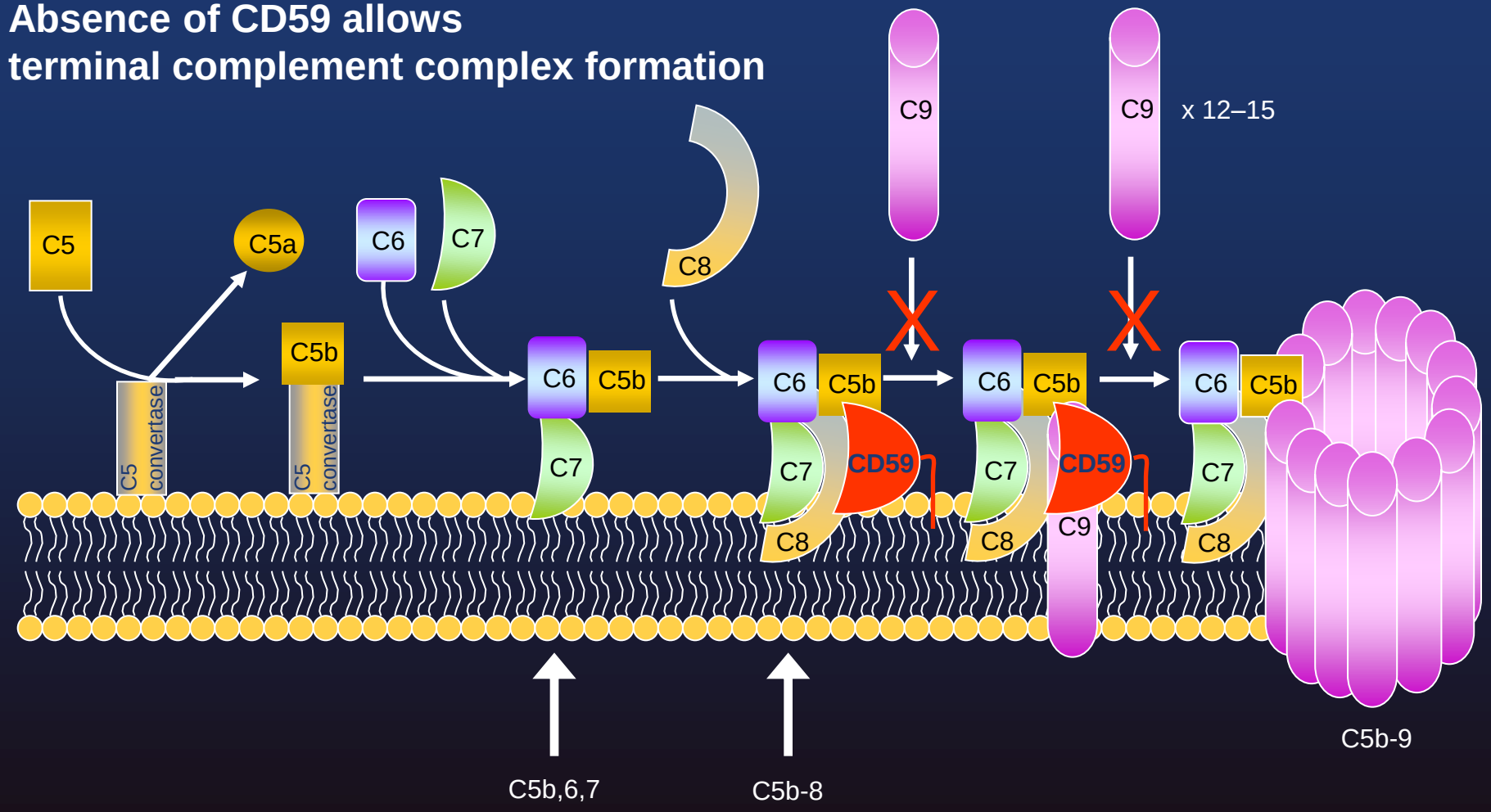
CD55

- Prevents formation and augments instability of the C3 convertases, attenuating the complement cascade



1. McKeage K. *Drugs*. 2011;71(17):2327-2345. Adapted from: Johnson RJ et al. *J Clin Pathol: Mol Pathol.* 2002;55:145-152. 2. Brodsky R. Paroxysmal In: *Hematology - Basic Principles and Practices*. 4th ed. R Hoffman; EJ Benz; S Shattil et al. eds. Philadelphia, PA: Elsevier Churchill Livingstone; 2005;419-427. Nocturnal Hemoglobinuria.

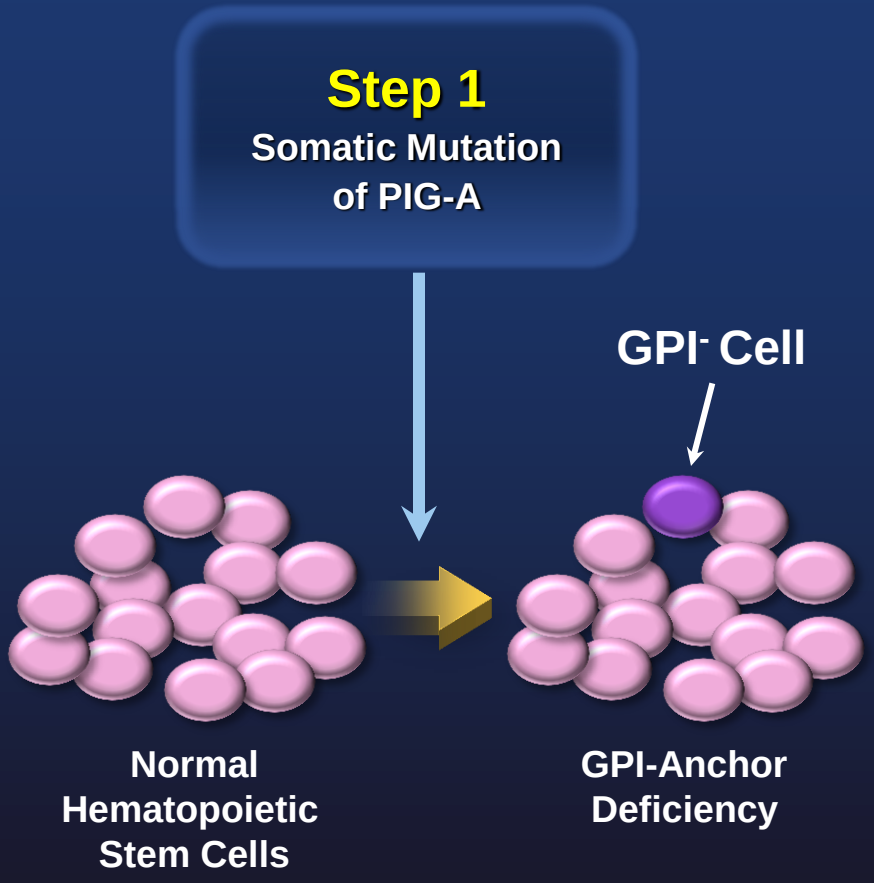
GPI deficiency results in Hemolytic Anemia
(lack of CD59 or CD55)



PNH, paroxysmal nocturnal haemoglobinuria

Adapted from Abbas AK *et al*. *Cellular and Molecular Immunology*, 3rd ed. WB Saunders: Philadelphia, 1991

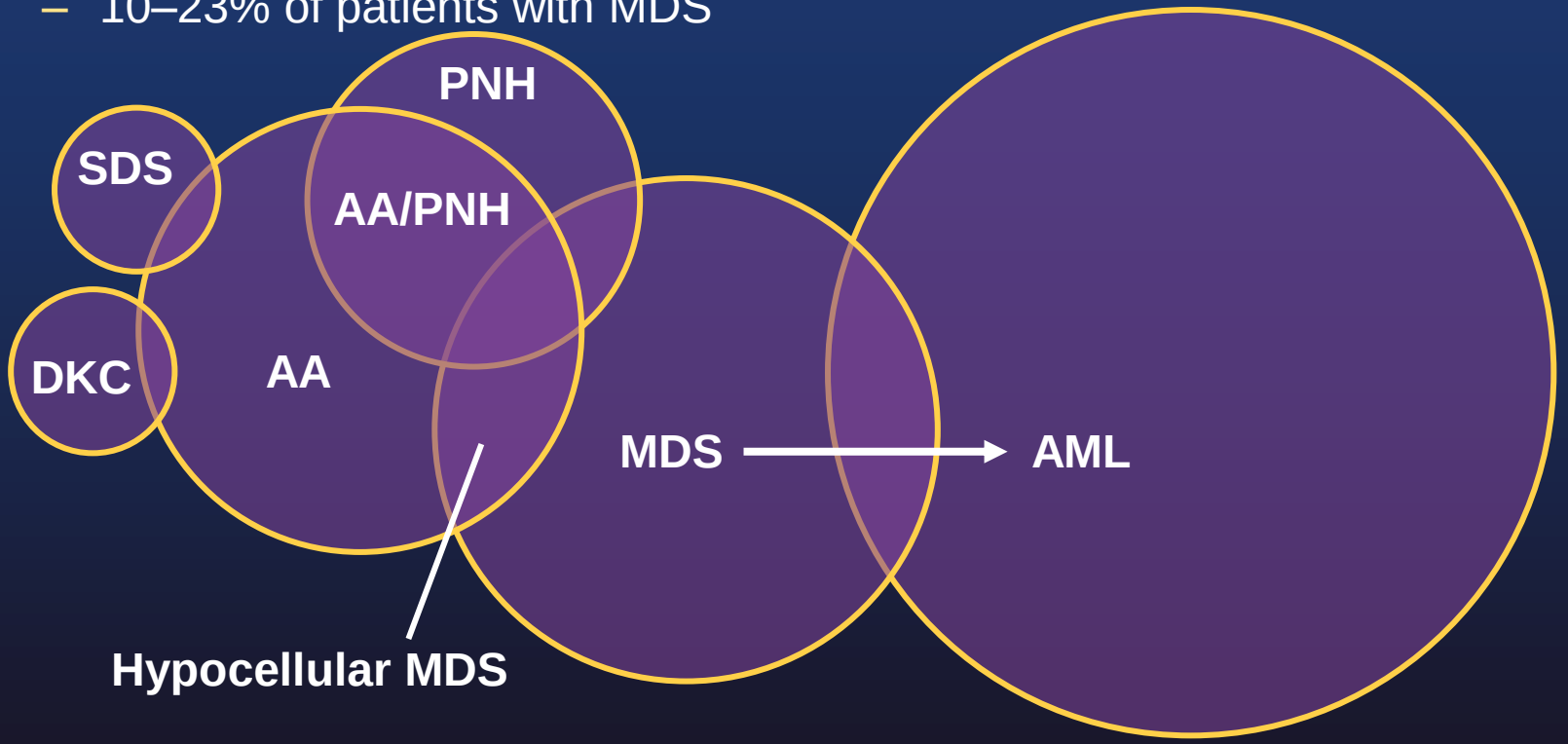
Expansion of PNH Clone



Adapted from Inoue N et al, Int J Hematol 2003;77 p107

Expansion of PNH Clone

- PNH clone is more common in patients with bone marrow failure syndromes[2–5]
  - 25–45% of patients with aplastic anaemia
  - 10–23% of patients with MDS

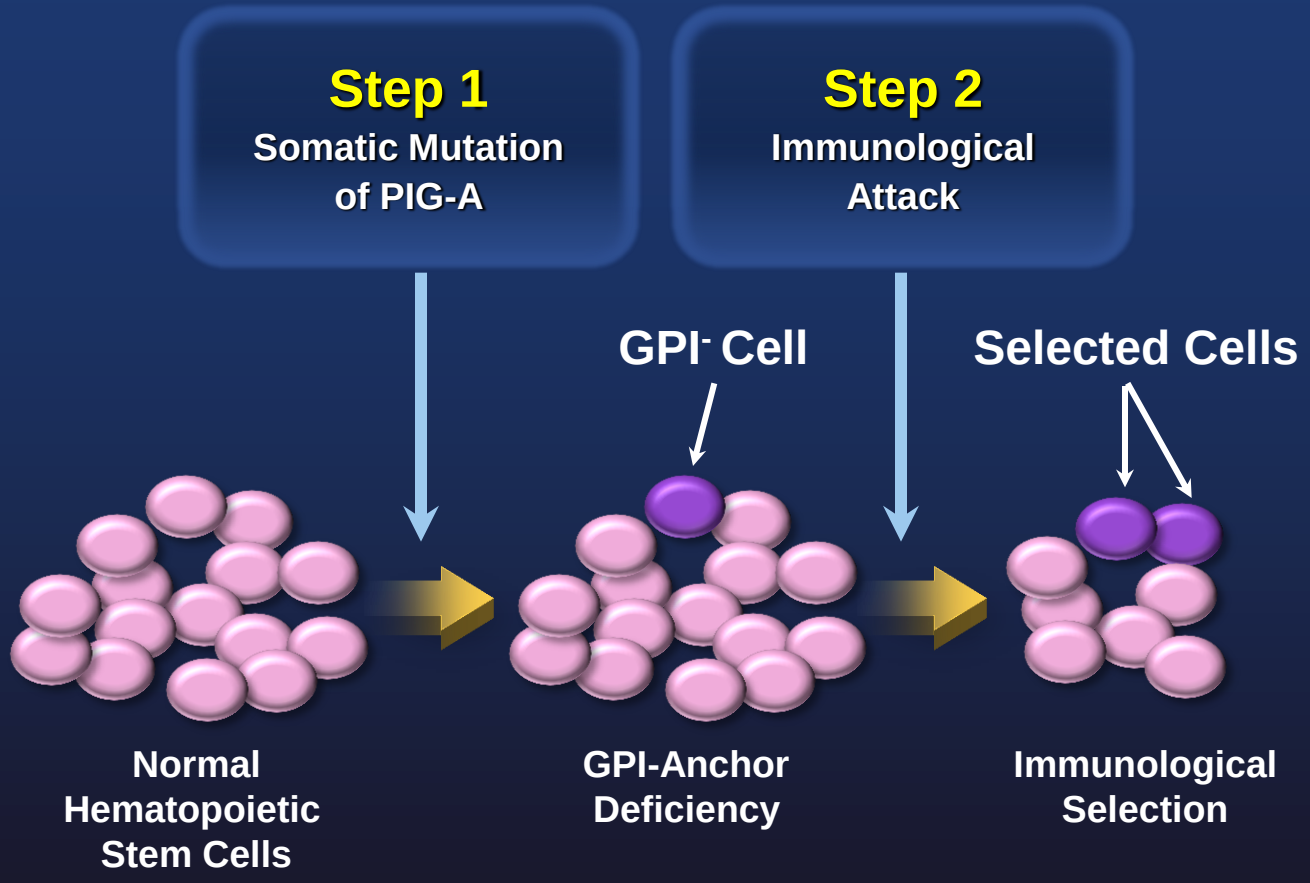


AA, aplastic anaemia; AML, acute myelogenous leukaemia;
DKC, dyskeratosis congenita; SDS, Shwachman-Diamond syndrome;
MDS, myelodysplastic syndrome;
PNH, paroxysmal nocturnal haemoglobinuria

Young, NS *et al. Blood* 2006;108:2509-2519

1. Araten DJ *et al*. *Proc Natl Acad Sci USA* 1999;96:5209–14;
2. Johnson RJ, Hillmen P. *Mol Pathol* 2002;55:145–52;
3. Wang H *et al*. *Blood* 2002;100:3897–902;
4. Iwanga M *et al*. *Br J Haematol* 1998;102:465–74;
5. Maciejewski JP *et al*. *Br J Haematol* 2001;115:1015–22

Expansion of PNH Clone



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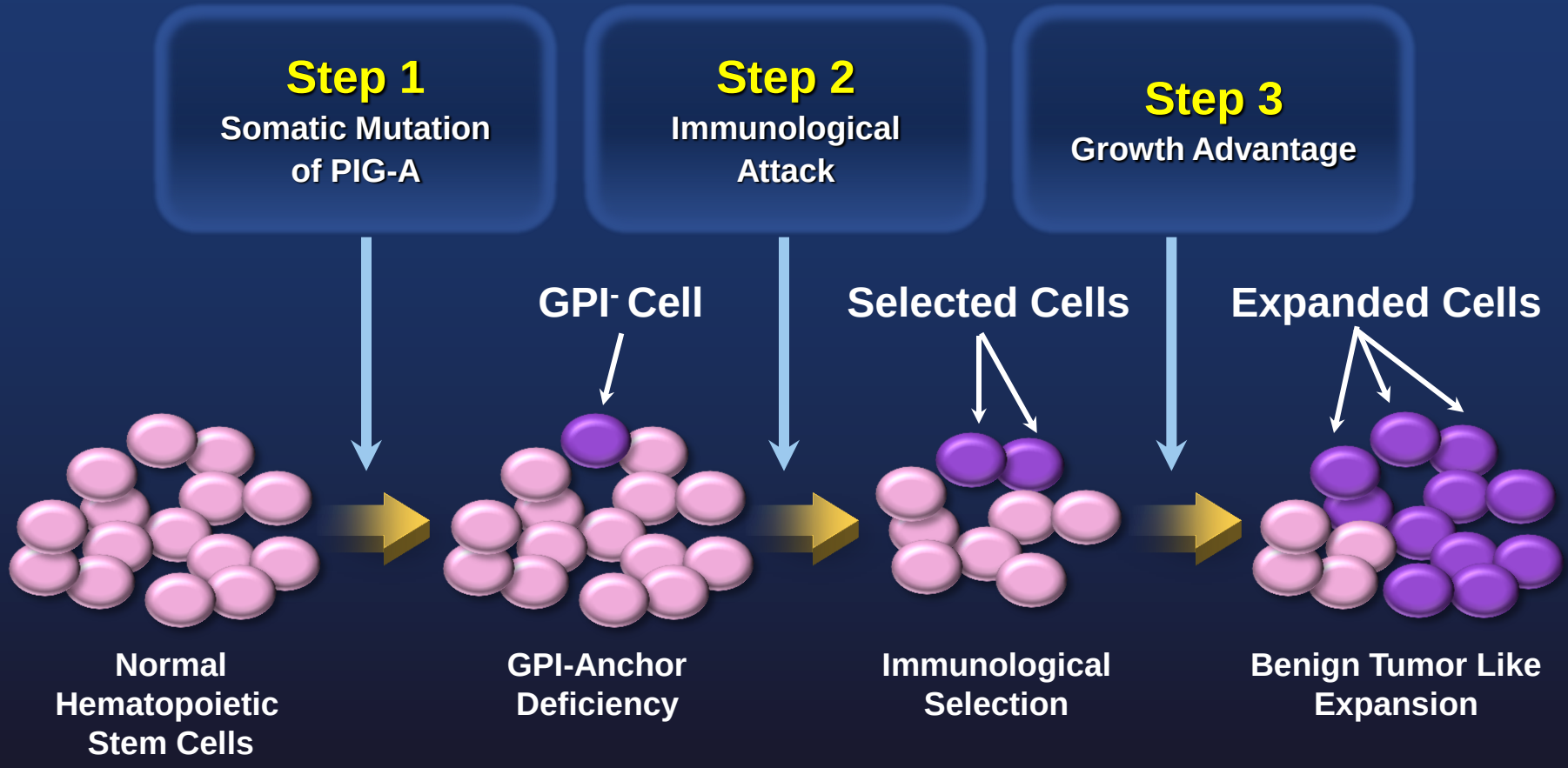
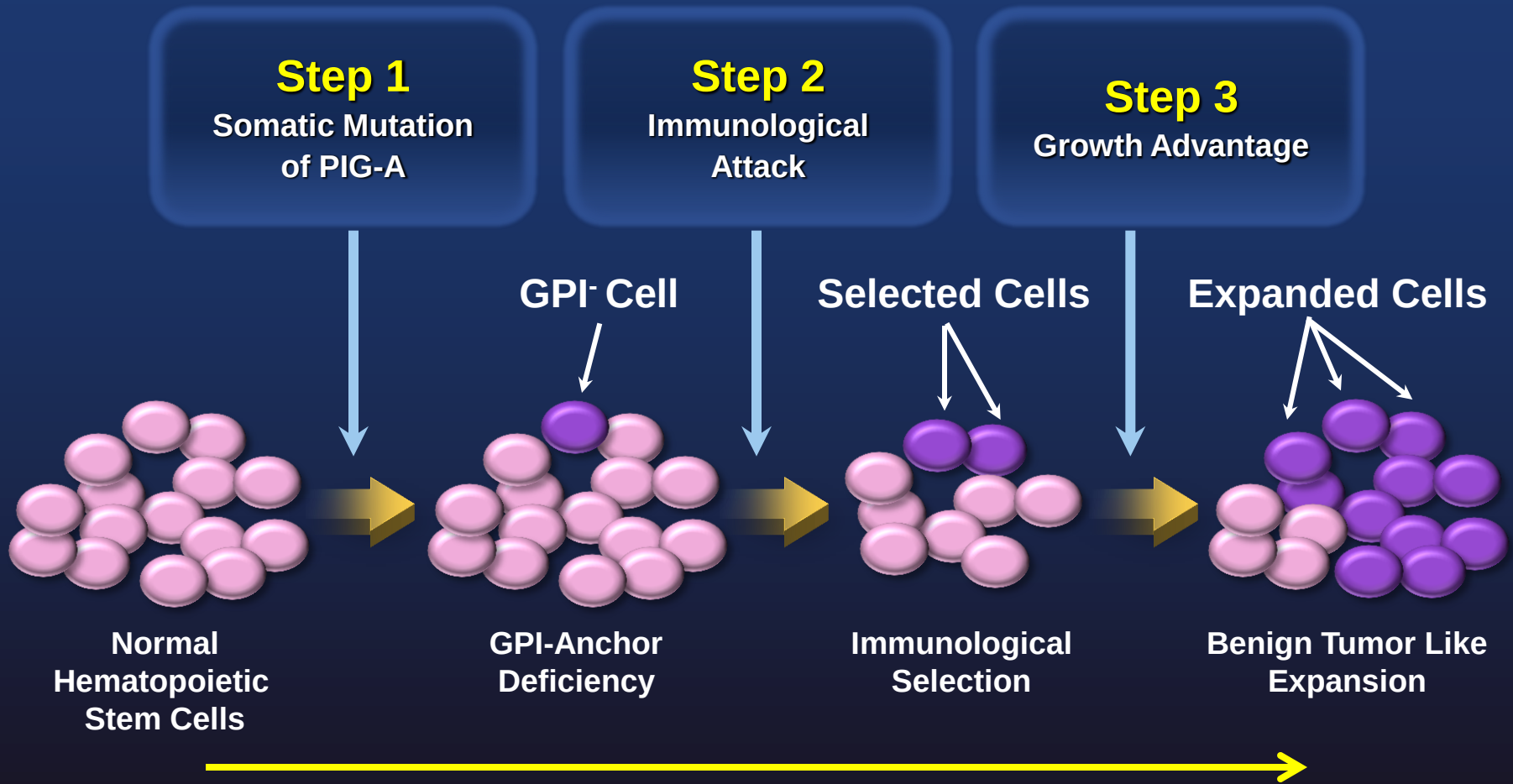
Expansion of PNH Clone



HMGA2, transcription factor gene
Benign Mesenchymal tumors (?)

Adapted from Inoue N et al, Int J Hematol 2003;77 p107

Expansion of PNH Clone



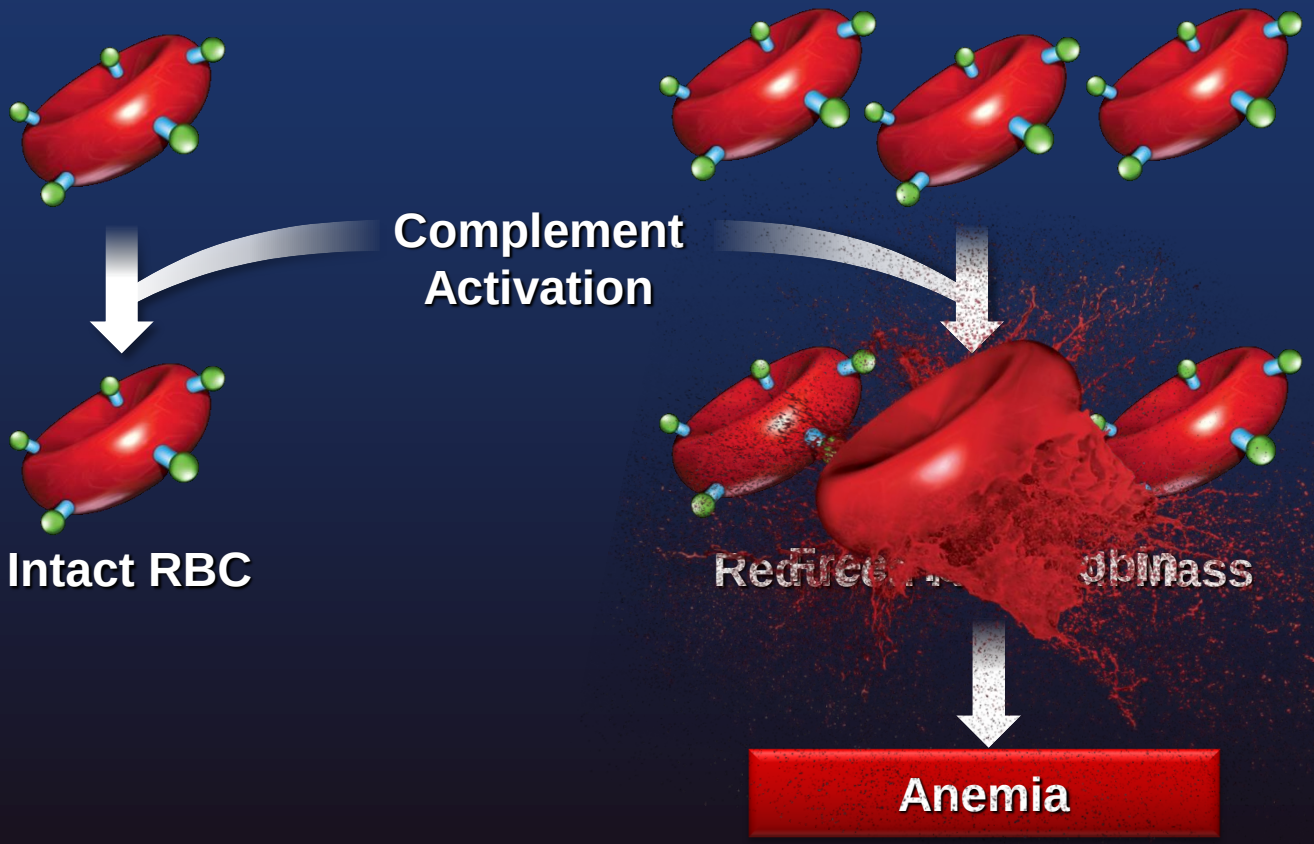
Aplastic anemia > AA PNH syndrome > Hemolytic PNH

Cytopenia	Cytopenia Low level of Hemolysis	Cytopenia Hemolysis Thrombosis

Historically Viewed as a Hemolytic Anemia

Normal red blood cells are protected from complement attack by a shield of terminal complement inhibitors

Without this protective complement inhibitor shield, PNH red blood cells are destroyed



1. International PNH Interest Group. *Blood.* 2005;106:3699-3709. 2. Brodsky R Paroxysmal Nocturnal Hemoglobinuria. In: *Hematology - Basic Principles and Practices*. 4th ed. R Hoffman; EJ Benz; S Shattil et al, eds. Philadelphia, PA: Elsevier Churchill Livingstone; 2005; 419-427. 3. Rother RP et al. *JAMA.* 2005;293:1653-1662. 4. Socie G et al. *Lancet.* 1996;348:573-577. 5. Hill A et al. *Br J Haematol.* 2007;137:181-192.

Chronic Uncontrolled Complement Activation Leads to Devastating Consequences

Normal red blood cells are protected from complement attack by a shield of terminal complement inhibitors

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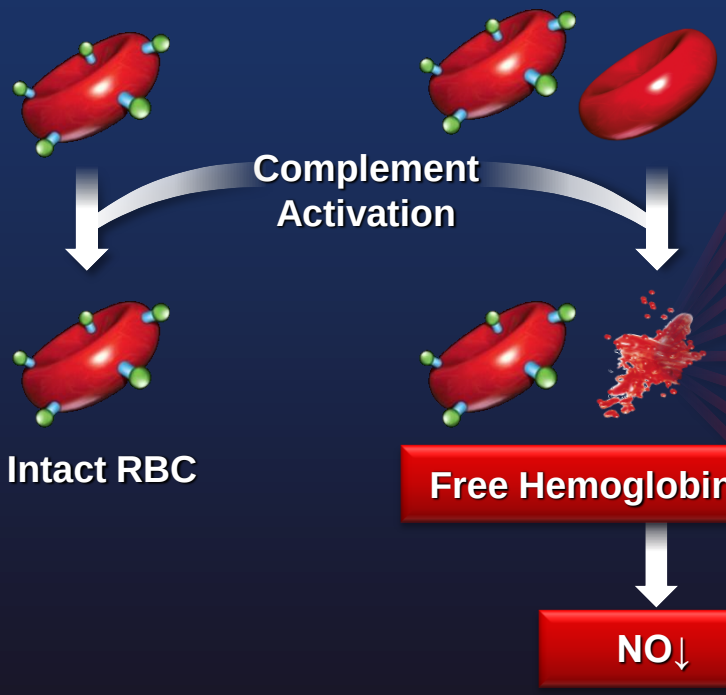

- Thrombosis
- Renal Failure
- Pulmonary Hypertension
- Abdominal Pain
- Dyspnea
- Dysphagia
- Fatigue
- Hemoglobinuria
- Erectile Dysfunction

1. International PNH Interest Group. *Blood.* 2005;106:3699-3709. 2. Brodsky R. Paroxysmal Nocturnal Hemoglobinuria. In: *Hematology - Basic Principles and Practices*. 4th ed. R Hoffman; EJ Benz; S Shattil et al, eds. Philadelphia, PA: Elsevier Churchill Livingstone; 2005;419-427. 3. Rother RP et al. *JAMA.* 2005;293:1653-1662. 4. Socie G et al. *Lancet. 1*996;348:573-577. 5. Hill A et al. *Br J Haematol.* 2007;137:181-192. 6. Lee JW et al. *Hematologica* 2010;95(s2): Abstract #505 and 506. 7. Hill A et al. *Br J Haematol*. 2010; May;149(3):414-425. 8. Hillmen P et al. *Am J Hematol*. 2010;85:553-559.

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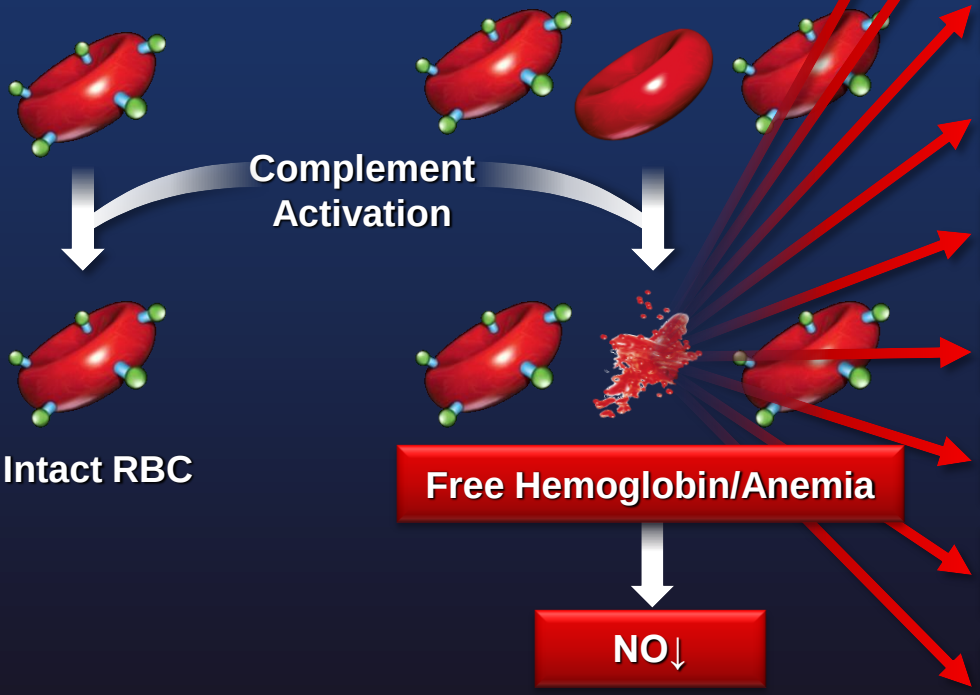


- Thrombosis
- Renal Failure
- Pulmonary Hypertension
- Abdominal Pain
- Dyspnea

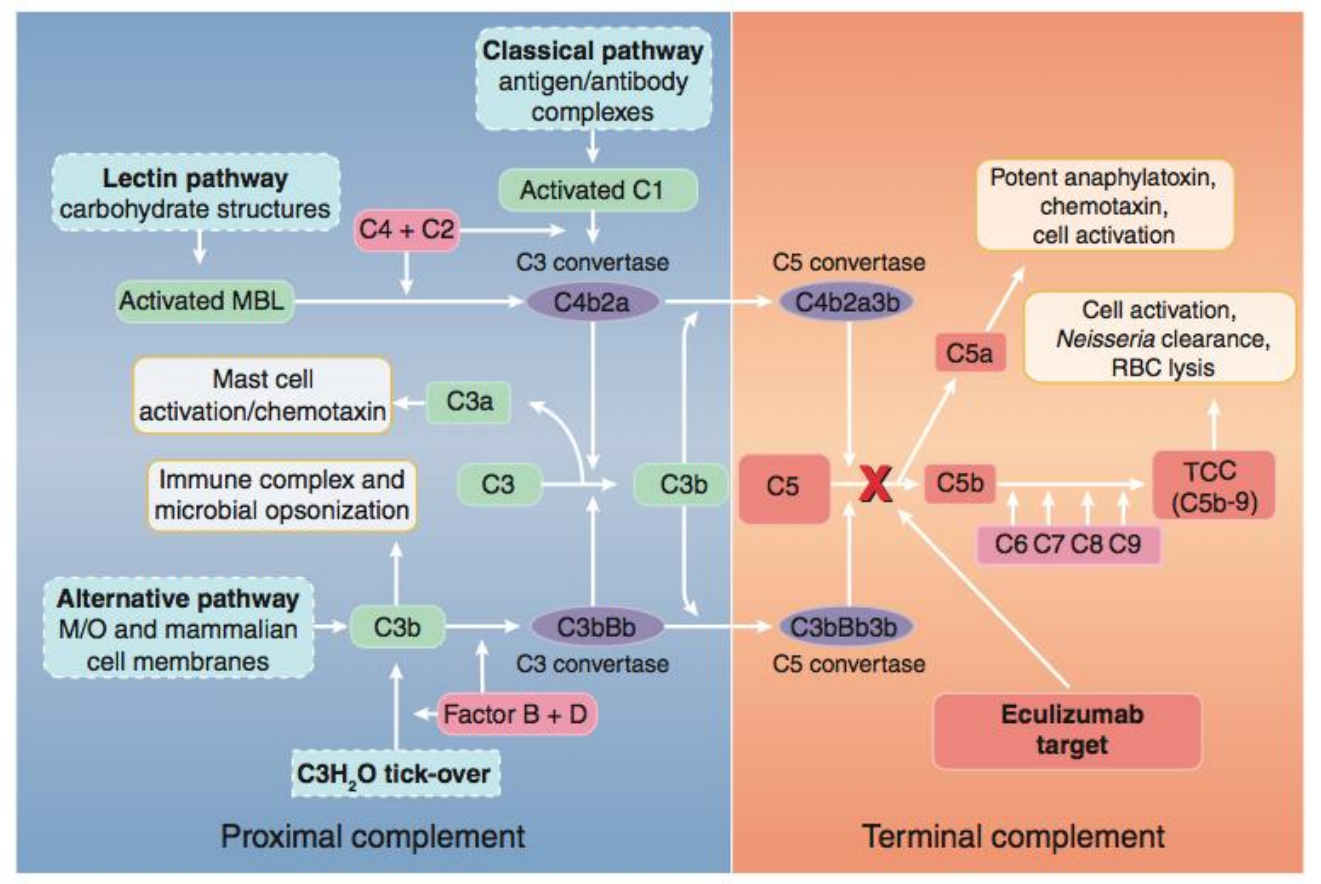
Significant Impact on Survival

- Dysphagia
- Fatigue
- Hemoglobinuria
- Erectile Dysfunction

Significant Impact on Morbidity

1. International PNH Interest Group. *Blood.* 2005;106:3699-3709. 2. Brodsky R. Paroxysmal Nocturnal Hemoglobinuria. In: *Hematology - Basic Principles and Practices*. 4th ed. R Hoffman; EJ Benz; S Shattil et al, eds. Philadelphia, PA: Elsevier Churchill Livingstone; 2005;419-427. 3. Rother RP et al. *JAMA.* 2005;293:1653-1662. 4. Socie G et al. *Lancet. 1*996;348:573-577. 5. Hill A et al. *Br J Haematol.* 2007;137:181-192. 6. Lee JW et al. *Hematologica* 2010;95(s2): Abstract #505 and 506. 7. Hill A et al. *Br J Haematol*. 2010; May;149(3):414-425. 8. Hillmen P et al. *Am J Hematol*. 2010;85:553-559.

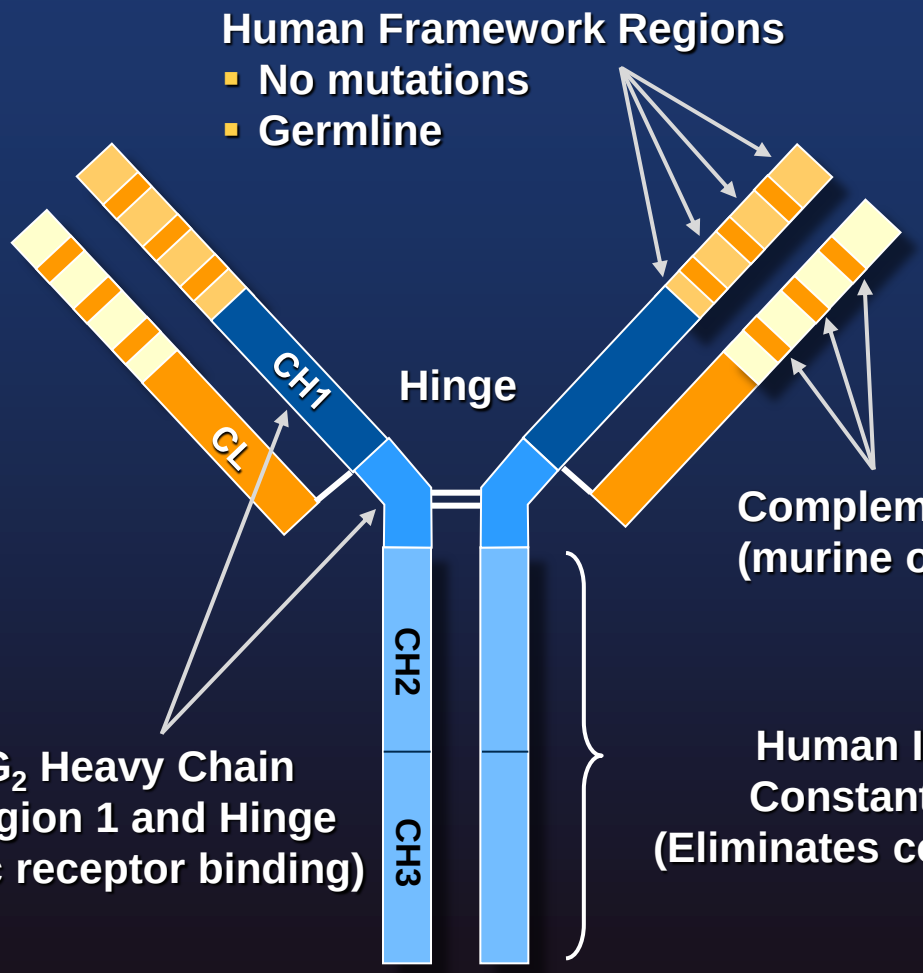
Eculizumab Humanized
First in Class Anti - C5 Antibody



Rother R et al. *Nat Biotech*. 2007;25:1256.

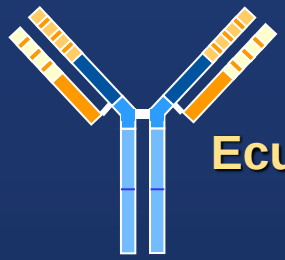
Murine anti-C5 antibody: *m5G1.1mAb*

Eculizumab Humanized
First in Class Anti - C5 Antibody

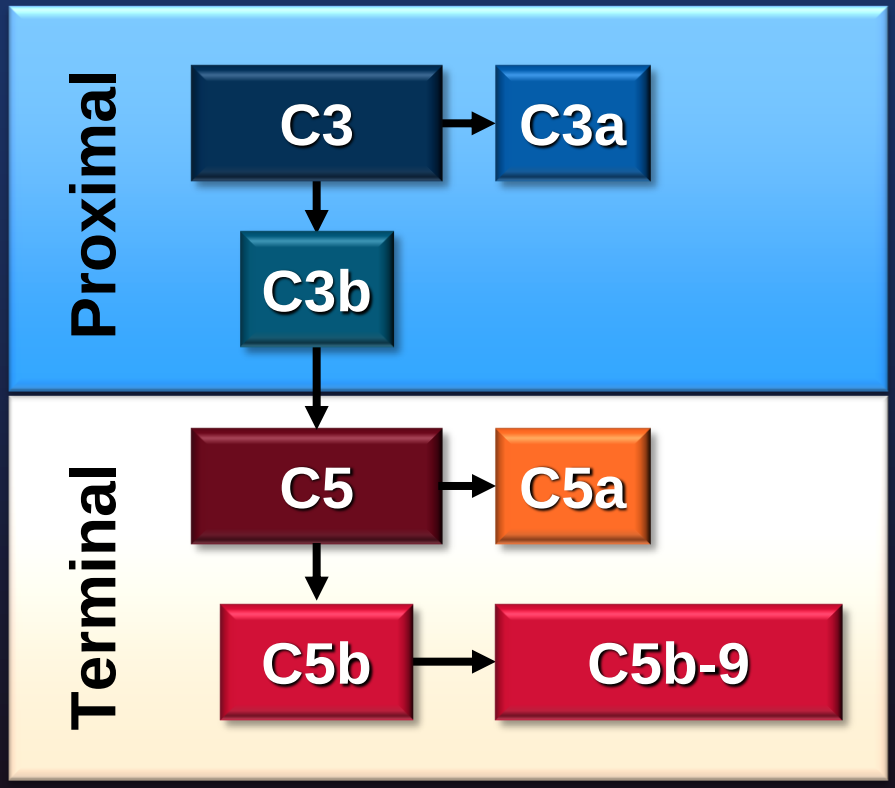


Rother R et al. *Nat Biotech*. 2007;25:1256.

Eculizumab Blocks Terminal Complement[1,2]



Complement Cascade[2,3]

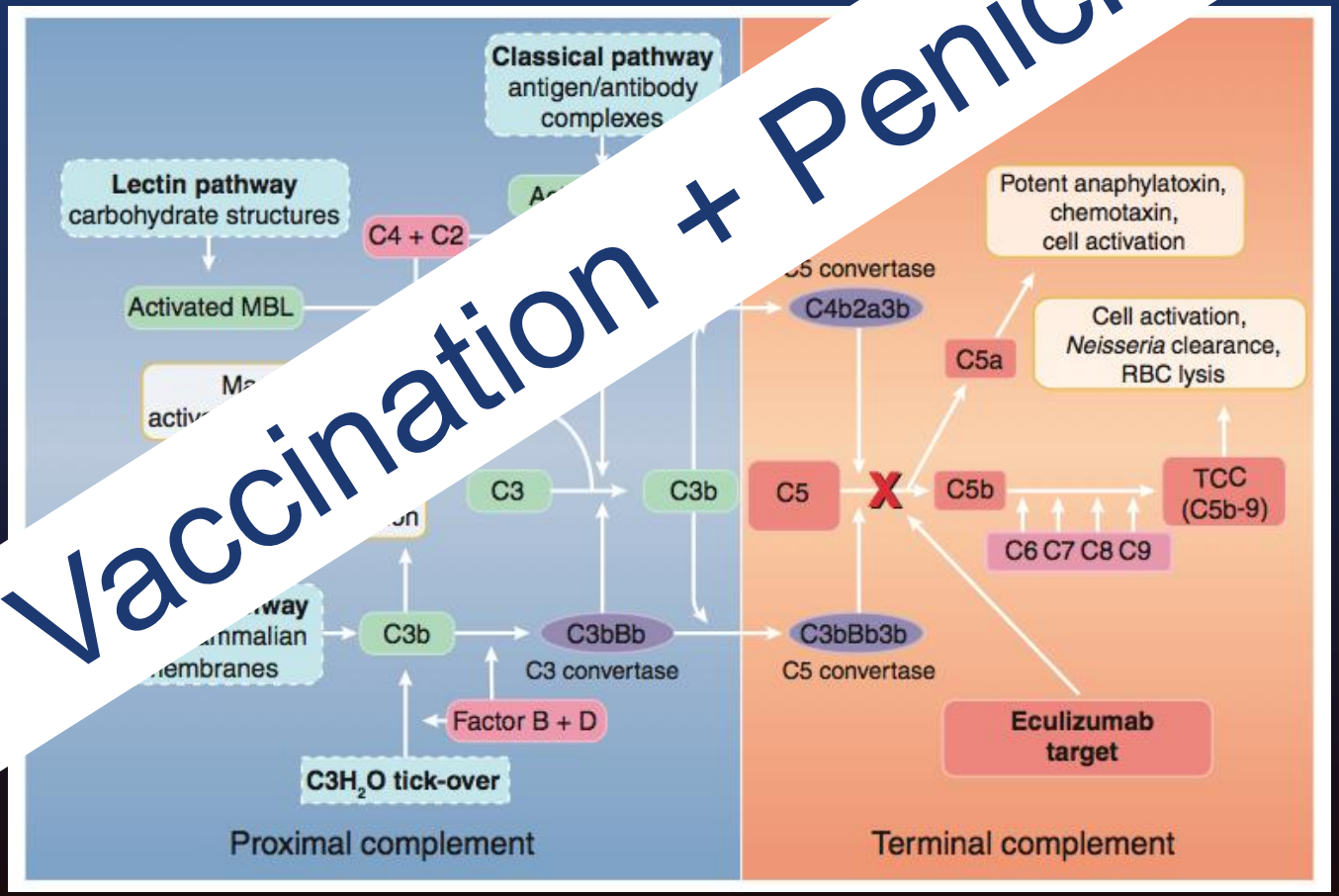


- Eculizumab binds with high affinity to C5[1,2]
- Terminal complement - C5a and C5b-9 activity blocked[1,2]
- Proximal functions of complement remain intact[1,2]
  - Weak anaphylatoxin[2,4]
  - Immune complex clearance[2]
  - Microbial opsonization[2]

1. Soliris® (eculizumab) [package insert; 2011. 2. Rother RP et al. *Nature Biotech*. 2007;25(11):1256-1264.
3. Walport MJ. *N Engl J Med*. 2001;344(14):1058-1066. 4. Figueroa JE, Densen P. *Clin Microbiol Rev*. 1991;4(3):359-395.

Safety: Warnings and Precautions (cont.)

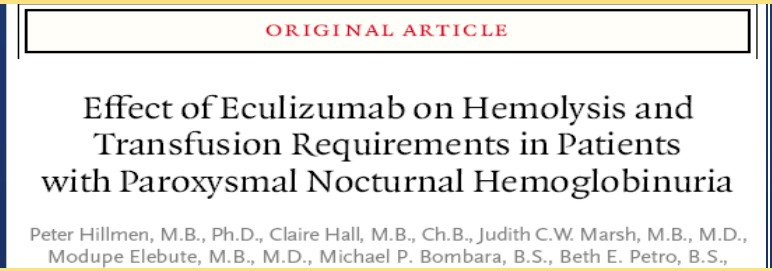
- SOLIRIS blocks terminal complement activation
  patients may have increased susceptibility t
  especially with encapsulated bacteria



Vaccination + Penicillin

Eculizumab Experience in PNH Clinical Trials

Pilot Study – Hillmen *et al. NEJM*, 2004
N = 11



ORIGINAL ARTICLE

Effect of Eculizumab on Hemolysis and Transfusion Requirements in Patients with Paroxysmal Nocturnal Hemoglobinuria

Peter Hillmen, M.B., Ph.D., Claire Hall, M.B., Ch.B., Judith C.W. Marsh, M.B., M.D., Modupe Elebute, M.B., M.D., Michael P. Bombara, B.S., Beth E. Petro, B.S.,

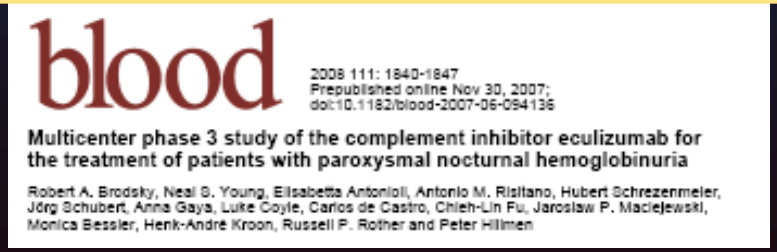
TRIUMPH – Hillmen *et al. NEJM,* 2006
Pivotal Phase III, Double-Blind, Placebo-Controlled Trial, N = 87

ORIGINAL ARTICLE

The Complement Inhibitor Eculizumab in Paroxysmal Nocturnal Hemoglobinuria

Peter Hillmen, M.B., Ch.B., Ph.D., Neal S. Young, M.D., Jörg Schubert, M.D., Robert A. Brodsky, M.D., Gerard Socié, M.D., Ph.D., Petra Muus, M.D., Ph.D., Alexander Röth, M.D., Jeffrey Szer, M.B., B.S., Modupe O. Elebute, M.D.,

SHEPHERD – Brodsky *et al. Blood*. 2008
Broader patient population, including those receiving minimal transfusions or with thrombocytopenia, N = 97



blood

2008 111: 1840-1847
Prepublished online Nov 30, 2007;
doi:10.1182/blood-2007-06-094136

Multicenter phase 3 study of the complement inhibitor eculizumab for the treatment of patients with paroxysmal nocturnal hemoglobinuria

Robert A. Brodsky, Neal S. Young, Elisabetta Antonioli, Antonio M. Risitano, Hubert Schrezenmeier, Jörg Schubert, Anna Gaya, Luke Coyle, Carlos de Castro, Chieh-Lin Fu, Jaroslaw P. Maciejewski, Monica Bessler, Henk-André Kroon, Russell P. Rother and Peter Hillmen

Long-Term Extension Trial
Hillmen *Blood*. 2007
Evaluated long-term safety, efficacy and effect on thrombosis; Placebo patients switched to Soliris
N = 187

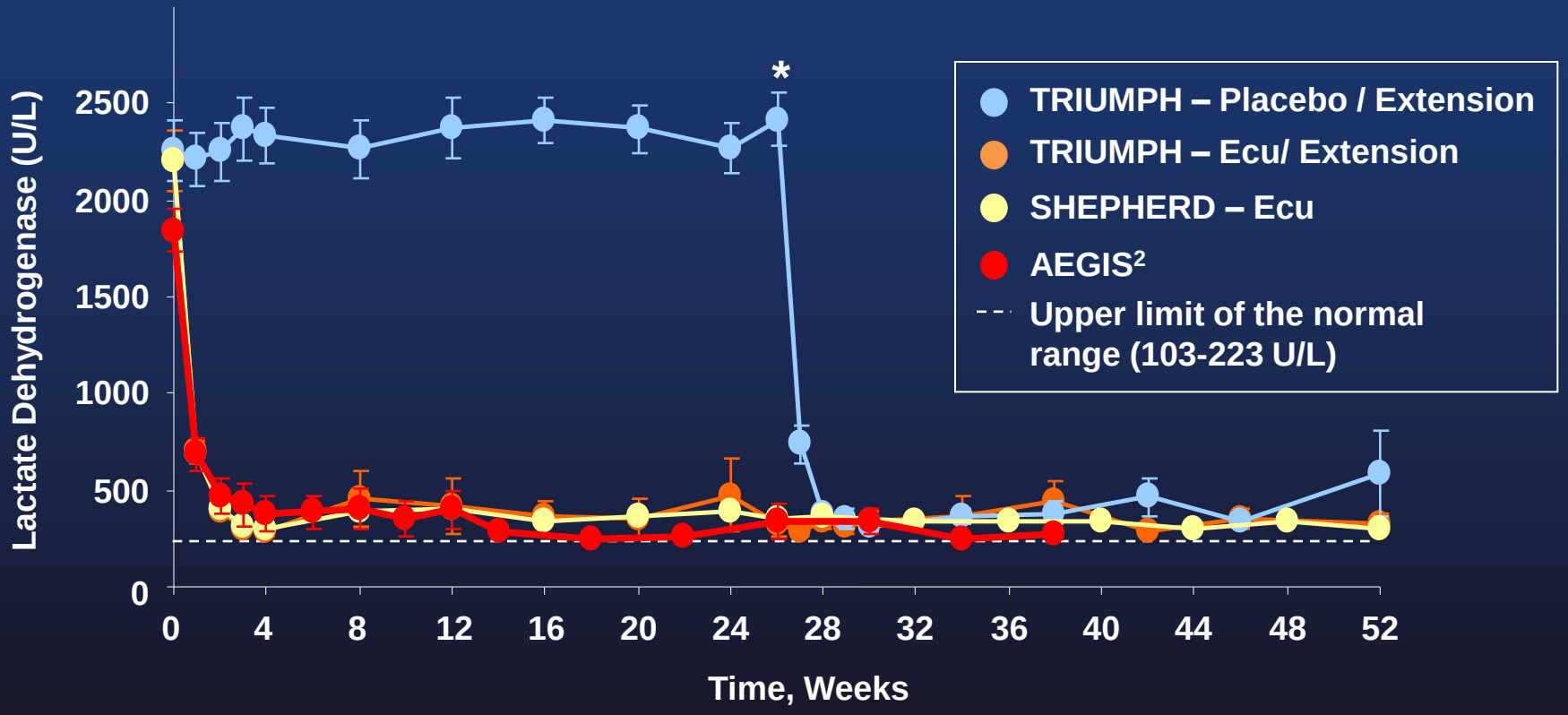
Effect of the complement inhibitor eculizumab on thromboembolism in patients with paroxysmal nocturnal hemoglobinuria

Peter Hillmen,[1] Petra Muus,[2] Ulrich Dührsen,[3] Antonio M. Risitano,[4] Jörg Schubert,[5] Lucio Luzzatto,[6] Hubert Schrezenmeier,[7] Jeffrey Szer,[8] Robert A. Brodsky,[9] Anita Hill,[1] Gerard Socié,[10] Monica Bessler,[11] Scott A. Rollins,[12] Leonard Bell,[12] Russell P. Rother,[12] and Neal S. Young[13]

[1]Leeds General Infirmary, Leeds, United Kingdom; [2]Radboud University Medical Center, Nijmegen, The Netherlands; [3]University Essen, Essen, Germany; [4]Federico II University, Naples, Italy; [5]Saarland University Medical School, Homburg-Saarland, Germany; [6]Istituto Toscano Tumori, Florence, Italy; [7]Institute of Transfusion Medicine, University Hospital, Ulm, Germany; [8]Royal Melbourne Hospital, Melbourne, Australia; [9]Johns Hopkins School of Medicine, Baltimore, MD; [10]Hôpital Saint-Louis and Institut National de la Santé et de la Recherche Médicale (INSERM), Paris, France; [11]Washington University, St Louis, MO; [12]Alexion Pharmaceuticals, Cheshire, CT; and [13]National Heart, Lung, and Blood Institute, Bethesda, MD

195 Patients With >250 Patient Years of Eculizumab Exposure

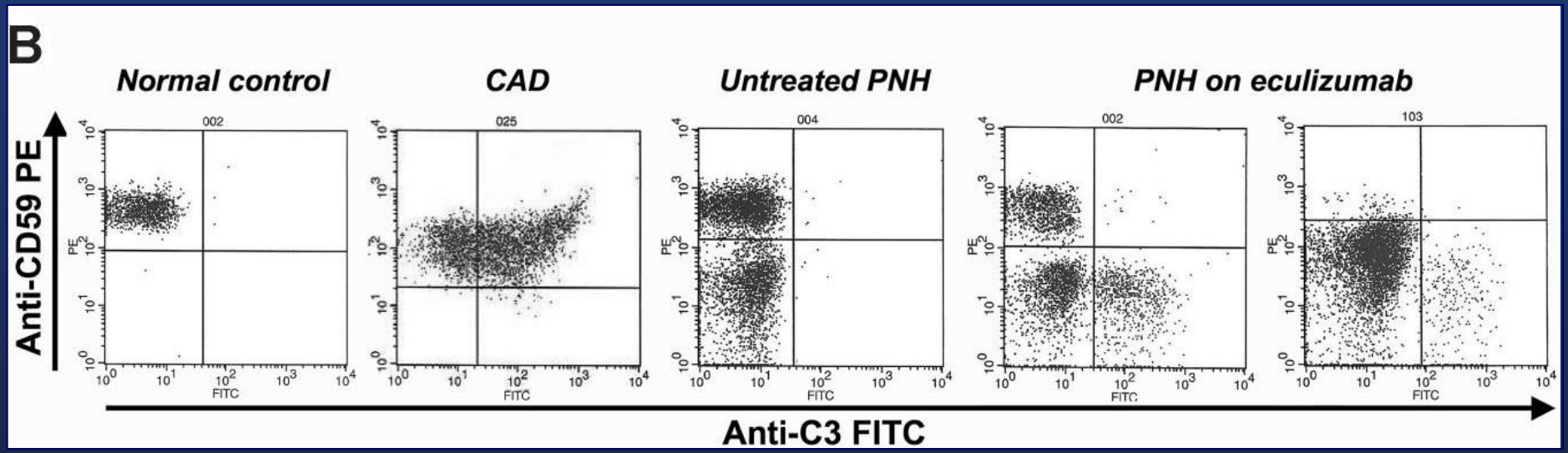
Inhibition of intravascular hemolysis (LDH)



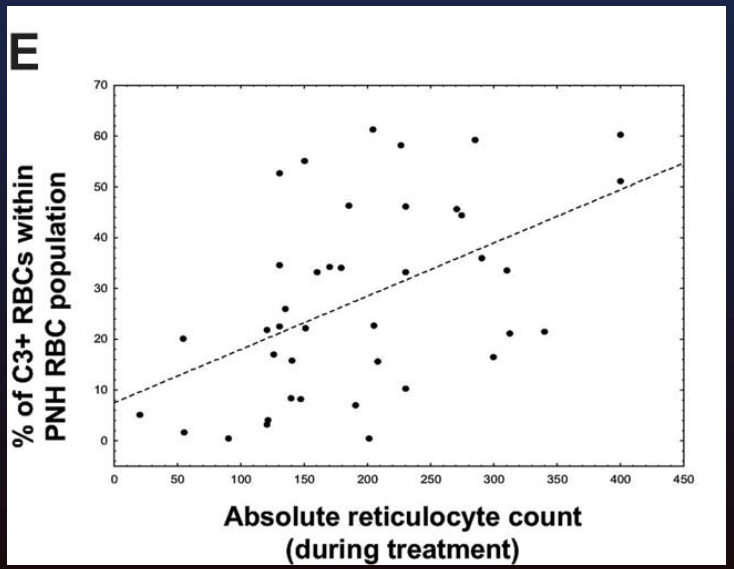
Transfusions reduction 85%

Hillmen P et al. *Blood*. 2007;110(12):4123-4128. 2. Kanakura Y et al. *Int J Hematol*. 2011;93:36-46.

Extra-vascular hemolysis??!!



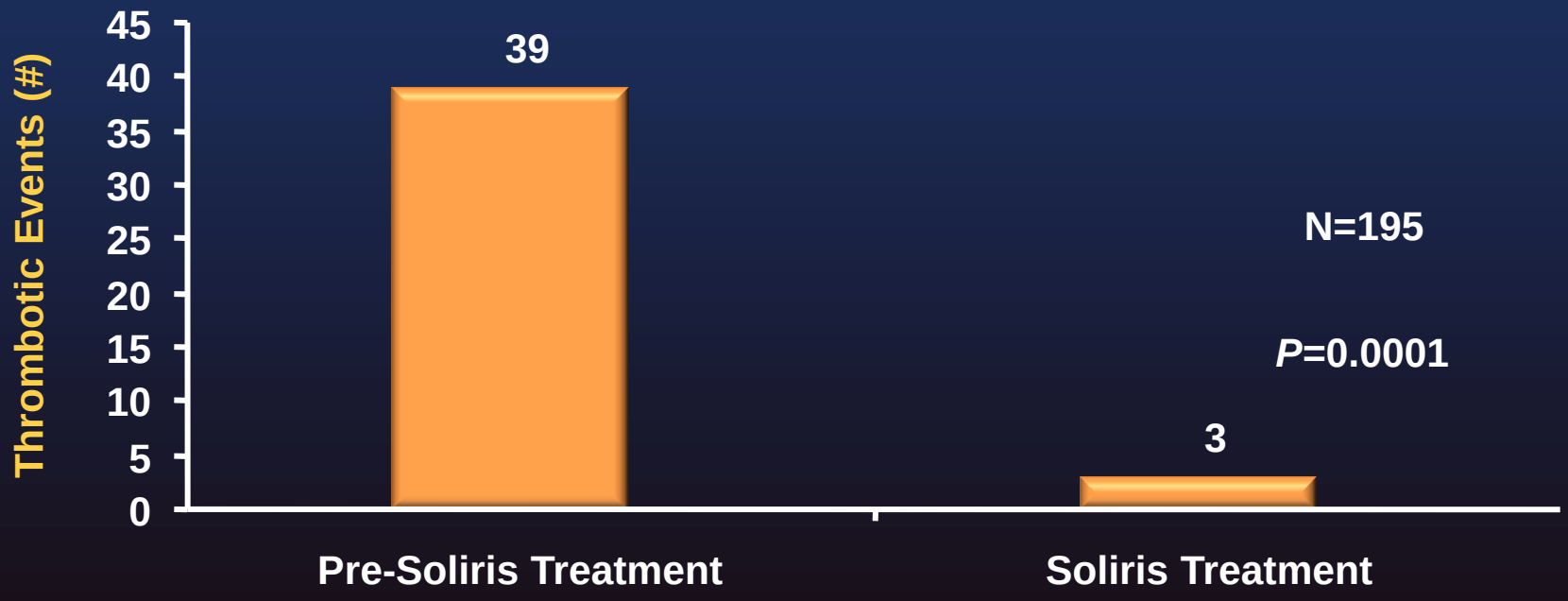
C3 opsonisation



Risitano *et al*, Blood 2010

92% Reduction in Thrombotic Events

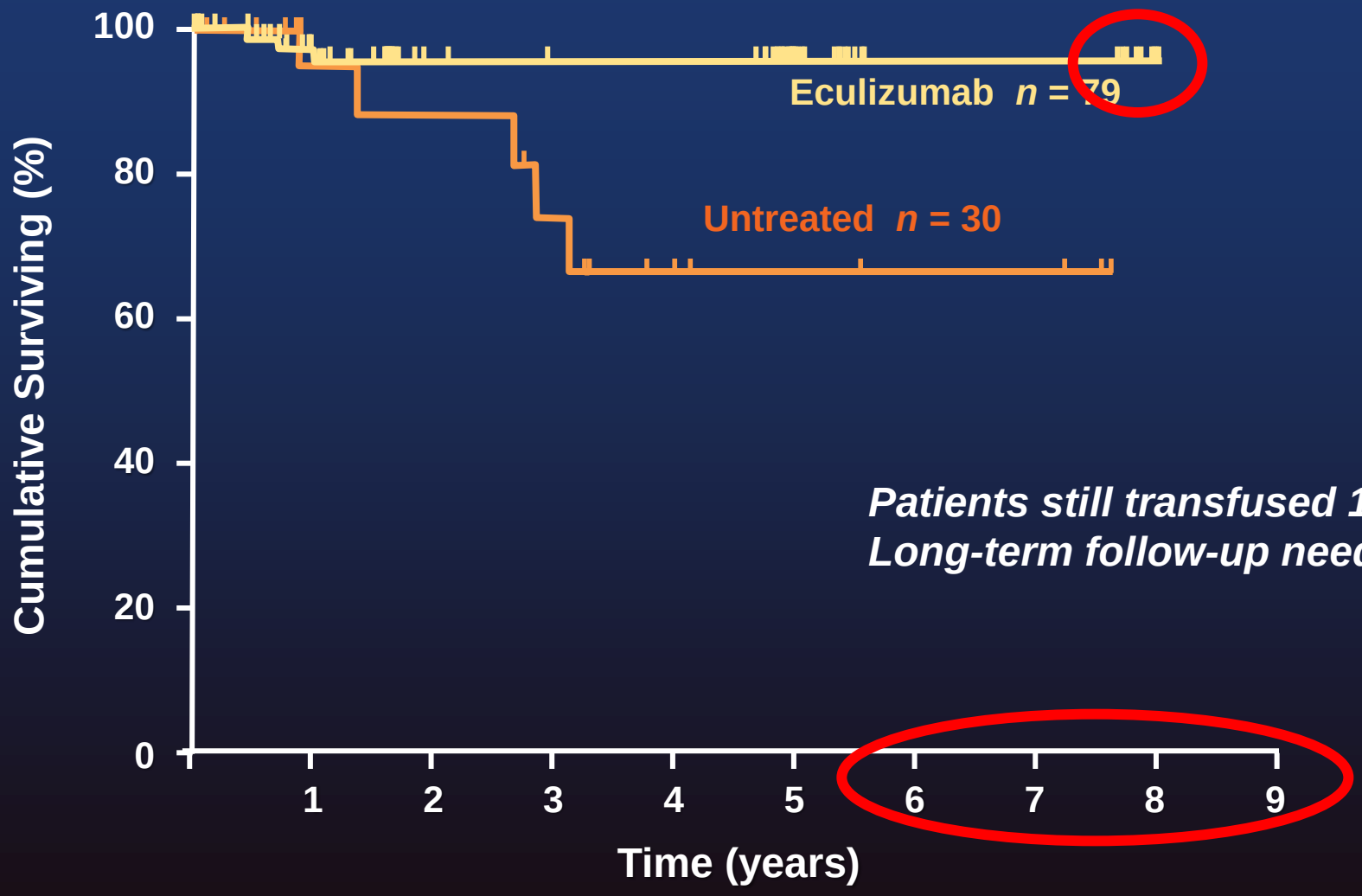
- 63% of patients received concomitant anticoagulants[1]
- The effect of anticoagulant withdrawal was not studied[2]
- Events observed in both venous and arterial sites[3]
- There were fewer thrombotic events with Soliris treatment than during the same period of time prior to treatment[2]



Please see full prescribing information for Soliris® (eculizumab).

1. Brodsky R *et al. Blood* 2008;111:1840–1847; 2. Soliris® (eculizumab) Summary of Product Characteristics. Alexion Europe SAS; 2013;
3. Hillmen P *et al. Blood* 2007;110:4123–4128.

Mortality With Eculizumab In Hemolytic PNH Patients

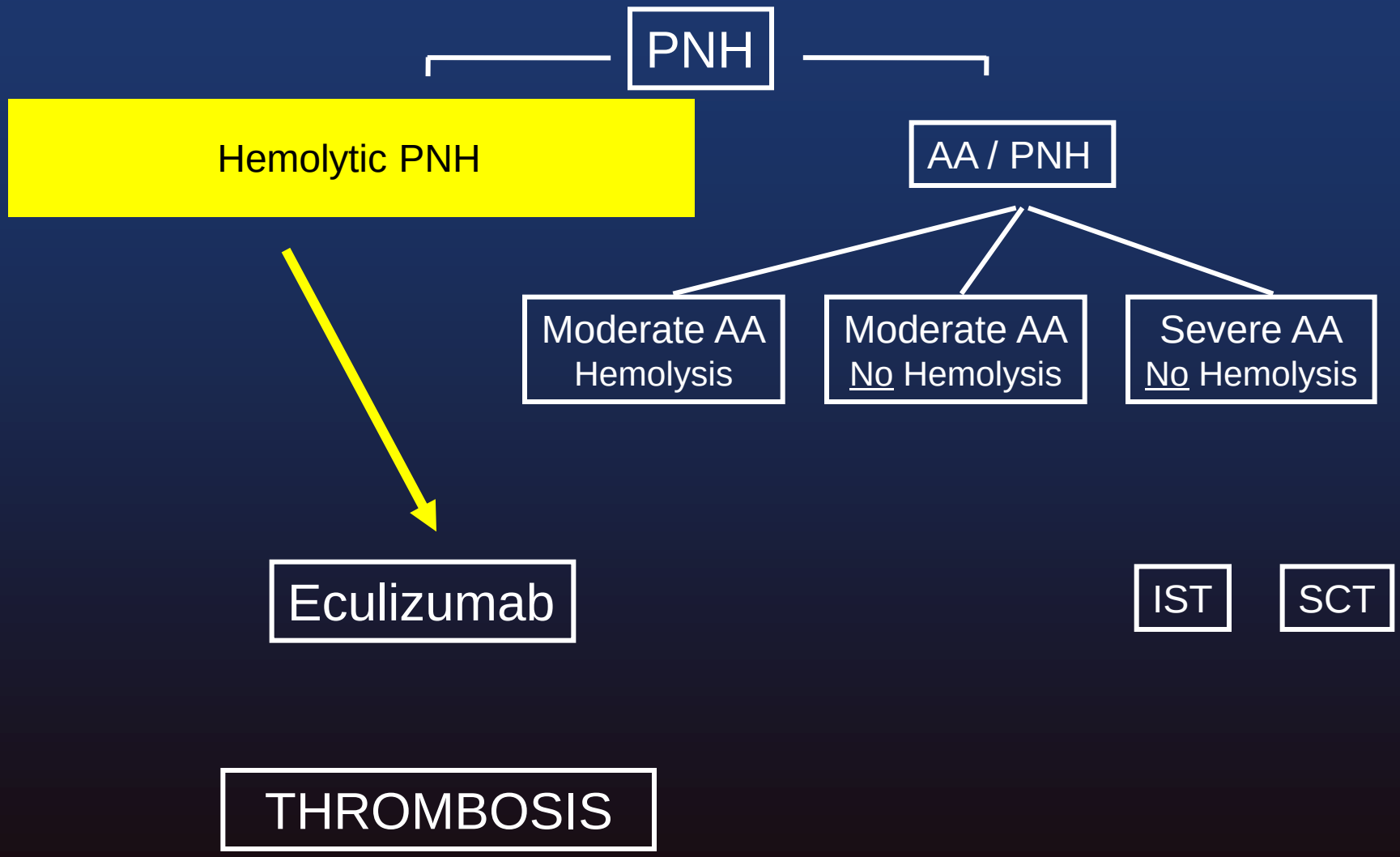


Patients still transfused 15-20%
Long-term follow-up needed!!

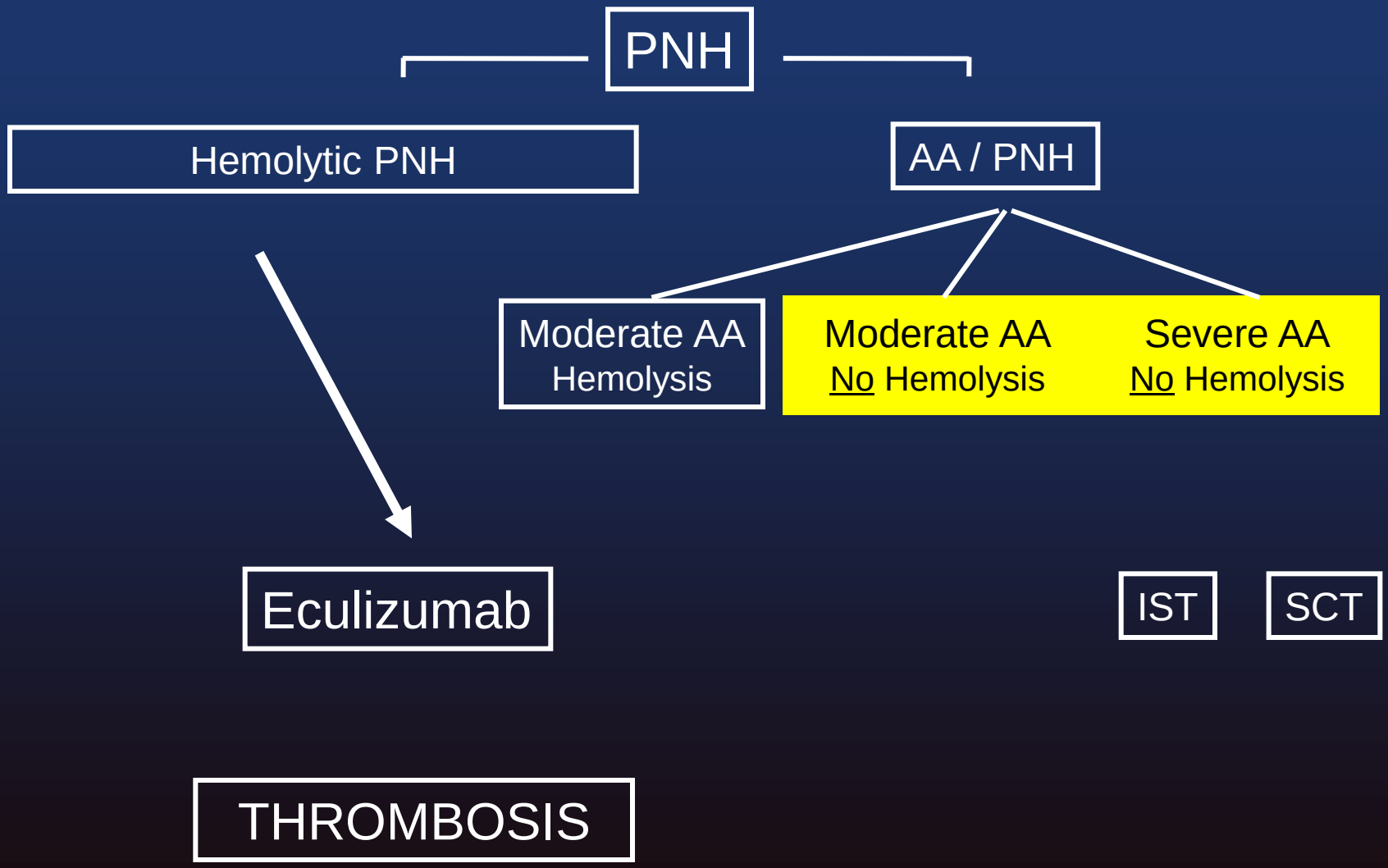
Kelly RJ et al. *Blood.* 2011

Mickael Loschi (on going)

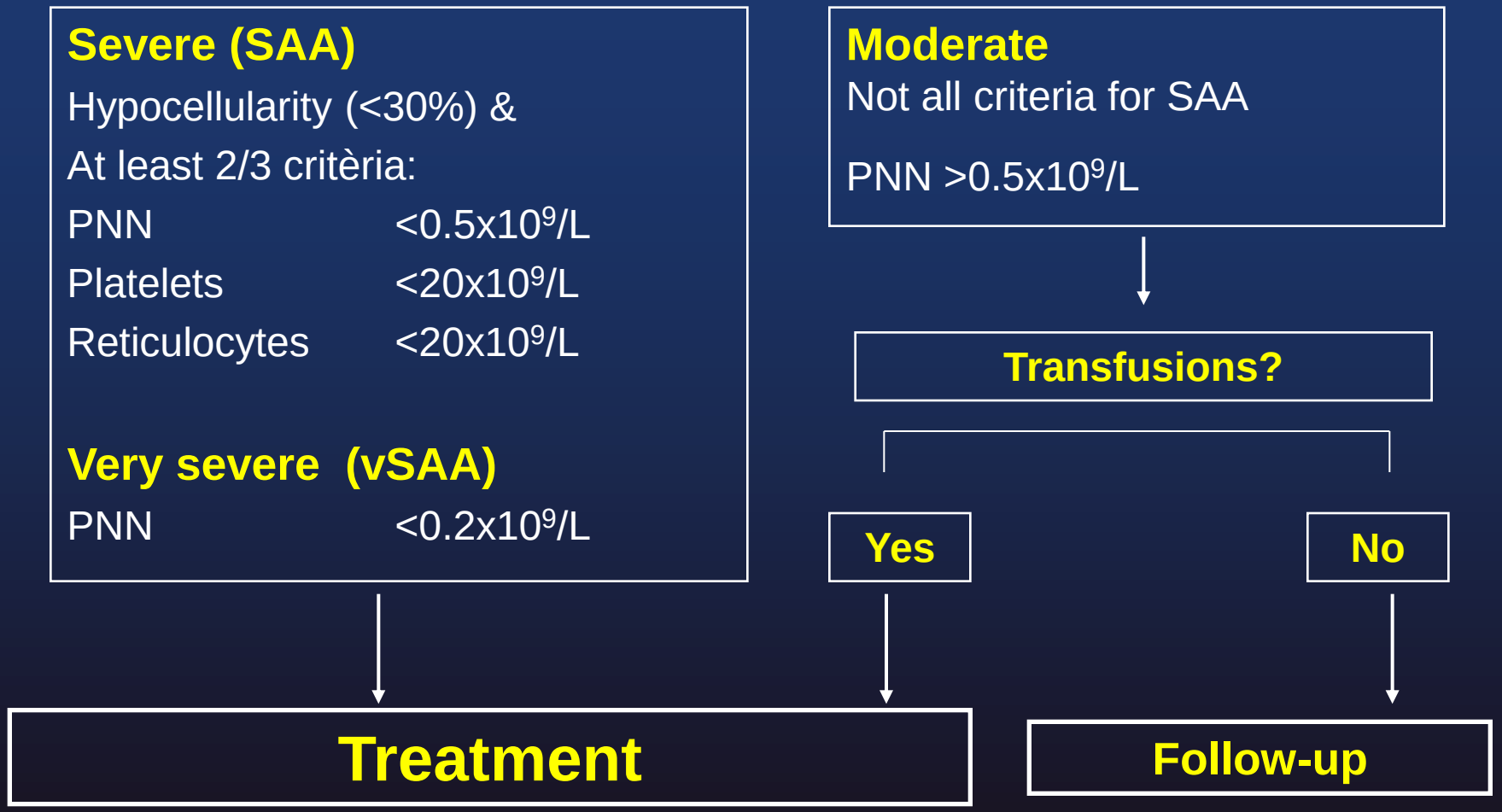
PNH management in 2013



PNH management in 2013

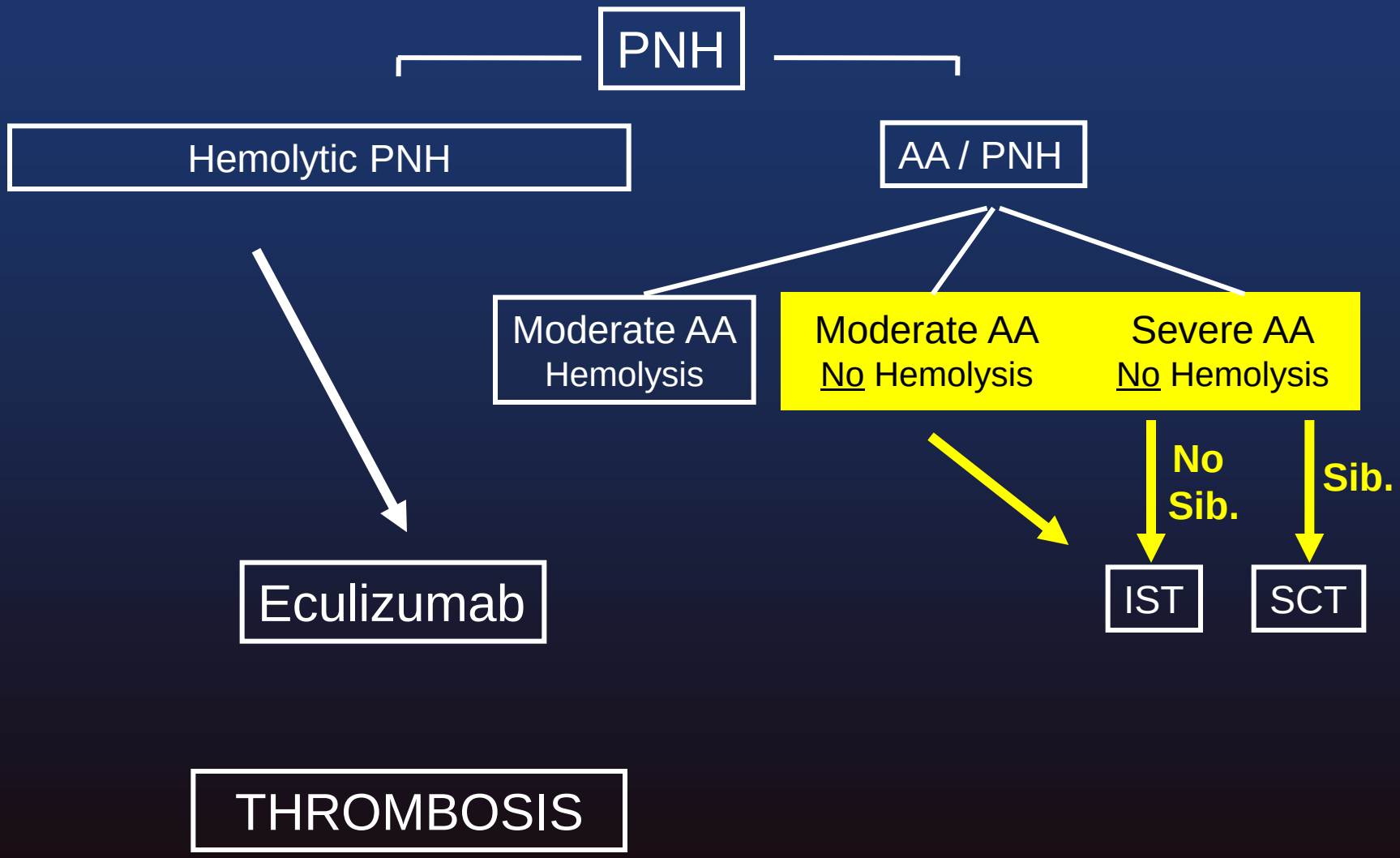


AA and treatment



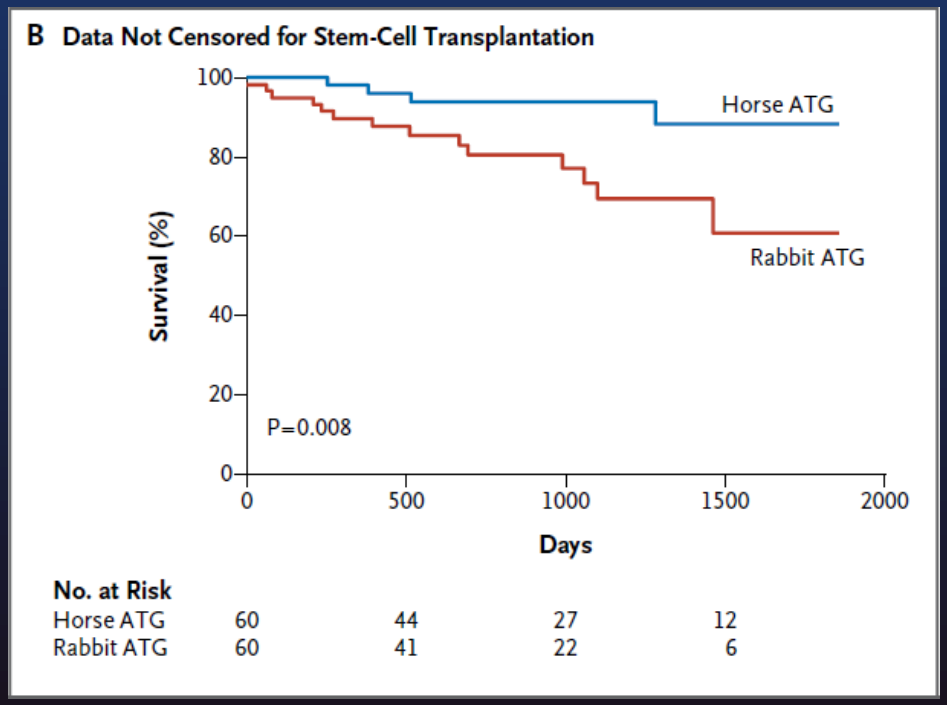
Camitta et al. *Blood* 1976

PNH management in 2013

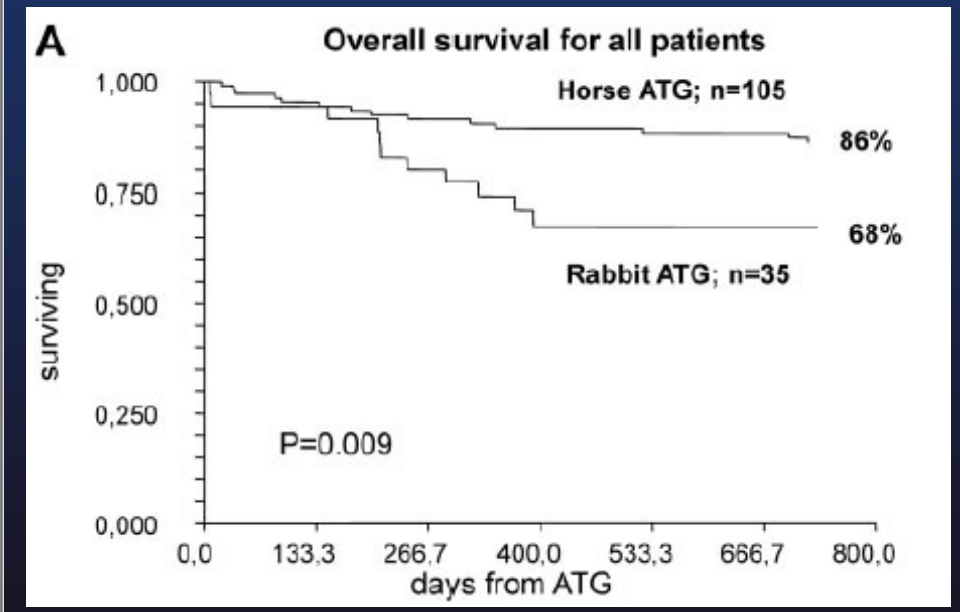


AA and no sibling donor

- ✓*Phase III prospective randomized study*
- ✓*First-line treatment*
- ✓*hATG + CyA (n=60) vs rATG + CyA (n=60)*
- ✓*OR at 6m 68% vs 37% (p<0.001)*



- ✓*Phase II prospective study*
- ✓*First-line treatment*
- ✓*rATG + CyA (n=35)*
- ✓*OR at 6m 40%*



Scheinberg P, *NEJM*, 2011; Marsh JC, *Blood* 2012

AA and no sibling donor

Etudes	Périodes	N	Age (médian)	Réponse	Rechute	Evolution Clonale	Survie
Allemagne	1986-1989	84	32	65%	19%	8%	58% à 11 ans
NIH	1991-1998	122	35	61%	35%	11%	55% à 7 ans
EGMBT	1991-1998	100	16	77%	12%	11%	87% à 5 ans
Japon	1992-1997	119	9	68%	22%	6%	88% à 3 ans
Allemagne/Australie	1993-1997	114	9	77%	12%	6%	87% à 4 ans
Japon	1996-2000	101	54	74%	42%	8%	88% à 4 ans
NIH	1999-2003	104	30	62%	37%	9%	80% à 4 ans
NIH	2003-2005	77	26	57%	26%	10%	93% à 3 ans

Réponse=60%

Young et al. *Blood* 2006

AA and no sibling donor

Etudes	Périodes	N	Age (médian)	Réponse	Rechute	Evolution Clonale	Survie
Allemagne	1986-1989	84	32	65%	19%	8%	58% à 11 ans
NIH	1991-1998	122	35	61%	35%	11%	55% à 7 ans
EGMBT	1991-1998	100	16	77%	12%	11%	87% à 5 ans
Japon	1992-1997	119	9	68%	22%	6%	88% à 3 ans
Allemagne/Australie	1993-1997	114	9	77%	12%	6%	87% à 4 ans
Japon	1996-2000	101	54	74%	42%	8%	88% à 4 ans
NIH	1999-2003	104	30	62%	37%	9%	80% à 4 ans
NIH	2003-2005	77	26	57%	26%	10%	93% à 3 ans

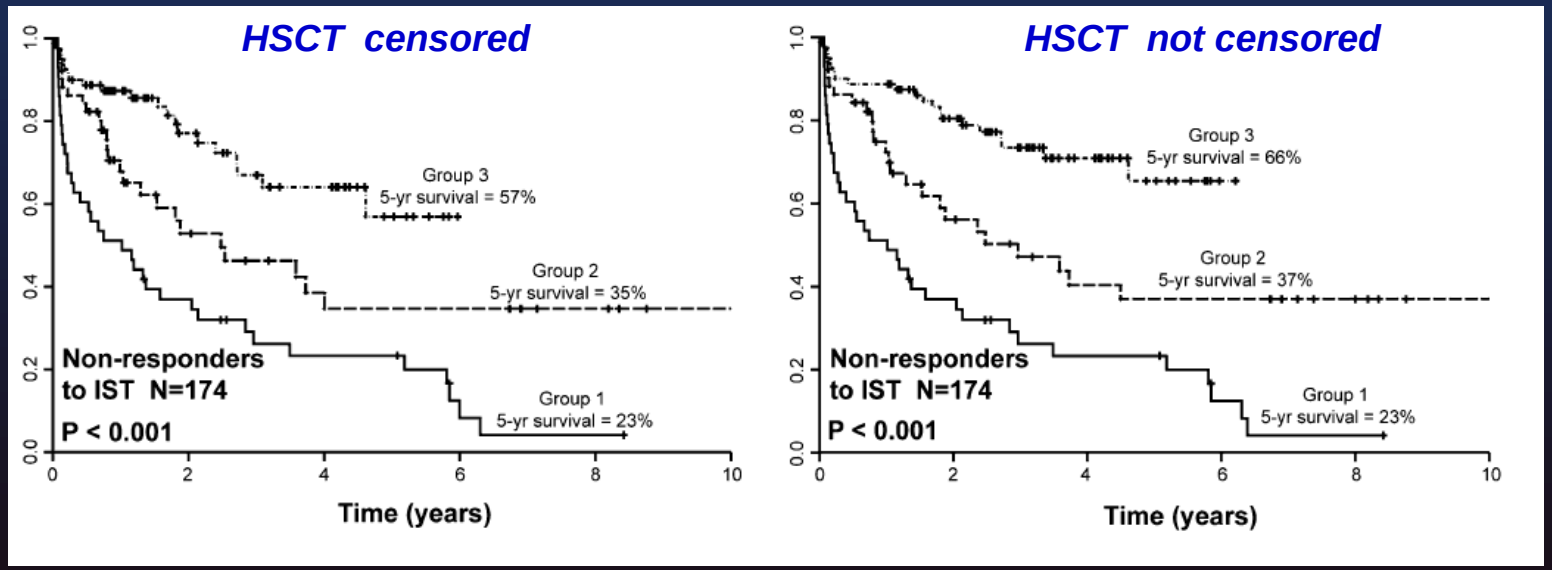
Young et al. *Blood* 2006

Réponse=60% > 30-40% réfractaires

Patients refractory to IST: survival

Don't forget what supportive care can do with nonresponders to Immunosuppressive therapy!

All patients	Group 1 (1989-1996)	Group 2 (1996-2002)	Group 3 (2002-2008)
174	43	51	80



Valdez *et al*, CID 2011

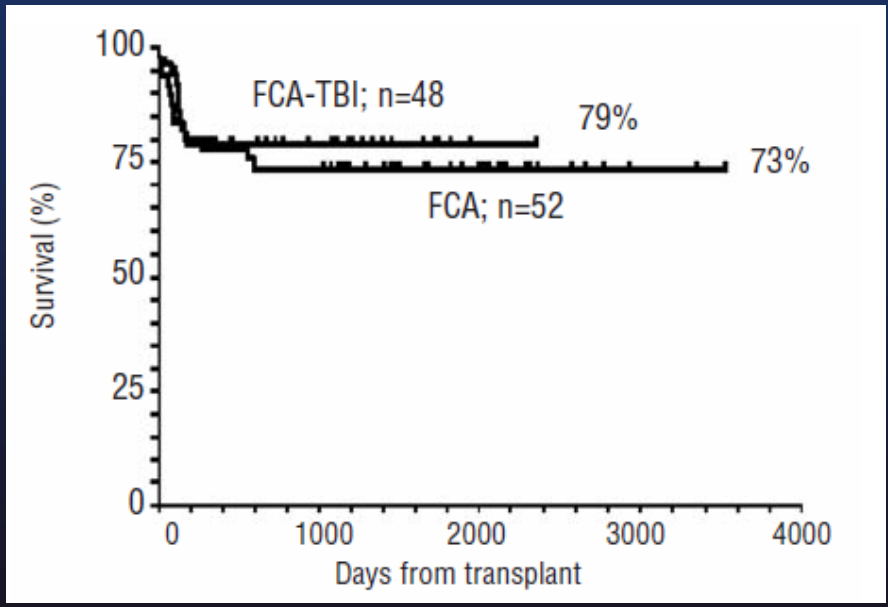
Patients refractory to IST: unrelated BMT

Fludarabine, cyclophosphamide, antithymocyte globulin, with or without low dose total body irradiation, for alternative donor transplants, in acquired severe aplastic anemia: a retrospective study from the EBMT-SAA working party

Andrea Bacigalupo,[1] Gerard Socie',[2] Edoardo Lanino,[3] Arcangelo Prete,[4] Franco Locatelli,[5] Anna Locasciulli,[6] Simone Cesaro,[7] Avichai Shimoni,[8] Judith Marsh,[9] Mats Brune,[10] Maria Teresa Van Lint,[1] Rosi Oneto,[1] and Jacob Passweg[13] for the Severe Aplastic Anemia Working Party of the European Group for Blood and Marrow Transplantation (SAA WP-EBMT)

Table 1. Clinical data of the 100 transplanted patients with SAA.

Patients	FCA n=52	FCA-TBI n=48	*P* value
Sex (male/female)	25/27	29/19	0.15
Median age	13 (3-51)	27 (7-53)	<0.001



Refractory after IS: YES

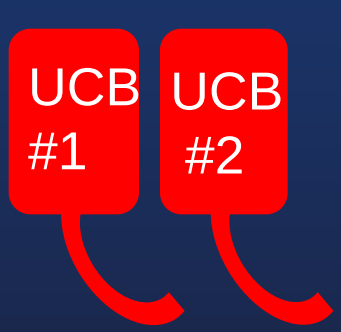
Haematologica 2010;95:976-982.

Patients refractory to IST: CB HSCT

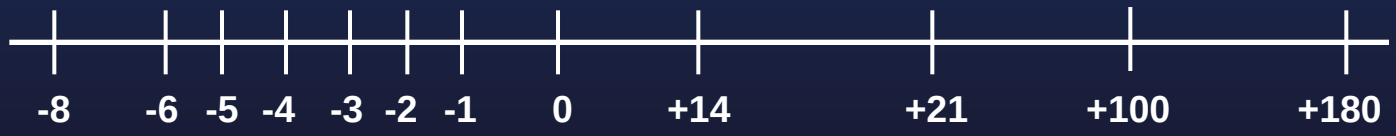
APCORD (SFGM-TC)

Conditioning regimen:

- > **Fludarabine, 120mg/m²**
- > **Endoxan, 120mg/Kg**
- > **ATG, 5 mg/Kg**
- > **TBI 2 Gy**



4-6/6 HLA-match UCB
TNCc: 4 x 10^7/kg



Anti CD20: 150mg/m² (D5)

G-CSF (D5)

15 patients inclus / 10 patients évaluables / 1 décès

Patients refractory to IST: Eltrombopag!

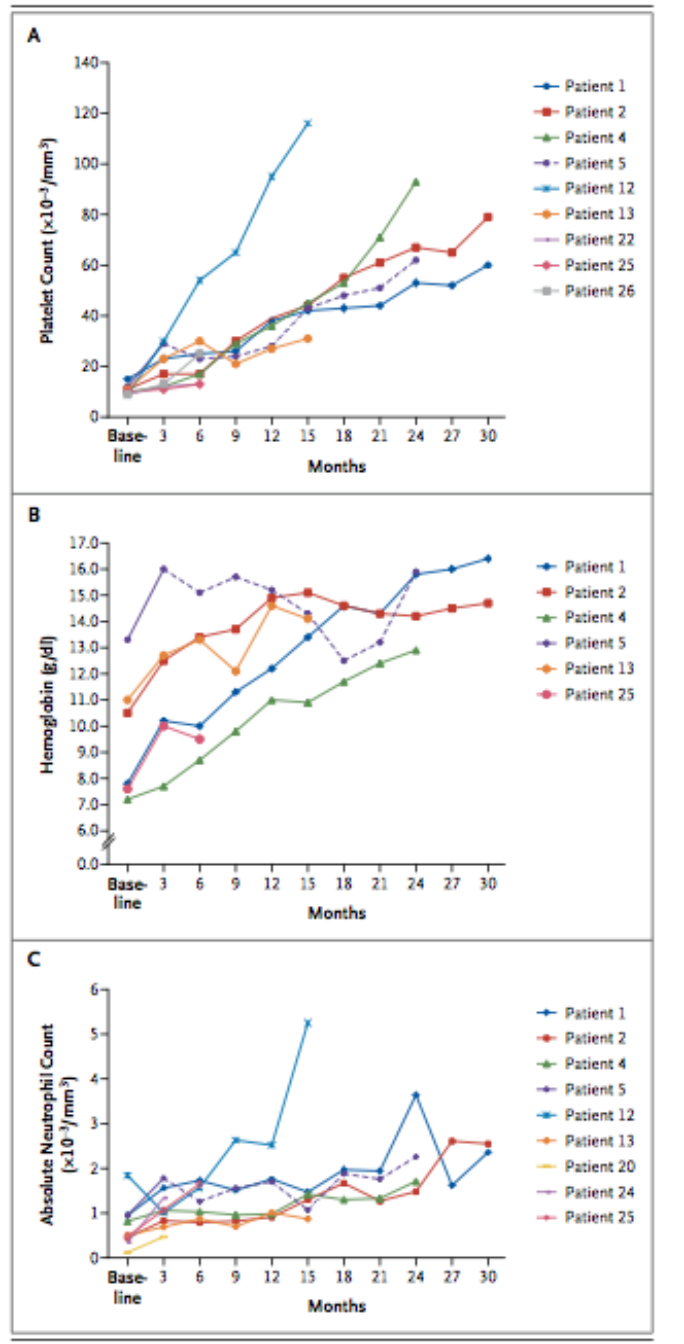
Eltrombopag and Improved Hematopoiesis in Refractory Aplastic Anemia

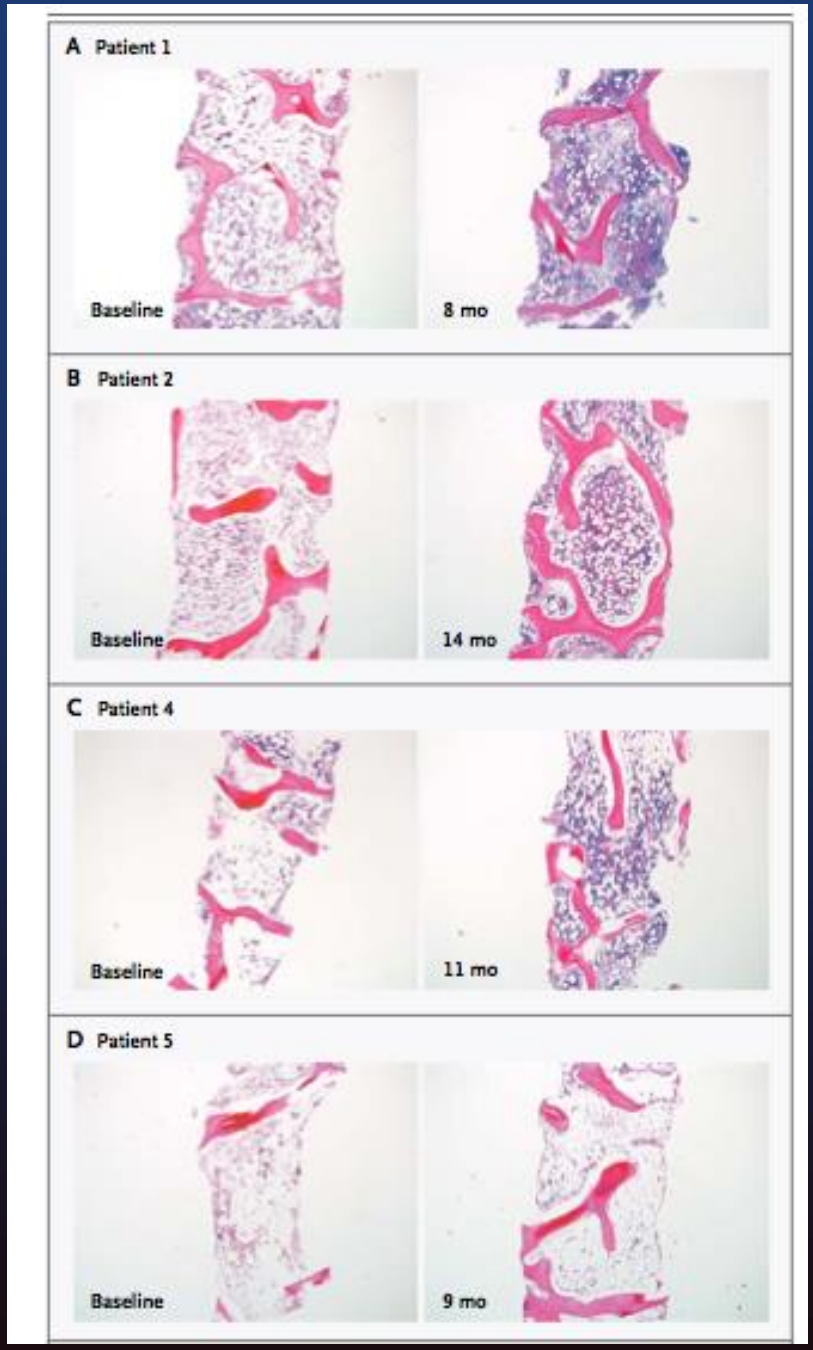
Matthew J. Olnes, M.D., Ph.D., Phillip Scheinberg, M.D., Katherine R. Calvo, M.D., Ronan Desmond, M.D., Yong Tang, M.D., Ph.D., Bogdan Dumitriu, M.D., Ankur R. Parikh, M.D., Susan Soto, B.S.N., Angelique Biancotto, Ph.D., Xingmin Feng, M.D., Ph.D., Jay Lozier, M.D., Ph.D., Colin O. Wu, Ph.D., Neal S. Young, M.D., and Cynthia E. Dunbar, M.D.

ABSTRACT

25 patients refractaires
50 à 175 mg/j
4 mois

44% de répondeurs: au moins une lignée


A
Platelet Count (×10⁻³/mm³)
Months
Baseline
Patient 1
Patient 2
Patient 4
Patient 5
Patient 12
Patient 13
Patient 22
Patient 25
Patient 26
B
Hemoglobin (g/dl)
Months
Baseline
Patient 1
Patient 2
Patient 4
Patient 5
Patient 13
Patient 25
C
Absolute Neutrophil Count (×10⁻³/mm³)
Months
Baseline
Patient 1
Patient 2
Patient 4
Patient 5
Patient 12
Patient 13
Patient 20
Patient 24
Patient 25


A Patient 1
Baseline
8 mo
B Patient 2
Baseline
14 mo
C Patient 4
Baseline
11 mo
D Patient 5
Baseline
9 mo

Agonistes de TPO??

- HSC and progenitor cells also expressed c-MPL on their cell surface
- Addition of rTPO expands the pool of HSC in vitro

Zeigler et al, Blood 1994

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- Souris KO for MPL or TPO ligand

Zeigler et al, Blood 1994; Alexander et al, Blood 1996; Kimura PNAS 1998

Agonistes de TPO??

- HSC and progenitor cells also expressed c-MPL on their cell surface
- Addition of rTPO expands the pool of HSC in vitro
- Souris KO for MPL or TPO ligand
- Congenital amegakaryocytic thrombocytopenia (MPL mutations)

Zeigler et al, Blood 1994; Alexander et al, Blood 1996; Kimura PNAS 1998; Geddis AE et al, pediatric blood cancer 2011

Agonistes de TPO (études cliniques)

- **Patients Réfractaires à toutes IST**
  - Phase I-II en cours (NIH)
  - Etude retrospective française (…)

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  - Etude observationnelle
  - SAL (lapin) ciclosporine eltrombopag (J15>J100)

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- **1ère ligne ET NON ELIGIBLE A LA GREFFE**
  - ATG (cheval) ciclosporine Eltrombopag (J15>J100)
  - Objectif primaire: RC à 3 mois, 7% >21%
  - Promoteur: EBMT; financement GSK, 190 patients
  - Ouverture Mai 2014

HPN/AA thérapeutiques innovantes

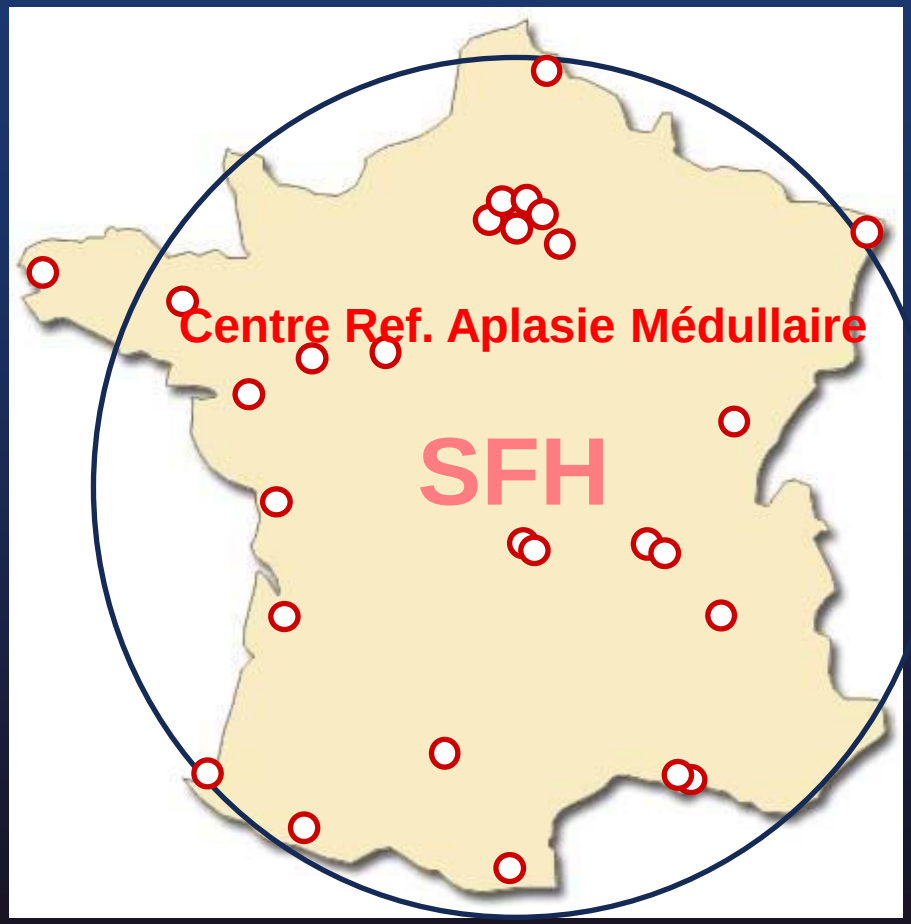
- **Eculizumab**
  - Long-terme+++
- **Eltrombopag (Romiplostine?)**
  - Tout début de l'histoire…!
  - Evolution clonale sous traitement ?
- **Attention à ne pas oublier le traitement de référence…**
  - Allogreffe 10/10 si jeune …

François Marie Arouet

dit ~~Zadig~~ et Voltaire
(1694 –1778)

«Les médecins administrent des médicaments dont ils savent très peu, à des malades dont ils savent moins, pour guérir des maladies dont ils ne savent rien »

Merci!



Participating centers

Sans oublier Marie Oger !!!!!!!!!!!!

Et si l'AIH faisait un peu d'HPN…

- **Appel à cas clinique (Septembre 2013)**
- **Selection des meilleurs cas pour présentation orale en Juin 2013**
  - 4 orateurs
- **Présence d'experts internationaux**
  - A. Hill
  - A. Risitano
  - G. Socié
- **Places ASH 2014 (1), EHA 2015 (1), EBMT 2015 (1) mais aussi SFH, SFGM-TC…**

Projet soutenu par les laboratoires Alexion