Aplasie médullaire: Spécificités liées à la présence d'un clone HPN

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APLASIE MEDULLAIRE
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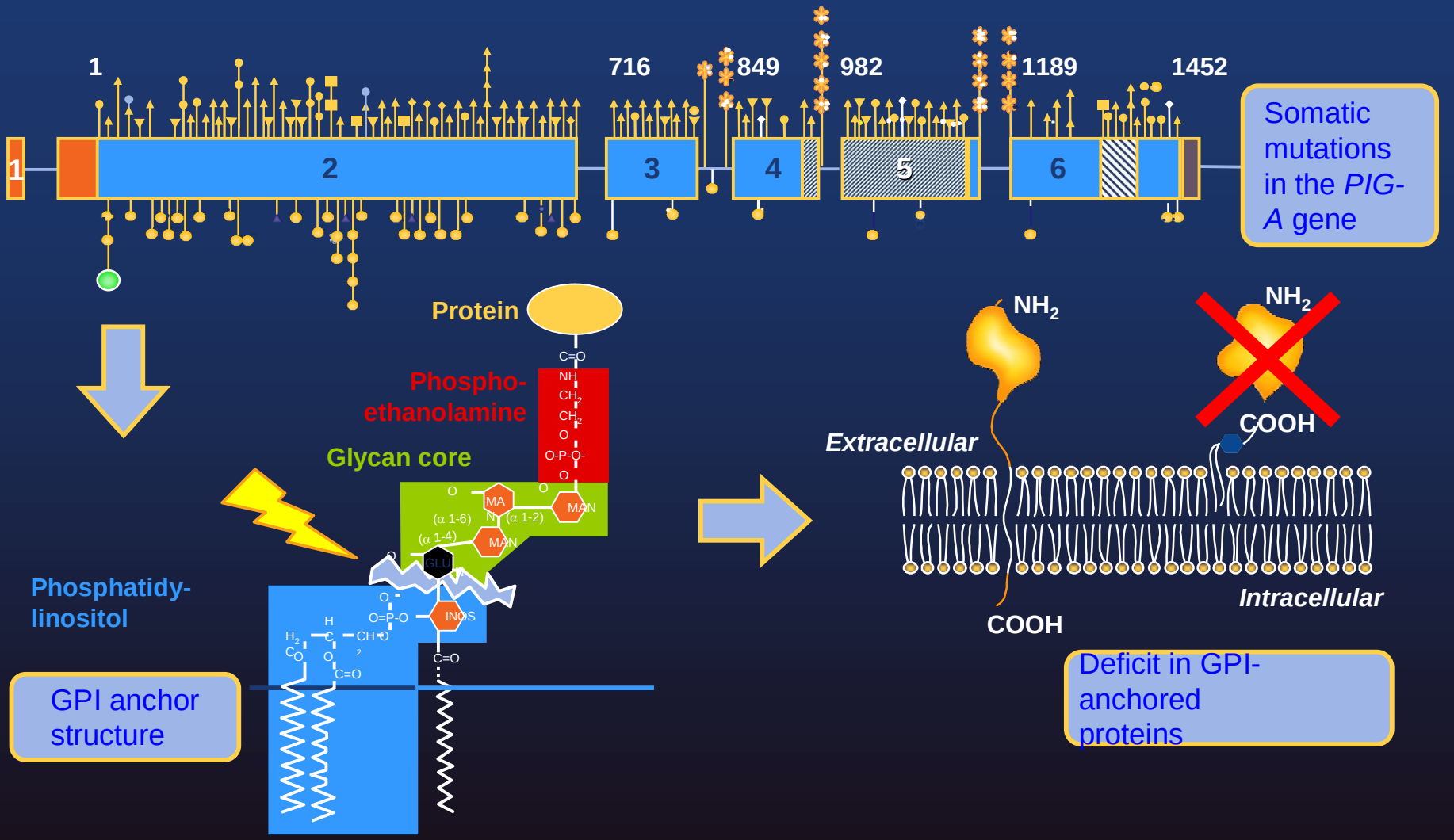
Paroxysmal Nocturnal Hemoglobinuria (PNH):

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.

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

The Defect in PNH

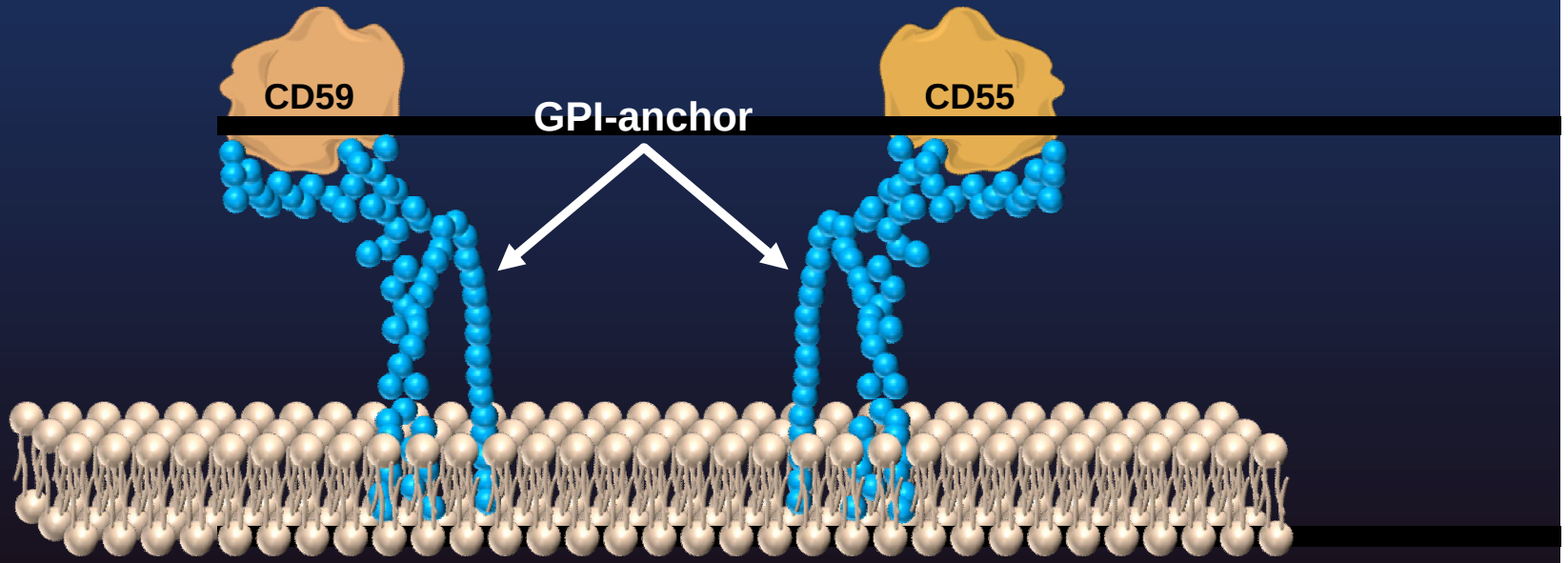
PNH is an acquired hemolytic disorder characterized by the somatic mutation of the PIG A gene

CD59

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

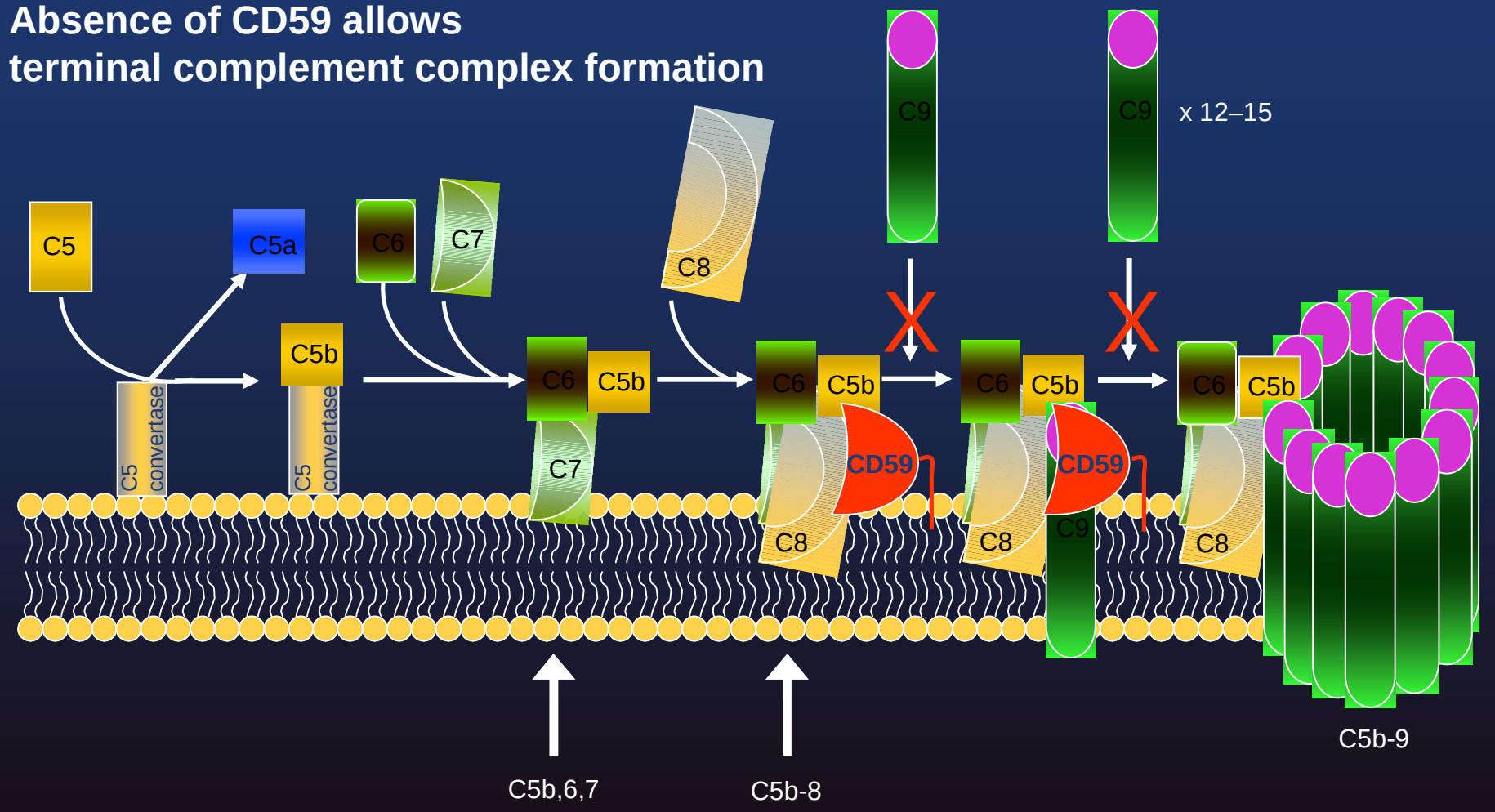
CD55

- 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.

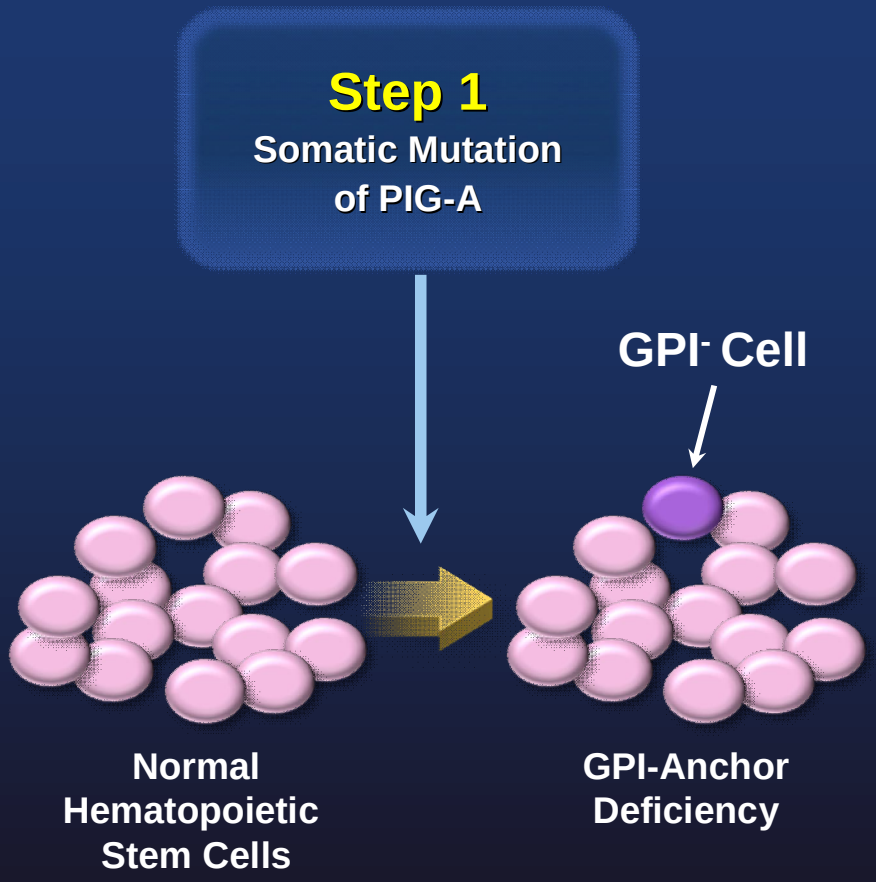
GPI deficiency results in Hemolytic Anemia
(lack of CD59 or CD55)



PNH, paroxysmal nocturnal haemoglobinuria

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

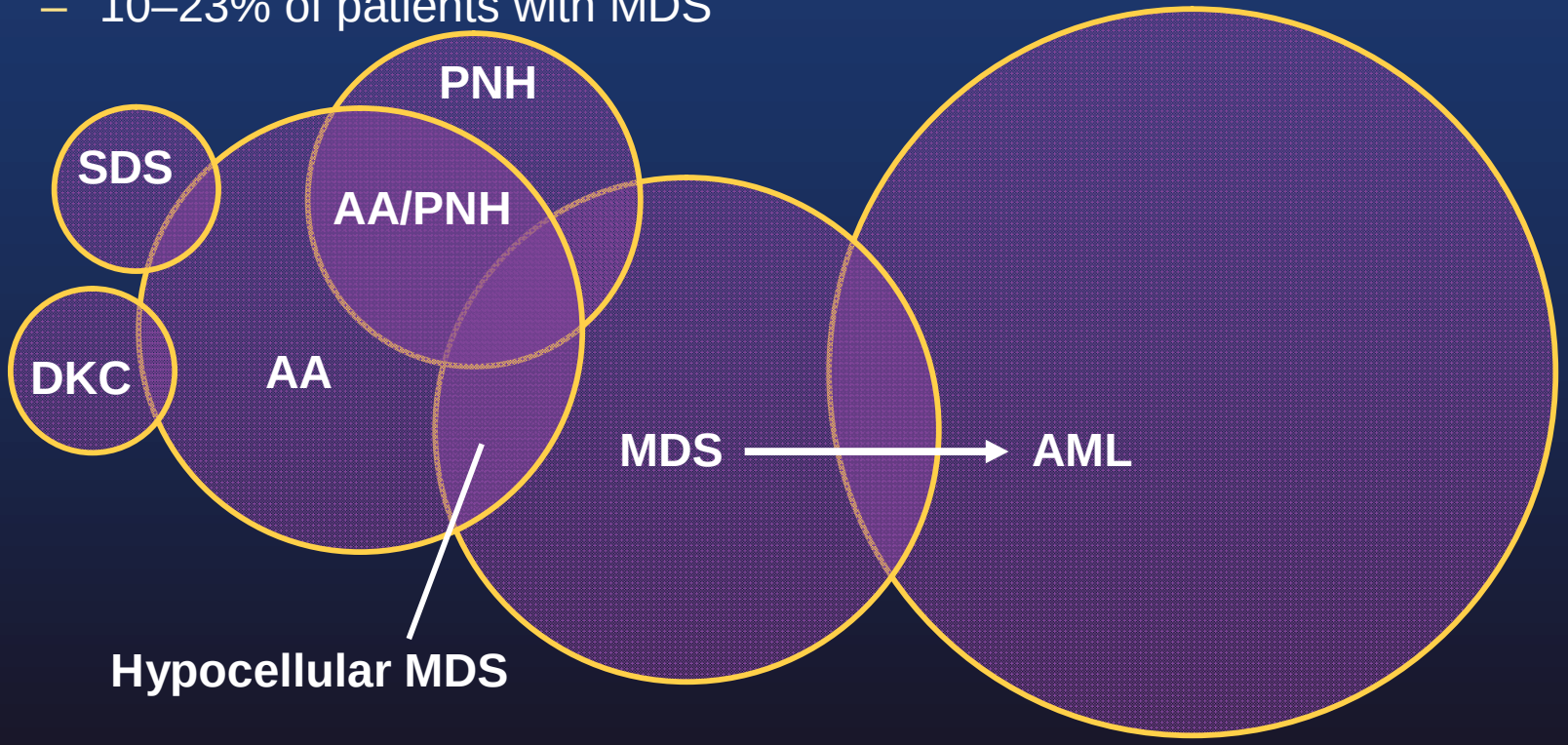
Expansion of PNH Clone



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

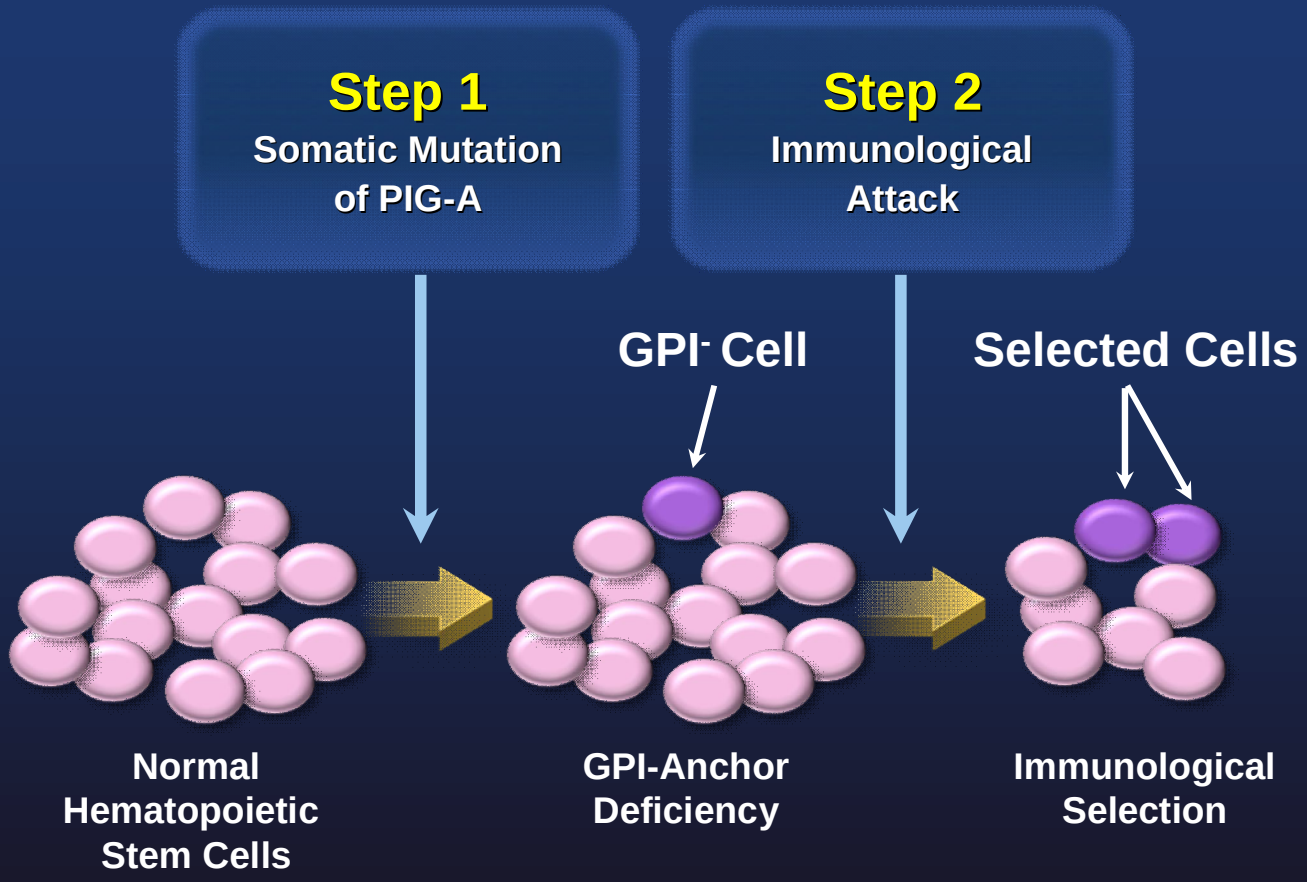


AA, aplastic anaemia; AML, acute myelogenous leukaemia;
DKC, dyskeratosis congenita; SDS, Shwachman-Diamond syndrome;
MDS, myelodysplastic syndrome;
PNH, paroxysmal nocturnal haemoglobinuria

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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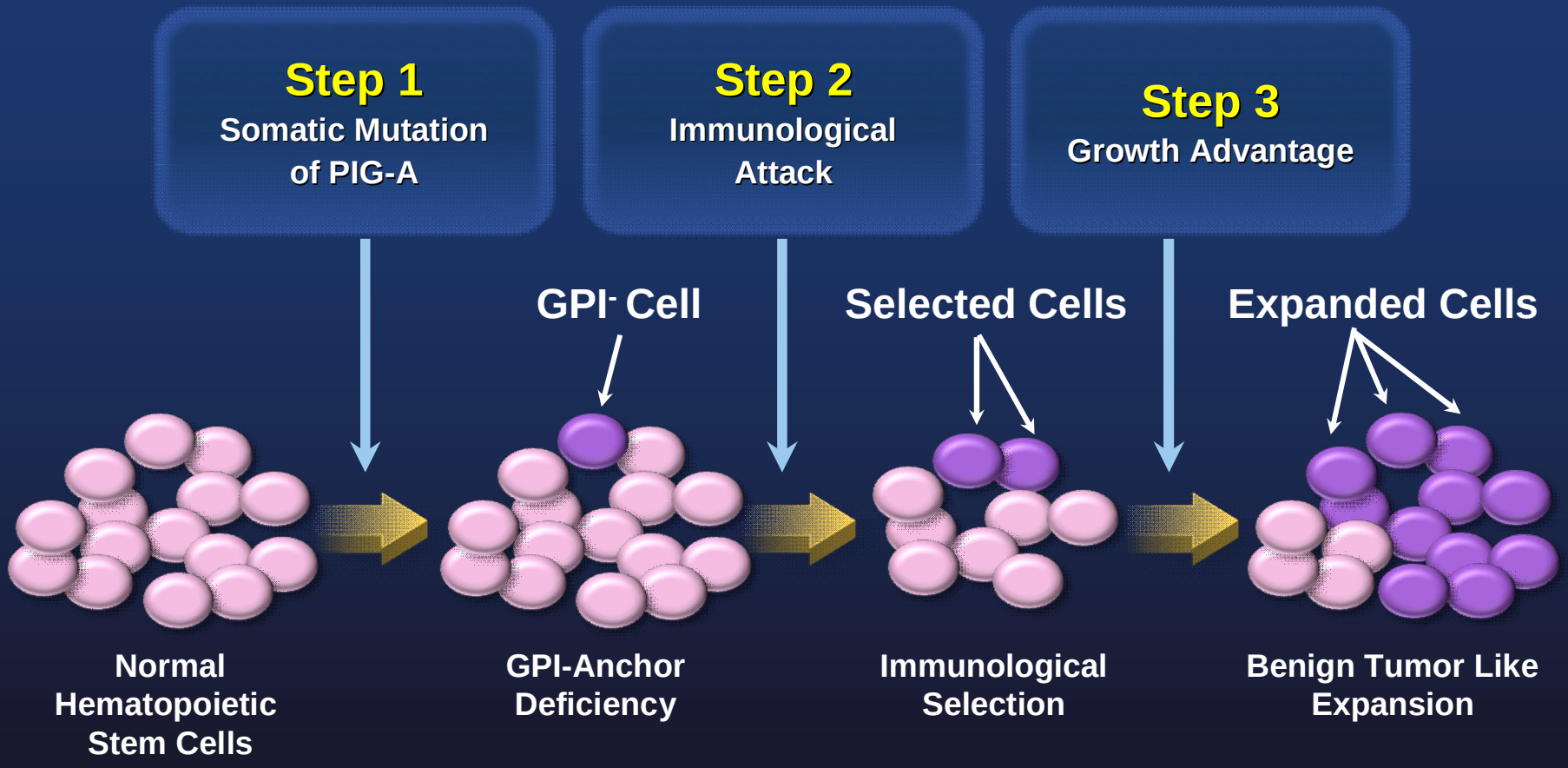
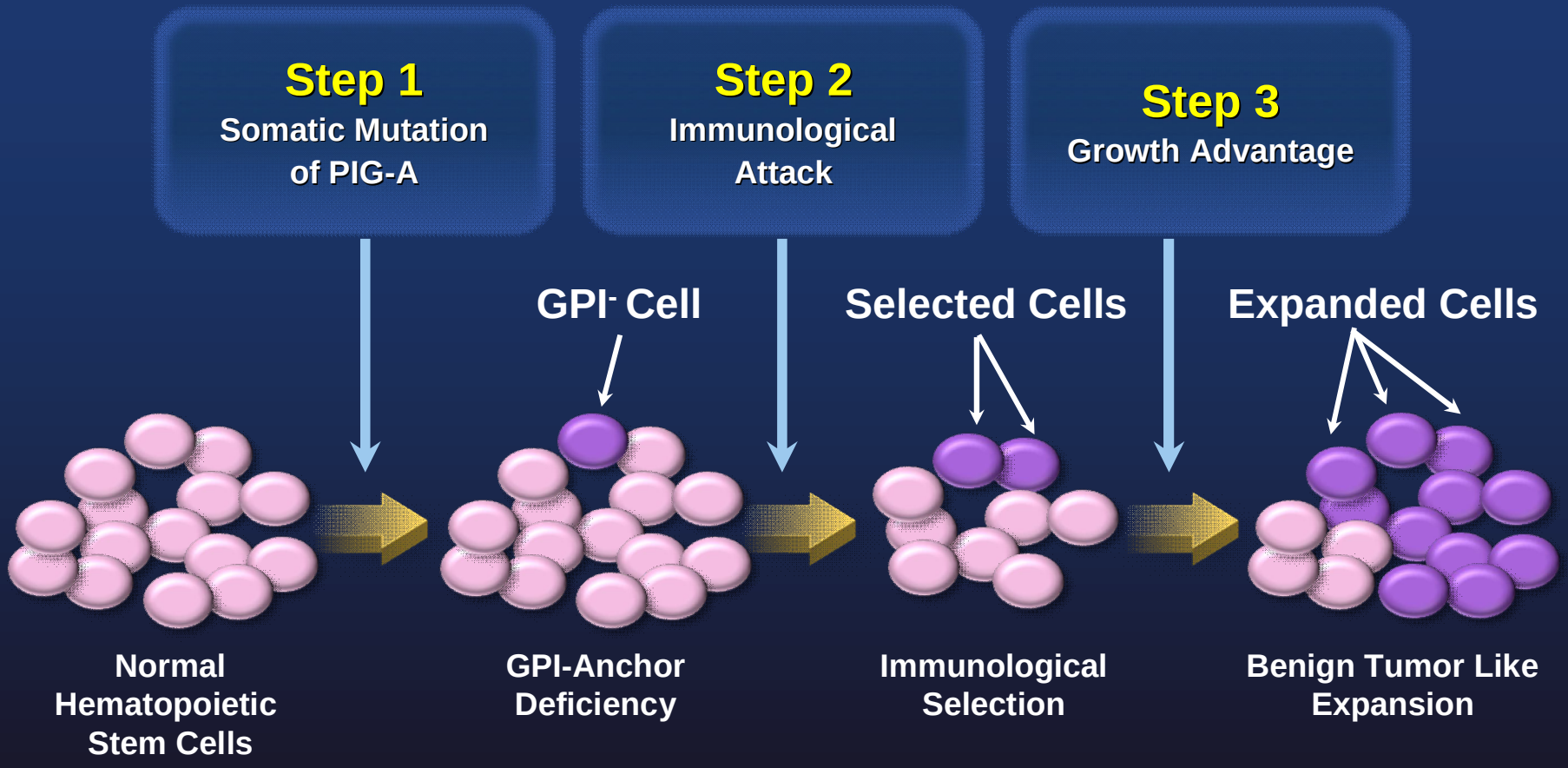


HMGA2, transcription factor gene
Benign Mesenchymal tumors (?)

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

Message 1: clone HPN = argument en faveur d'une aplasie acquise

AA & PNH

> 1/3 des patients avec AA auront un test de Ham positif

> 1/3 des patients avec AA ont des cellules GPI (-) au diagnostic ou durant l'évolution

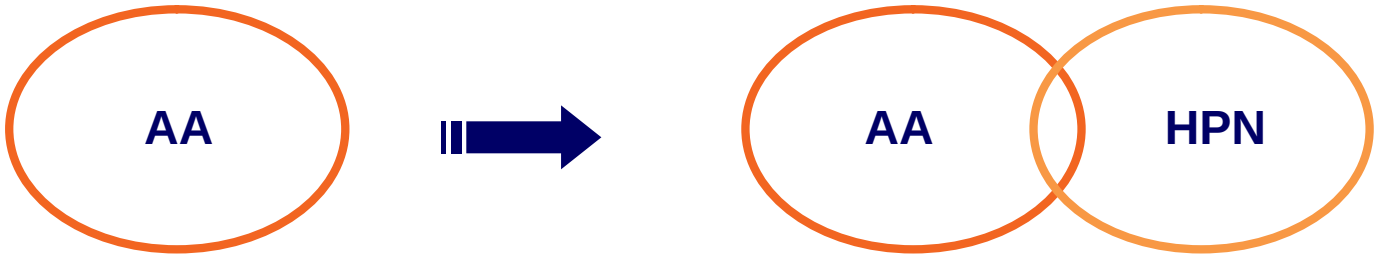
> On retrouve les mêmes mutations PIG-A, chez les AA avec des cellules GPI (-) et chez les HPN de novo

1/3 des AA considérées comme idiopathiques
= AA/HPN (cellules GPI négatives ; PIG-A mutées)

AA & PNH

HPN <u>après</u> Aplasie médullaire

Groupes	Références	N / total (%)
Basel	*Br.J.Haematol* 1988	25%
EBMT	*Br J Haematol* 1989	20%
French	*Blood* 1990	10%
SFH	*Lancet* 1996	30%



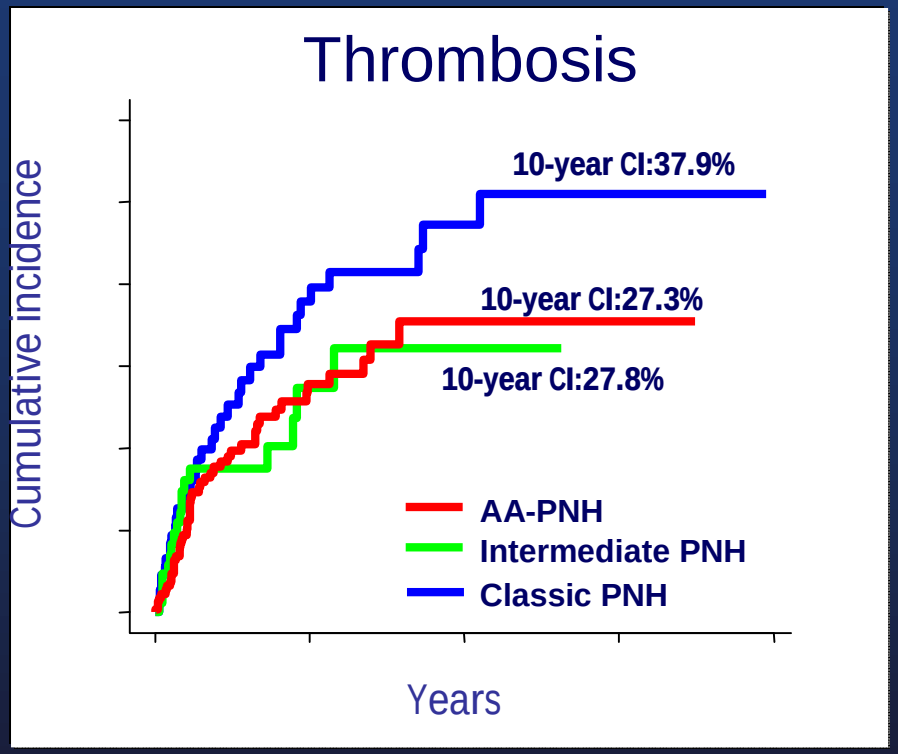
Message 2: clone HPN = une fois/an chez un malade avec aplasie acquise

30-40% des aplasies ont ou auront un clone HPN

et

20% des malades évoluent du stade aplasie vers le stade HPN hémolytique classique

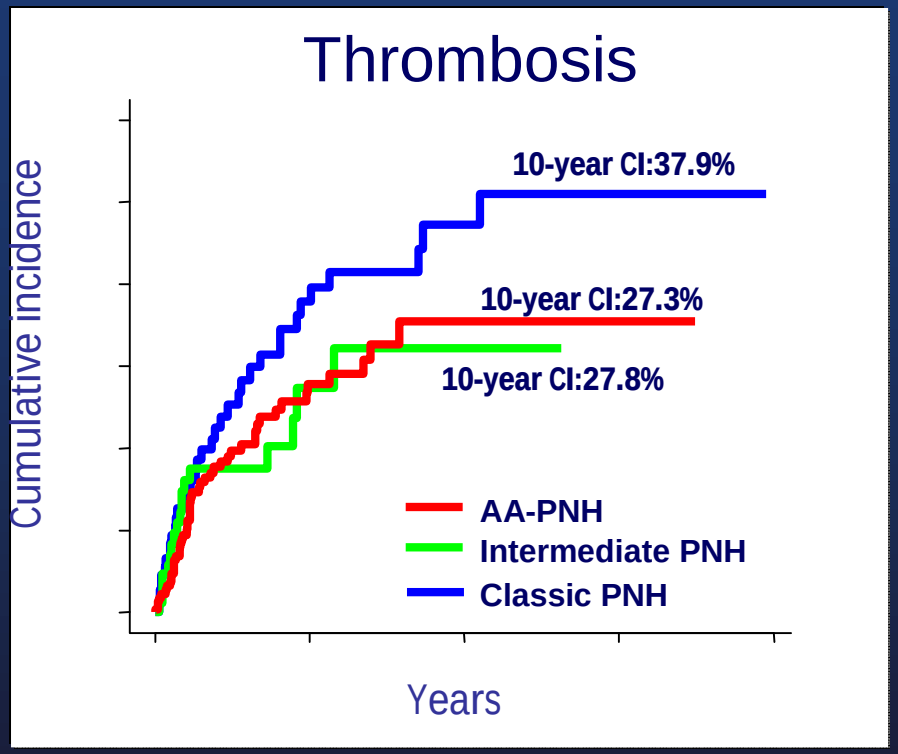
Trombosis in PNH



Socié *et al*, Lancet 1996; Peffault de Latour *et al*, Blood 2008

Trombosis in PNH

Thrombosis Risk Factors	RR	*p*
Age >55	1.8	.01
Thrombosis (DG)	3.7	<.001
Warfarin (prophylaxis)	5.2	<.001
Transfusions	1.7	.01
IST	0.5	.02



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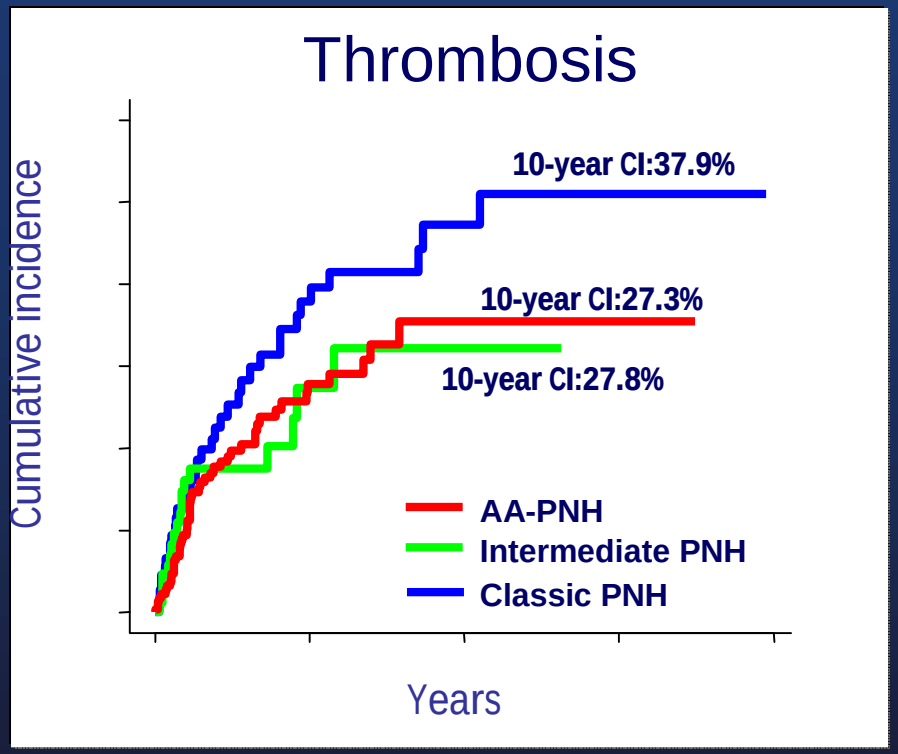

- **Thrombosis**
  - ✓ **CI ~ 30% in AA-PNH (!)**
  - ✓ **No prophylaxis (Eculizumab?)**

Socié *et al*, Lancet 1996; Peffault de Latour *et al*, Blood 2008

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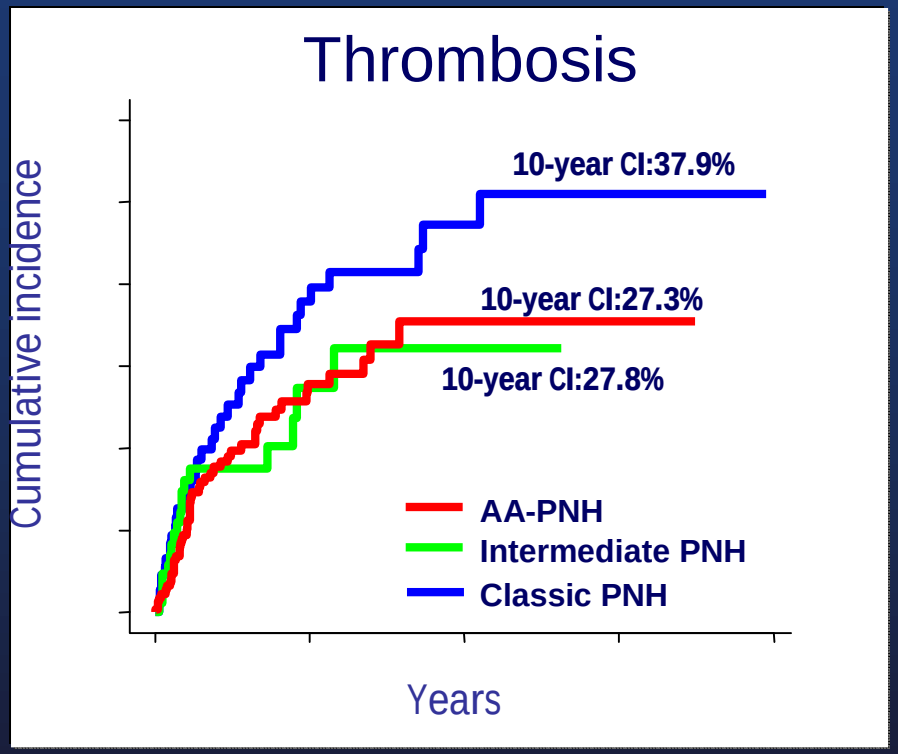


- **Thrombosis**
  - ✓ **CI ~ 30% in AA-PNH (!)**
  - ✓ **No prophylaxis (Eculizumab?)**
  - ✓ **The major life-threatening complication affecting outcome in PNH**

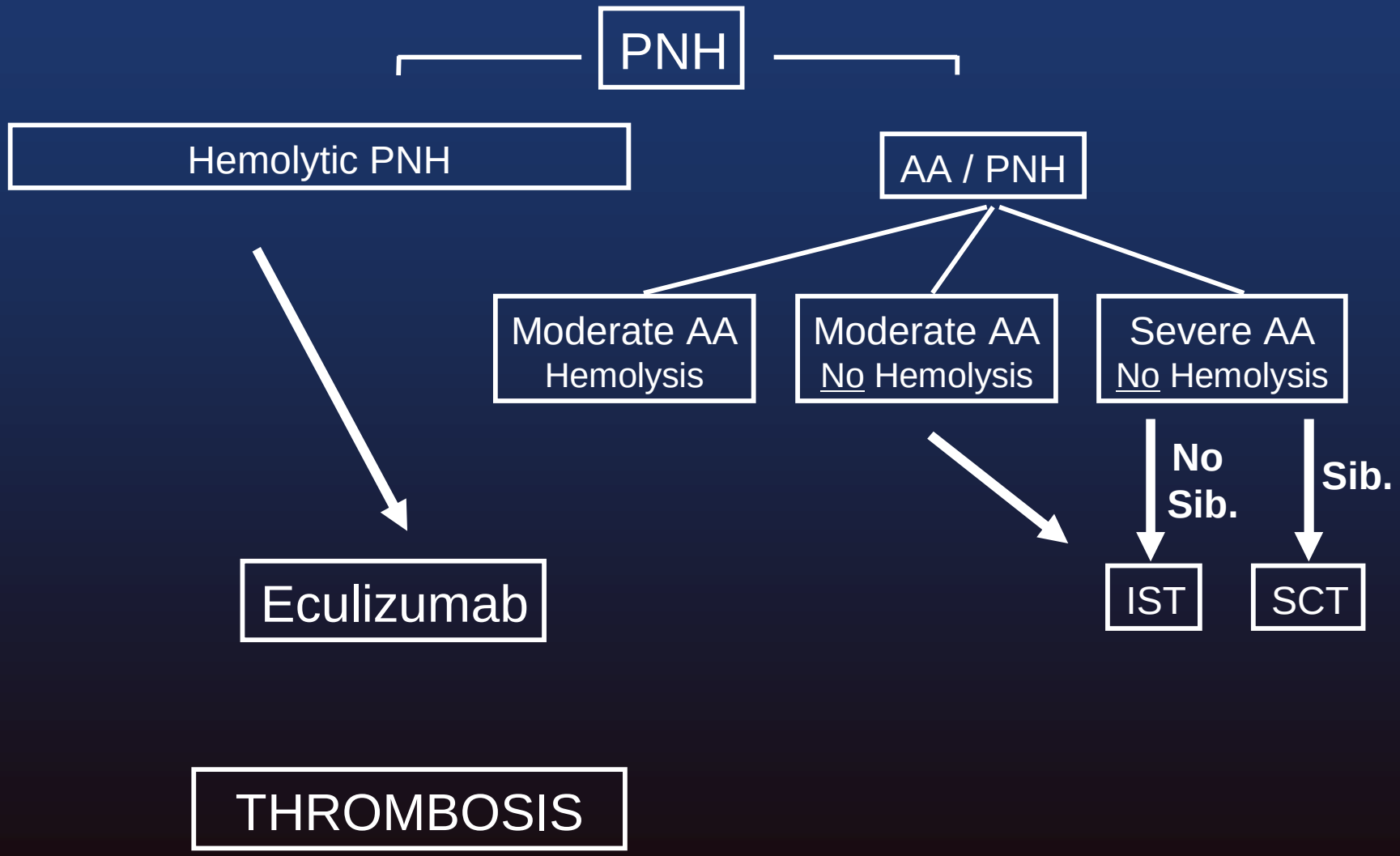
Socié *et al*, Lancet 1996; Peffault de Latour *et al*, Blood 2008

Message 3: clone HPN et AA

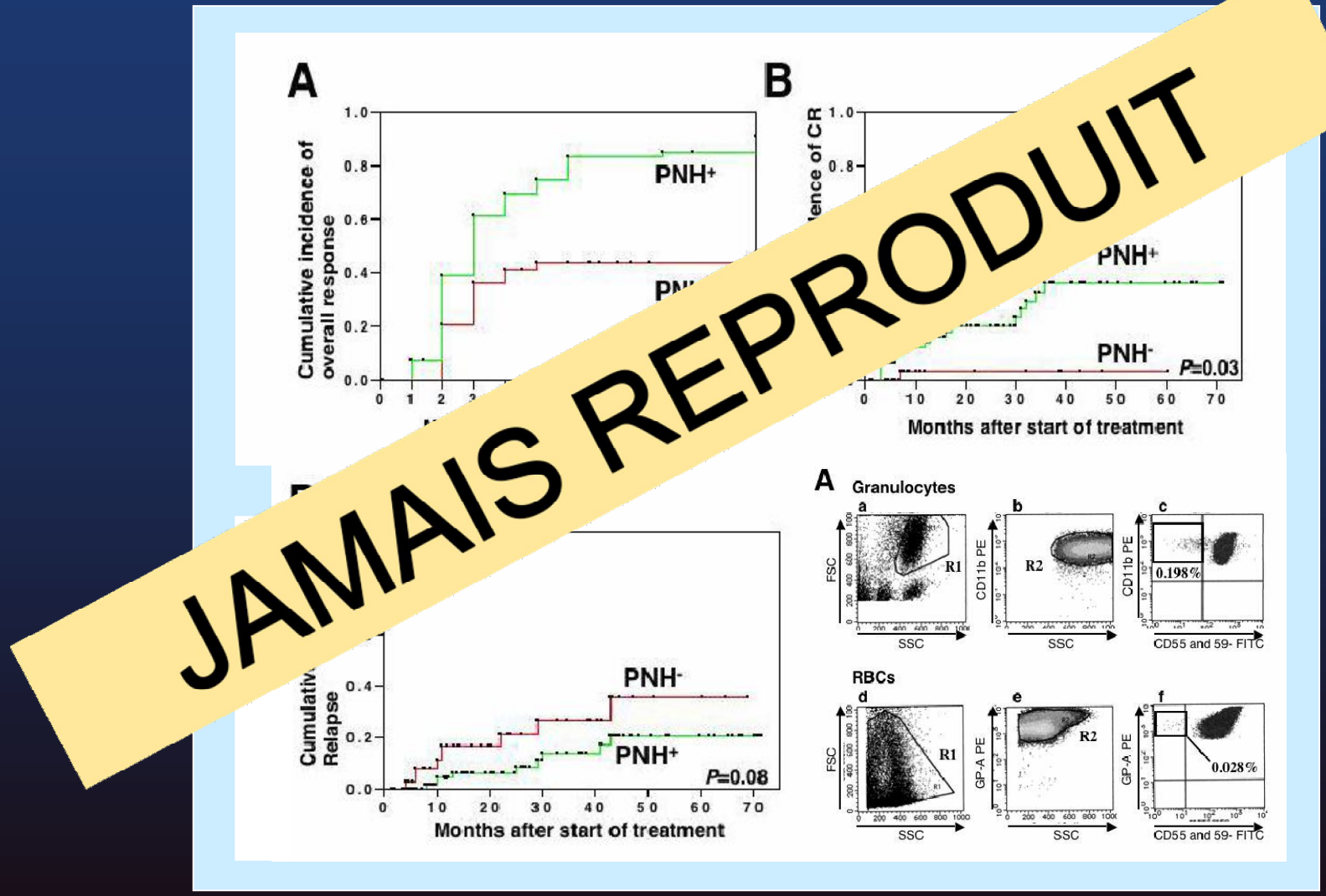
=

attention thrombose

PNH management in 2013



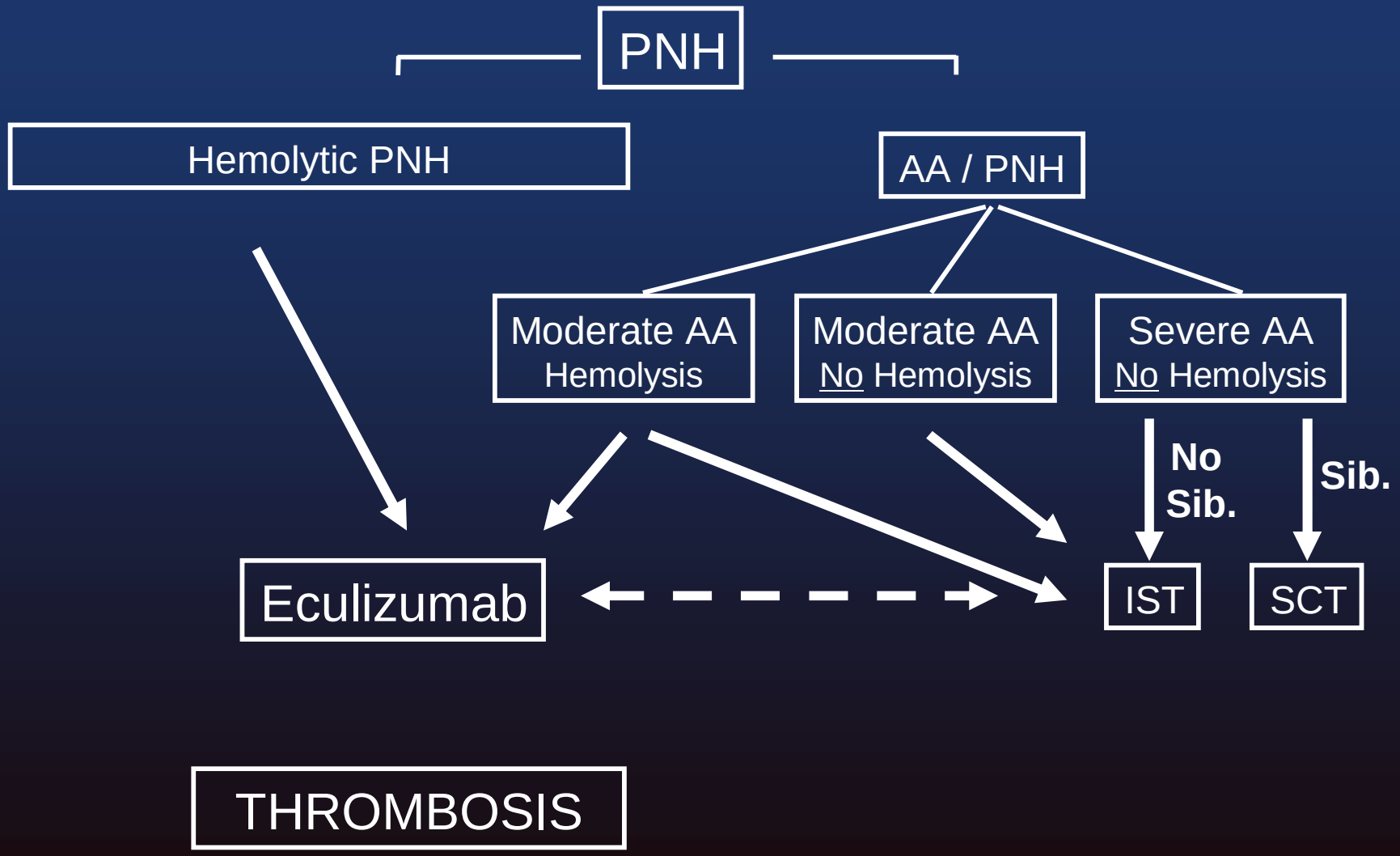
PNH management in 2013



Nakano et al. Minor population of CD55-CD59-blood cells predicts response to immunosuppressive therapy and prognosis in patients with aplastic anemia. Blood 2006; 107 : 1308-1314

Message 4: AA avec ou sans HPN = même traitement si pas d'hémolyse

Take home messages



Message 5: AA/HPN avec hémolyse =

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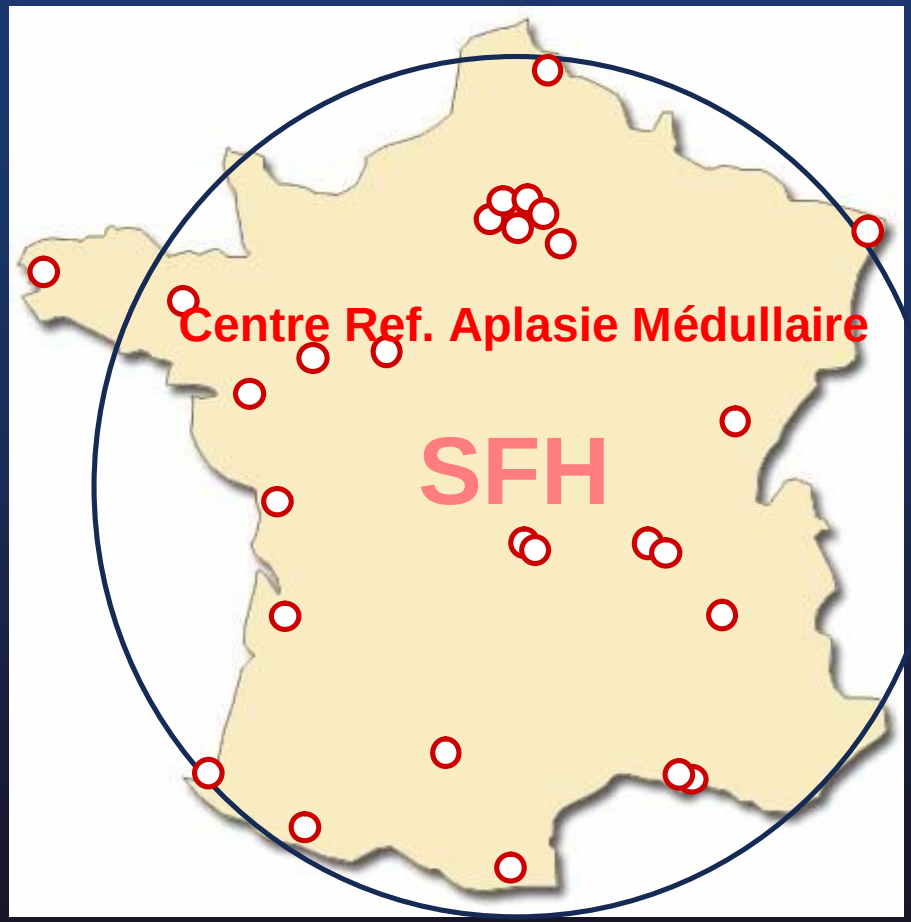
Conclusions

- 1: En faveur d'une AA acquise
- 2: 30-40% des AA et évolution possible vers HPN classique dans 20% des cas
- 3: Risque de thrombose
- 4: AA avec ou sans HPN = même traitement si pas d'hémolyse

Merci!



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Participating centers

EBMT
European Group for Blood and Marrow Transplantation

Société Française de Greffe de Moelle et de thérapie cellulaire