Paroxysmal Nocturnal Hemoglobinuria in 2013

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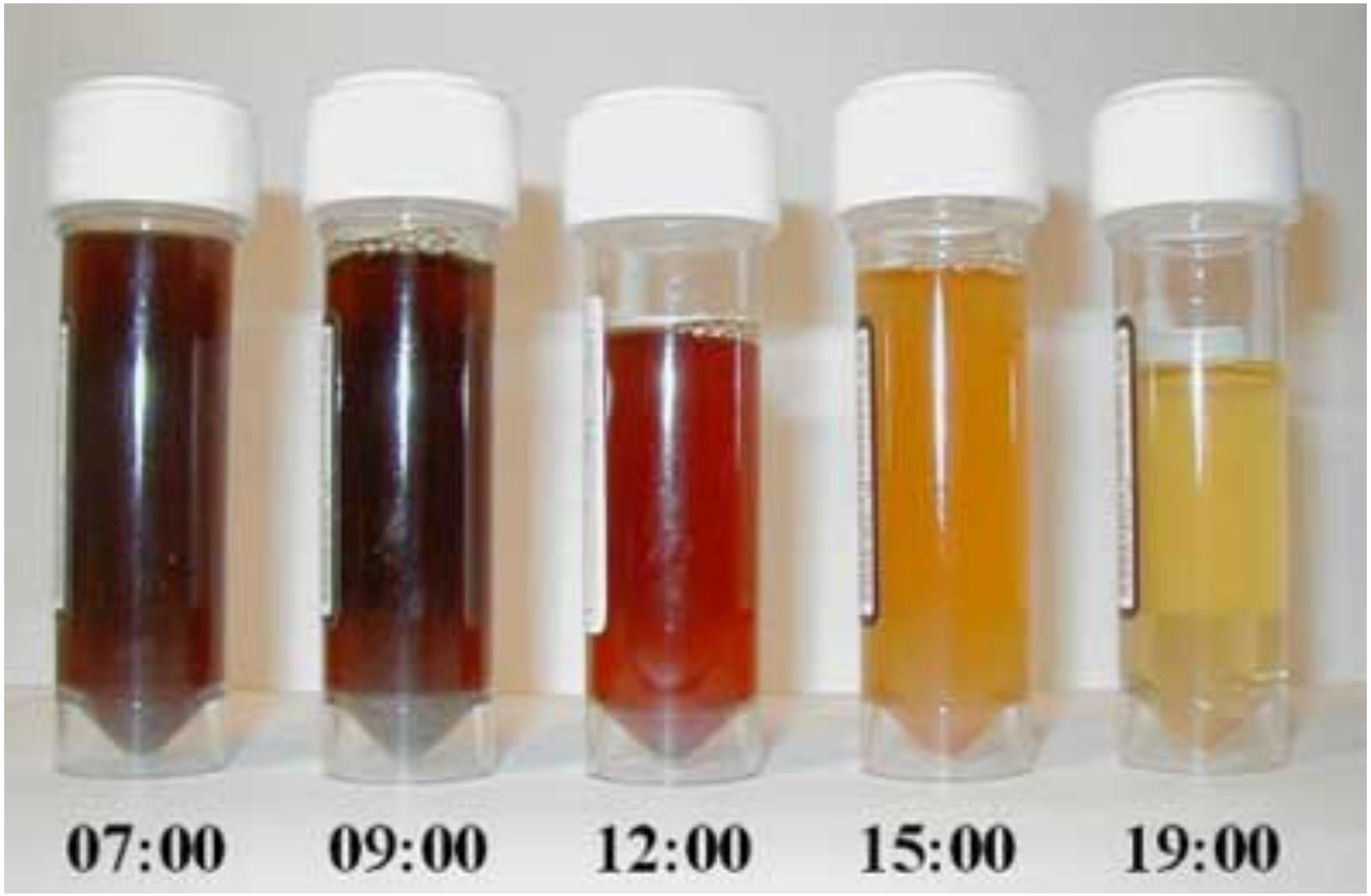
PNH

- Introduction
- History
- Clinical Manifestations
- Pathogenesis
- Diagnosis
- Treatment
- PNH network and PNH registry
- Conclusions



Toronto General Hospital Morning Report

Hall mark features of PNH

- Nocturnal hemoglobinuria related to intermittant hemolytic anemia
- Bone marrow failure resulting in pancytopenia
- Thrombophilia resulting in increased risk for thrombosis

Paul Struebing. Paroxysmale Haemoglobinurie. Deutsche Medizinische Wochenschrift 1882:8:1

- 1st patient reported
- 29 year old cart maker with dark urine after sleep.
- Patients plasma was red and urine contained a yellowish brown pigment
- Dr Strubing suggested that red cells destroyed within the blood stream.

History

1882	Description of first PNH case (P.Strubing)
1939	Complement mediated lysis and development of Hams test (T.Ham)
1966	Description sugar lysis test (R Hartmann)
1969	Characterisation of Decay Accelerating Factor (DAF) (E. Hoffman)
1973	First allogeneic BMT for PNH (R.Storb)
1989	Characterisation of MIRL (CD59) and GPI anchor (C Parker)
2003	Cloning of PIG-A gene (T Kinoshita)
2007	FDA approval of eculizumab

Demographics and Survival

- Median age at presentation: 34 years
- Incidence 1-10 cases per million population
- Overall survival at 10 years 76%, at 20 years approx 50% (de Latour et al Blood 2008) (before eculizumab)
- Often begins with anemia
- Episodic hemolysis at night or hemolysis precipitated by infection, surgery and transfusion

Clinical Manifestations

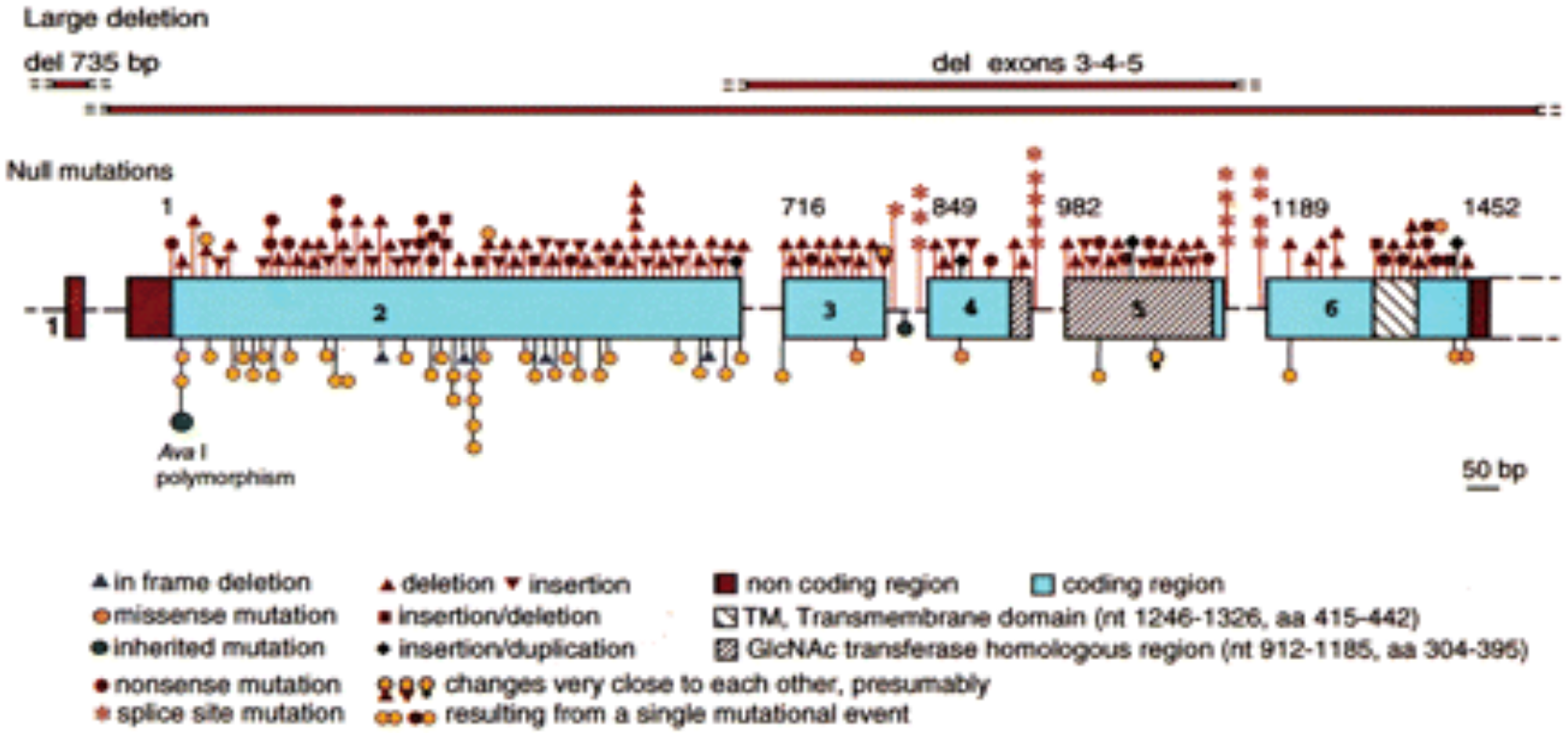
- **Due to intravascular hemolysis:**
  - Anemia, hemoglobinuria, fatigue, renal failure, recurrent urinary tract infection, Abdominal pain, bloating, back pain, headache, Esophagospasms, erectile dysfunction, cholelithiasis
- **Due to thrombosis:**
  - Venous thrombosis: Abdominal vein thrombosis, portal hypertension, esophageal varices, cerebral vein thrombosis, retinal vein thrombosis, deep vein thrombosis, pulmonary emboli
  - *Rare:* Arterial thrombosis
- **Due to bone marrow failure:**
  - Anemia, infections, bleeding, Myelodysplastic syndrome *Rare:* Transformation to acute myeloid leukemia (AML)

Adapted from Bessler M, Hematology 2008

Pathophysiology of PNH

- Acquired hemolytic anemia with venous thrombosis, pancytopenia and risk of transformation to MDS and AML suggests mutation of hemopoietic stem cells
- Glycosyl phosphatidyl inositol (GPI) anchor deficiency on hemopoietic cells
- related to PIG-A gene mutation (phosphatidyl inositol glycan complementation class A)
- PNH cells have cell surface deficiency in all proteins that use the GPI anchor

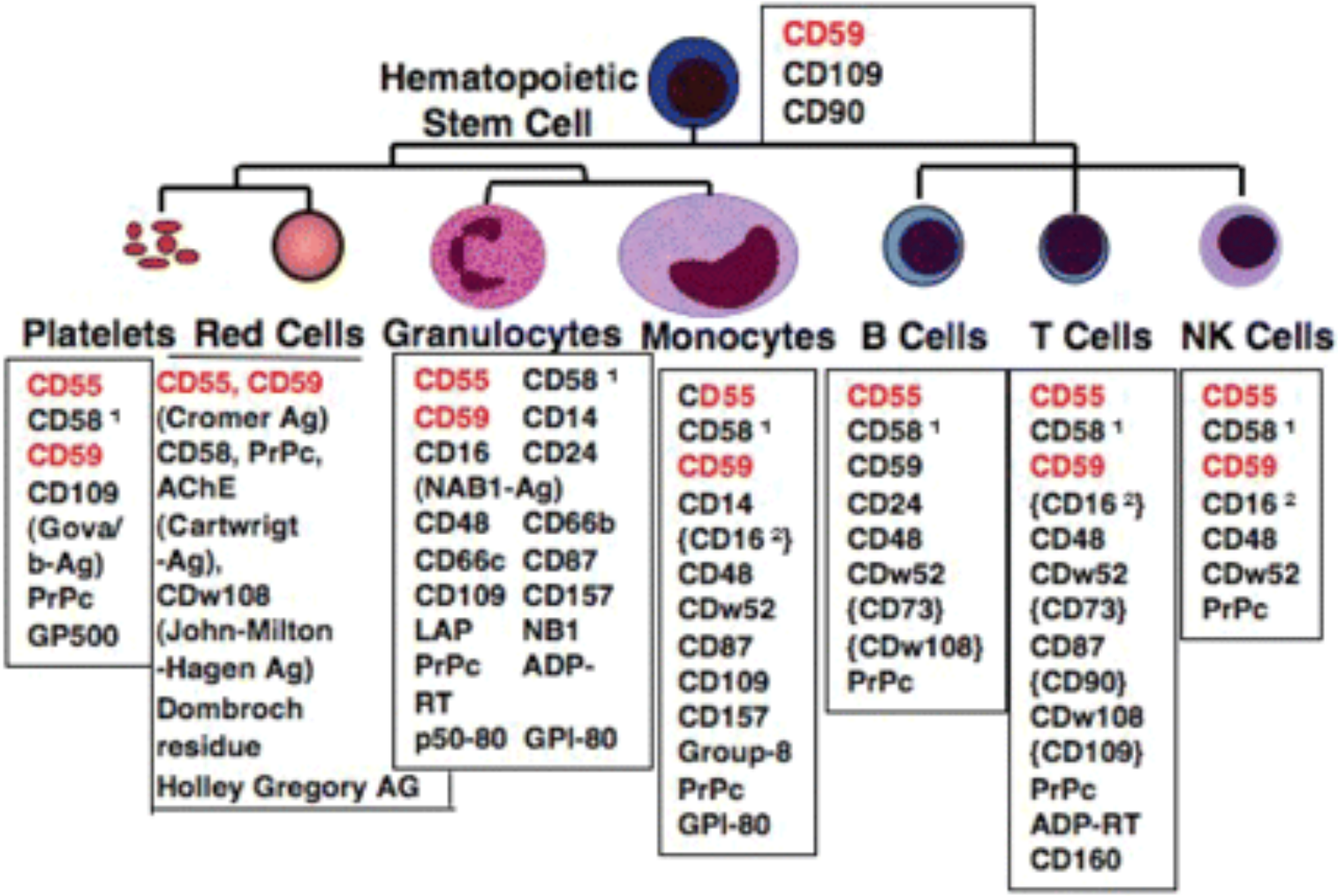
Schematic representation of the structure and mutations in the PIGA gene



Short arm of chromosome X
17kb long
6 exons
Only 1 mutation sufficient to abolish GPI linked protein expression
To date over 180 mutations identified
Majority of mutations lead to loss of glycosyltransferase activity and inactive PIGA protein

Hematology 2008;2008:491-506

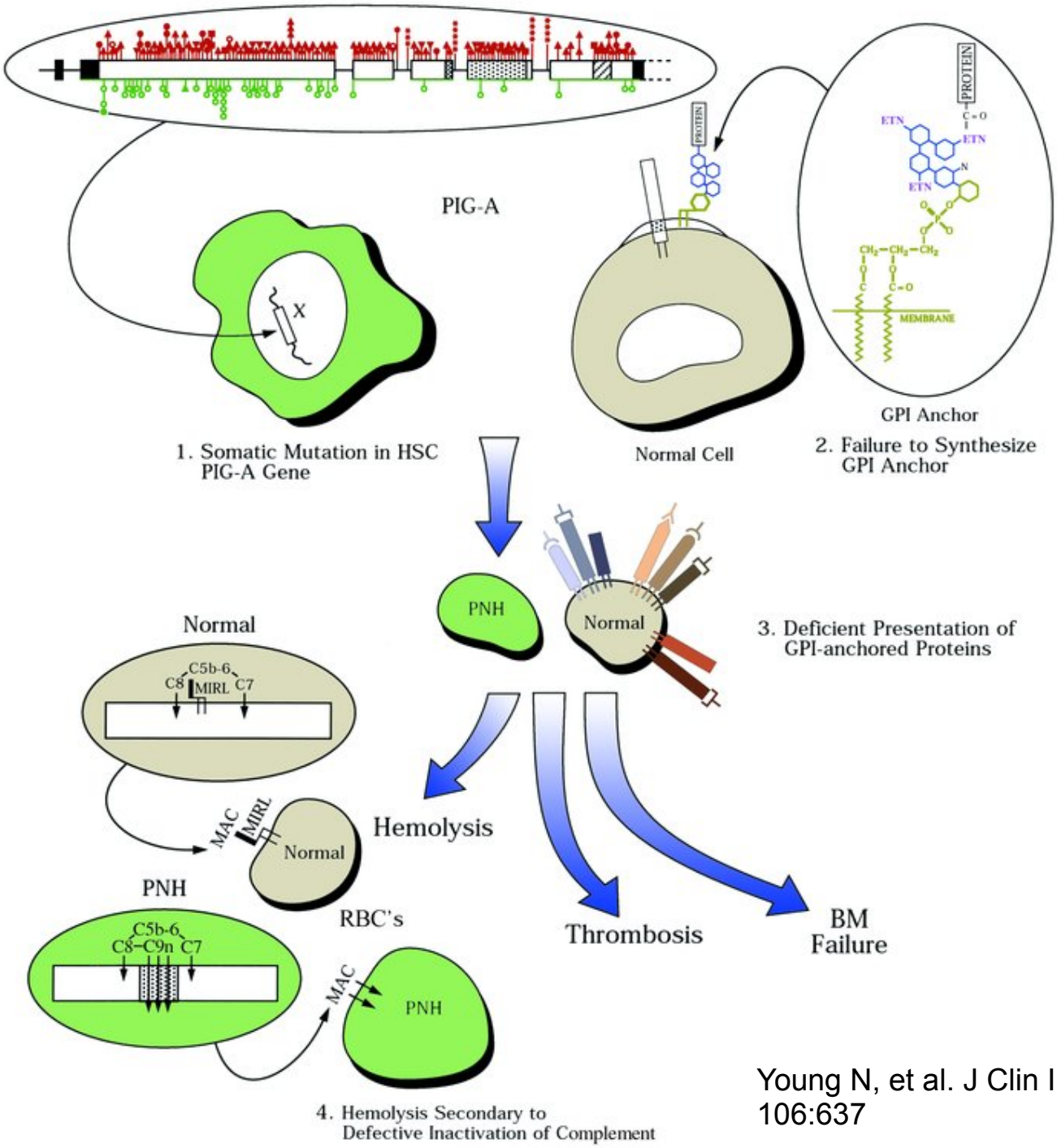
GPI-anchored surface proteins on human hematopoietic cells



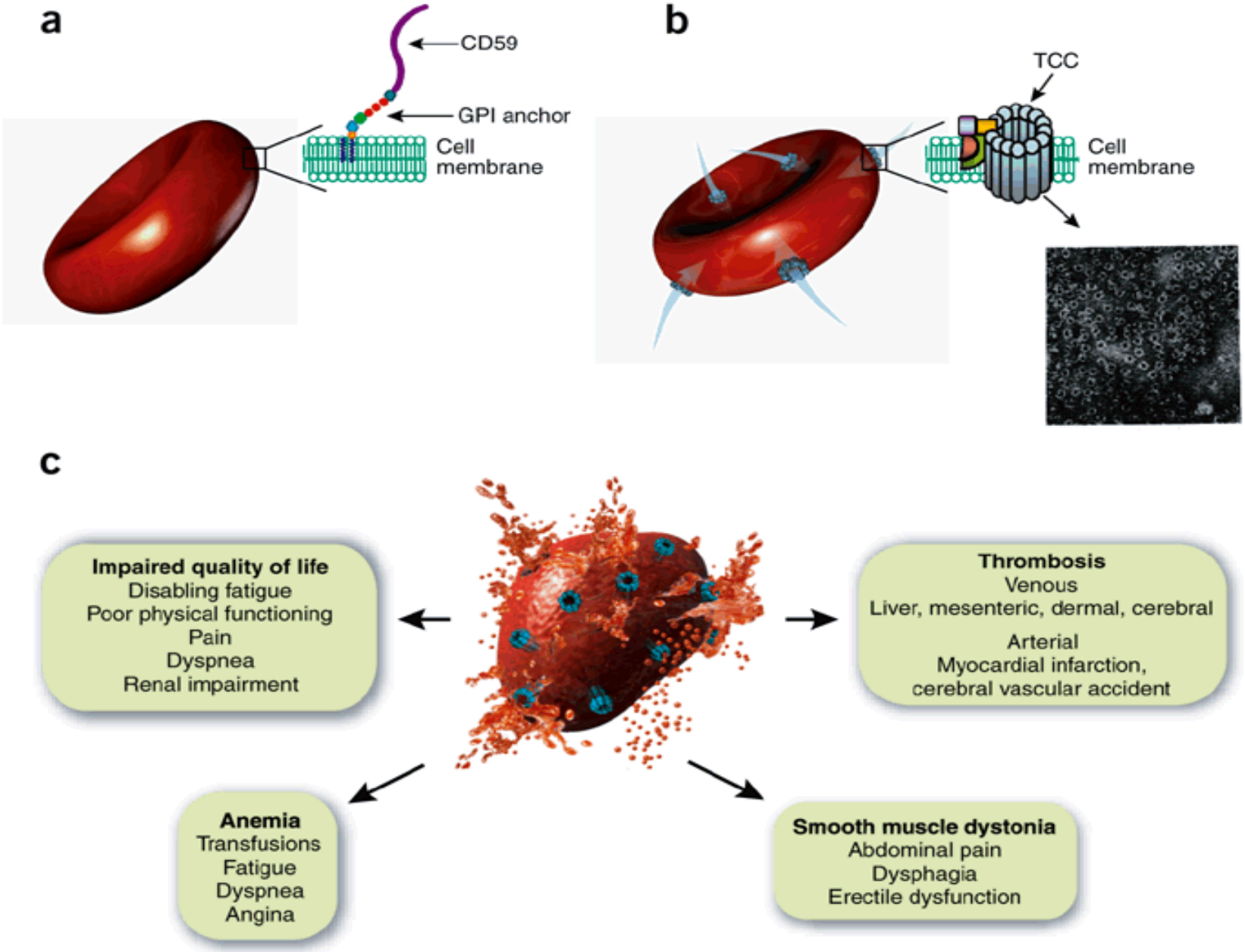
Hematology 2008;2008:491-506

Complement system

- Biochemical cascade which helps antibodies to eliminate pathogens
- Part of the innate immune system (non adaptable)
- proteases cleave specific proteins and initiate a cascade of cleavages
- End result of cascade is amplification of immune response and activation of cell killing membrane attack complex (or terminal complement complex)



Young N, et al. J Clin Invest 2000; 106:637

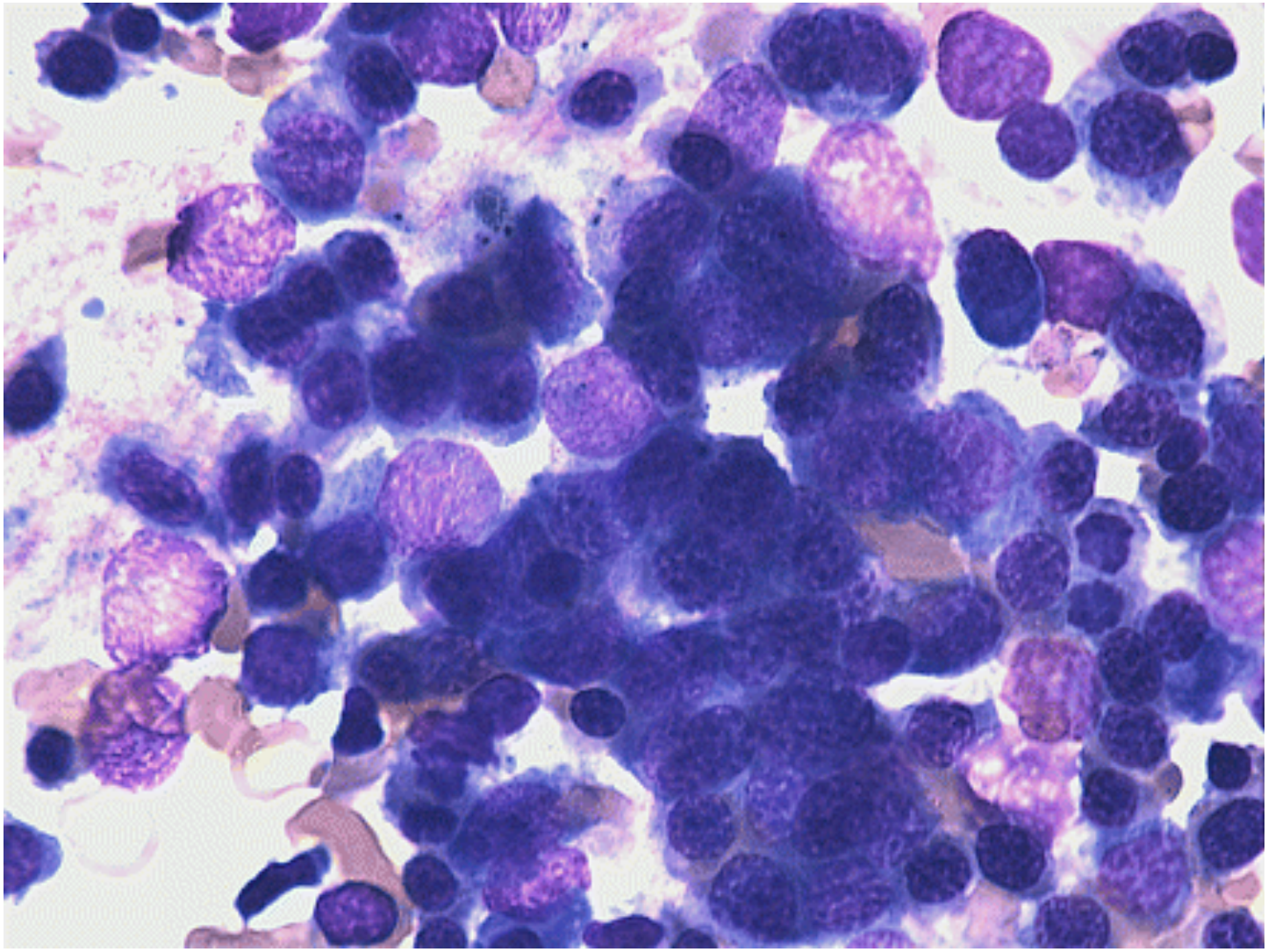


Podack et al. J Cell Biochem 1986;30:133-170

To summarize

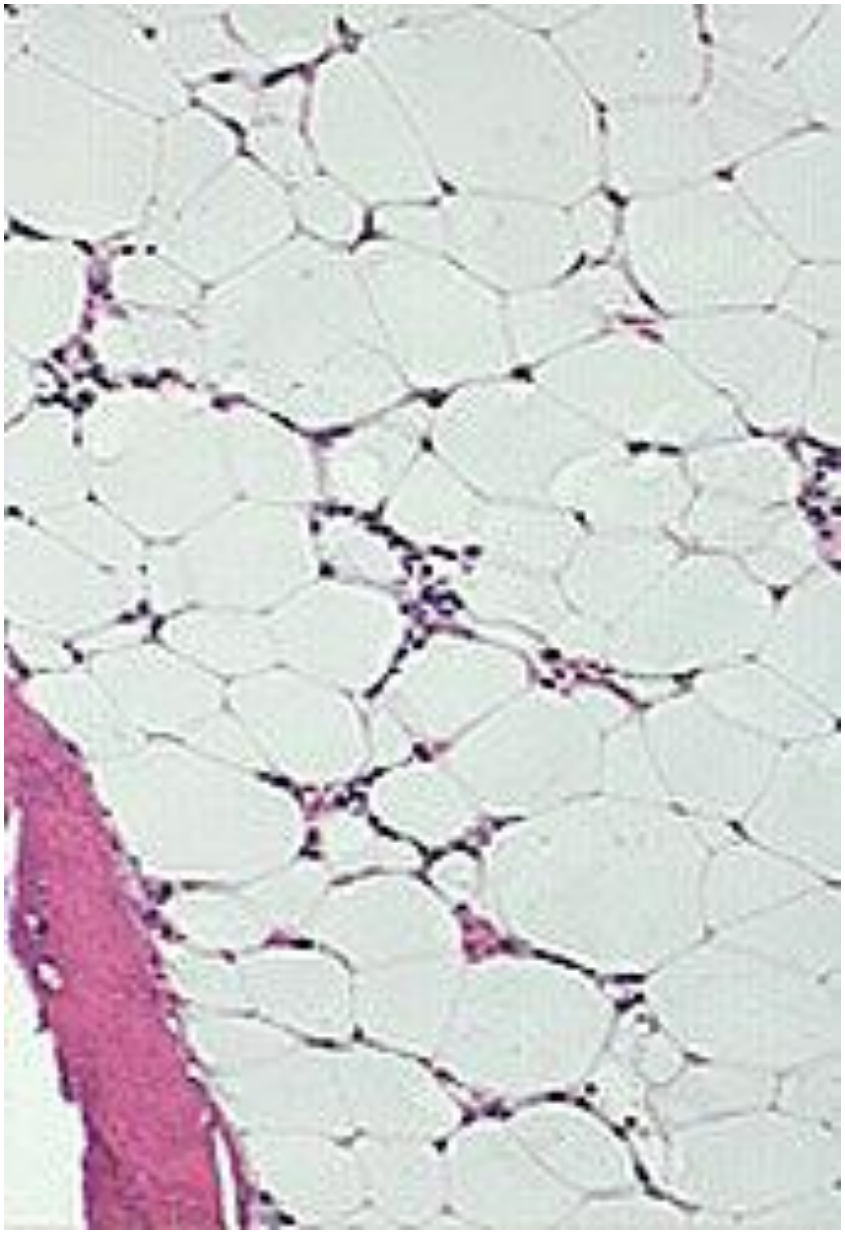
- PNH phenotype is caused by PIG-A gene mutation
- This leads to a lack of GPI anchor bound proteins on cell surface
- This leads to increased susceptiblity of red cells to complement mediated hemolysis (lack of MIRL and DAF)
- This leads to in vivo activation of clotting by increased platelet aggregation (? Related to nitric oxyde depletion), thrombin generation and expression of tissue factor by endothelial cells
- This leads to pancytopenia presumably due to deficient production of hemopoietic stem cells
- Hall mark of PNH are hemolysis, pancytopenia and thrombosis

Diagnosis of PNH



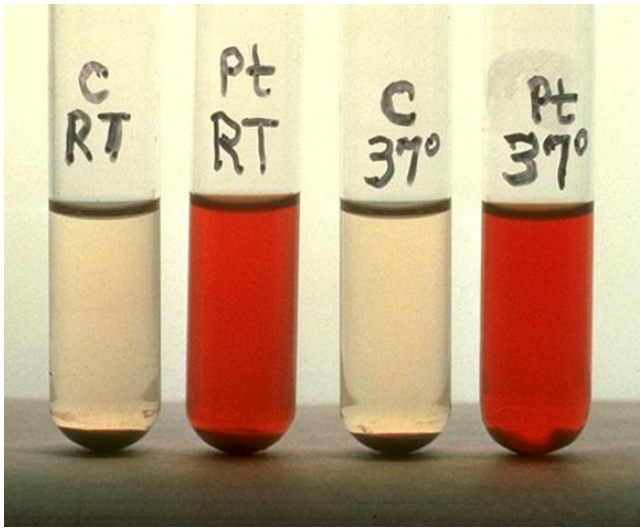
Maslak, P. ASH Image Bank 2009;2009:8-00165

Bone Marrow biopsy from PNH patient



Laboratory tests for diagnosis (traditionally)

- Ham Test: complement activation by acidification of serum leads to lysis of patients red cells

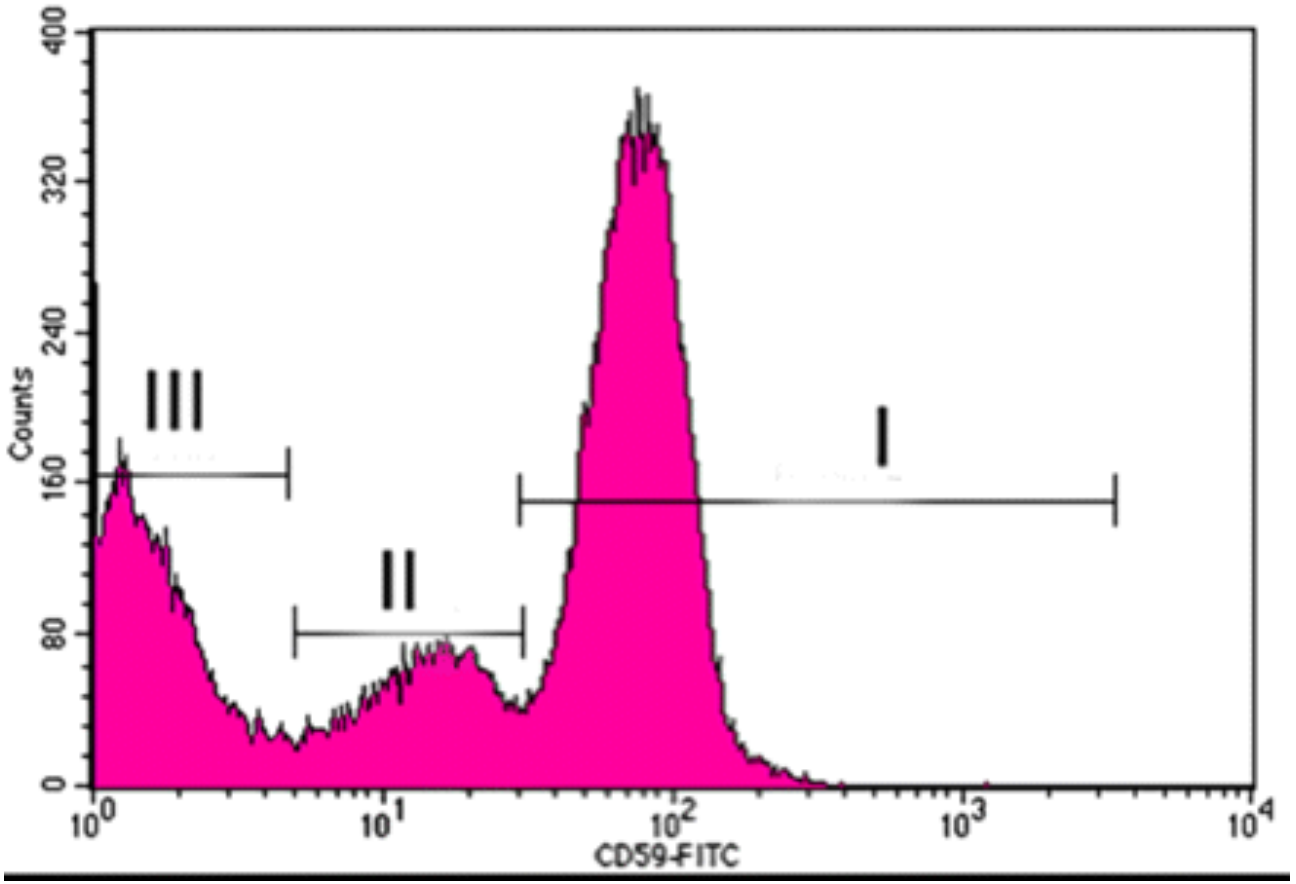


- Sucrose lysis test: complement activation by isotonic sucrose solution

Laboratory tests (today)

- Flow cytometric analysis
  - CD59 and CD55 on red cells
  - CD59 and CD55 on granulocytes
  - FLAER (fluorescently labeled aerolysin)
- PIG-A gene mutation analysis

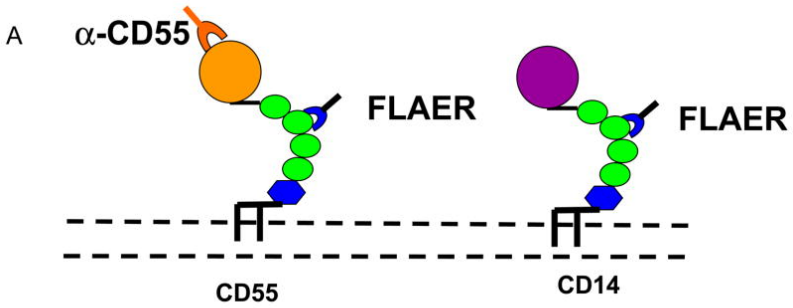
Flow cytometric demonstration of the absence of CD59 on erythroid cells

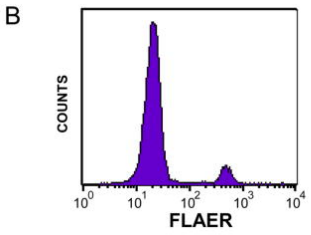


Maslak, P. ASH Image Bank 2009;2009:8-00165

FLAER (fluorescently labeled aerolysin)

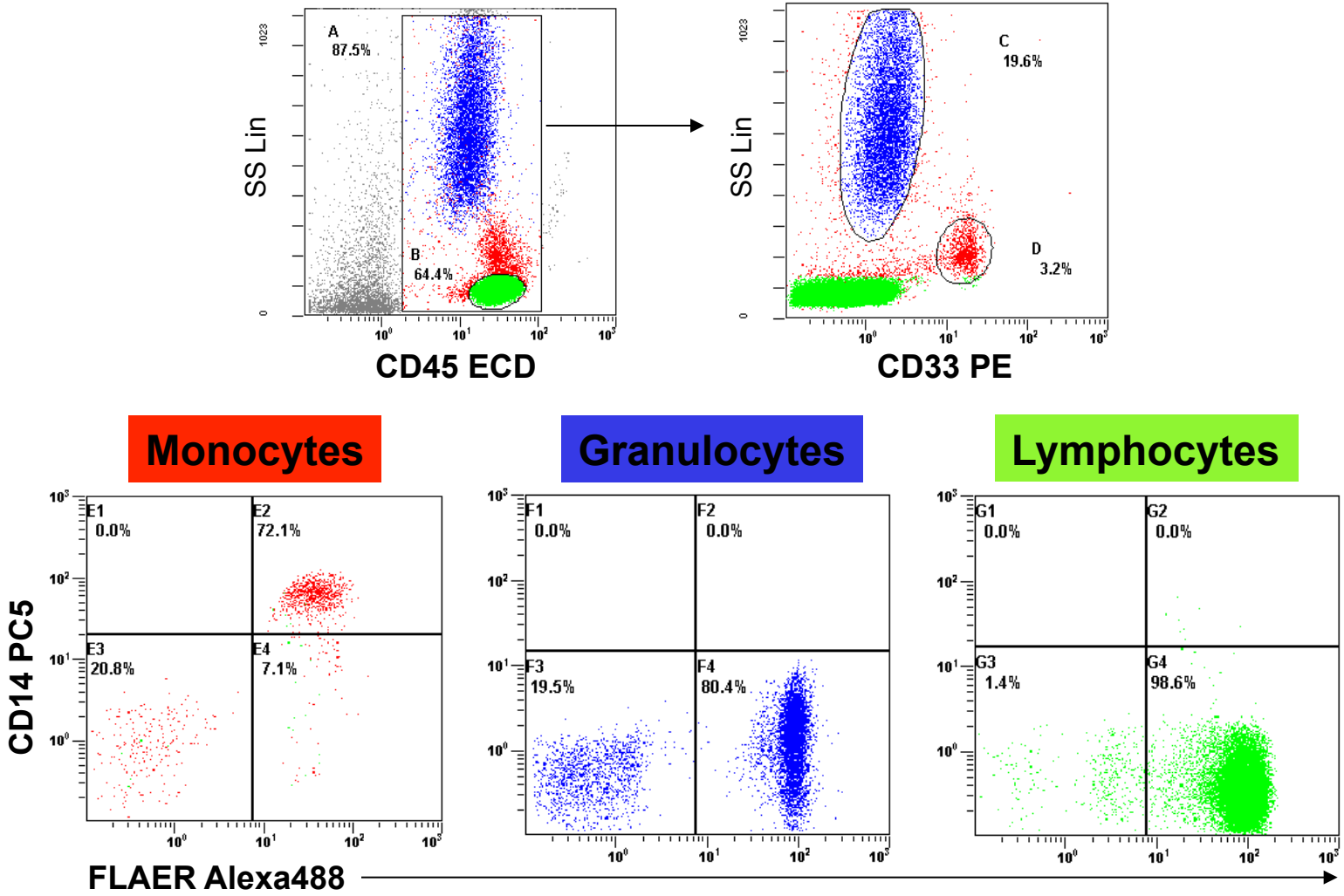
- Bacterial toxin (Aerolysin) binds to GPI linked cell surface structures
- secreted by Aeromonas hydrophilia
- Fluorochrome labeled form of aerolysin (=FLAER)
- Highly sensitive to detect GPI anchor deficient granulocytes (0.5%)





Test 2

Quantification des GPI-AP par la fixation de FLAER (Toxine bactérienne inactivée) sur les leucocytes seulement



Sensibilté: Avec ce test on parle de déficience en GPI-AP à partir de 0.5% de cellules négatives pour le FLAER et on rapporte dans ce cas la présence d'un clone PNH dans les leucocytes.
Pour le patient ci-dessus il y a présence d'un clone PNH de 20% de déficience sur les monocytes et les granulocytes (On ne tient pas compte des lymphos pour l'analyse)

R. Terra HMR 2010

Treatment of PNH

- Observation (ie PNH clone <10%)
- Supportive care (transfusions, folic acid, iron)
- Glucocorticoids or androgens
- Anticoagulation and antibiotics
- ATG/cyclosporine
- Eculizumab
- Allogeneic bone marrow transplantation

Supportive Care

- Red cell transfusions
- Iron and folic acid supplementation
- Prophylactic anticoagulation
  - Suggested in patients with large PNH clone (granulocytes >50%) and platelet counts > 100 x 10/9/l
  - Suggested in high risk periods ie perioperative, immobilisation

Glucocorticoids

- Non proven
- Meachanism of action unclear, possibly decreasing complement activation
- Variable dosing schedules (prednisone 0.25-1mg/kg daily or every 2nd)
- Appears particularly useful to decrease severity of acute hemolytic crisis
- Androgens (danazol) may decrease anemia

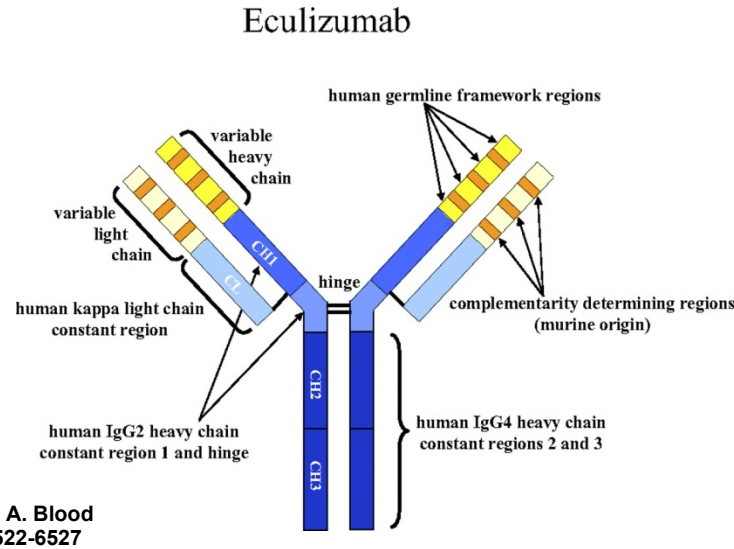
ATG/cyclosporine

- Cytopenias caused by immune mediated suppression of normal cells (GPI positive) producing growth advantage to PNH cells.
- Cyclosporine in small series of patients could improve cytopenias but not hemolytic features of PNH (H van Kamp, et al. Br J Hematol 1995;89:79-82)
- Patients with severe AA and minor populations of CD55-/ CD59- cells appear to respond well to ATG treatment (Sugimori C et al, Blood 2006;15:1308-14, N=83, Response rate 91%)
- Immunosuppressive therapy should be considered in all patients with severe aplastic anemia and PNH features (except if allo transplant considered)
- Immunosuppressive therapy appear to improve cytopenias but not other characteristics of PNH

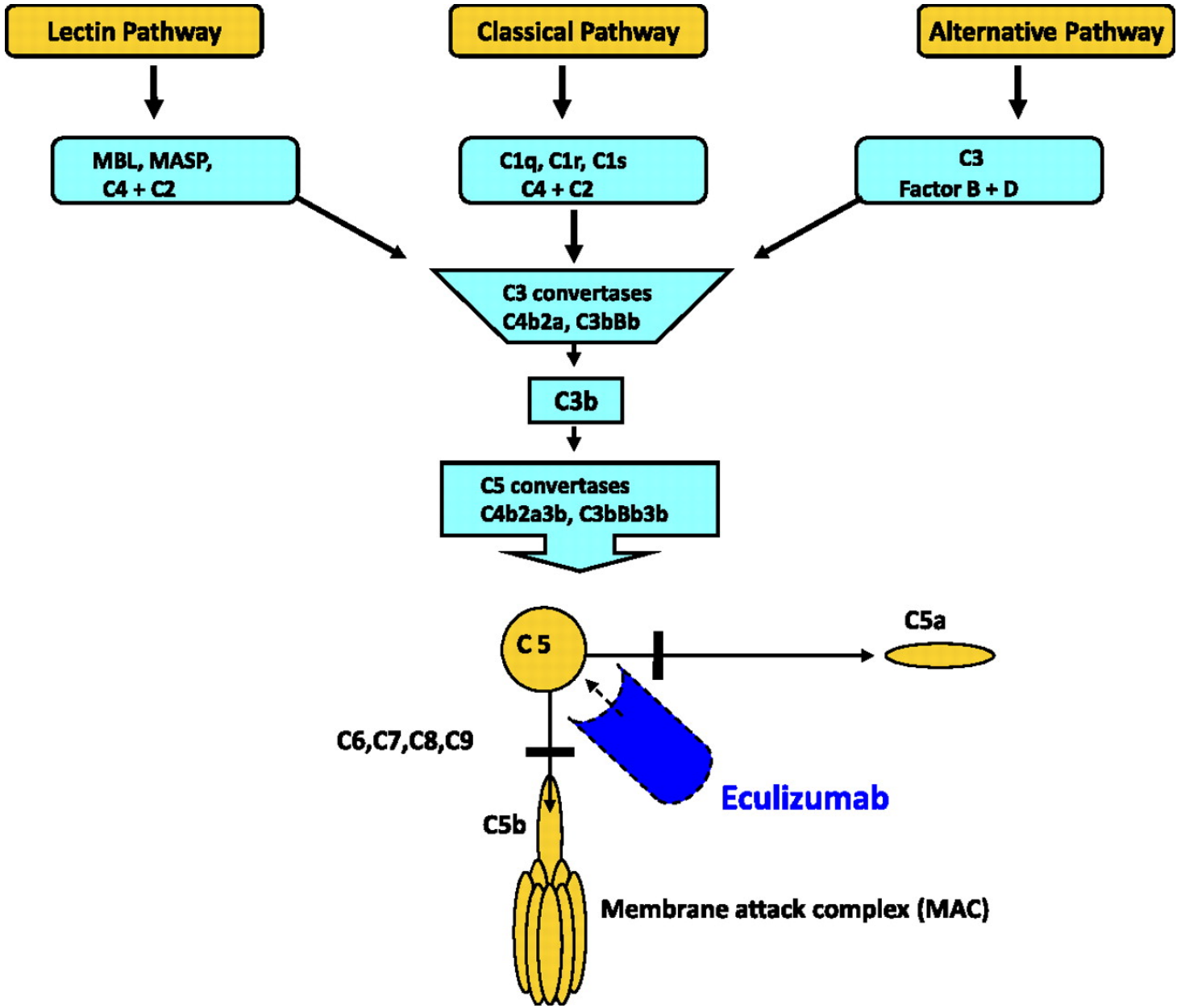
Eculizumab

- Humanized monoclonal IgG kappa antibody
- Binds to human C5 complement protein
- Prevents cleavage to C5a, formation of lytic complement cascade and membrane attack complex (MAC)
- Hybrid of IgG2 and IgG4 (unable to activate complement)
- Remains bound to target

  until removed from circulation



Brodsky, R. A. Blood 2009;113:6522-6527



Brodsky, R. A. Blood 2009;113:6522-6527

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

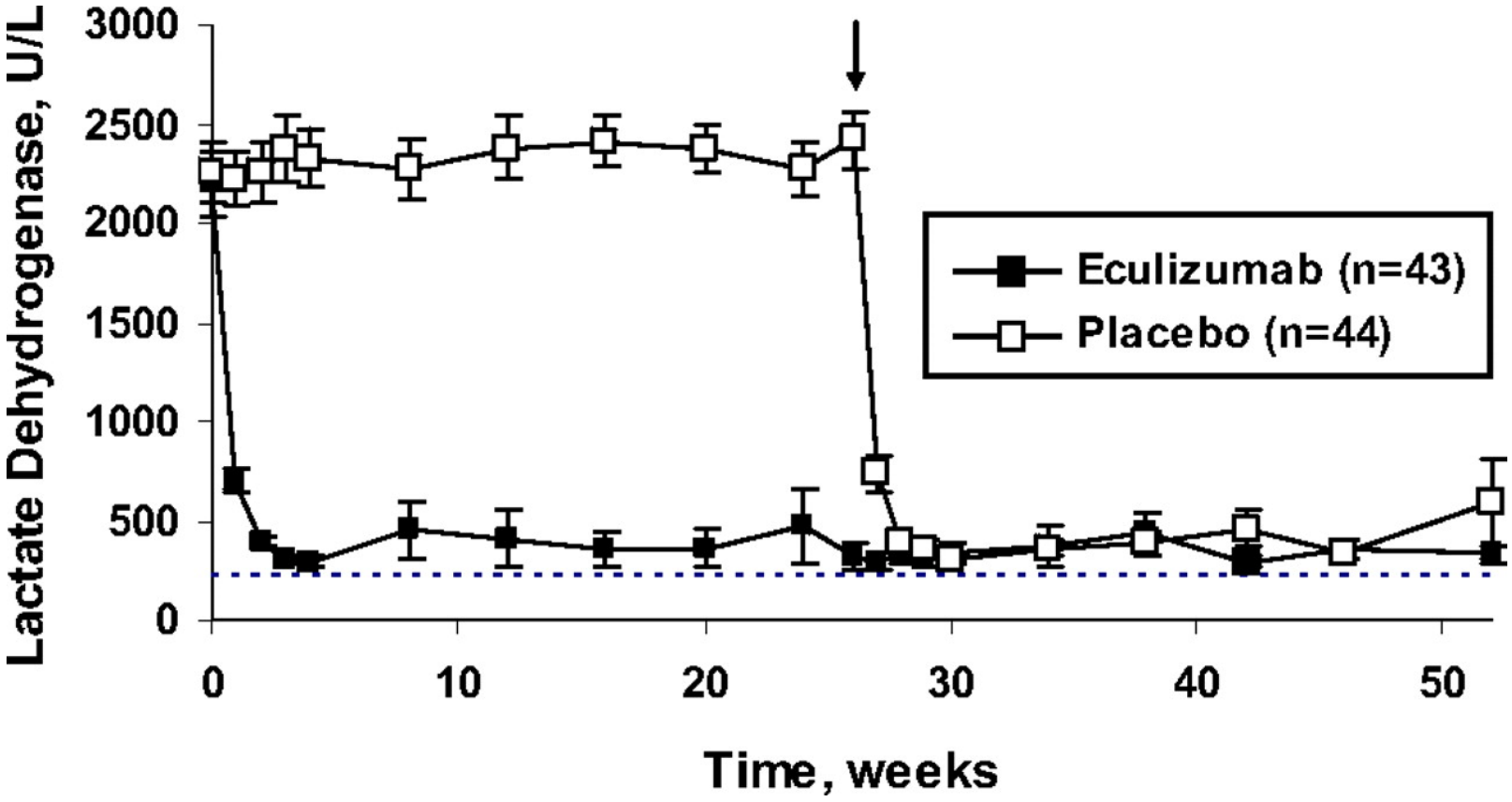
Effect of the complement inhibitor eculizumab on thromboembolism in patients with paroxysmal nocturnal hemoglobinuria

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

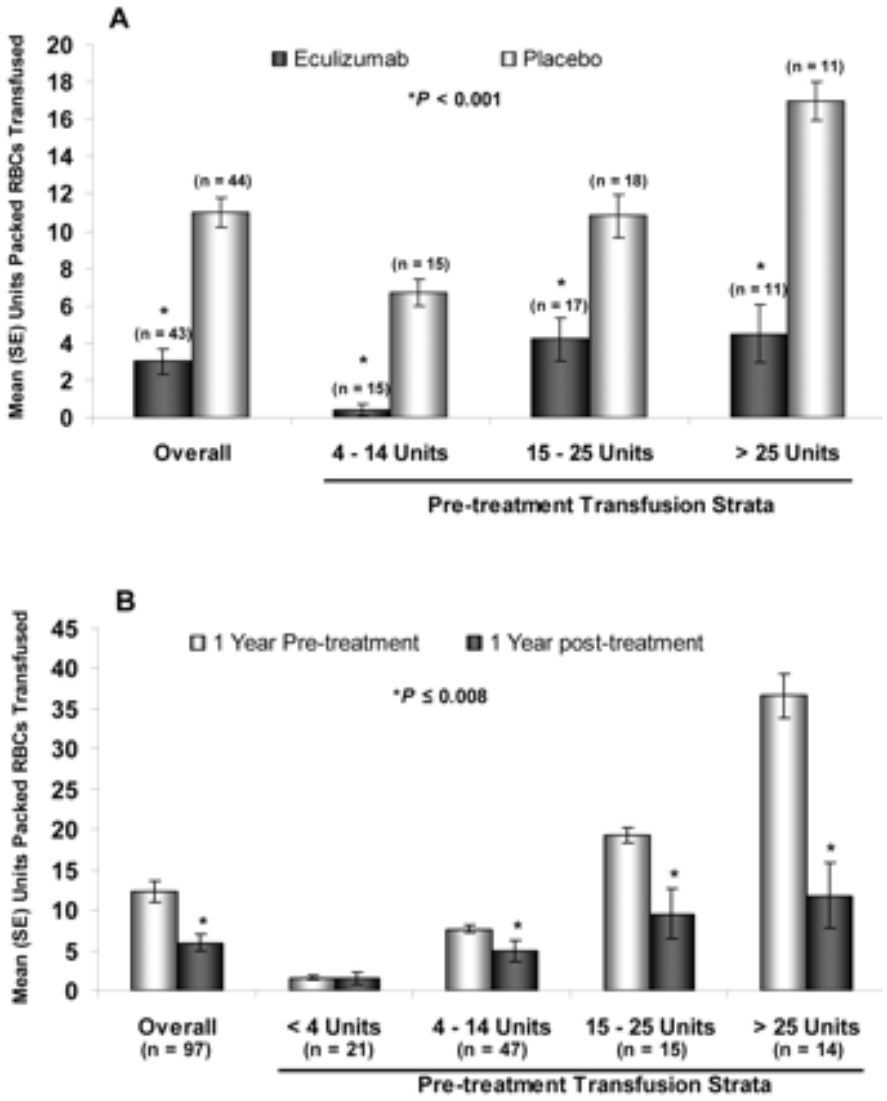
195 Patients With >250 Patient Years of Eculizumab Exposure

Reduction in intravascular hemolysis (LDH) during treatment with eculizumab



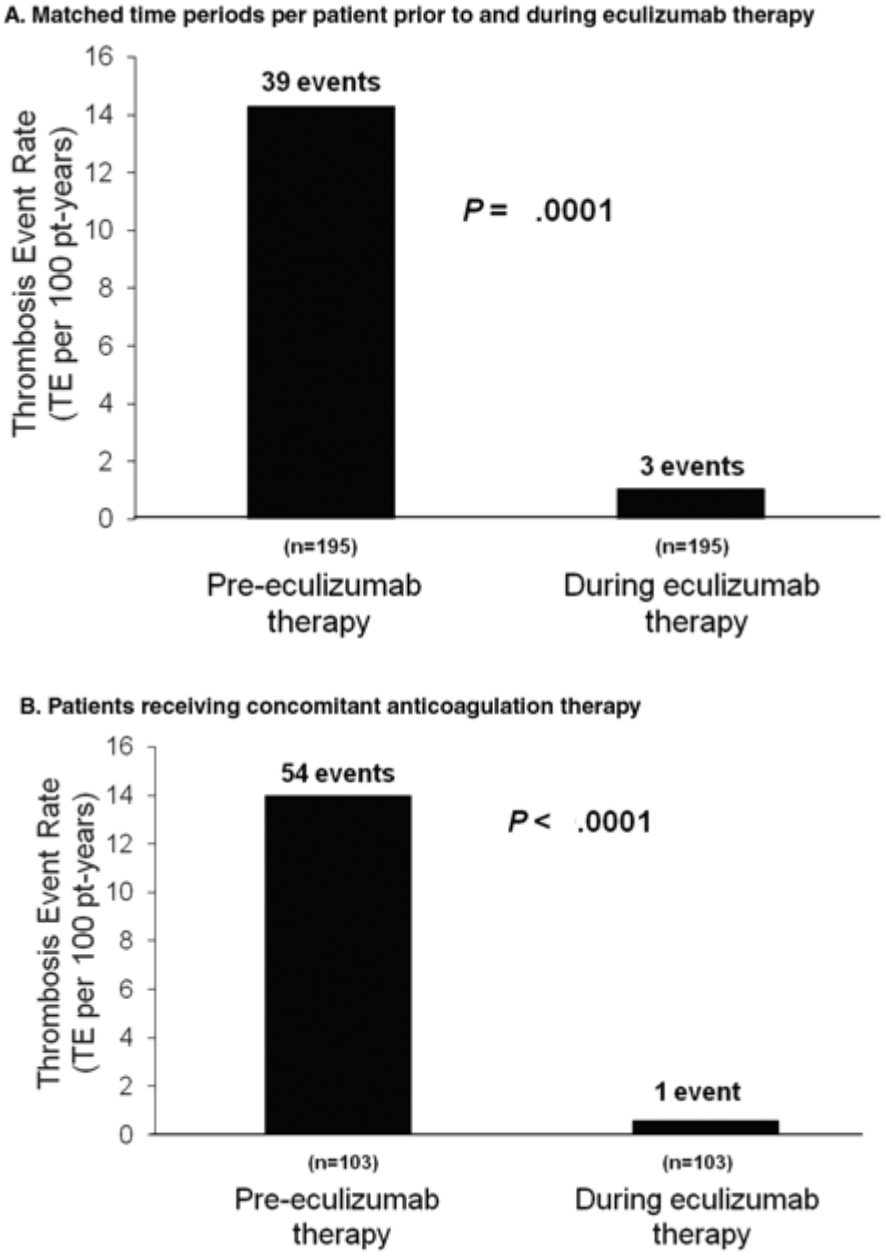
Hillmen P et al. NEJM 2006;355:1233-1243

Mean (SE) units packed red blood cells transfused by pre-treatment transfusion strata during the TRIUMPH and SHEPHERD studies



Hillmen, P. Hematology 2008;2008:116-123

Analysis of thrombosis before and during eculizumab therapy



Hillmen, P. Hematology 2008;2008:116-123

Eculizumab

- Treat patients with
  - Moderate to severe symptoms of PNH
  - Patients who have developed or are at high risk of thrombotic events and/or renal dysfunction
- improvement of quality of life at a cost of twice monthly infusions
- Increased risk of infections with encapsulated bacteria (Neisseria species) therefore vaccination mandatory

CME article

Long-term treatment with eculizumab in paroxysmal nocturnal hemoglobinuria: sustained efficacy and improved survival

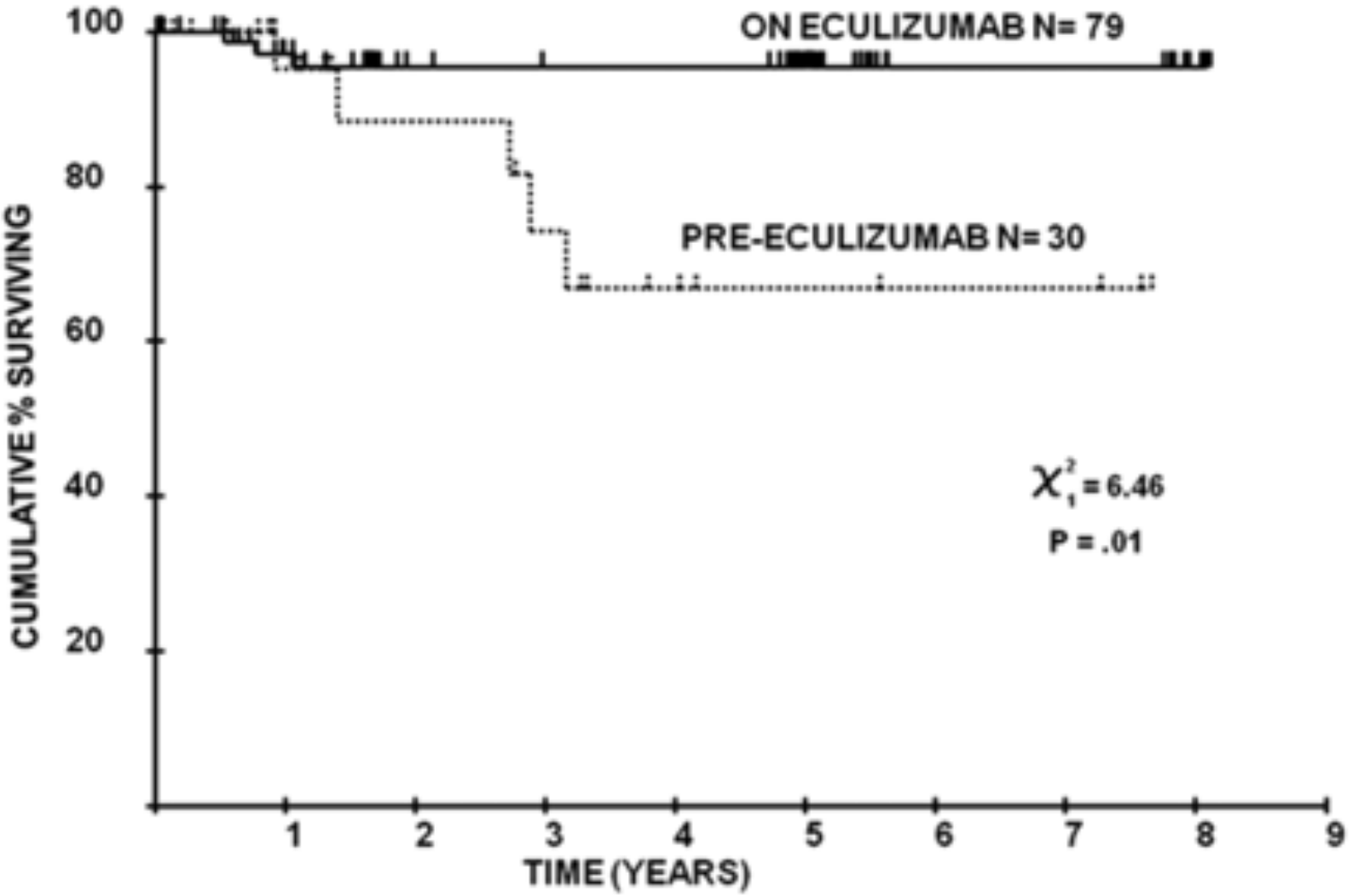
Richard J. Kelly,[1] Anita Hill,[1] Louise M. Arnold,[1] Gemma L. Brooksbank,[1] Stephen J. Richards,[2] Matthew Cullen,[2] Lindsay D. Mitchell,[3] Dena R. Cohen,[4] Walter M. Gregory,[4] and Peter Hillmen[1]

[1]Department of Haematology, Leeds Teaching Hospitals, Leeds, United Kingdom; [2]HMDS Laboratory, Leeds Teaching Hospitals, Leeds, United Kingdom; [3]Department of Haematology, Monklands Hospital, Airdrie, United Kingdom; and [4]Clinical Trials Unit, University of Leeds, Leeds, United Kingdom

- 79 patients treated with eculizumab in Leeds between 2002-2010, mean duration of 39 months
- Assessment every 3 months in Leeds
- Control group for comparison: 30 patients fulfilling criteria for eculizumab treatment, treated in Leeds, 7 years prior to availability of eculizumab
- Comparison of survival data of eculizumab treated patients with age and sex matched control averages obtained from 2001 UK census data

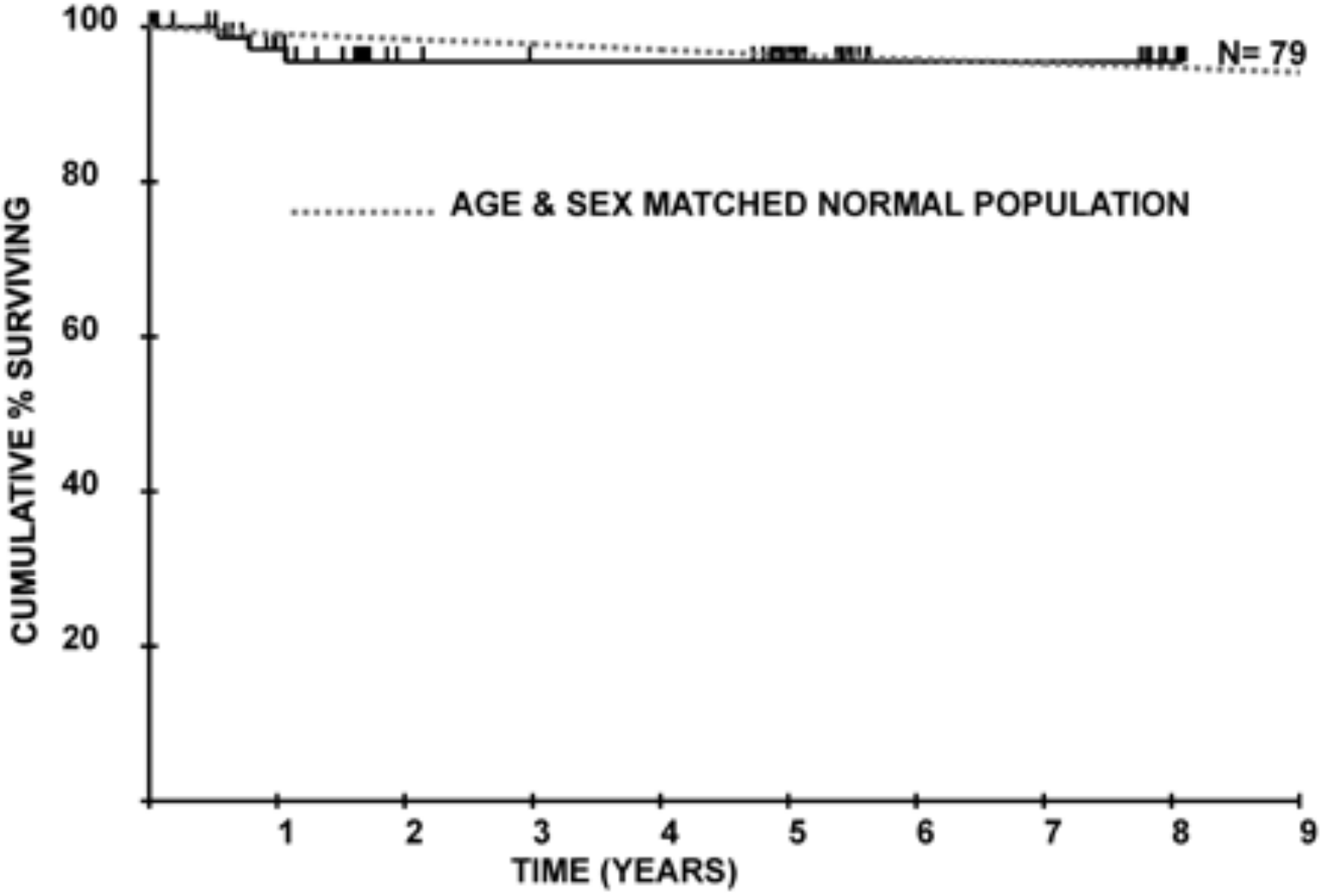
Kelly RJ et al. Blood 2011;117(25):6786

Overall survival of patients before and after eculizumab



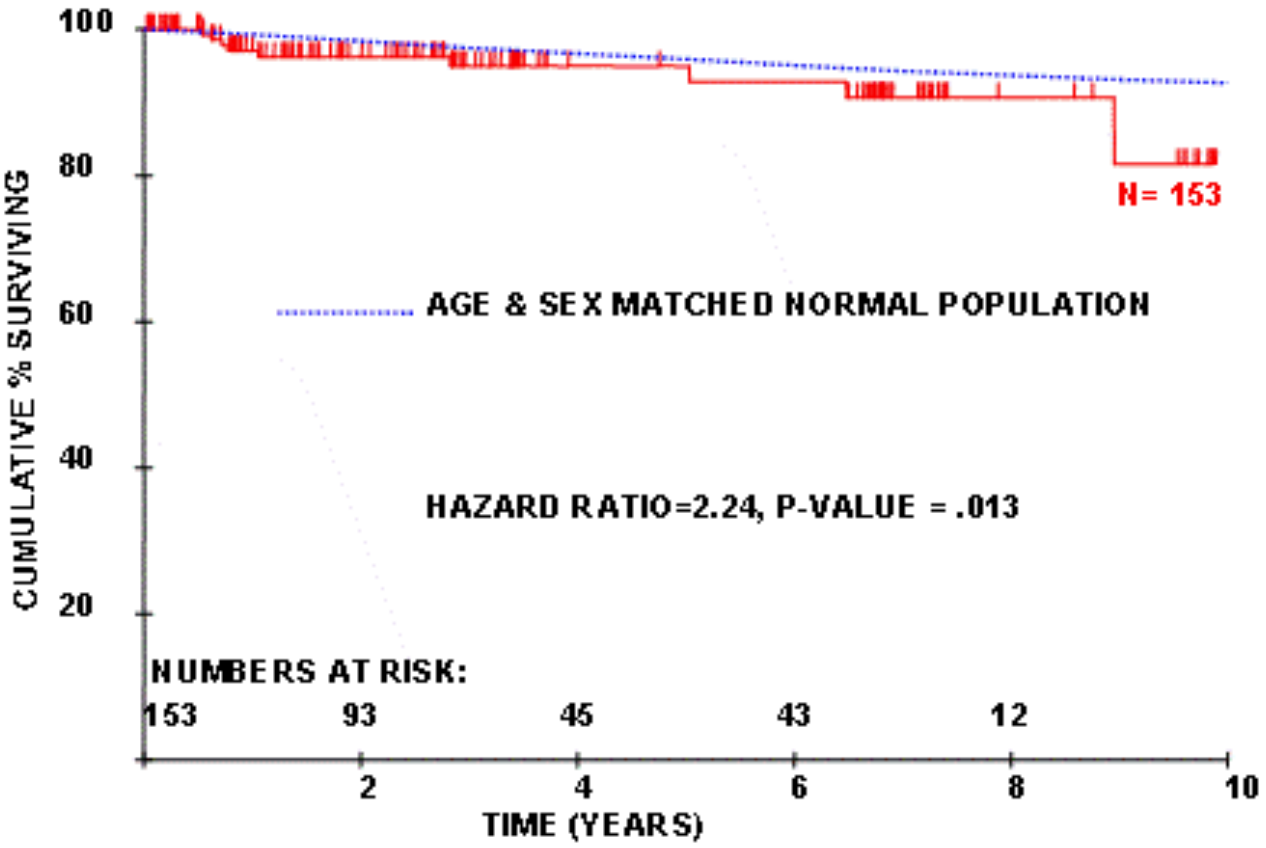
Kelly RJ et al. Blood 2011;117(25):6786

Overall Survival on eculizumab compared with normal population



Kelly RJ et al. Blood 2011;117(25):6786

Figure 1 Kaplan-Meier survival plot for UK PNH patients on eculizumab compared to age and sex matched controls



Survival after 10 years is slightly inferior to controls with causes of death related to bone marrow failure and not hemolysis or thrombosis

Mean duration of eculizumab treatment 42 months

A Hill et al. ASH 2012 Abstract 3472

Conclusions Leeds

- Eculizumab alters dramatically the natural course of PNH
- Overall survival is improved to a similar level than the general population
- Mean duration of eculizumab treatment of 39 months (1-98)

Allogeneic bone marrow transplantation

- Currently only curative treatment option for PNH
- Appealing as clonal diseases can be cured by allogeneic bone marrow transplantation
- Associated with significant morbidity and mortality
- Difficulty lies in patient selection and because of small numbers of published patients in choice of preparative regimen and graft

Paroxysmal Nocturnal Hemoglobinuria and refractory marrow failure treated by marrow transplantation. R. Storb, RS Evans, ED Thomas, CD Bruckner, RA Clift, A Fefer, P Neiman, SE Wright. Br J Hematol 1973;24(6): 743-50

S*ummary*. A patient with pancytopenia and paroxysmal nocturnal haemoglobinuria (PNH) following exposure to insecticide spray developed complete marrow failure after inhalation of vapours containing benzol. There was no sign of spontaneous recovery after more than 6 mth of conventional and supportive therapy. The patient was treated with the immunosuppressive agent cyclophosphamide, 50 mg/kg on each of four days, followed in 36 hr by transplantation of marrow from a sibling compatible at the major human histocompatibility locus (HL-A). Intermittent methotrexate therapy was given for 102 days after grafting to prevent graft-versushost disease. The patient showed prompt haemopoietic engraftment indicated by restoration of marrow cellularity and a rise in peripheral blood cell counts beginning on day 11 after the graft. The patient is alive and well with normal haemopoietic function and continued absence of PNH more than 1 yr and 4 mth after transplantation.

BMT and PNH publications

- Vast majority are case reports with 1-5 patients
- Variable preparative regimens
- Variable graft source (syngeneic, related or unrelated)
- Only few studies with more than 10 patients

British Journal of Haematology, 1999, 104, 392–396

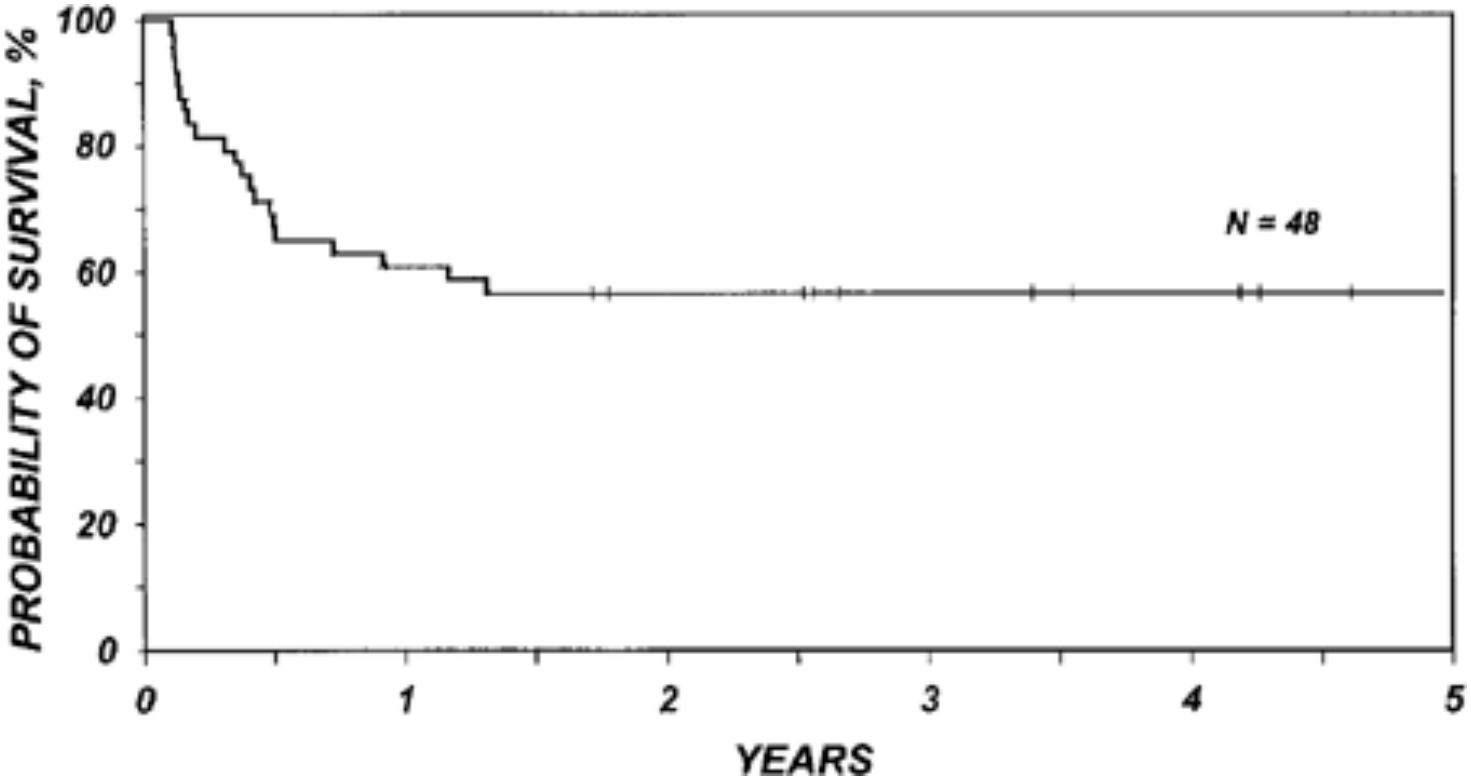
Bone marrow transplants for paroxysmal nocturnal haemoglobinuria

Radovan Sašo,[2] Judith Marsh,[2] Lidija Čevreska,[3] Jeffrey Szer,[4] Robert Peter Gale,[5] Philip A. Rowlings,[1] Jakob R. Passweg,[6] Melodee L. Nugent,[1] Lucio Luzzatto,[7] Mary M. Horowitz[1] and Edward C. Gordon-Smith[2] [1]*International Bone Marrow Transplant Registry, Health Policy Institute, Medical College of Wisconsin, Milwaukee, Wisconsin, U.S.A.,* [2]*Department of Haematology, St George's Hospital Medical School, London, U.K.,* [3]*Department of Haematology, Medical Faculty of Skopje, Skopje, Macedonia,* [4]*Division of Bone Marrow Transplantation, Royal Melbourne Hospital, Australia,* [5]*Division of Bone Marrow and Stem Cell Transplantation, Salick Health Care Inc., Los Angeles, California, U.S.A.,* [6]*Kantonnspital Basel, Basel, Switzerland, and* [7]*Department of Human Genetics, Memorial Sloan-Kettering Cancer Center, New York, N.Y., U.S.A.*

Received 18 May 1998; accepted for publication 12 November 1998

- 57 patients reported to the International Bone Marrow Transplant registry, 48 with HLA identical sibling donors
- Transplanted between 1978-1995
- Median age 28 (10-47)
- Severe aplastic anemia pretransplant in 32%
- Conditioning regimen:
  - Bu-Cy 30 (53%)
  - Cy-TBI +/- other 12 (21%)
  - Limited field radiation – Cy 11 (19%)

Figure 1. Survival after 48 HLA-identical sibling bone marrow transplants for PNH



Saso R et al. Br J Hem 199;104:392-396

Hematopoietic stem cell transplantation for paroxysmal nocturnal hemoglobinuria: long-term results of a retrospective study on behalf of the Gruppo Italiano Trapianto Midollo Osseo (GITMO)

Stella Santarone,[1] Andrea Bacigalupo,[2] Antonio M. Risitano,[3] Elena Tagliaferri,[4] Erminia Di Bartolomeo,[1] Anna Paola Iori,[5] Alessandro Rambaldi,[6] Emanuele Angelucci,[7] Alessandra Spagnoli,[8] Federico Papineschi,[9] Stefania Tamiazzo,[10] Marta Di Nicola,[11] and Paolo Di Bartolomeo[1]

- Retrospective study of 26 patients
- Median age 32 years
- Between 1988-2006
- HLA matched donor for 22, 1 MUD, 3 MM donors
- Classic and AA/PNH phenotypes (AA alone in 4 patients)
- Bu-CY in 15 patients, RICT in 11
- Cumulative TRM 26% for myeloablative and 63% for RICT approach

Santarone S, et al. Haematologica 2010;95(6):983

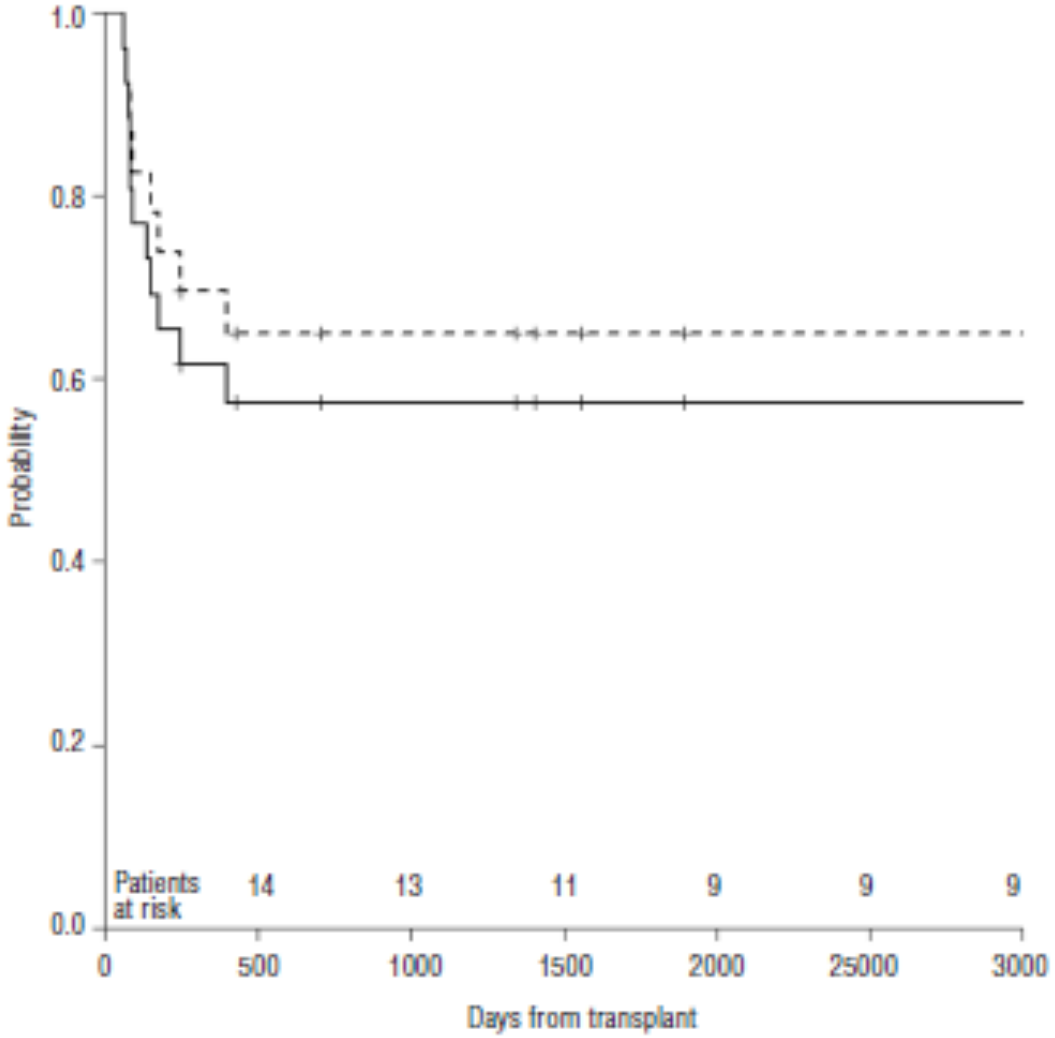


Figure 1. Kaplan-Meier probabilitiy of disease-free survival for 23 patients transplanted from HLA-identical sibling donor (65%, dotted line) and for all 26 patients (57%, continuous line).

Santarone S, et al. Haematologica 2010;95(6):983

Allogeneic stem cell transplantation in paroxysmal nocturnal hemoglobinuria

Régis Peffault de Latour,[1] Hubert Schrezenmeier,[2] Andrea Bacigalupo,[3] Didier Blaise,[4] Carmino A. de Souza,[5] Stephane Vigouroux,[6] Roelf Willemze,[7] Louis Terriou,[8] Andre Tichelli,[9] Mohamad Mohty,[10] Sophie de Guibert,[11] Judith C. Marsh,[12] Jakob Passweg,[13] Jean Yves Mary,[14]* and Gerard Socié[1,15]*

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On behalf of the Severe Aplastic Anemia Working Party (SAA WP) of the European Group for Blood and Marrow Transplantation (EBMT) and the French Society of Hematology (SFH)

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Study Design

- Retrospective multicenter study conducted by SAA working party of EBMT
- Evaluation of outcomes and risk factors affecting survival in 211 patients receiving allogeneic stem cell transplantation
- Reported to the EBMT between 1978-2007 by 83 centers
- Previously reported data on 402 non transplanted patients reported to the SFH and diagnosed between 1950-2005 used as comparison
- Update of previously published abstracts (ASH 2008 and 2011)

Table 1. Characteristics of patients and their transplants (n=211).

Characteristics	n/N (%) or median (IQR[a]), N
Gender, female	106/211 (50%)
Age at transplantation, years	30 (23-39)
PNH natural history before SCT, months	20 (7-59), 192
Clone size at transplantation (<3 months before SCT)	56 (32-90), 56
Classification of PNH at transplantation	
Classical PNH	85/191 (45%)
PNH in the setting of another bone marrow disorder	103/191 (54%)[e]
Indications for SCT[vw]	
Severe aplastic anemia	118/191 (62%)
Recurrent severe hemolytic crises	64/191 (70%)
Thrombosis[§]	47/191 (25%)
Mesenteric veins	17
Budd Chiari	14
Central nervous system	6
Pulmonary embolism	3
Deep vein thrombosis	2
Myelodysplastic syndrome/acute myeloid leukemia	13/191 (7%)
Donor type	
HLA-identical sibling	136/210 (65%)
Source of stem cells[α]	
Bone marrow	135/210 (64%)
Peripheral blood stem cells	71/210 (34%)
Conditioning regimen	
Cyclophosphamide + busulfan	47/144 (33%)
Cyclophosphamide + total body irradiation (≥ 8 Gray)	22/144 (15%)
Cyclophosphamide + anti-thymocyte globulin	32/144(22%)
Fludarabine-based regimen	42/144 (29%)
GvHD prophylaxis	
Cyclosporine ± methotrexate	154/211 (73%)

*IQR: Interquartile range; *Three cases of subclinical PNH; [v]More than one indication for stem cell transplantation (SCT) was possible; [w]Nine patients were transplanted for renal failure and 18 for other reason; [§]Site was lacking for five cases; [α]Four patients received cord blood as the source of stem cells.

Table 2. Characteristics of non-transplanted patients.

Characteristics	n/N (%) or median (IQR[a]), N
Gender, female	222/402[b] (55%)
Age at diagnosis, years	36 (25-51)
Clone size	30 (15-52), 132
Complications	
Aplastic anemia	59/402
Thrombosis	106/402
Budd Chiari	44
Central nervous system	33
Deep vein thrombosis	31
Pulmonary embolism	7
Myelodysplastic syndrome/acute leukemia	21/402
Treatment	
Immunosuppressive treatment (≥1)[c]	96/402 (24%)

[a]IQR: Interquartile range; 408 patients were eligible but five did not have follow-up and one was not evaluated for complications; [c]Immunosuppressive therapy means one course of antithymoglobulin and/or cyclosporine.

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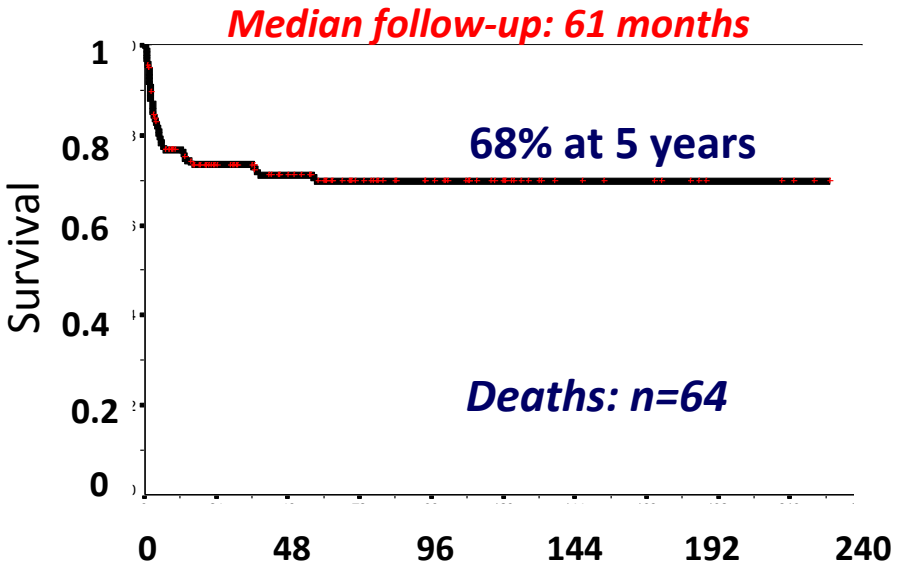
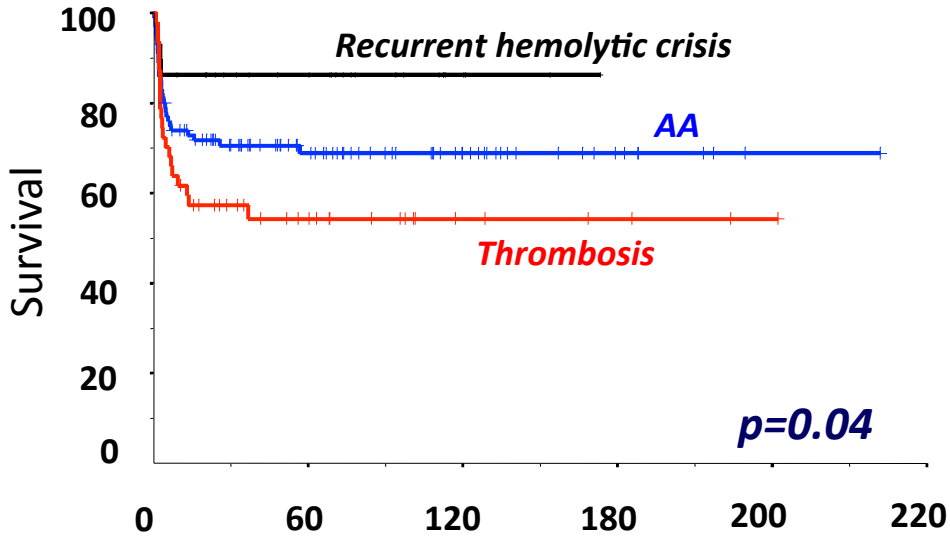
Results

- Median follow up 61 months
- Engraftment failure in 14 (7%)
- Acute GVHD in 85 (40%)
- Chronic GVHD in 57 (27%), extensive in 24 (11%)
- PNH relapse in 1 patient
- Overall survival probability at 5 years 68%

Overall Survival (OS)

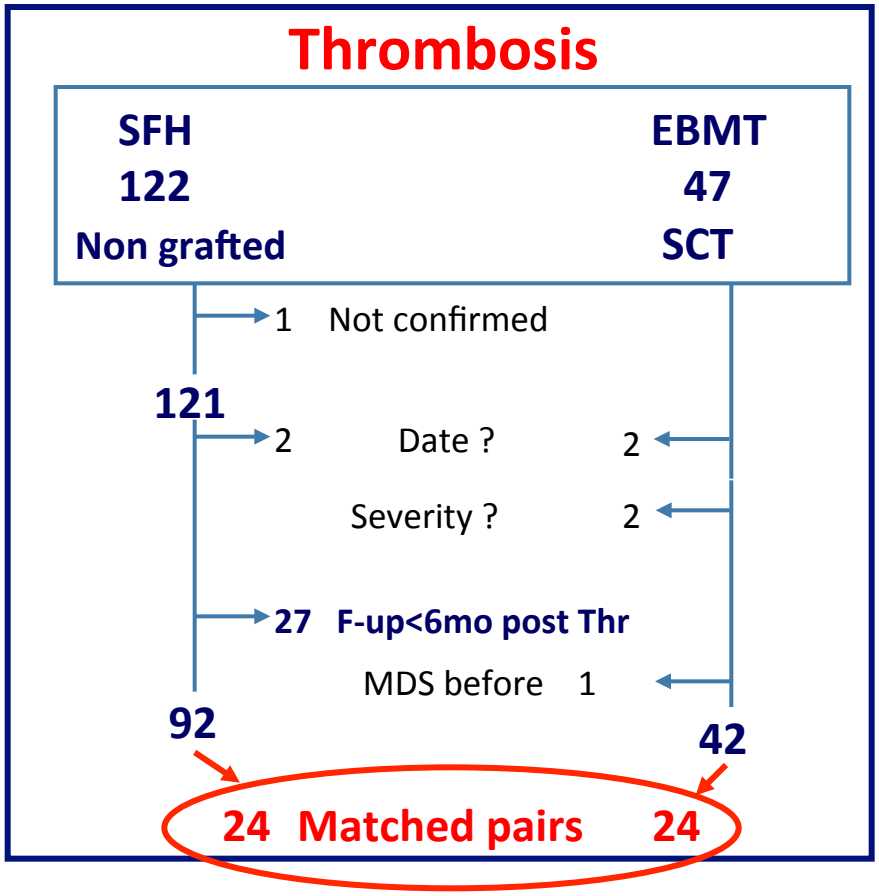


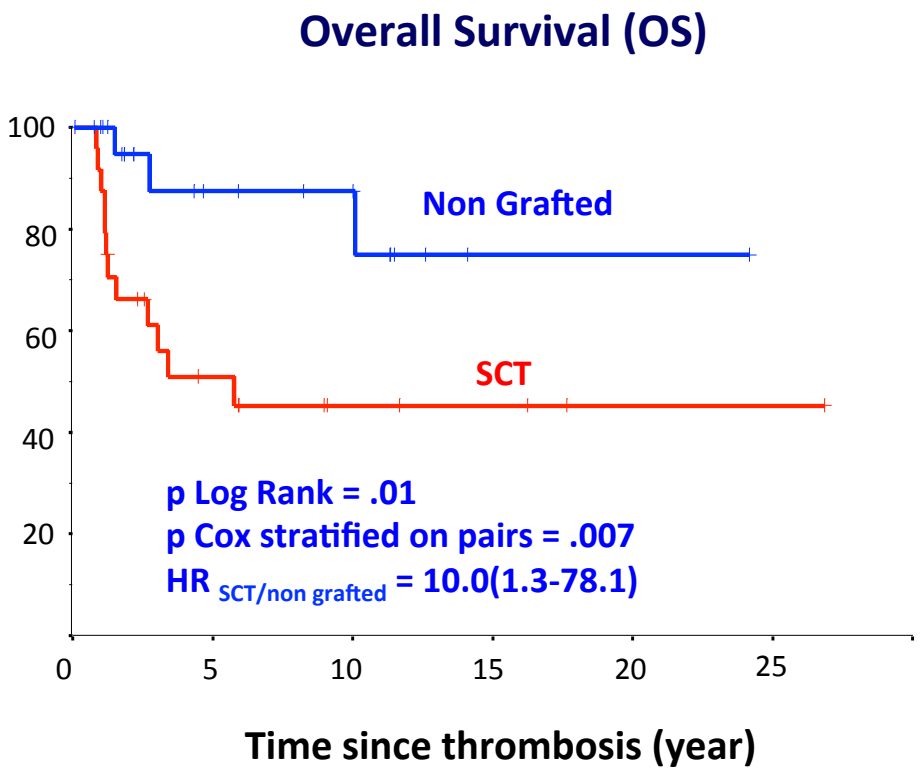
Factor associated with OS



Matching between non SCT patients (SFH registry) and SCT patients (EBMT promise)

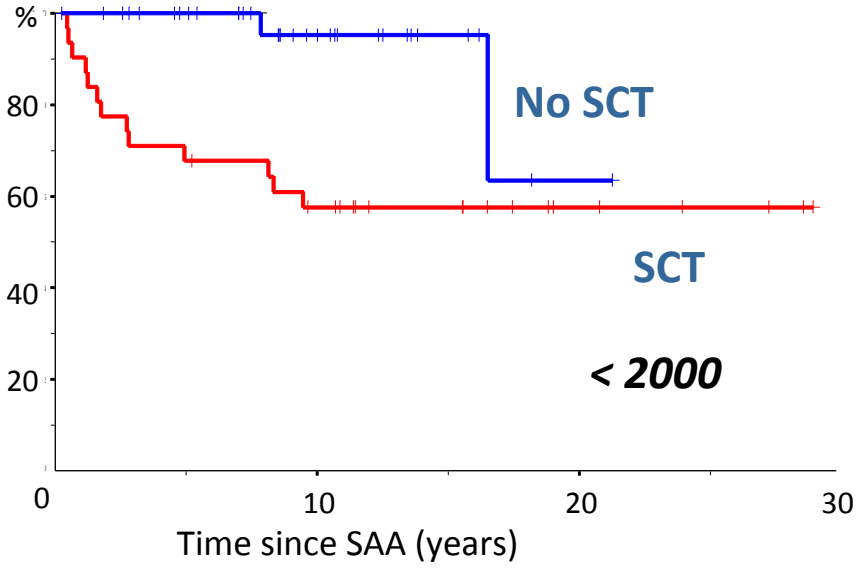
- ✓ Complications (Severity of thrombosis)
- ✓ Age at thrombosis and decade
- ✓ Delay between PNH diagnosis and complication

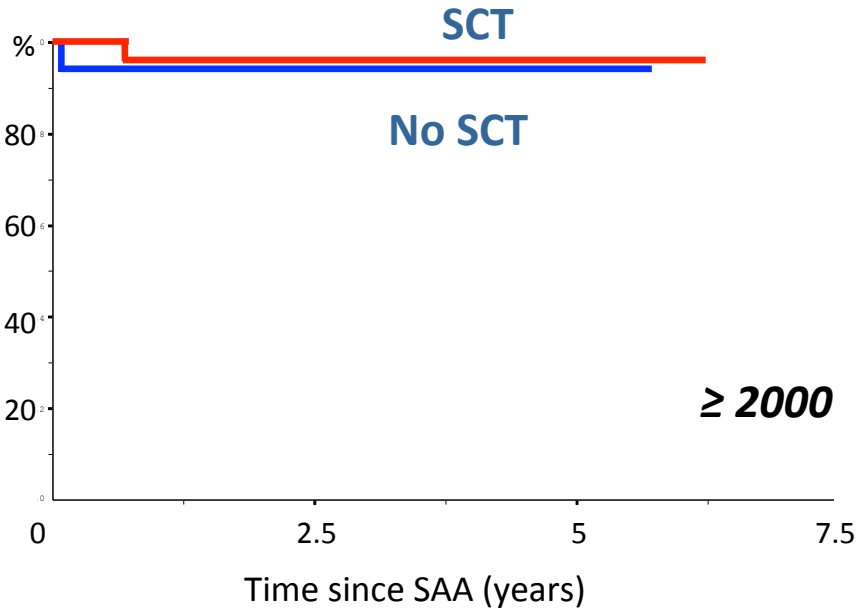

Thrombosis
SFH
122
Non grafted
EBMT
47
SCT
1 Not confirmed
121
2 Date ?
2
Severity ?
2
27 F-up<6mo post Thr
MDS before 1
92
42
24 Matched pairs
24


Overall Survival (OS)
100
80
60
40
20
0
5
10
15
20
25
Non Grafted
SCT
p Log Rank = .01
p Cox stratified on pairs = .007
HR SCT/non grafted = 10.0(1.3-78.1)
Time since thrombosis (year)

Differences between IST alone & sib/no IST:

	SFH (non SCT)	
Period (<*vs.* ≥ 2000)	*0.17*	**0.05**





Conclusions BMT

- Allogeneic BMT can cure PNH
- Overall survival rates up to 70%
- SCT is not standard of care in PNH patients with thromboembolic events
- Severe aplastic anemia - PNH patients should be considered for transplant
- PNH patients with hemolytic crisis +/- moderate aplastic anemia should be treated with eculizumab

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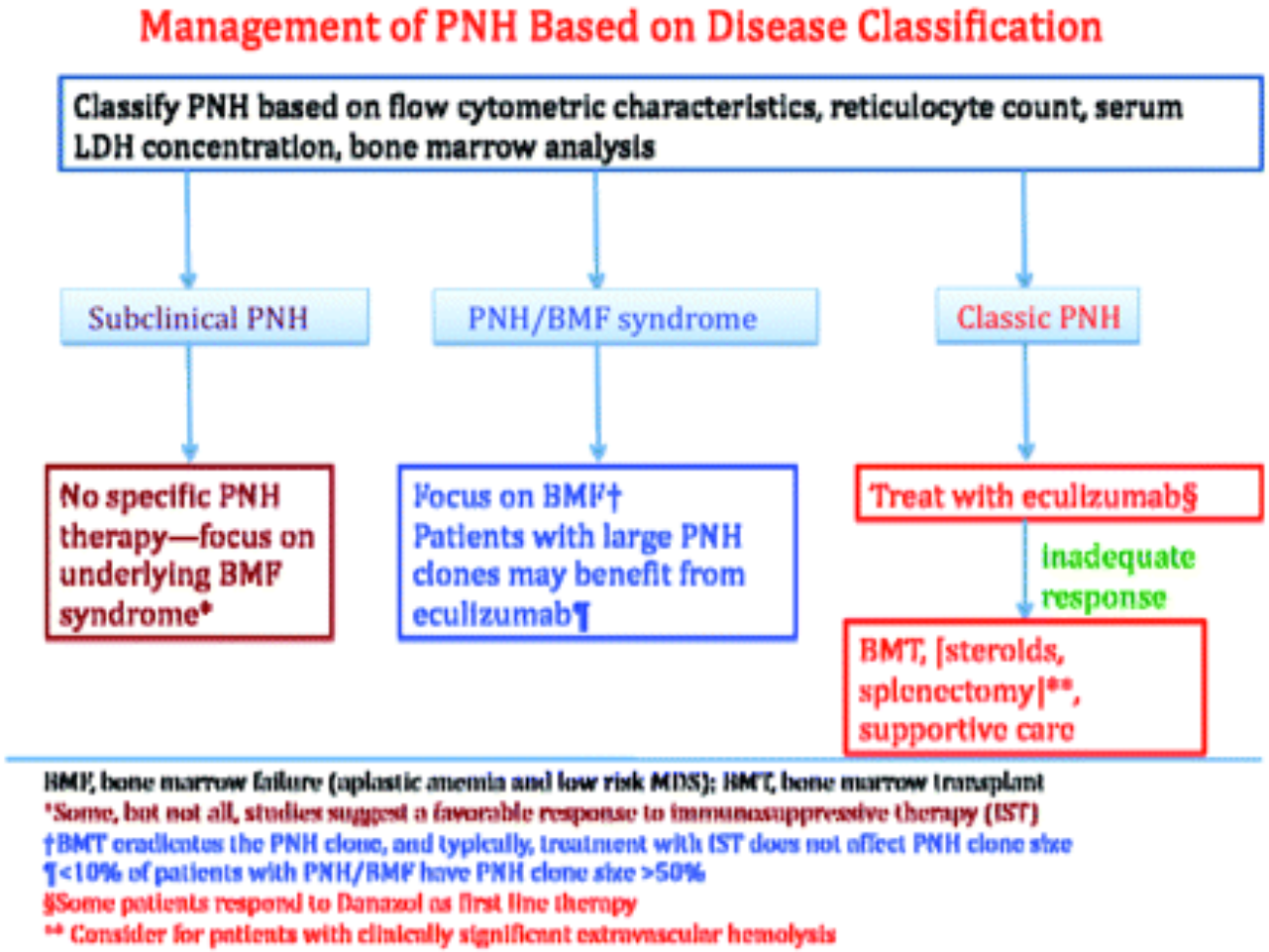
Treatment algorithm based on disease classification



Parker et al Hematology 2011

CANADIAN

PNH

NETWORK

Excellence in PNH Education and Care

Who Are We?

Hematologists with established benign hematology programs

Oncologists with established programs in bone marrow failure

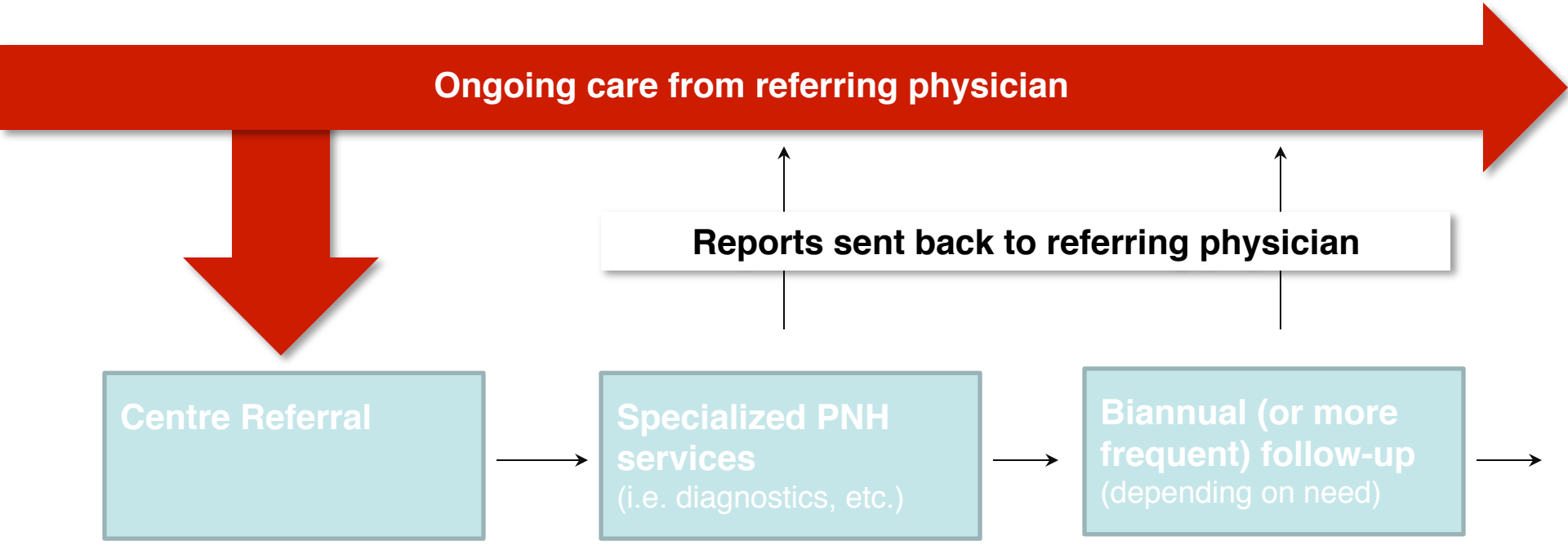
All with experience in:

PNH diagnosis • PNH assessment • Treatment and follow-up

(including experience with eculizumab (Soliris®))

PNH Referral Centre Locations

Our Shared Care Approach



Shared care allows the patient to remain with the referring physician, while benefitting from access to specialized PNH services.

What we stand for

Our Vision

"Patients in Canada must receive world-leading care that extends over case recognition, diagnosis and treatment follow-up."

Our Mission

1. To maintain the highest standard of clinical practice in the management of PNH

2. To provide continuing health education on the evolving management of PNH patients

3. To participate in PNH registry to gain further understanding of the natural history of PNH

PNH Registry

A global, observational, noninterventional study collecting safety, effectiveness, and quality of life data on PNH

Analyzed by a collaborative scientific board, chaired by Professor Peter Hillmen (Hematologist, Leeds Teaching Hospitals, England)

Benefits of your participation:

- Enhance understanding of PNH disease and treatment
- Capture the long-term outcomes of patients in order to better guide and assess treatments and the safety of Soliris®
- Expand robust, international database on PNH for scientific exchange and publications

PNH Registry

Enrolled to date:

- Over **1800** patients globally
- Patients from: the United States, Canada, Argentina, Denmark, the Netherlands, the United Kingdom, Belgium, France, Germany, Spain, Switzerland, Finland, Sweden, Australia, New Zealand, and Taiwan

Who can contribute?

- ALL physicians managing patients with PNH, *regardless of therapy*

Who is eligible?

- All patients who have been diagnosed with PNH or have evidence of a positive PNH clone
- All patients with PNH should consider enrolment!

Conclusions

- PNH is a ultrarare clonal disorder resulting in hemolysis, thrombosis and pancytopenia
- Diagnosis by flow cytometry (FLAER)
- Treatment either observation, supportive care, complement blockade with eculizumab or in certain cases allogeneic stem cell transplantation
- Referral to a PNH network center and participation in the PNH registry is encouraged


Thank you for your attention