Novità in tema di terapia delle emofilie

Marco Marietta - Modena

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Relazioni con soggetti portatori di interessi commerciali in campo sanitario

Ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Regolamento Applicativo dell'Accordo Stato-Regione del 5 novembre 2009, io sottoscritto **Dott. Marco Marietta** dichiaro che negli ultimi due anni ho avuto i seguenti rapporti ricevendo compens individuali con soggetti portatori di interessi commerciali in campo sanitario:

- **Partecipazione ad Advisory Board per l' Azienda Novo-Nordisk**
- **Relazioni a congressi per la ditta Kedrion, Orphan, Novo-Nordisk, Werfen**

Da dove veniamo? Che siamo? Dove andiamo?

Paul Gauguin, 1897

Da dove veniamo? Che siamo? Dove andiamo?

Paul Gauguin, 1897

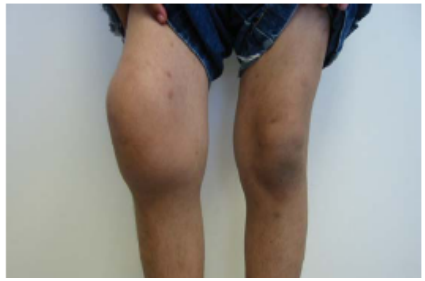
Haemophilia treatment

pre-1930 | 1940 | 1950 | 1960 | 1970 | 1980 | 1990

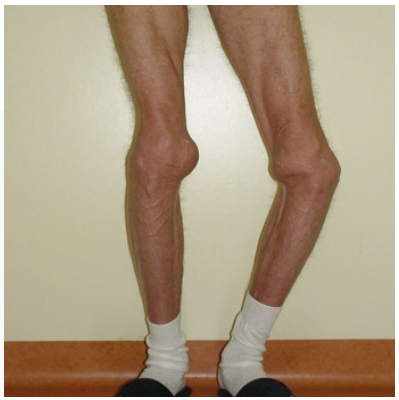
Immobilization, ice, rest, analgesia

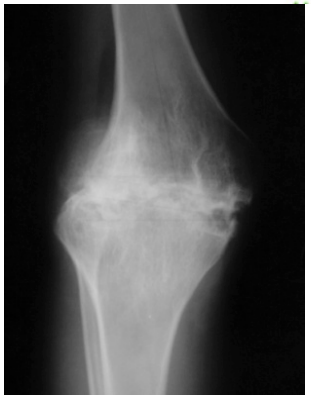
Plasma

Whole blood transfusion



Cryoprecipitate





1970

Limited plasma-derived replacement material

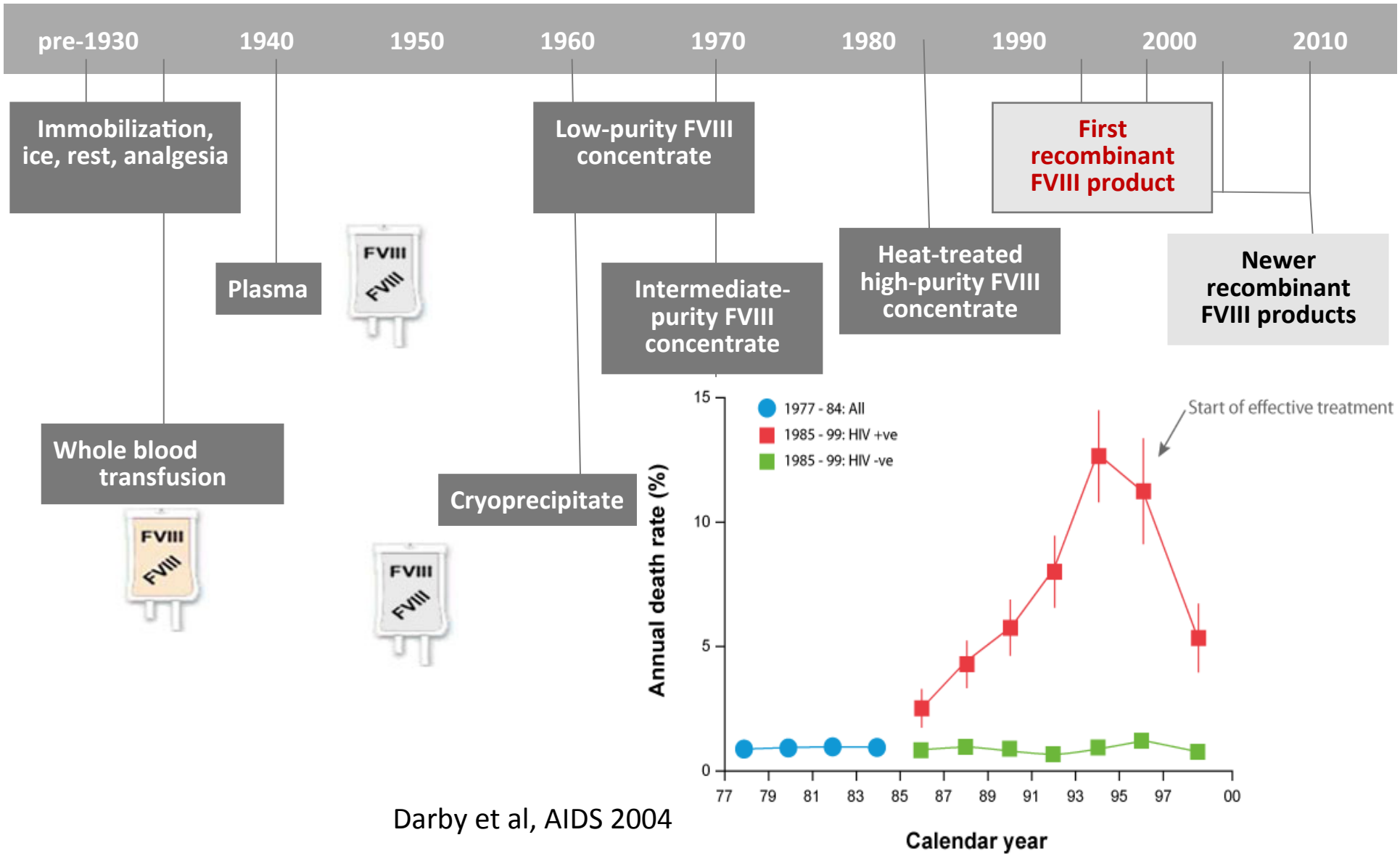
Mainly on-demand, in-hospital treatment

Early crippling arthropathy

Bleeding-related deaths: 47% (NL)

Life expectancy:
59 yrs (Sweden)
25 yrs (Finland)

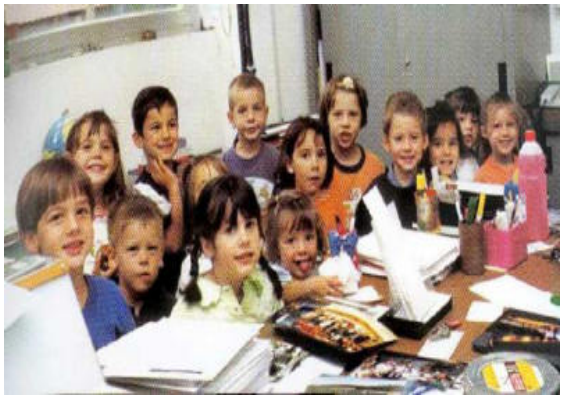
Haemophilia treatment

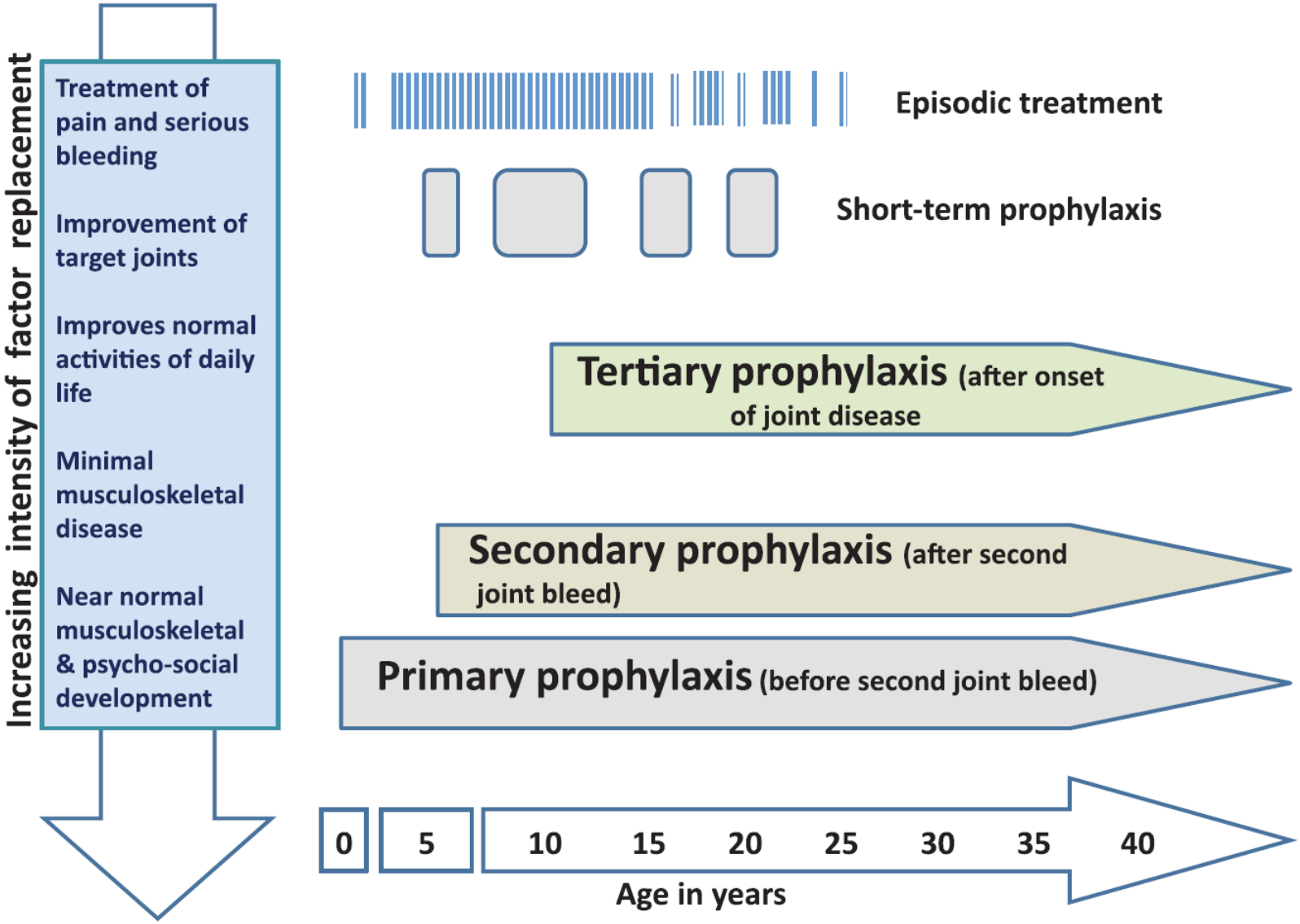


Darby et al, AIDS 2004

Haemophilia treatment

2000
Plasma-derived and recombinant concentrates largely available
Diffusion of prophylaxis Home Treatment
Minimal joint disease in patients on prophylaxis
Bleeding-related deaths: <10% (NL)
Life expectancy: 71 yrs (Italy, NL)





Adapted from Blood Transfus 2008 Sep;6 Suppl 2:s4-11

All that glisters is not gold,

Often have you heard that told

William Shakespeare
The Merchant of Venice

All that is gold does not glitter,
Not all those who wander are lost

JRR Tolkien
The Lord of the Rings

Current challenges for treatment of hemophilia

- ✓ Venous access: intravenous route of administration
- ✓ Infusion frequency: half-life FVIII ~ 12 hrs, FIX ~20 hrs
- ✓ Inhibitors
- ✓ Costs and availability of concentrates
- ✓ Barrier to highly demanding regimens:
  - **Prophylaxis**
  - **Immune tolerance induction**
  - **Major surgery**

Da dove veniamo? Che siamo? Dove andiamo?

Paul Gauguin, 1897

J Thromb Haemost 2016; 14: 2095–106.

Advances in the treatment of bleeding disorders

Table 1 New therapeutic agents for hemophilia A and B

Deficiency	Product	Technology	Mean $t_{1/2}$ (h) (minimum–maximum)	Clearance ($mL\,h^{-1}\,kg^{-1}$)	Estimated time to 1% after dose of 50 IU kg^{-1} (days)
Hemophilia A	BAY94-9027	Site-specific PEGylation (60-kDa PEG)	18.4 (13.7–28.1)	1.4	5
	N8-GP	Site-specific glycoPEGylation (40-kDa PEG)	19 (11.6–27.3)	1.4	6.5
	Adynovate (BAX 855)	Controlled PEGylation (2 × 20-kDa PEG)	14.3–16.0	2.47	4
	Eloctate, Elocta (rFVIII-Fc)	Fc fusion	18.8 (14.3–24.5)	2	4.9
	rFVIII-SingleChain (CSL 627)	Single-chain rFVIII	14.5	2.64	NA
Hemophilia B	N9-GP	Site-directed glycoPEGylation (40-kDa PEG)	93 (85–111)	0.7	22
	Alprolix (rFIX-Fc)	Fc fusion	82.1 (71.4–94.5)	3.2	11.2
	Idelvion (rFIX-FP)	Albumin fusion	91.57	0.75	14

REVIEW ARTICLE

J Thromb Haemost 2016; **14**: 2095–106.

Advances in the treatment of bleeding disorders

F. PEYVANDI,*† I. GARAGIOLA† and E. BIGUZZI*

Table 2 Dose and frequency of treatment for the control of acute bleeding in patients with hemophilia A and B [16,20,29]

	Dose (IU kg^{-1})		Frequency of dosing (h)	
Type of bleeding	rFVIII standard	rFVIII EHL	rFVIII standard	rFVIII EHL
Minor/moderate	20–30	20–30	12–24	24–48
Major (life-threatening hemorrhages)	40–50	40–50	8–24	12–24

	Dose (IU kg^{-1})		Frequency of dosing (h)	
Type of bleeding	rFIX standard	rFIX EHL	rFIX standard	rFIX EHL
Minor/moderate	40–60	30–60	12–24	48
Major (life-threatening hemorrhages)	60–80	80–100	12 to 24	24 for the first 3 days, and then every 48

EHL, extended half-life; rFIX, recombinant factor IX; rFVIII, recombinant factor VIII.

J Thromb Haemost 2016; 14: 2095–106.

Advances in the treatment of bleeding disorders

F. PEYVANDI,*† I. GARAGIOLA† and E. BIGUZZI*

Table 3 Dose and frequency for standard and extended half-life (EHL) products in the management of hemophilia A patients undergoing minor and major surgical procedures

	Dose (IU kg^{-1})	Frequency (h)	Duration of therapy (days)
rFVIII standard product			
Minor	25–40	Every 12–24	1–3
Major			
Preoperative	40–50	A single-dose injection	
Postoperative	30–40	Every 8–24	1–7
FVIII EHL			
Minor	62.50*	Every 24	1
Major			
Preoperative and intraoperative	58.3†	A single-dose injection	
	58.8‡	Every 24	7

Table 4 Dose and frequency for standard and extended half-life (EHL) products in the management of hemophilia B patients undergoing minor and major surgery procedures

	Dose (IU kg^{-1})	Frequency (h)	Duration of therapy (days)	References
rFIX standard product				
Minor	50–80	Every 24	1	[29]
Major				
Preoperative	60–80	A single-dose injection		[29]
Postoperative	40–60	Every 8–24	7	[29]
FIX EHL				
Minor	50–80	A single injection may be sufficient. Repeat as needed after 24–48 h		
Major				
Preoperative	84.16*	A single-dose injection		[32]
	80	A single-dose injection		[35]
	87†	A single-dose injection		[37]
Postoperative	49.12–64.61*	24–48	1–14	[32]
	40	24–96	13	[35]
	51	24–72	14	[37]

AJH Educational Material

2017 Clinical trials update: Innovations in hemophilia therapy

Jan Hartmann[1] and Stacy E. Croteau[2]*

- ✓ EHL factor concentrates build on the familiar management strategies of conventional factor concentrates
- ✓ The challenges of frequent IV infusions, patient adherence, and inhibitor risk remain.
- ✓ The degree to which the addition of these various moieties increase, decrease, or have a neutral effect on immunogenicity remains under investigation.

Am. J. Hematol. 91:1252–1260, 2016.

AJH Educational Material

2017 Clinical trials update: Innovations in hemophilia therapy

Jan Hartmann[1] and Stacy E. Croteau[2]*

- ✓ Interestingly, uptake of these products in the immediate postlicensure period has been modest
- ✓ EHL products have accentuated the variability of patient half-life.
- ✓ The real-world impact of EHL products on health-related quality of life and health economics are also under investigation

Am. J. Hematol. 91:1252–1260, 2016.

Da dove veniamo? Che siamo? ***Dove andiamo?***

Paul Gauguin, 1897

Why is hemophilia an excellent target for gene therapy

- ✓ Single gene disorder
- ✓ Small absolute amounts of clotting factors in normal plasma (fVIII 50 ng/ml, fIX 5 μg/ml)
- ✓ 1/10 of these values sufficient for normal hemostasis
- ✓ Biologically active factors can be produced in a wide variety of cells
- ✓ Large animal models are available (hemophilic dogs)

Product	Vector	Promotor–transgene	Clinical trial status	Human response
Factor VIII				
BMN270	AAV5	Active Factor VIII with B domain deletion of Refacto™	Enrollment suspended	8 patients dosed; 6 at high dose level, 6×10^{13} vg/kg, with FVIII activity level of 4–60% with maximum of 16 weeks of follow-up, prophylactic corticosteroids initiated with patient 4 and beyond
Factor IX				
AAV8-hFIX19	ssAAV8	HCRhATT-hFIXco	Enrollment completed	No study results posted
SPK-9001 (SPX-FIX)	novel AAV vector	high specific activity FIX variant	Enrolling	4 patients dosed at initial dose level (5×10^{11} vg/kg) with FIX activity ranging from 26 to 41% with 7 to 26 weeks of follow up
scAAV2/8-LP1-hFIXco	scAAV2/8	LP1-hFIXco	Enrolling	10 patients dosed in 3 dosing cohorts, mean steady state FIX activity 2.9–7.2% with follow-up of at least 16 months.
AskBio009 (BAX 335)	scAAV8	TTR-FIXR338L (Padua)	Enrollment closed	7 patients dosed in 3 dosing cohorts, 2 patients with transient FIX activity > 50%, only 1 persisted (medium dose cohort, 1×10^{12} vg/kg)
DTX101	AAVrh10	hFIX	Enrolling	No study results posted
AMT-060	AAV5	LP1-hFIXco	Enrolling	5 patient enrolled in initial dose level (5×10^{12} gc/kg), two with at least week 12 follow-up had FIX expression levels of 4.5–5.5%
SB-FIX	AAV2/6	ZNF mediated gene editing Three components of SB-FIX (ZFN1, ZFN2, and FIX cDNA donor)	Anticipated	No study results posted

Am. J. Hematol. 91:1252–1260, 2016.

AJH

AJH Educational Material

2017 Clinical trials update: Innovations in hemophilia therapy

Jan Hartmann[1] and Stacy E. Croteau[2]*

- ✓ Cell-based approach to gene therapy for hemophilia uses Lentiviral vectors and several cell types : liver sinusoidal endothelial cells, stem cells derived from bone marrow, blood-outgrowth endothelial cells, and endothelial progenitor cells
- ✓ It requires cytoablative agents to create a niche for hematopoietic stem cells transduced ex vivo → harm?
- ✓ Trials only in in murine models of HA with inhibitors
- ✓ Use of platelet-specific promoters enables expression of FVIII within the α-granules of platelets → delivery at the site of hemostatic need

Am. J. Hematol. 91:1252–1260, 2016.

Buscar el levante por el poniente…

Cristoforo Colombo

UPDATES IN CLINICAL TRIALS FOR HEMATOLOGICAL DISEASES

AJH Educational Material

2017 Clinical trials update: Innovations in hemophilia therapy

Jan Hartmann[1] and Stacy E. Croteau[2]*

Nonfactor Replacement Strategies: "Disruptive Therapies"

- Emicizumab
- Concizumab
- APC-specific serpin

FVIII-specific human (CAR) T-regulatory cells

Am. J. Hematol. 91:1252–1260, 2016.

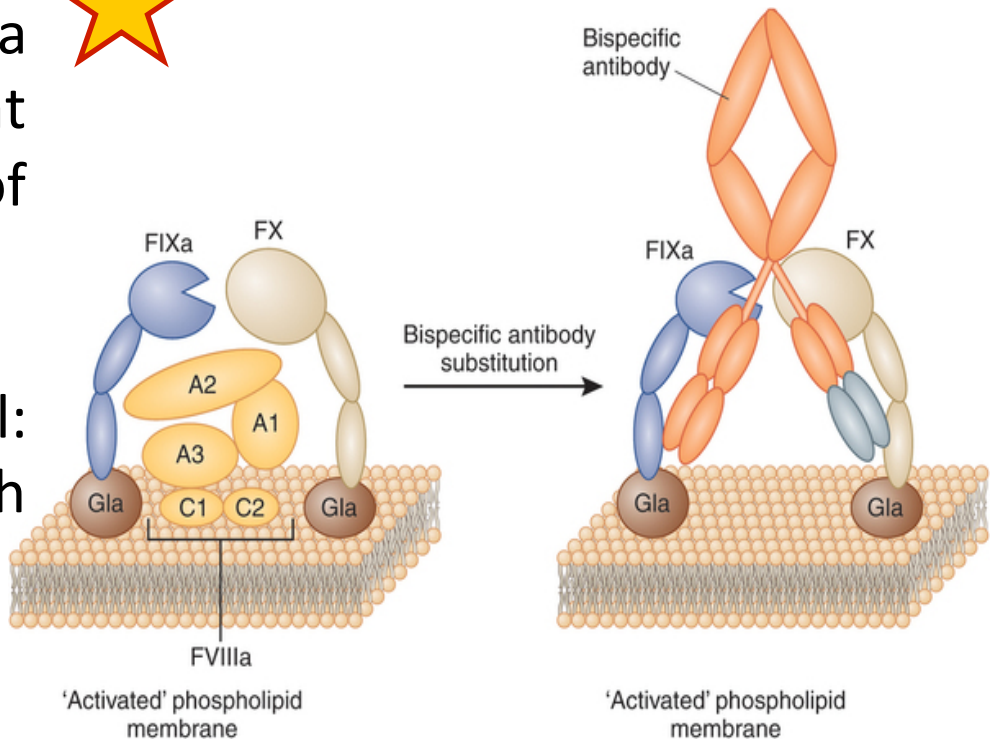
Anti-factor IXa/X bispecific antibody (ACE910): hemostatic potency against ongoing bleeds in a hemophilia A model and the possibility of routine supplementation

J Thromb Haemost 2014; **12**: 206–13

A. MUTO,* K. YOSHIHASHI,* M. TAKEDA,* T. KITAZAWA,* T. SOEDA,* T. IGAWA,* Y. SAKAMOTO,* K. HARAYA,* Y. KAWABE,* M. SHIMA,† A. YOSHIOKA‡ and K. HATTORI*

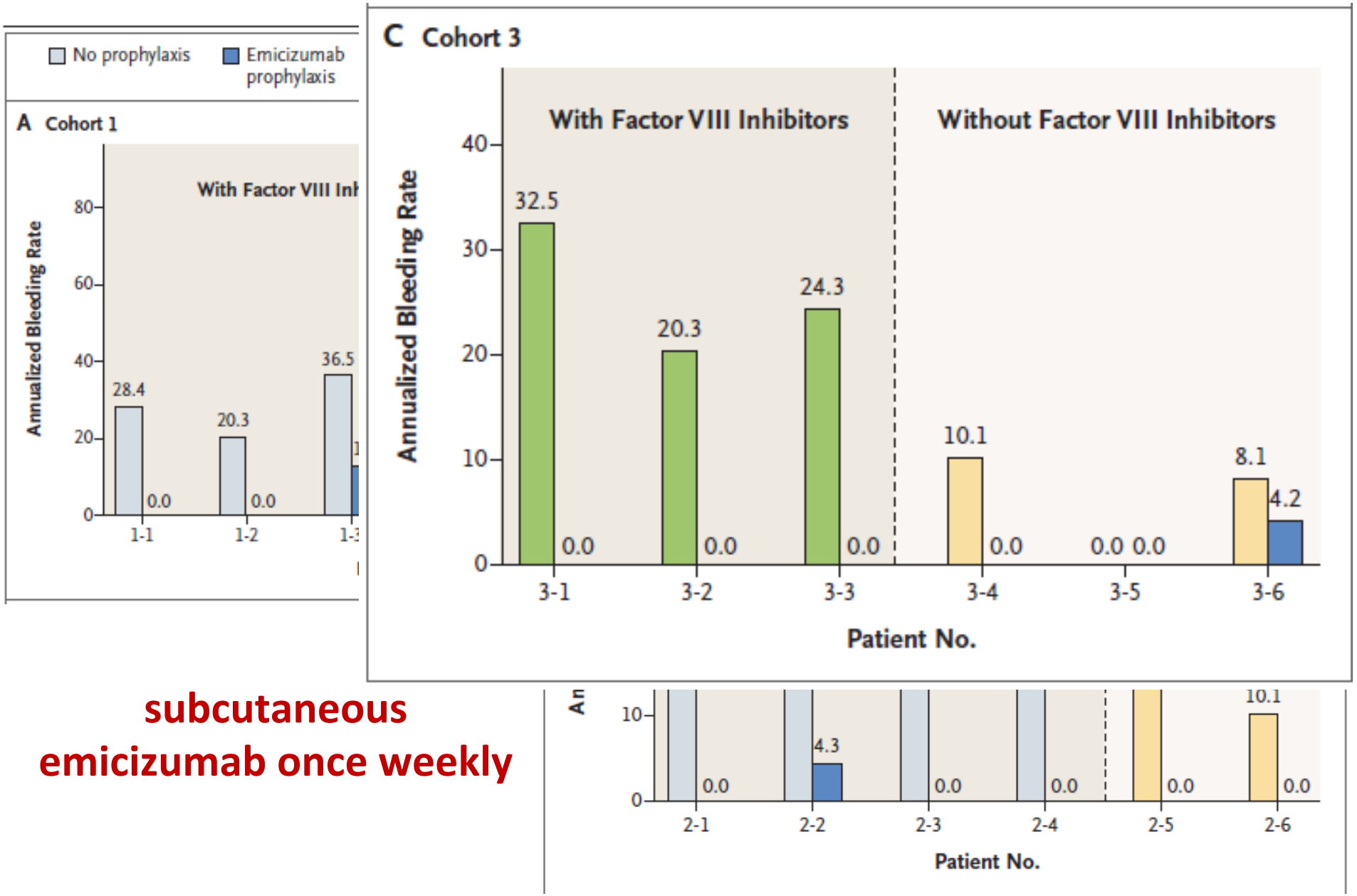
- ACE910 **(emicizumab)** is a bispecific Ab to FIXa and FX that mimics the cofactor function of FVIII

- In non-human primate model: prolonged half-life and high subcutaneous bioavailability



The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med 2016;374:2044-53.



subcutaneous emicizumab once weekly

ORIGINAL ARTICLE

J Thromb Haemost 2015; **13**: 743–54.

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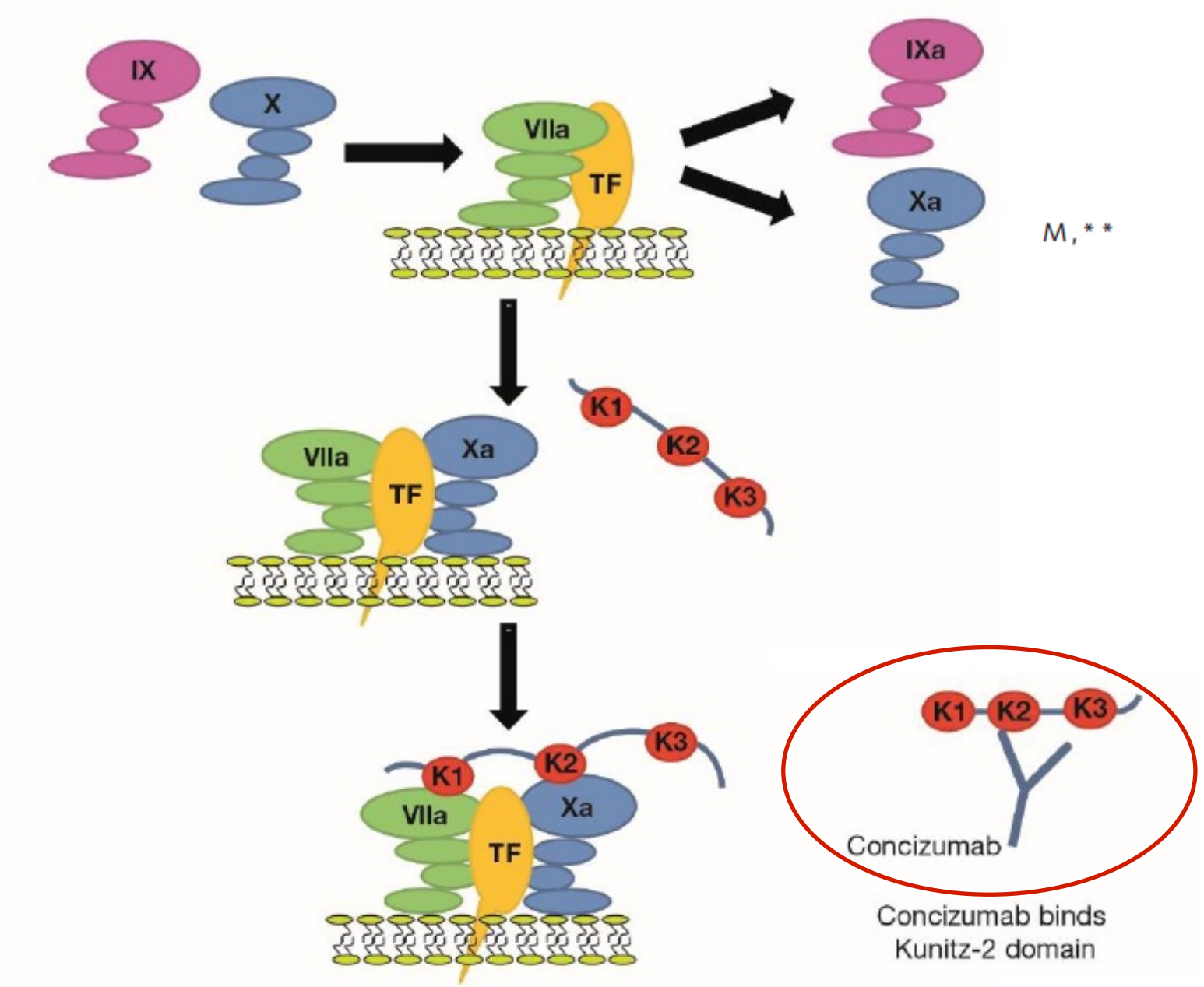
P. CHOWDAR

M, * *



ORIGINAL ARTICLE

J Thromb Haemost 2015; 13: 743–54.

Safety and pharmacokinetics of anti-TFPI antibody (concizumab) in healthy volunteers and patients with hemophilia: a randomized first human dose trial

P. CHOWDARY,* S. LETHAGEN,†‡ U. FRIEDRICH,† B. BRAND,§ C. HAY,¶ F. ABDUL KARIM,**

- ✓ Phase 1, multicenter, randomized, double-blind, placebo controlled trial
- ✓ Escalating single i.v. or s.c. doses of concizumab were administered to 28 healthy volunteers and 24 hemophilia patients

ORIGINAL ARTICLE

J Thromb Haemost 2015; 13: 743–54.

Safety and pharmacokinetics of anti-TFPI antibody (concizumab) in healthy volunteers and patients with hemophilia: a randomized first human dose trial

P. CHOWDARY,* S. LETHAGEN,†‡ U. FRIEDRICH,† B. BRAND,§ C. HAY,¶ F. ABDUL KARIM,**

Results:

- ✓ Concizumab had a favorable safety profile after single i.v. or s.c. administration
- ✓ No serious adverse events nor anti-concizumab antibodies were reported
- ✓ Nonlinear pharmacokinetics was observed due to target-mediated clearance.
- ✓ A concentration-dependent procoagulant effect of concizumab was observed

Regular Article

blood

THROMBOSIS AND HEMOSTASIS

(*Blood.* 2017;129(1):105-113)

Design and characterization of an APC-specific serpin for the treatment of hemophilia

Stéphanie G. I. Polderdijk,[1] Ty E. Adams,[1] Lacramioara Ivanciu,[2] Rodney M. Camire,[2] Trevor P. Baglin,[3] and James A. Huntington[1]

- ✓ An alternative approach to hemophilia treatment is selective inhibition of APC
- ✓ The endogenous inhibitors of APC are members of the serpin family: protein C inhibitor (PCI) and α1-antitrypsin (α_1 AT); however, both exhibit poor reactivity and selectivity for APC.
- ✓ The Authors mutated residues in and around the scissile P1-P19 bond in PCI and α_1 AT, resulting in serpins with the desired specificity profile.

Regular Article

blood

THROMBOSIS AND HEMOSTASIS

(*Blood.* 2017;129(1):105-113)

Design and characterization of an APC-specific serpin for the treatment of hemophilia

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Table 4. Platelet and fibrin deposition in a cremaster arteriole laser-induced injury model

Sample	No. of mice	Total injuries	Clot formation					
			No clot		Platelets only		Platelets + fibrin	
			No.	%	No.	%	No.	%
PBS	5	8	8	100	0	0	0	0
KRK α_1AT (7.5 mg/kg)	4	18	2	11.1	6	33.3	10	55.6
KRK α_1AT (15 mg/kg)	3	20	0	0	3	15	17	85

PBS PBS KRK 7.5 mg/kg KRK 15 mg/kg

Regular Article

(*Blood*. 2017;129(2):238-245)

THROMBOSIS AND HEMOSTASIS

- ✓ In this study, an FVIII-specific chimeric antigen receptor (ANS8 CAR) was engineered using a FVIII-specific scFv derived from a synthetic phage display library.
- ✓ Transduced ANS8 CAR T cells specific for the A2 domain proliferated in response to FVIII and ANS8 CAR Tregs were able to suppress the proliferation of FVIII-specific T effector cells with specificity for a different FVIII domain *in vitro*.
- ✓ These data suggest that engineered cells are able to promote bystander suppression
- ✓ Importantly, ANS8 CAR-transduced Tregs also were able to suppress the recall antibody response of murine splenocytes from FVIII knockout mice to FVIII *in vitro* and *in vivo*.
- ✓ ***In conclusion, CAR-transduced Tregs are a promising approach for future tolerogenic treatment of hemophilia A patients with inhibitors.***

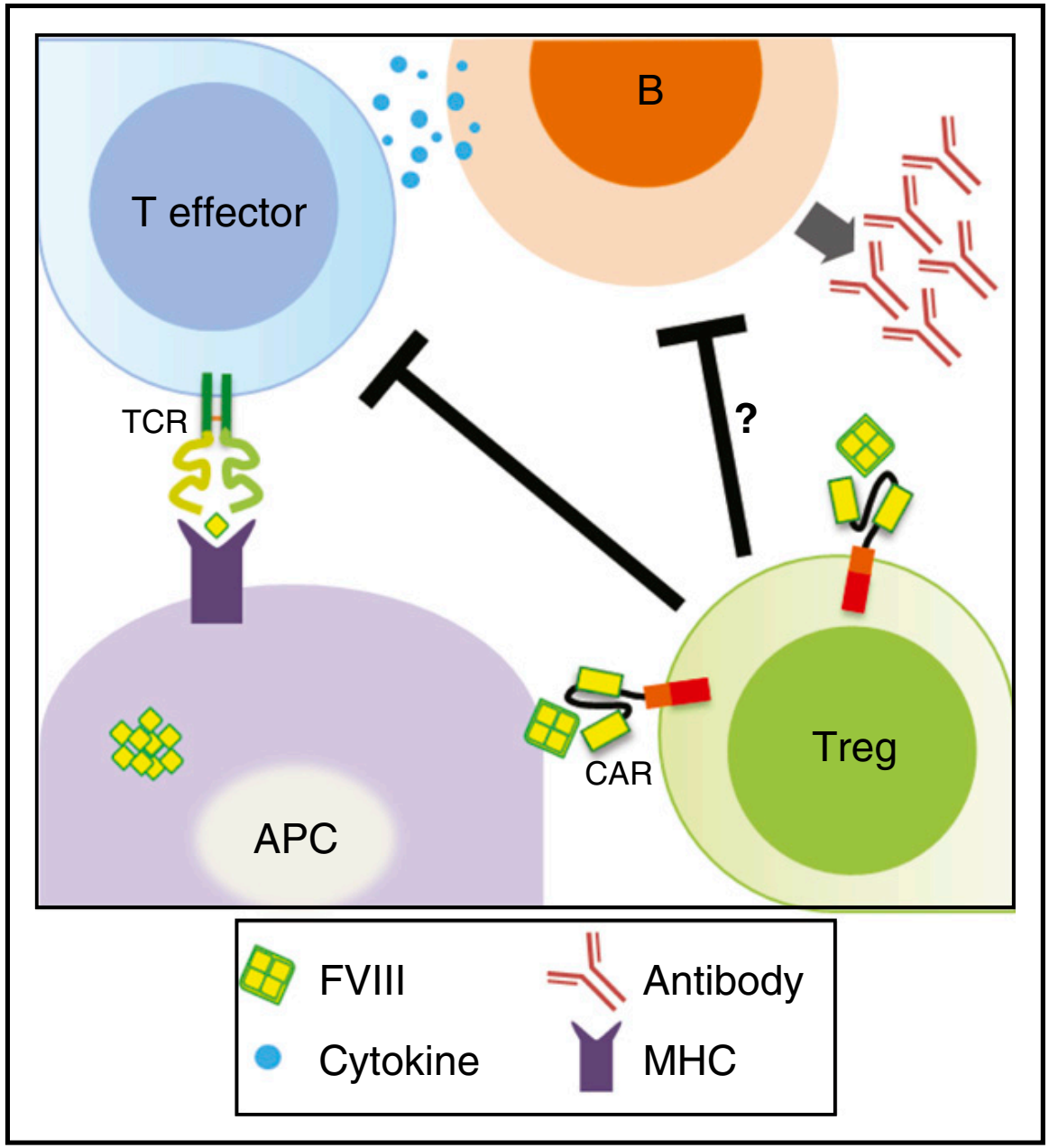
Regular Article

(*Blood*. 2017;129(2):238-245)

THROMBOSIS

FVIII-specif ... ory cells suppress T-

Jeongheon Yoon,[1,*] ... vid W. Scott[1]



Ed il mare concederà a ogni uomo nuove speranze,
come il sonno porta i sogni.
Cristoforo Colombo

Haemophilia

Haemophilia (2012), **18** (Suppl. 4), 1–12 DOI: 10.1111/j.1365-2516.2012.02822.x

ORIGINAL ARTICLE

WFH: Closing the global gap – achieving optimal care

MARK W. SKINNER

Looking just at people with haemophilia, we estimate only about 25% worldwide receive at least minimally adequate treatment. The percentage is far lower for those with VWD and the other bleeding disorders.

Non c'è progresso senza giustizia sociale

Jorge Maria Bergoglio