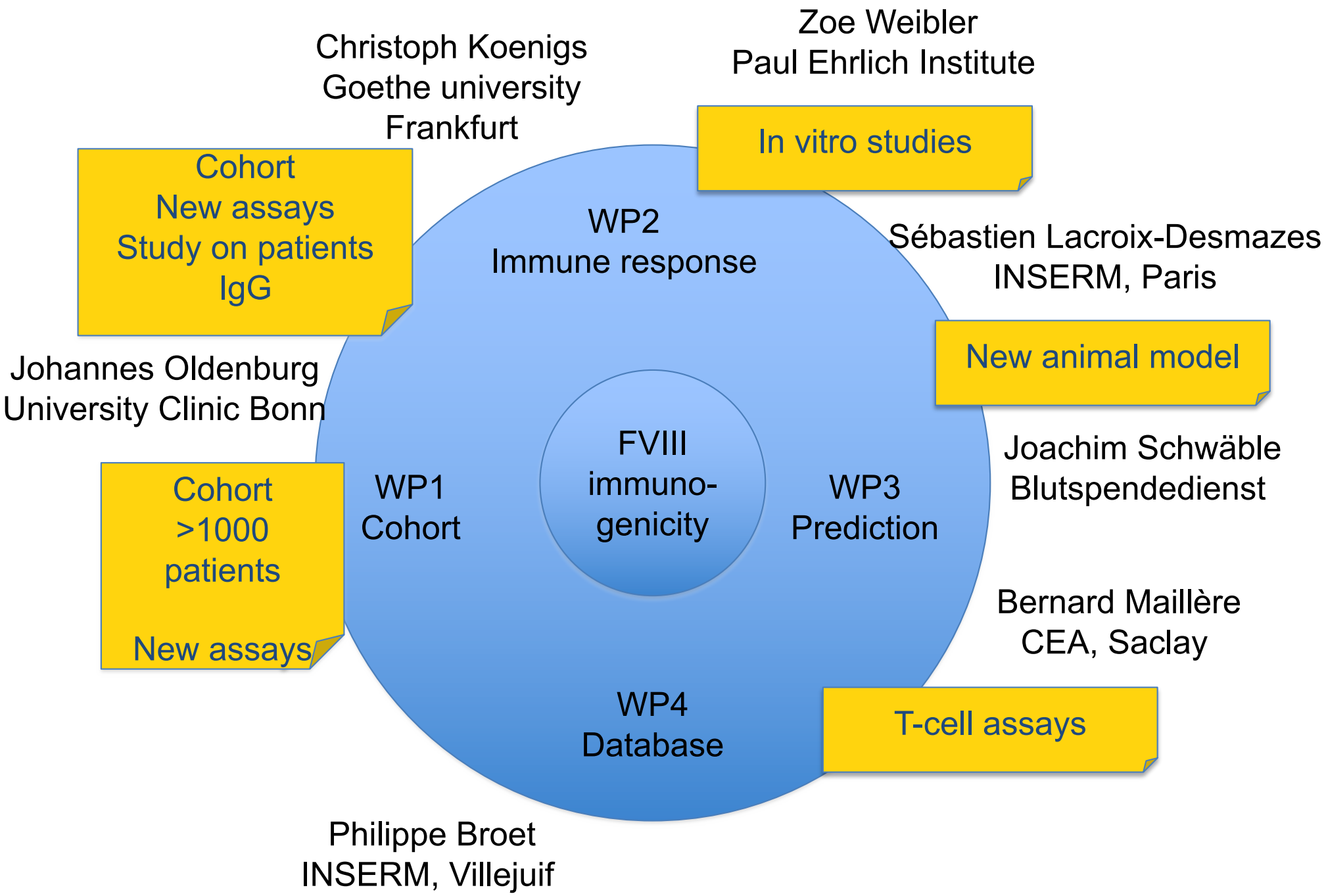
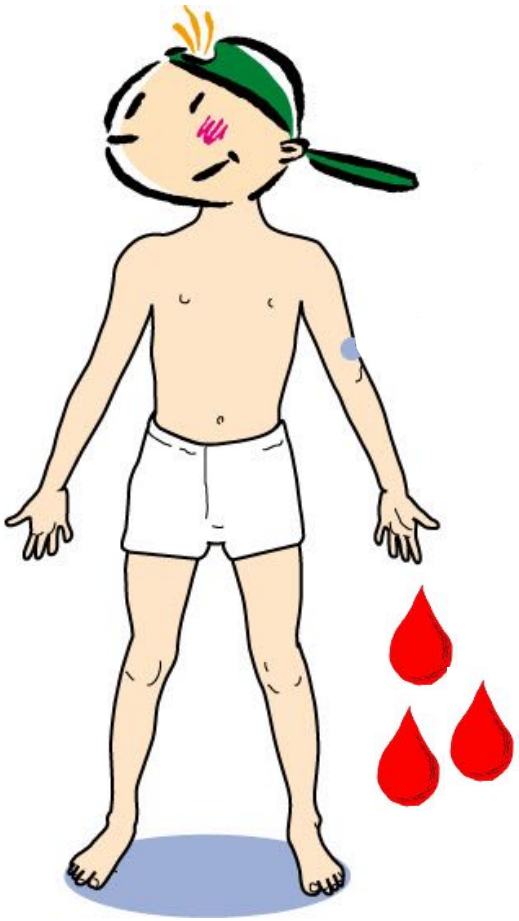
FVIII immunogenicity:
Lessons from 5 years of ABIRISK… and beyond

Sébastien LACROIX-DESMAZES

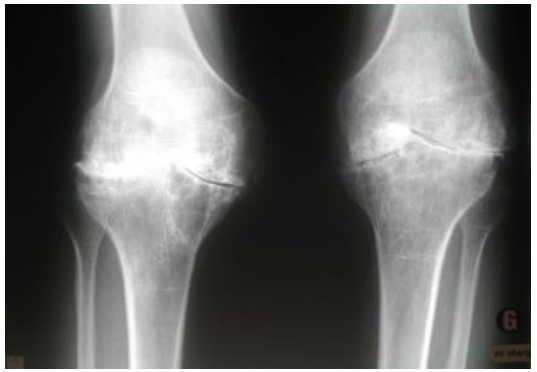
INSERM UMRS 1138,
Immunopathology and therapeutic immunointervention
CRC - Paris, France


Christoph Koenigs
Goethe university
Frankfurt
Zoe Weibler
Paul Ehrlich Institute
In vitro studies
Cohort
New assays
Study on patients
IgG
WP2
Immune response
Sébastien Lacroix-Desmazes
INSERM, Paris
New animal model
Johannes Oldenburg
University Clinic Bonn
FVIII
immuno-
genicity
WP1
Cohort
WP3
Prediction
Joachim Schwäble
Blutspendedienst
Cohort
>1000
patients
New assays
Bernard Maillère
CEA, Saclay
WP4
Database
T-cell assays
Philippe Broet
INSERM, Villejuif

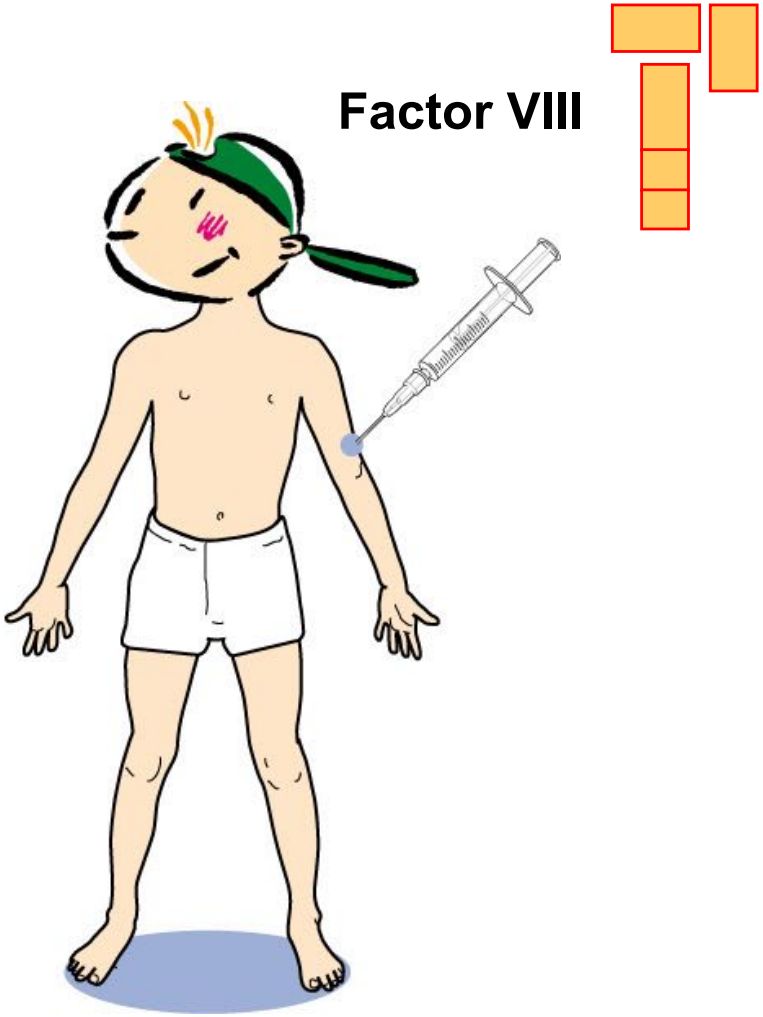
Hemophilia A



- Rare disease linked to the X chromosome
- Absence of functional factor VIII (FVIII)
  - severe: <1%
  - mild: 1-5%
  - moderate: 5-30%
- Serious hemorrhagic disease
  - Internal hemorrhages
  - Crippling hemarthrosis



Treatment of hemorrhages



- **Life expectancy**

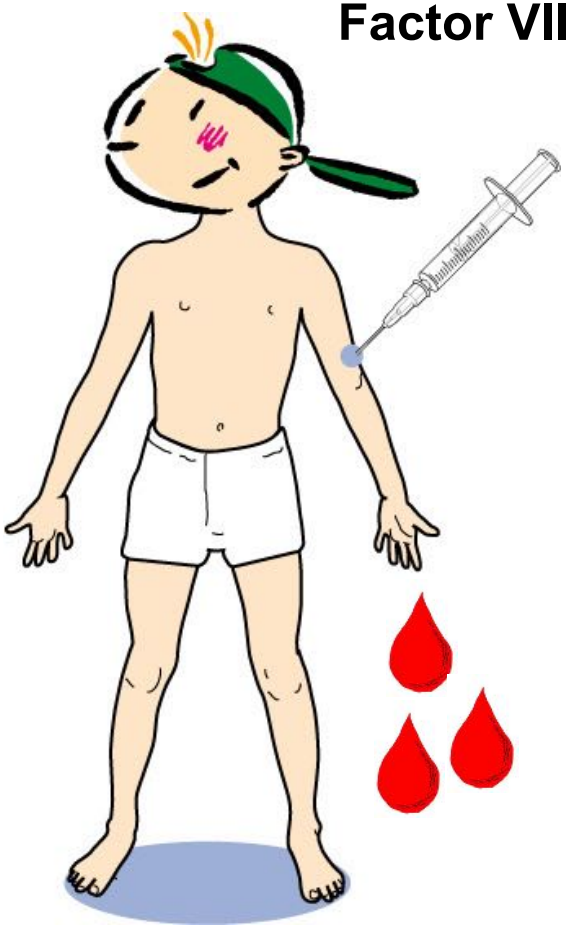
  20 years (1950) to >60 years

- **Quality of life**

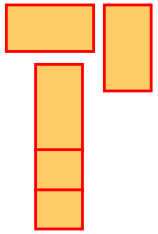
- **Average treatment cost**

  > 35 000 € / patient / year

Immune response to therapeutic factor VIII



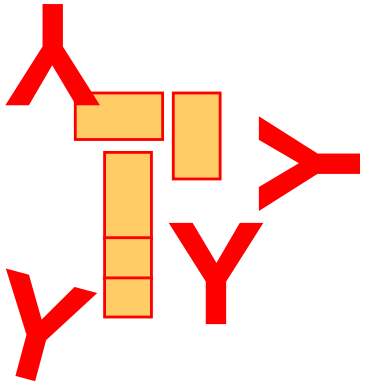
Factor VIII



Complication of treatment: neutralizing antibodies

- Occur in 5-50% (~30%) of the patients
- Inhibit therapeutic FVIII
- Treatment cost

  > 200 000 € / patient / year

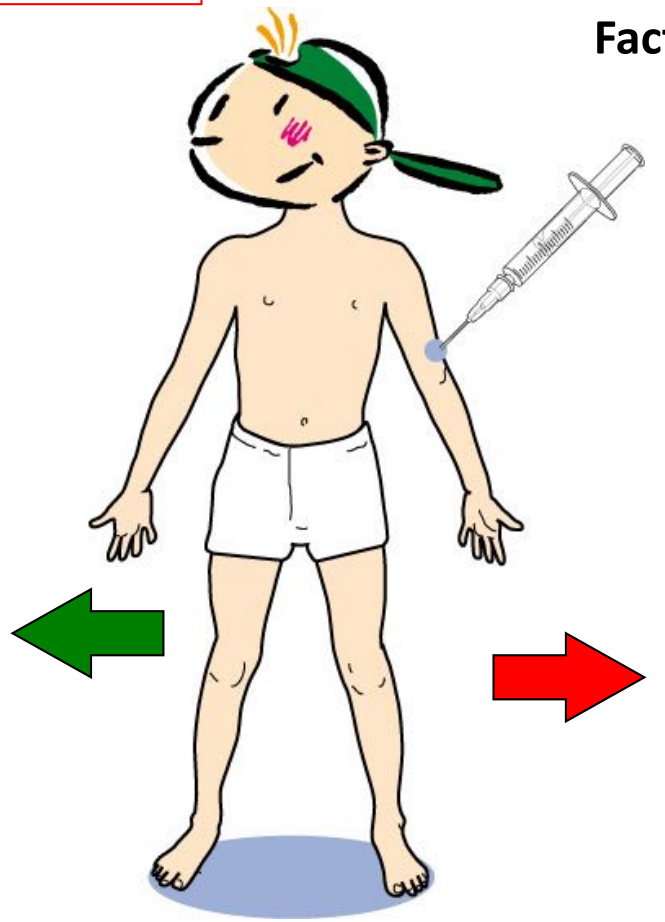


Anti-FVIII antibodies or "FVIII Inhibitors"

Immune response to therapeutic factor VIII

Why do 5 to 30% of the patients develop an immune response to FVIII?

Factor VIII

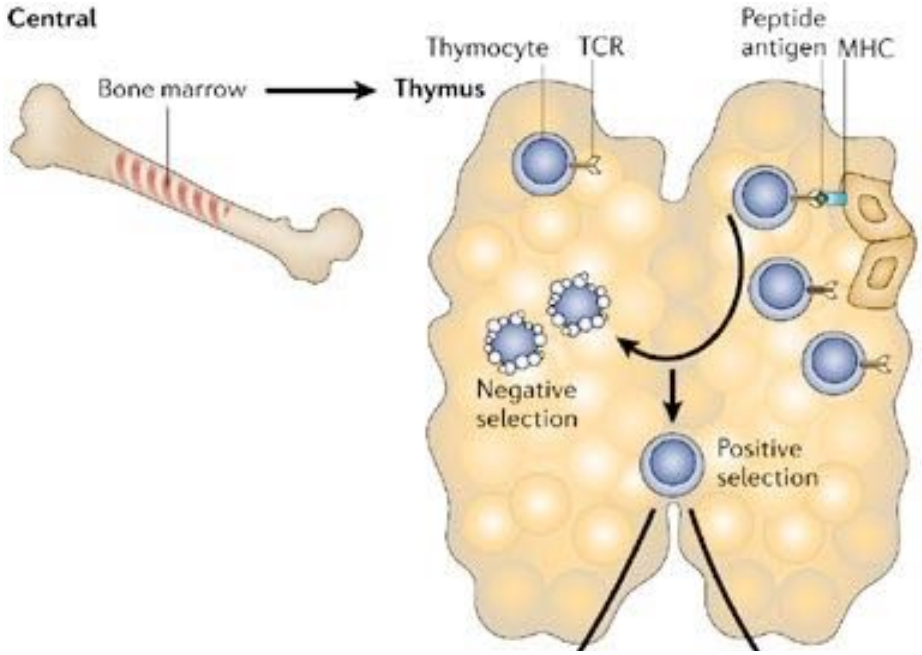


5-30% of the patients

70–95% of the patients

FVIII inhibitors

Central T-cell tolerance

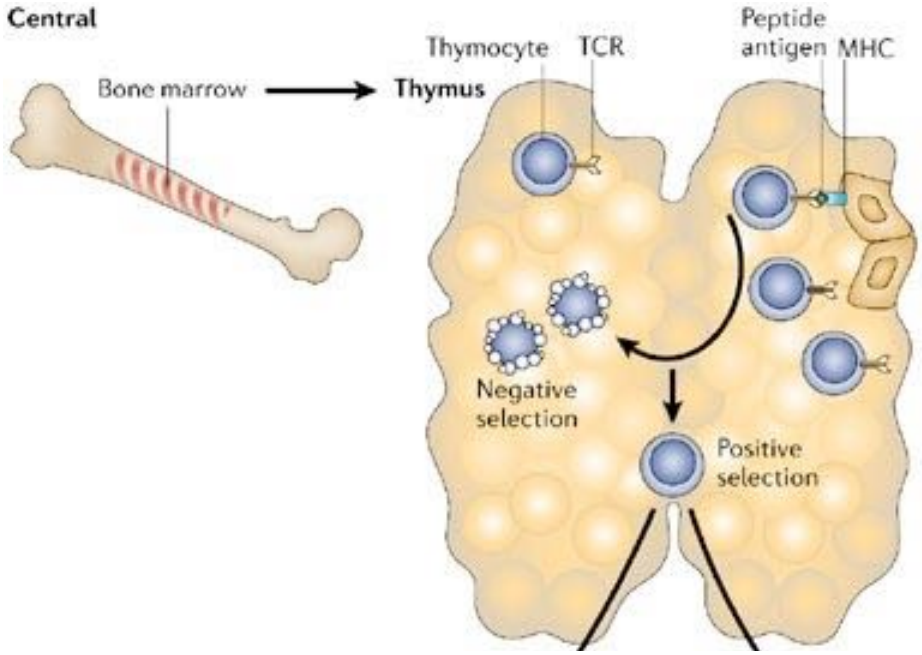


Positive selection: any antigen recognition?

Yes → **Survival**

No → **Elimination**

Central T-cell tolerance



Positive selection: any antigen recognition?

Yes → **Survival** → Negative selection: Strength of antigen recognition?

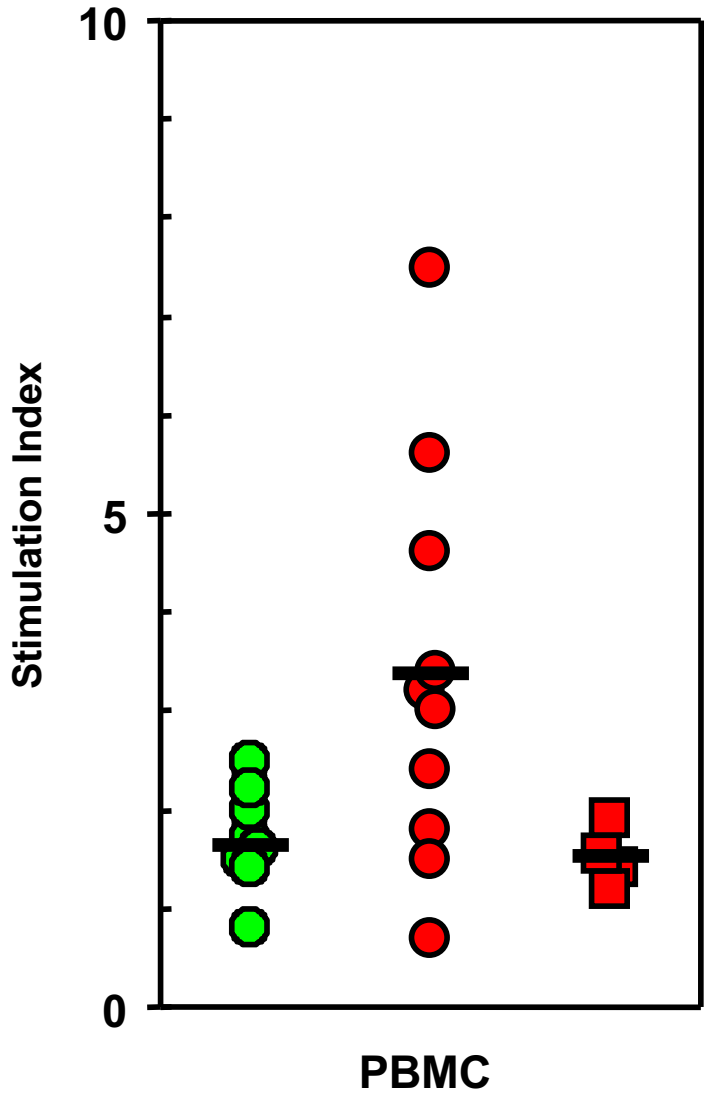
No → **Elimination**

+ / **-**

- **Elimination**
- **Regulatory T cells**
- **Effector T cells**

Central T-cell tolerance to FVIII

Natural FVIII-reactive CD4+ T cells in healthy individuals



Reding Thromb Haemost 1999
Reding Thromb Haemost 2000
Reding Thromb Haemost 2003
Reding Thromb Haemost 2004
Misra Thromb Haemost 2003

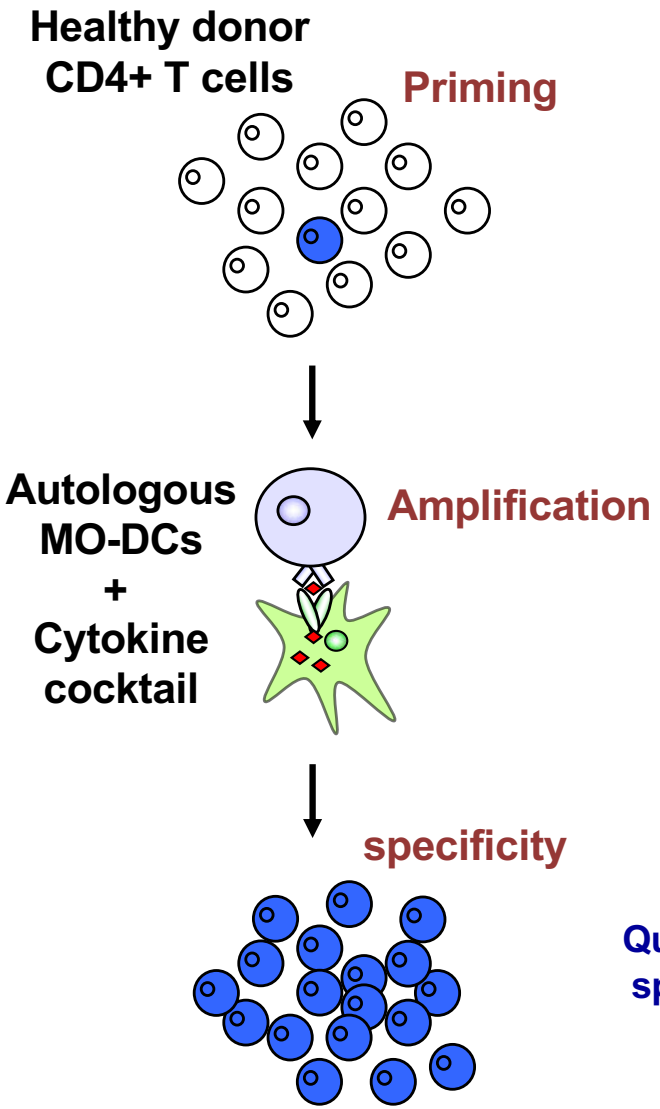
Healthy donors

Patients with inhibitors

Patients without inhibitors

CD4+ T cell amplification assay

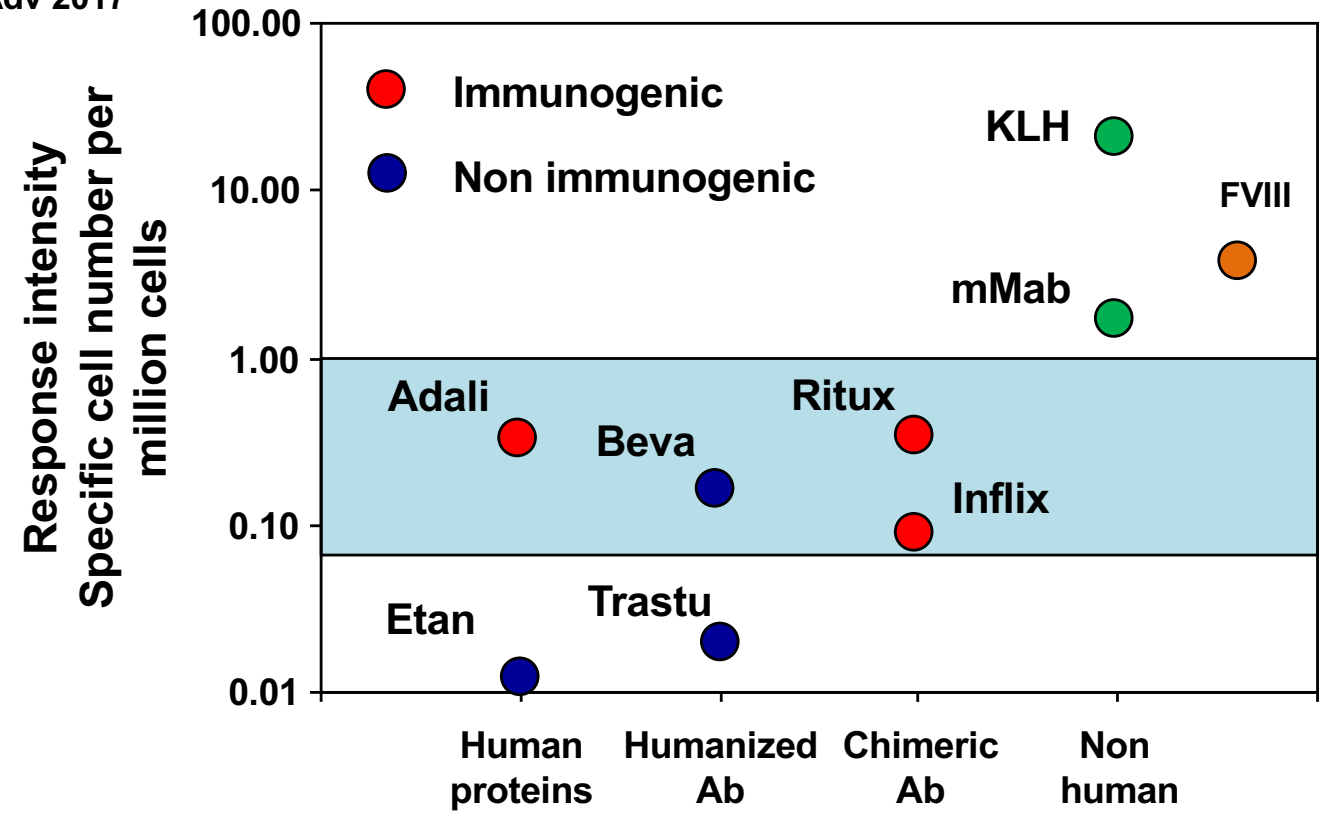
Number of FVIII-specific T cells



Number of FVIII-specific CD4+ T-cells in healthy subjects

Maillere FASEB J 2011

Maillere Blood Adv 2017

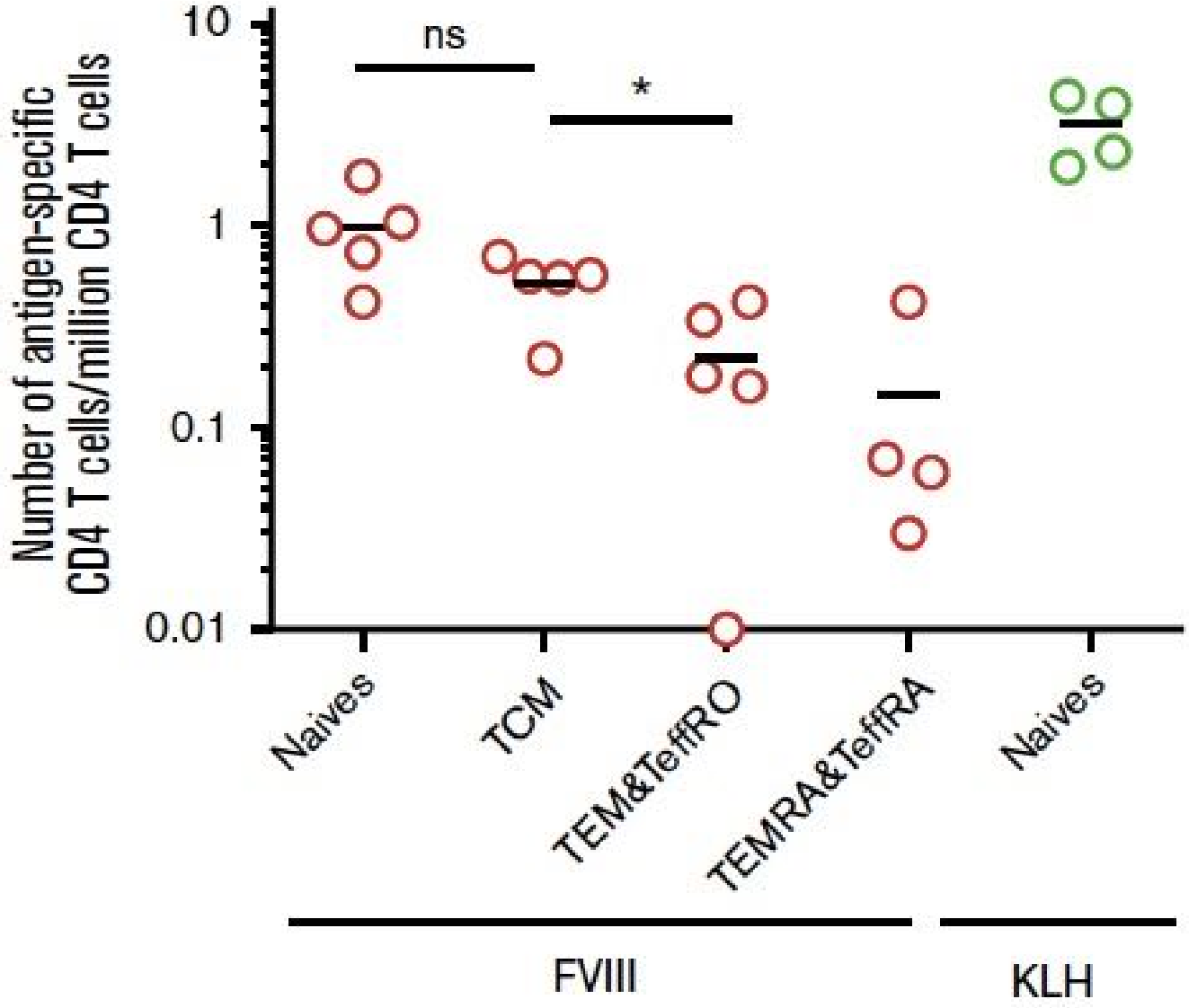


=> Discrimination between immunogenic and non-immunogenic proteins

=> FVIII: 2-4 LT CD4+/million de cellules

Number of FVIII-specific CD4+ T-cells in healthy subjects

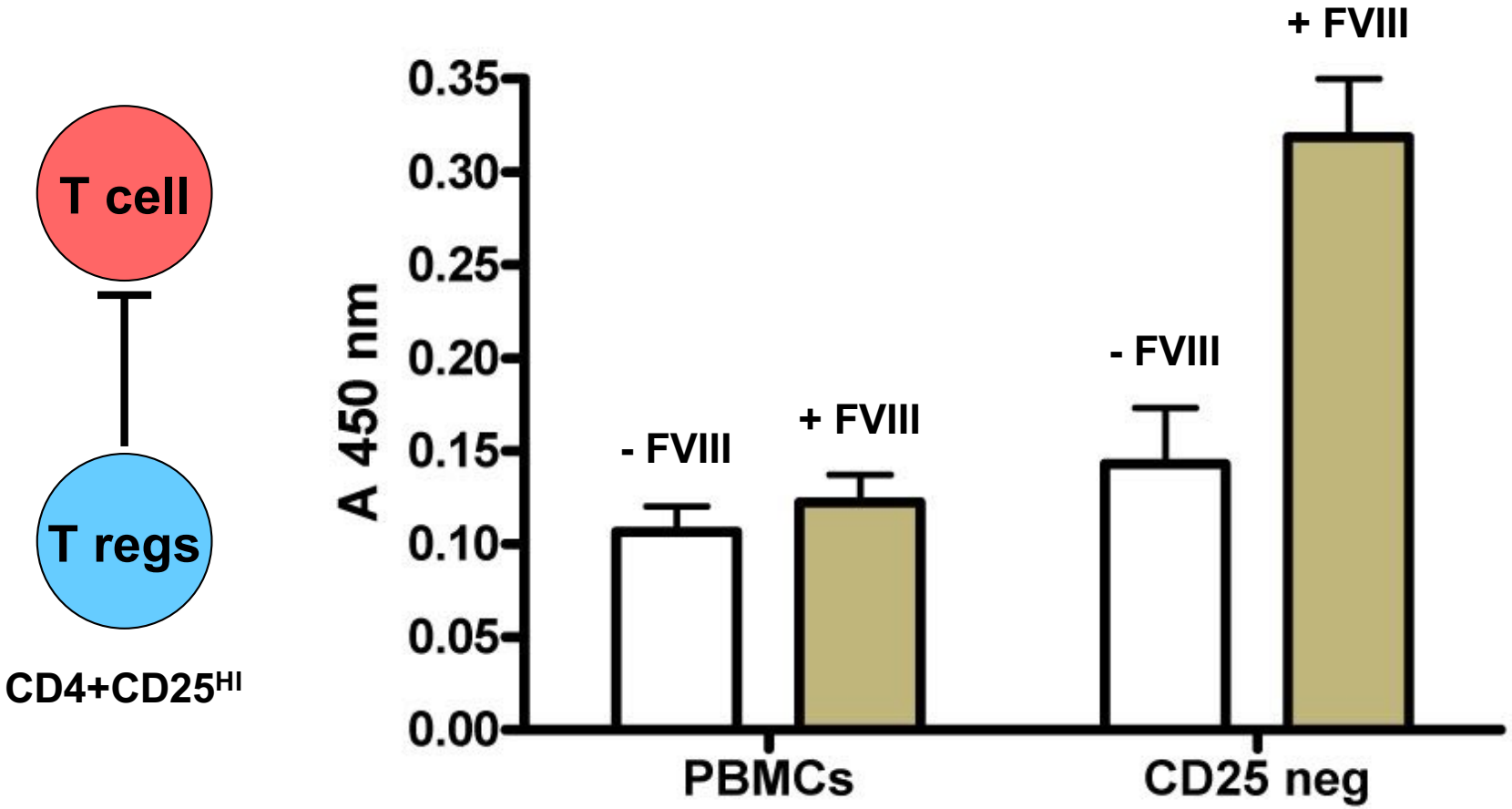
Maillere Blood Adv 2017



T-cell tolerance to FVIII

Natural regulatory CD4+ T cells in healthy individuals

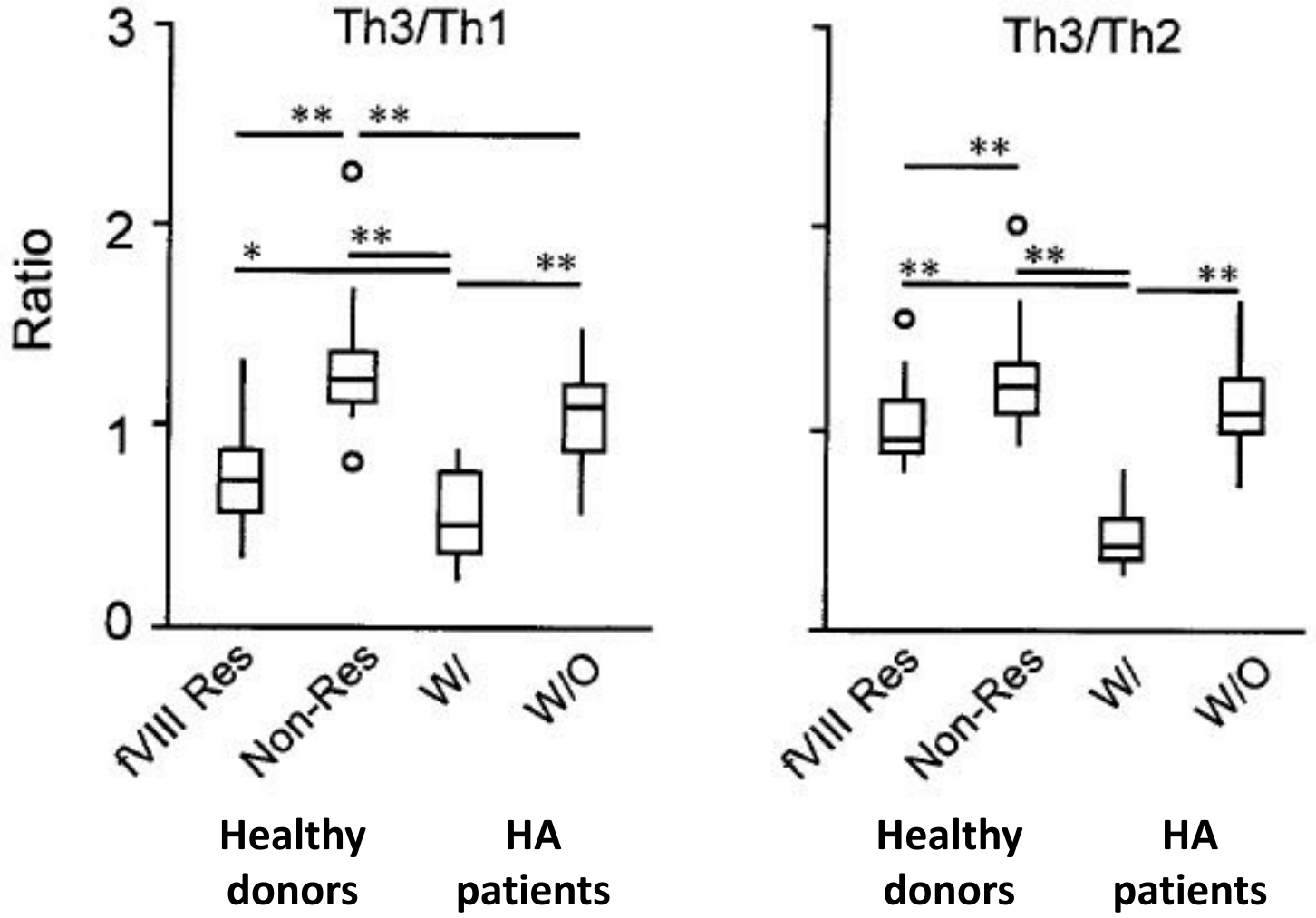
Kamate JTH 2007



Th1 CD4+ T cells: IFN-gamma
Th2 CD4+ T cells: IL-4
Th3 CD4+ T cells: TGF-ß

Peripheral T-cell tolerance to FVIII

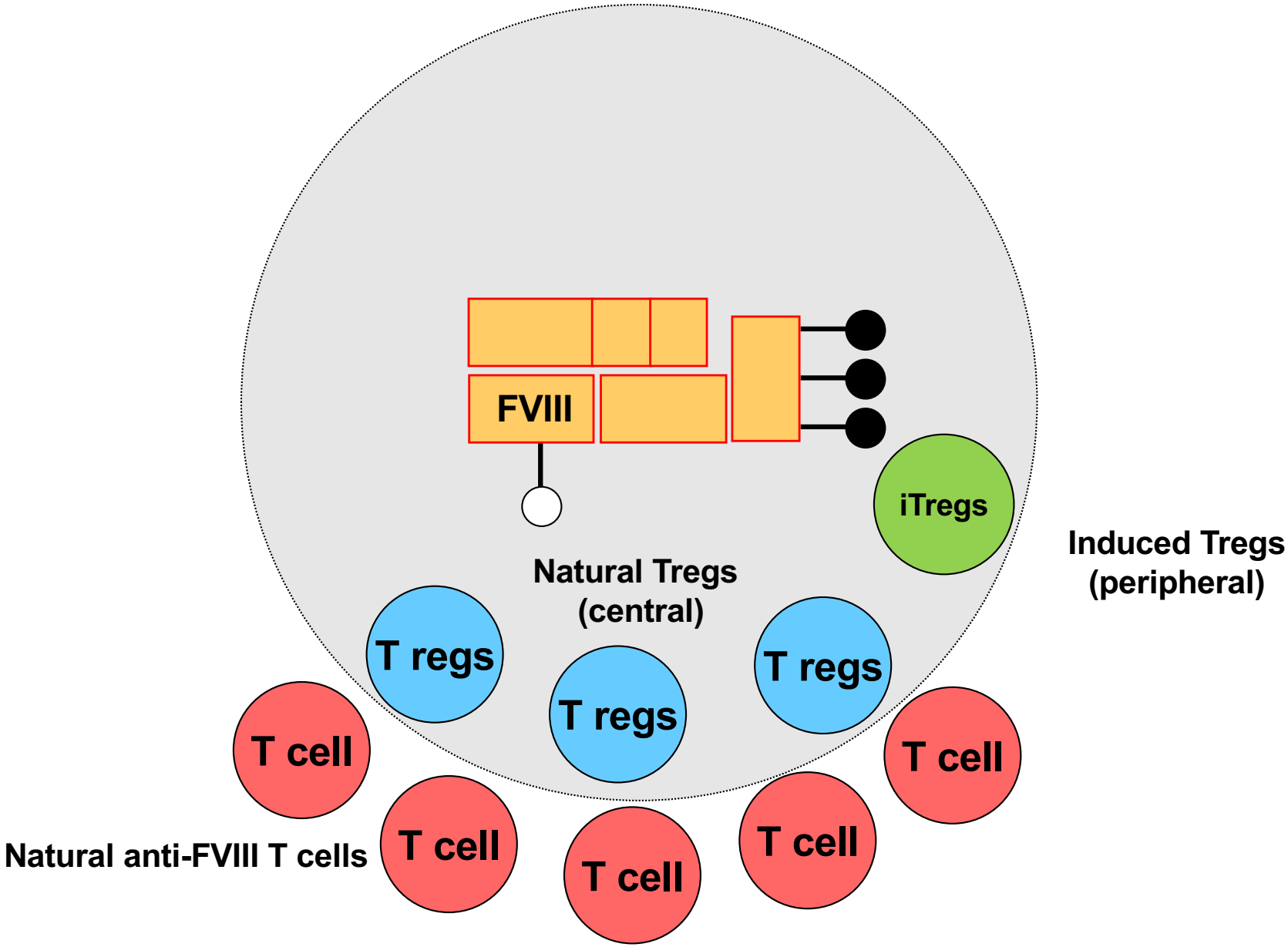
Hu Thromb Haemost 2007



Healthy donors **HA patients** **Healthy donors** **HA patients**

Recognition of FVIII under physiological conditions

T cell level



Selection of B lymphocytes

Elimination of autoreactive clones under physiological conditions

Centrale tolerance

- "receptor editing"

- Deletion of autoreactive B-cell clones

Peripheral tolerance

- Anergy

- Ignorance/Lack of CD4+ T cell help

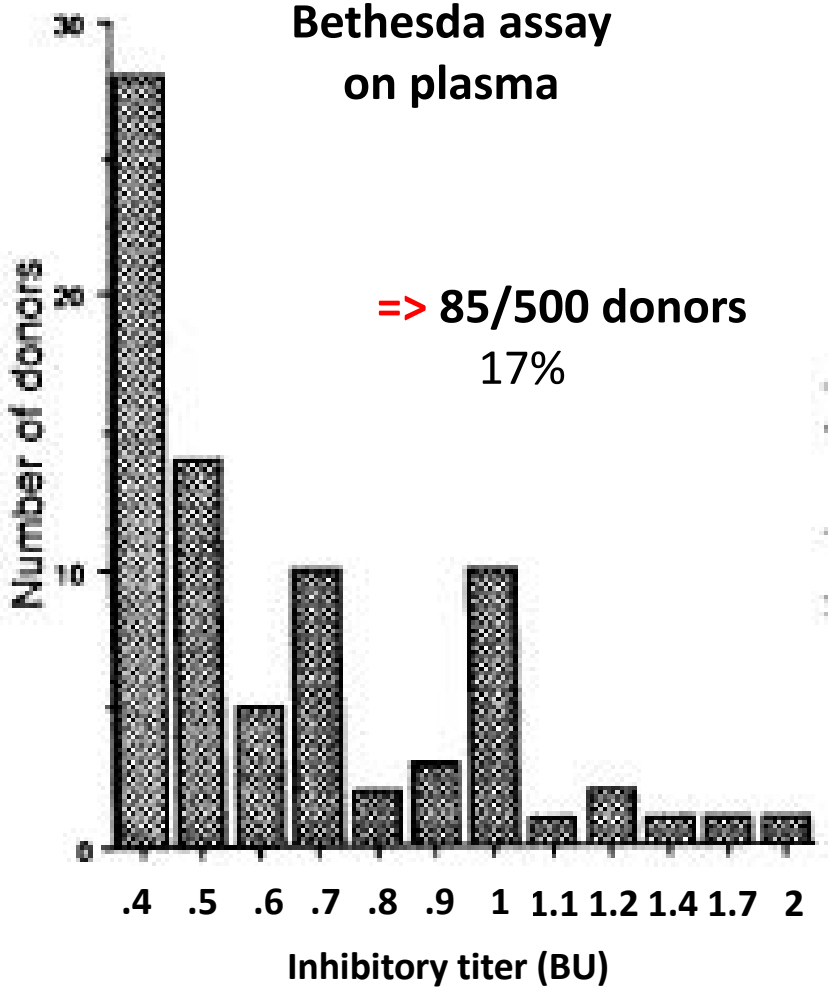
Proc. Natl. Acad. Sci. USA
Vol. 89, pp. 3795–3799, May 1992
Medical Sciences

Natural antibodies to factor VIII (anti-hemophilic factor) in healthy individuals

MARINA ALGIMAN*, GILLES DIETRICH†, URS E. NYDEGGER‡, DENIS BOIELDIEU*, YVETTE SULTAN*, AND MICHEL D. KAZATCHKINE†§

Bethesda assay on plasma

=> 85/500 donors
17%



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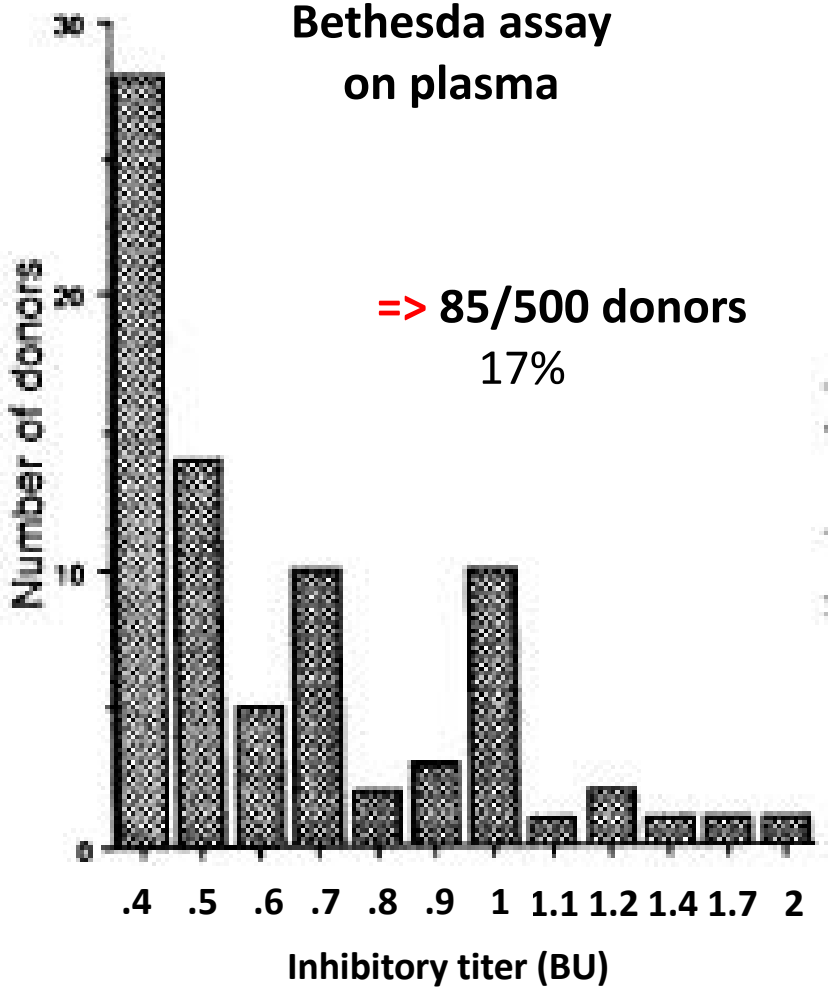
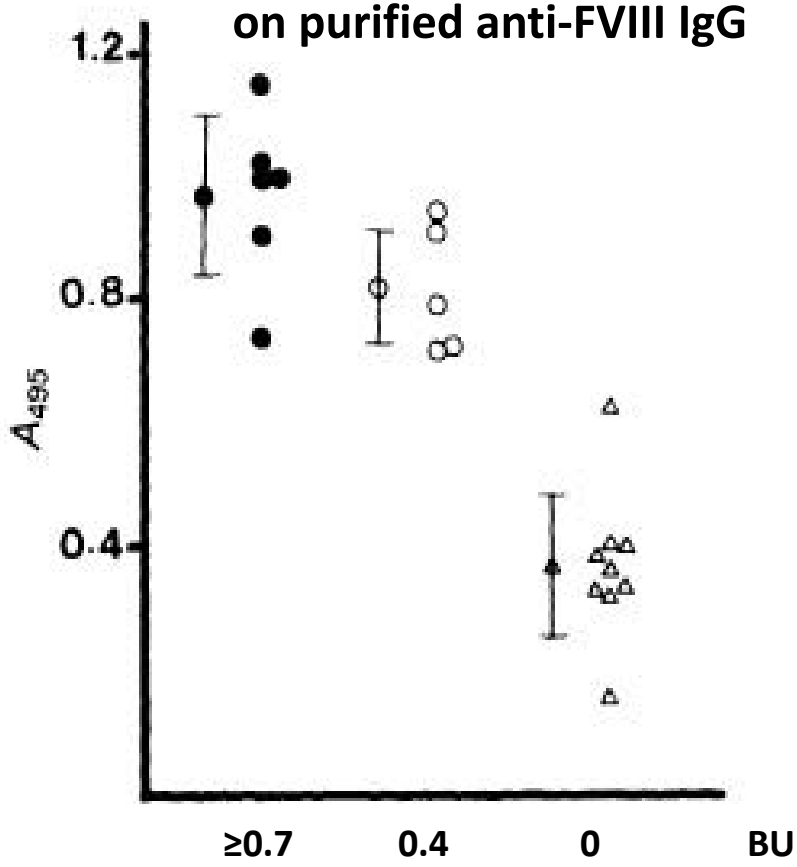


=> 85/500 donors
17%

ELISA on purified anti-FVIII IgG



THROMBOSIS AND HEMOSTASIS

Blood 2013

Distinct characteristics of antibody responses against factor VIII in healthy individuals and in different cohorts of hemophilia A patients

*Shawn F. J. Whelan,[1] *Christoph J. Hofbauer,[1] Frank M. Horling,[1] Peter Allacher,[1] Martin J. Wolfsegger,[1] Johannes Oldenburg,[2] Christoph Male,[3] Jerzy Windyga,[4] Andreas Tiede,[5] Hans Peter Schwarz,[1] Friedrich Scheiflinger,[1] and Birgit M. Reipert[1]

Prevalence of FVIII-binding IgG

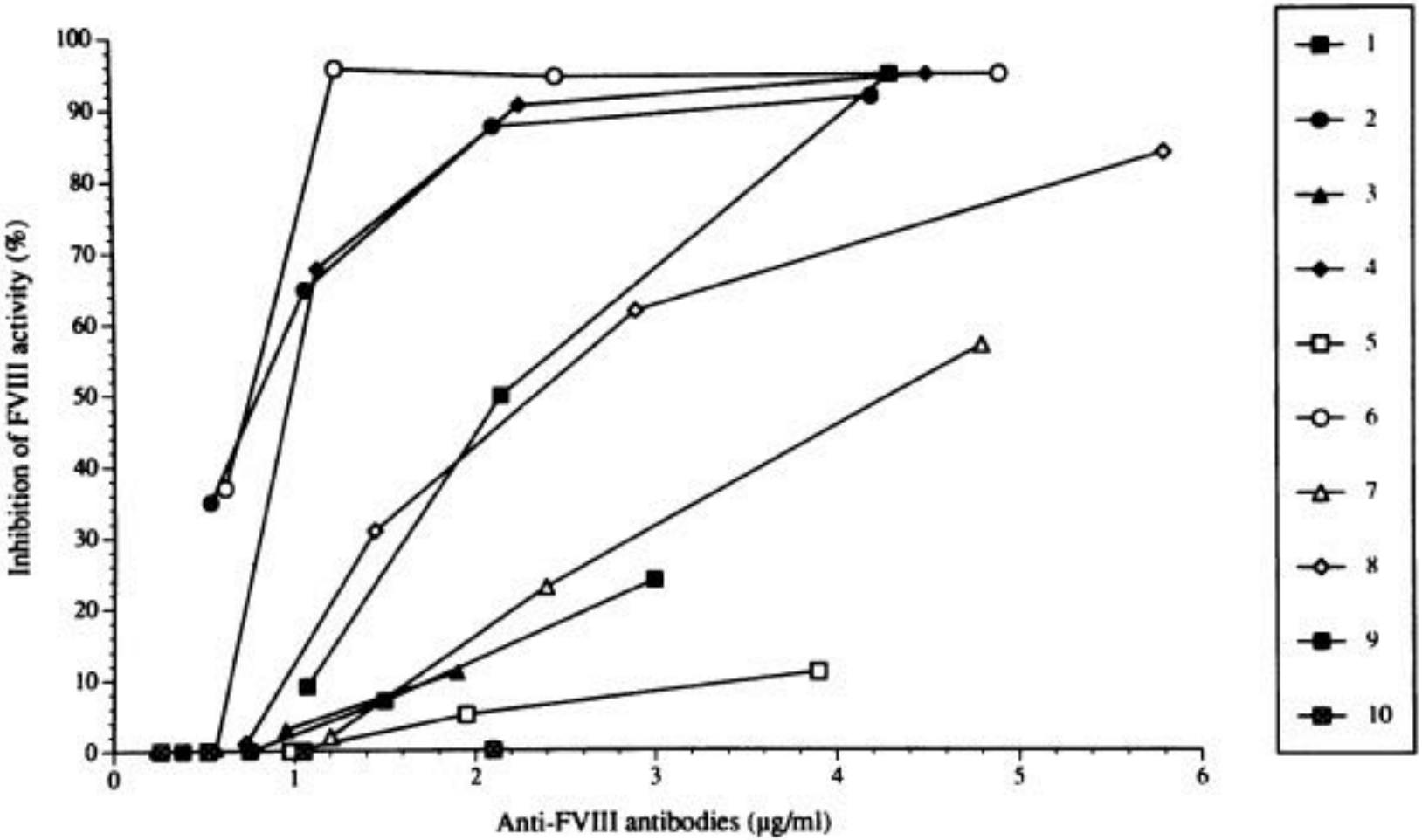
Healthy donors (#600)	**19%**	**IgG1, IgG3, IgA**
Inh-negative HA patients	**34%**	**IgG1, IgG3**
Inh-positive HA patients	**100%**	**IgG1, IgG4**

Healthy Subjects Produce both Anti–Factor VIII and Specific Anti-Idiotypic Antibodies

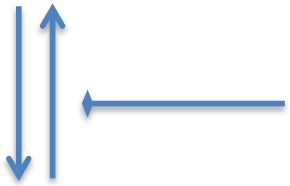
J Clin Invest 1994

Jean Guy Gilles and Jean-Marie R. Saint-Remy

Allergy and Clinical Immunology Unit, Institute of Cellular and Molecular Pathology, Université Catholique de Louvain, 1200 Brussels, Belgium



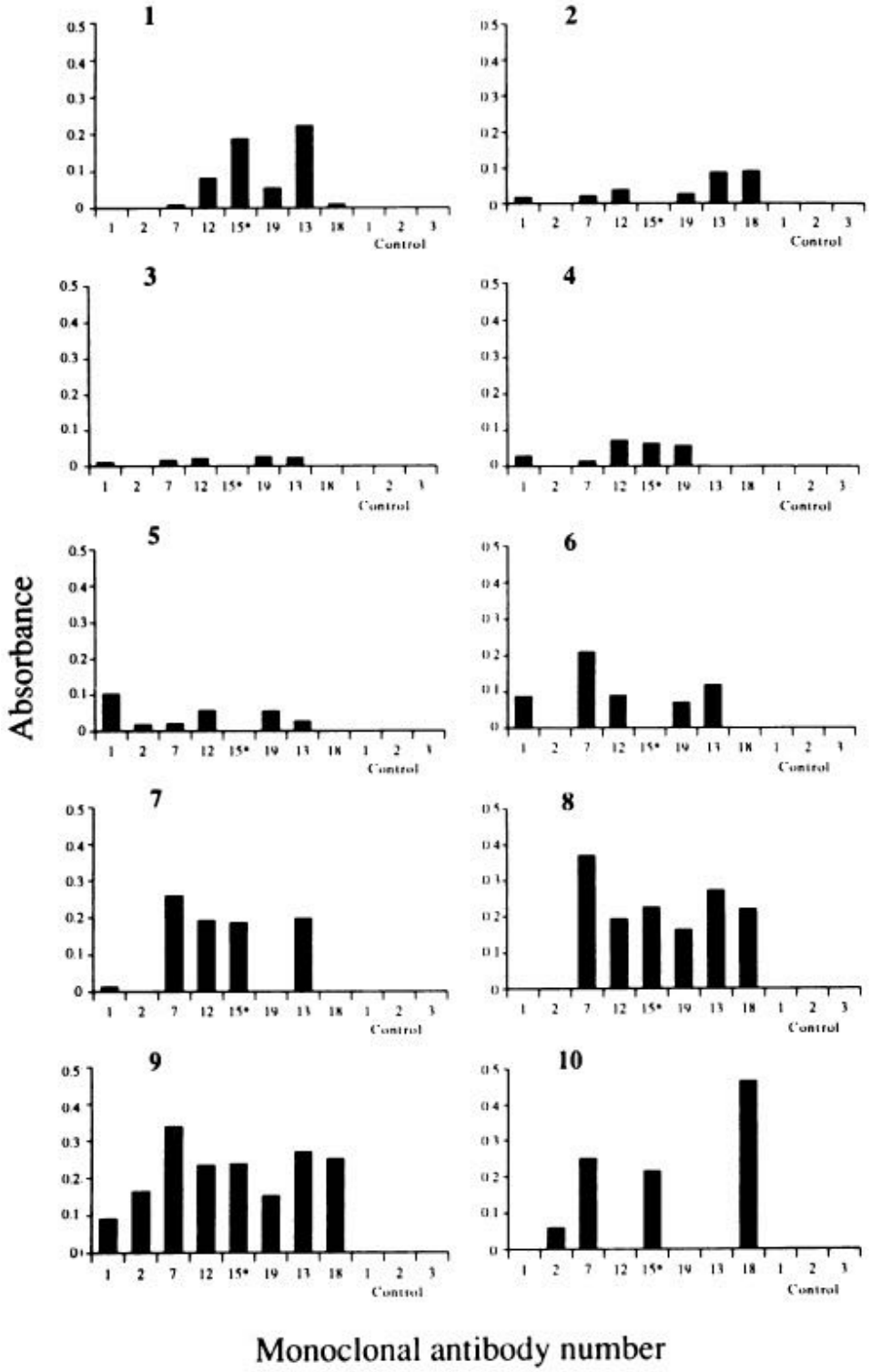
FVIII-biot



Anti-FVIII IgG-depleted fraction

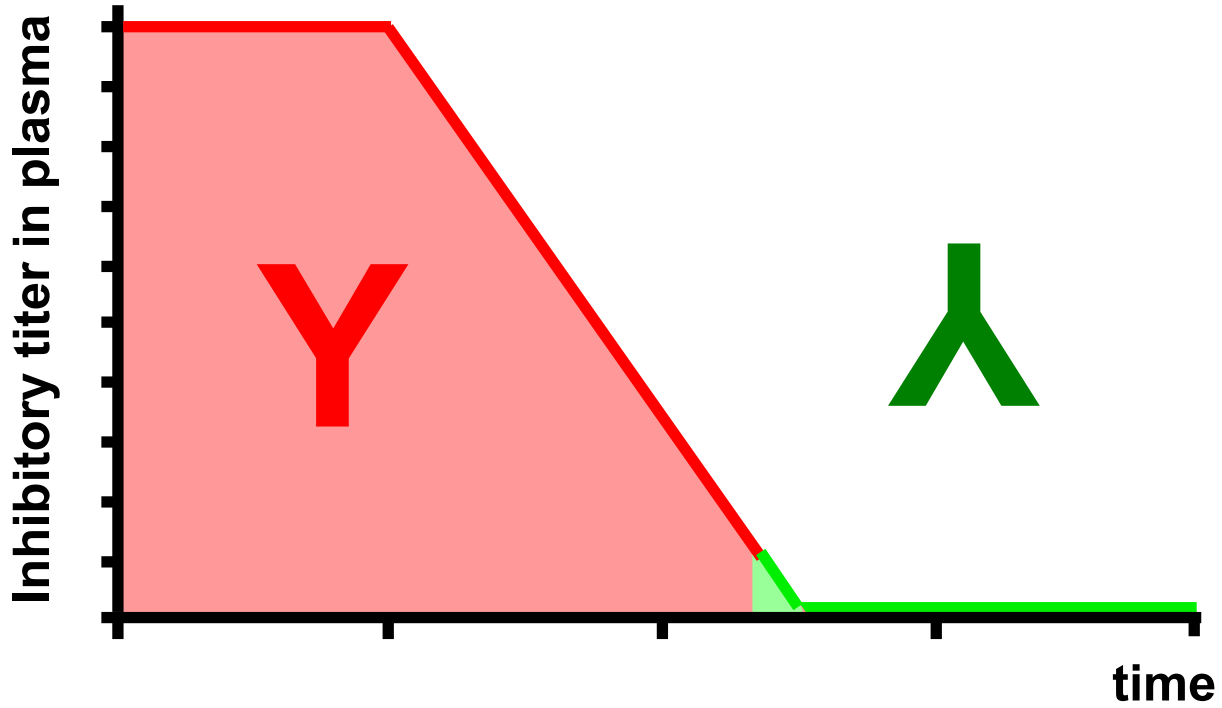
Y

Anti-FVIII mAb



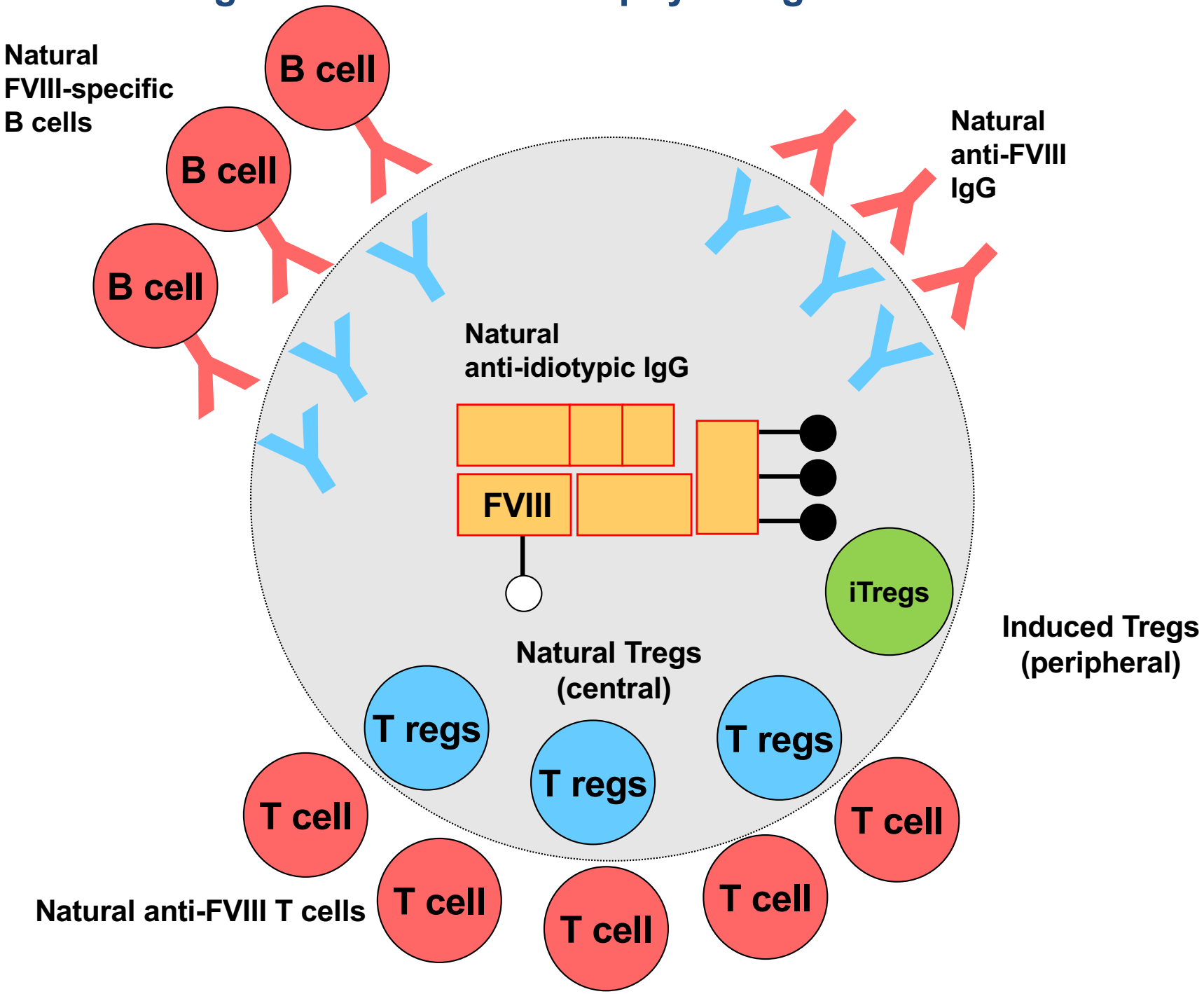
Remission in acquired hemophilia A

Sultan PNAS 1987

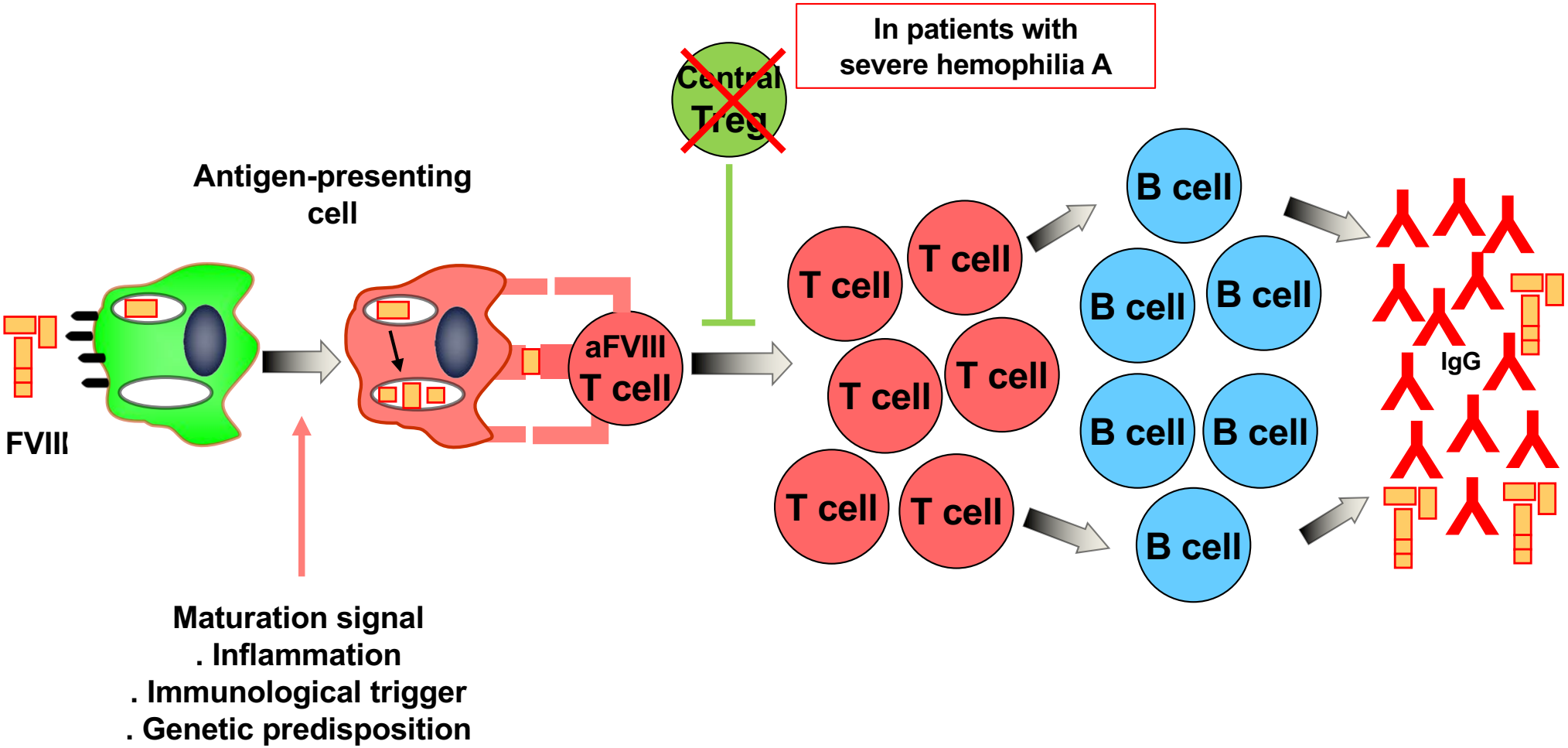


IgG	FVIII inhibition
Y	+
λ	-
Y + λ	-

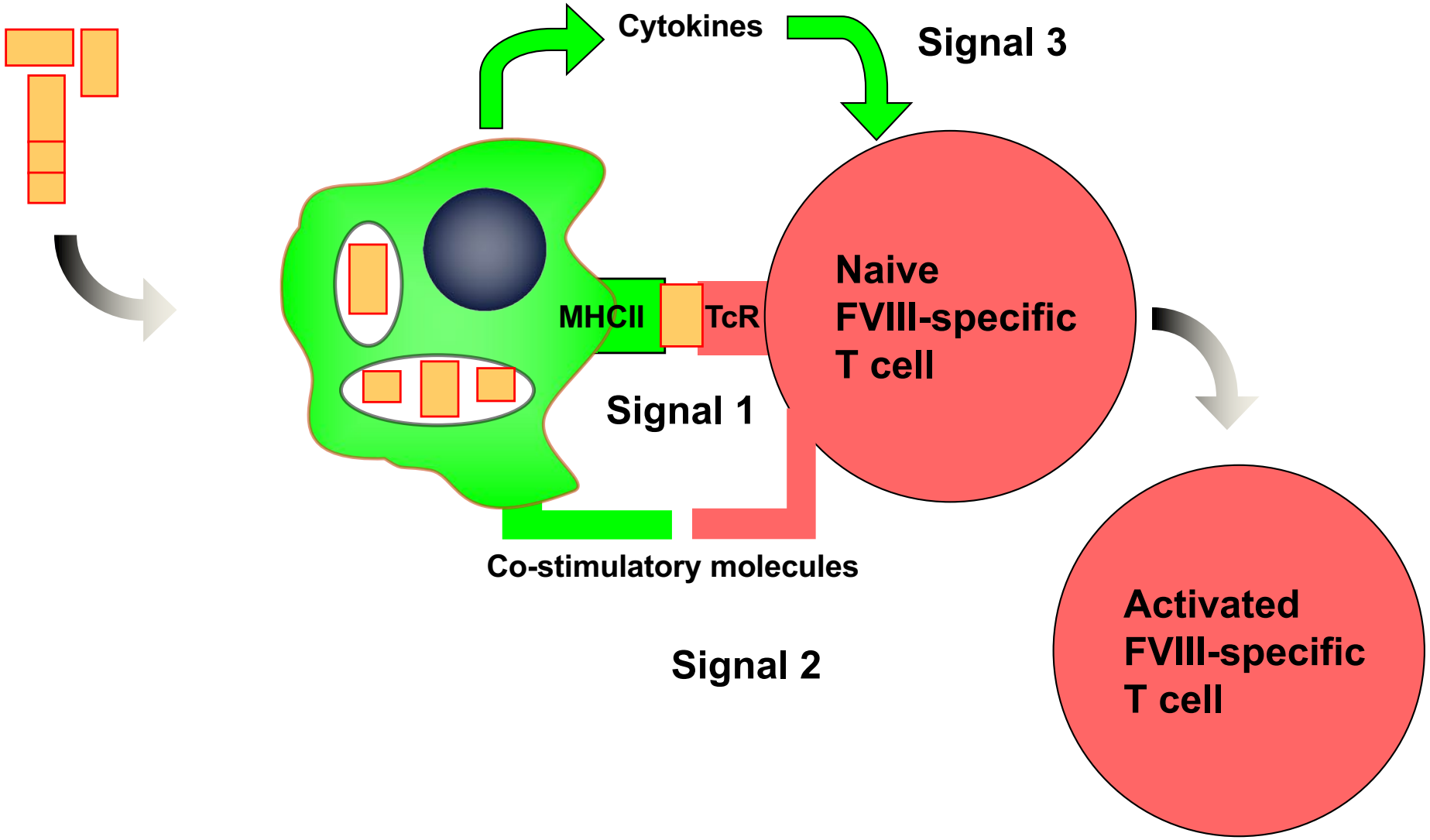
Recognition of FVIII under physiological conditions



Immune response to factor VIII



Immune response to factor VIII



Risk factors for the development of FVIII inhibitors

I. Risk factors related to the patient

- Severity of hemophilia A
- Type of mutation
- Ethnic group
- Familial history of inhibitor
- Age at first FVIII infusion
- HLA type

II. Risk factors related to the method

- Method of inhibitor detection
- Frequency of inhibitor investigation - transitory inhibitors
- Definition of strong/weak responder
- Presence of associated autoAb or anti-phospholipid Ab

III. Risk factors related to the product

- Purity of FVIII
- Method of industrial production
- Method of viral inactivation
- Associated medication (vaccination, IFNg…)

IV. Risk factors related to the administration

- Increase of the dose
- Type of bleeding
- Change in FVIII used for treatment
- Surgical procedure
- Associated infection/inflammation

ISTH sub-committee 2003

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ISTH sub-committee 2003

Risk factors for the development of FVIII inhibitors

Rating of risk factors for inhibitor development

Haemophilia
The Official Journal of the World Federation of Hemophilia,
European Association for Haemophilia and Allied Disorders and
the Hemostasis & Thrombosis Research Society

Haemophilia (2016), **22**, 657–666 DOI: 10.1111/hae.13075

Cor REVIEW ARTICLE

Non-genetic risk factors in haemophilia A inhibitor management – the danger theory and the use of animal models

K. M. LÖVGREN,*† H. SØNDERGAARD,‡ S. SKOV* and B. WIINBERG§
*Department of Veterinary Disease Biology University of Copenhagen, Frederiksberg; †Translational Haemophilia Pharmacology, Global Research, Novo Nordisk A/S, Maaloev; ‡Diabetes Complications Pharmacology, Global Research, Novo Nordisk A/S, Maaloev; and §Haemophilia Translational Biology, Global Research Novo Nordisk A/S, Maaloev, Denmark

Percentage of respondents rating the factor important (4) or very important (5) for inhibitor development

From EHTSB Survey Haemophilia 2010

Haemophilia
The Official Journal of the World Federation of Hemophilia,
European Association for Haemophilia and Allied Disorders and
the Hemostasis & Thrombosis Research Society

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REVIEW ARTICLE

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**Department of Veterinary Disease Biology University of Copenhagen, Frederiksberg; †Translational Haemophilia Pharmacology, Global Research, Novo Nordisk A/S, Maaloev; ‡Diabetes Complications Pharmacology, Global Research, Novo Nordisk A/S, Maaloev; and §Haemophilia Translational Biology, Global Research Novo Nordisk A/S, Maaloev, Denmark*

In haemophilia A (HA) management, antidrug antibodies, or inhibitors, are a serious complication that renders factor VIII (FVIII) replacement therapy ineffective, increases morbidity and reduces quality of life for affected patients. Inhibitor development aetiology is multifactorial and covers both genetic and therapy related risk factors. Many therapy-related risk factors have proven difficult to confirm due to several confounding factors and the small study populations available. However, clinical studies indicate that e.g. on-demand treatment and surgery affect inhibitor development, and explanations for this association are being investigated. A potential explanation is the danger signal effect, where the immune response is activated by endogenous or exogenous danger or damage signals present at the time and site of FVIII administration. The danger theory explains how alarm signals from stressed, injured or dying cells can activate an immune reaction, without the involvement of foreign antigens. Bleeds, trauma, surgery or concomitant infection could be events initiating danger signalling in HA patients, resulting in an immune reaction towards administered FVIII that otherwise would pass unnoticed. This role of danger in HA inhibitor formation has previously been suggested, but a thorough discussion of this subject is lacking. The present review will discuss the potential role of danger signals in haemophilia and inhibitor development, with focus on treatment related risk factors with a suspected danger signal aetiology; on-demand treatment, treatment during major bleeds or surgery, and treatment during infection or vaccination. Clinical studies as well as animal experiments addressing these factors will be reviewed.

Haemophilia

Haemophilia (2010), 16, 256–262 DOI: 10.1111/j.1365-2516.2009.02122.x

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GmbH,

Early prophylaxis/FVIII tolerization regimen that avoids immunological danger signals is still effective in minimizing FVIII inhibitor developments in previously untreated patients – long-term follow-up and continuing experience

G. AUERSWALD,* C. BIDLINGMAIER† and K. KURNIK†

*Prof. Hess Childrens Hospital, Klinikum Bremen-Mitte, Bremen, Germany; and †Klinikum der Universitaet Muenchen, Dr von Haunersches Childrens Hospital, Munich, Germany

Correspondence: Günter Auerswald, MD, Prof. Hess Childrens Hospital, Klinikum Bremen-Mitte, St-Jürgen-Strasse 1; D-28177 Bremen, Germany. Tel.: +49 (421) 497 3655; fax: +49 (421) 497 4631; e-mail: guenterauerswald@aol.com

Accepted after revision 25 August 2011

DOI: 10.1111/j.1365-2516.2011.02659.x

Randomized clinical studies have clearly demonstrated that regular prophylactic administration of factor VIII (FVIII), started at an early age, was able to prevent life-threatening bleeds, as well as, reduce physical impairment from haemophilic arthropathy in children with severe haemophilia A [1,2]. Current guidelines recommend that primary prophylaxis in children with severe haemophilia A should be started before the age of 2 years either without previous joint bleed

EPIC study based on this concept – terminated in 2012 due to 40% inh (Baxter set up)

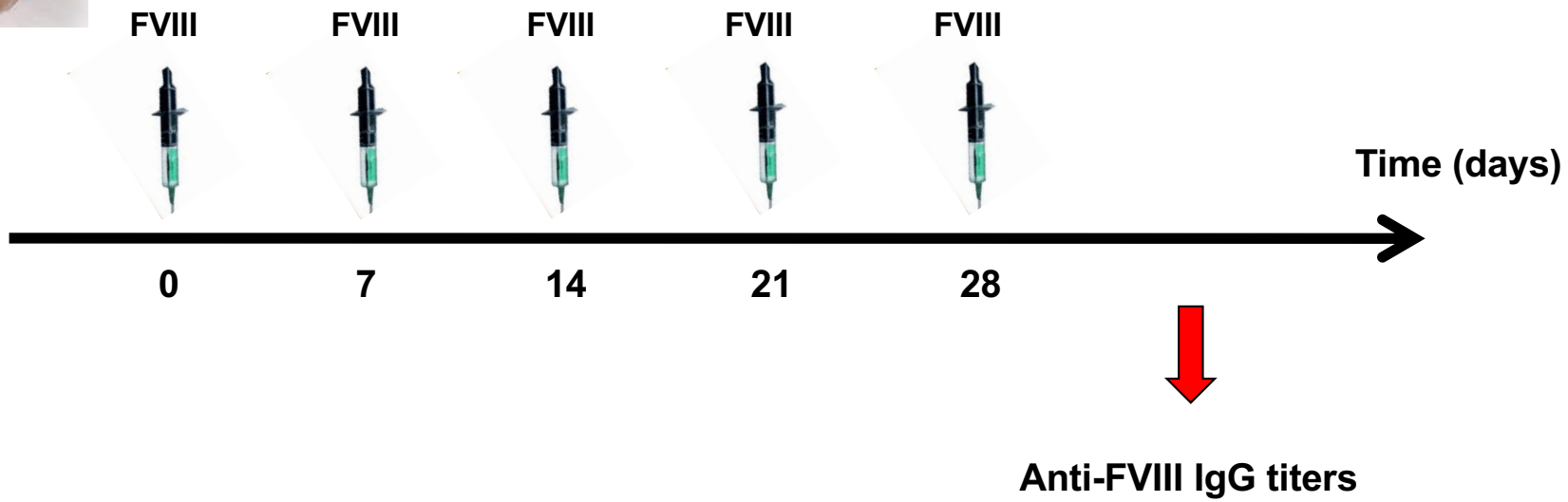
"Immunogenic" presentation of FVIII to naive CD4+ T cells

Desperately seeking danger signals

1. Antigen dose
2. Pro-coagulant activity of FVIII
3. FVIII antigen
4. Vaccination
5. Hemolysis/Acute bleeding
6. Control of inflammation

Ze model: FVIII-deficient mice

FVIII KO mice



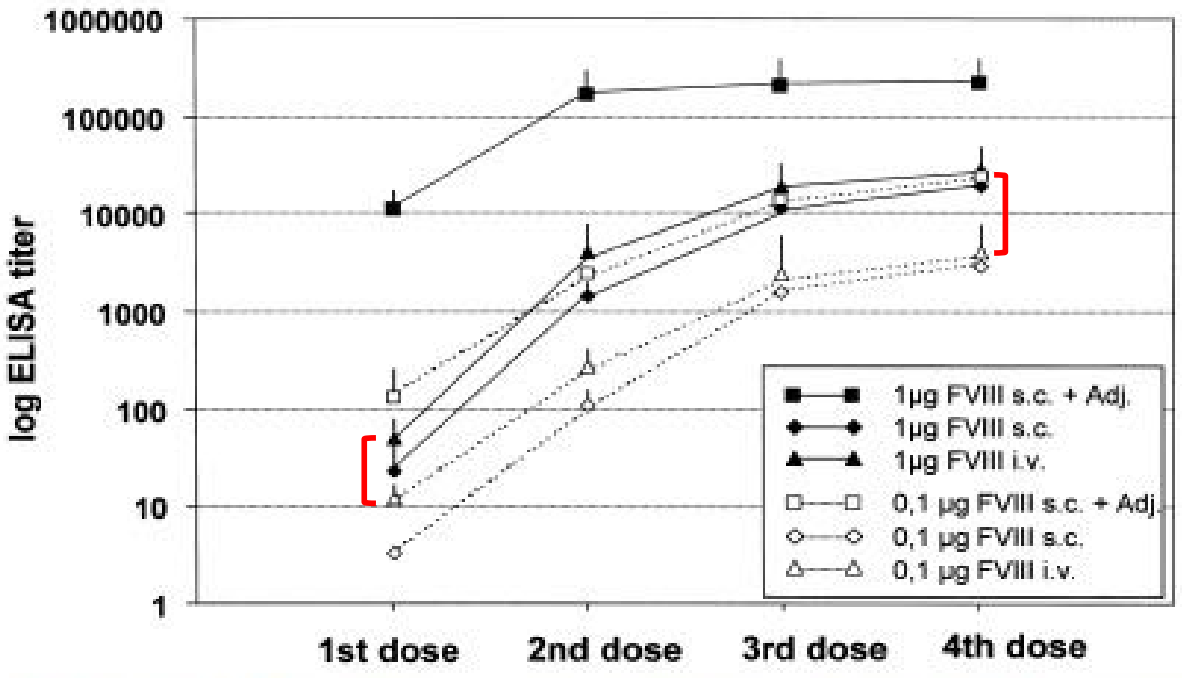
Antigen dose 1/5

Thromb Haemost 2000; 84: 826–32

Characterization of Antibodies Induced by Human Factor VIII in a Murine Knockout Model of Hemophilia A

Birgit M. Reipert, Rafi U. Ahmad, Peter L. Turecek, Hans P. Schwarz

Effect of dose on anti-factor VIII antibody formation determined by ELISA in FVIII-KO mice in response to human rFVIII



If 10 IU per 2 µg,
1 µg → 250 IU/kg
0.1 µg → 25 IU/kg

Antigen dose 1/5

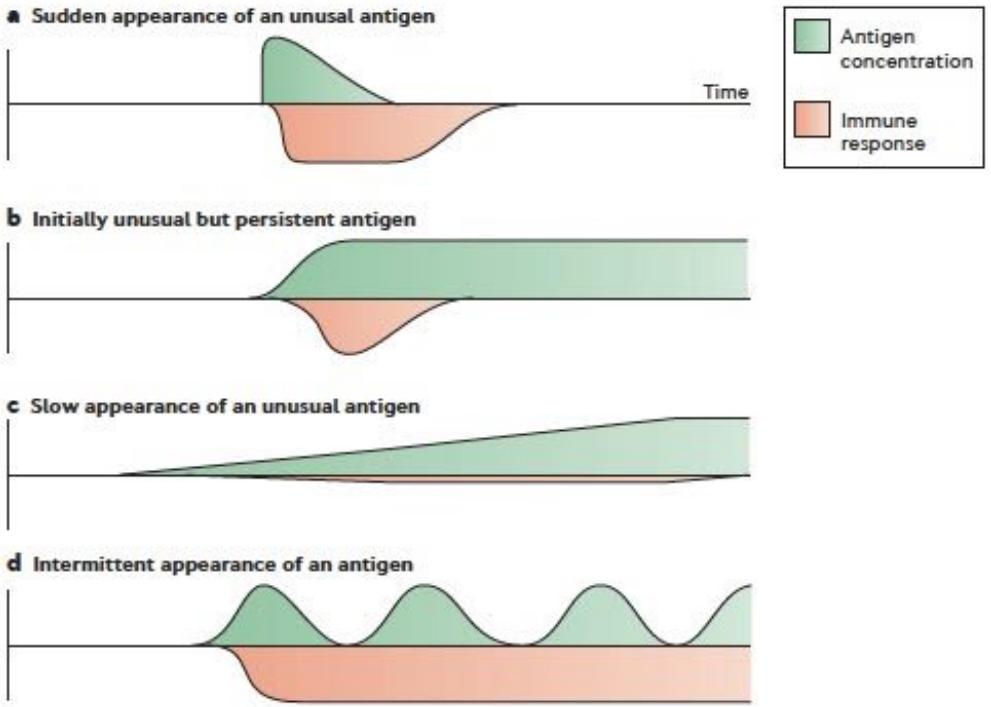
PERSPECTIVES

ESSAY

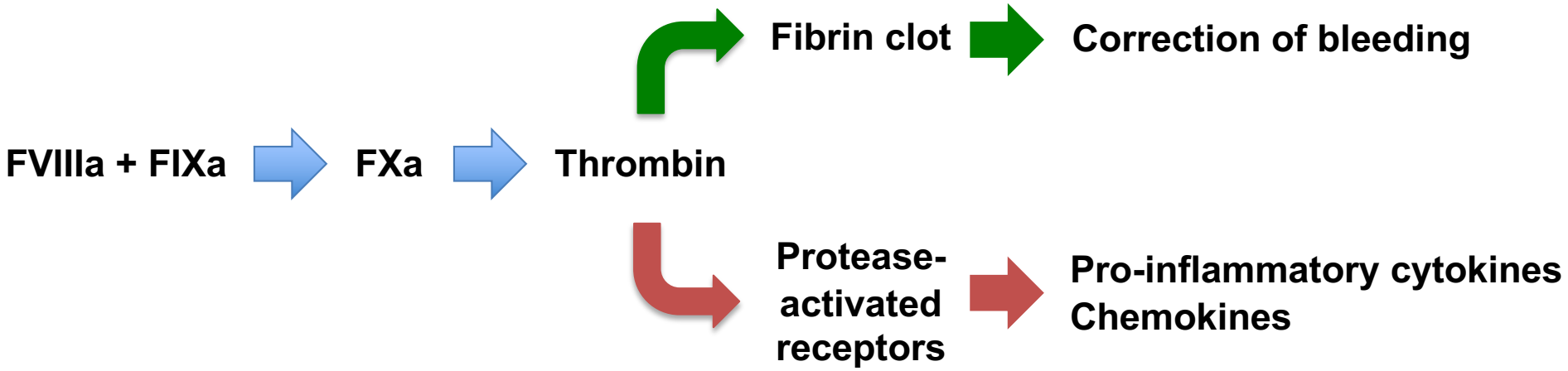
The speed of change: towards a discontinuity theory of immunity?

Thomas Pradeu, Sébastien Jaeger & Eric Vivier

NATURE REVIEWS | IMMUNOLOGY VOLUME 13 | OCTOBER 2013 | 765



Pro-coagulant activity of FVIII 2/5



Pro-coagulant activity of FVIII 2/5

A role for thrombin in the initiation of the immune response to therapeutic factor VIII

Jonathan Skupsky,[1] Ai-Hong Zhang,[1] Yan Su,[1] and David W. Scott[1-3]

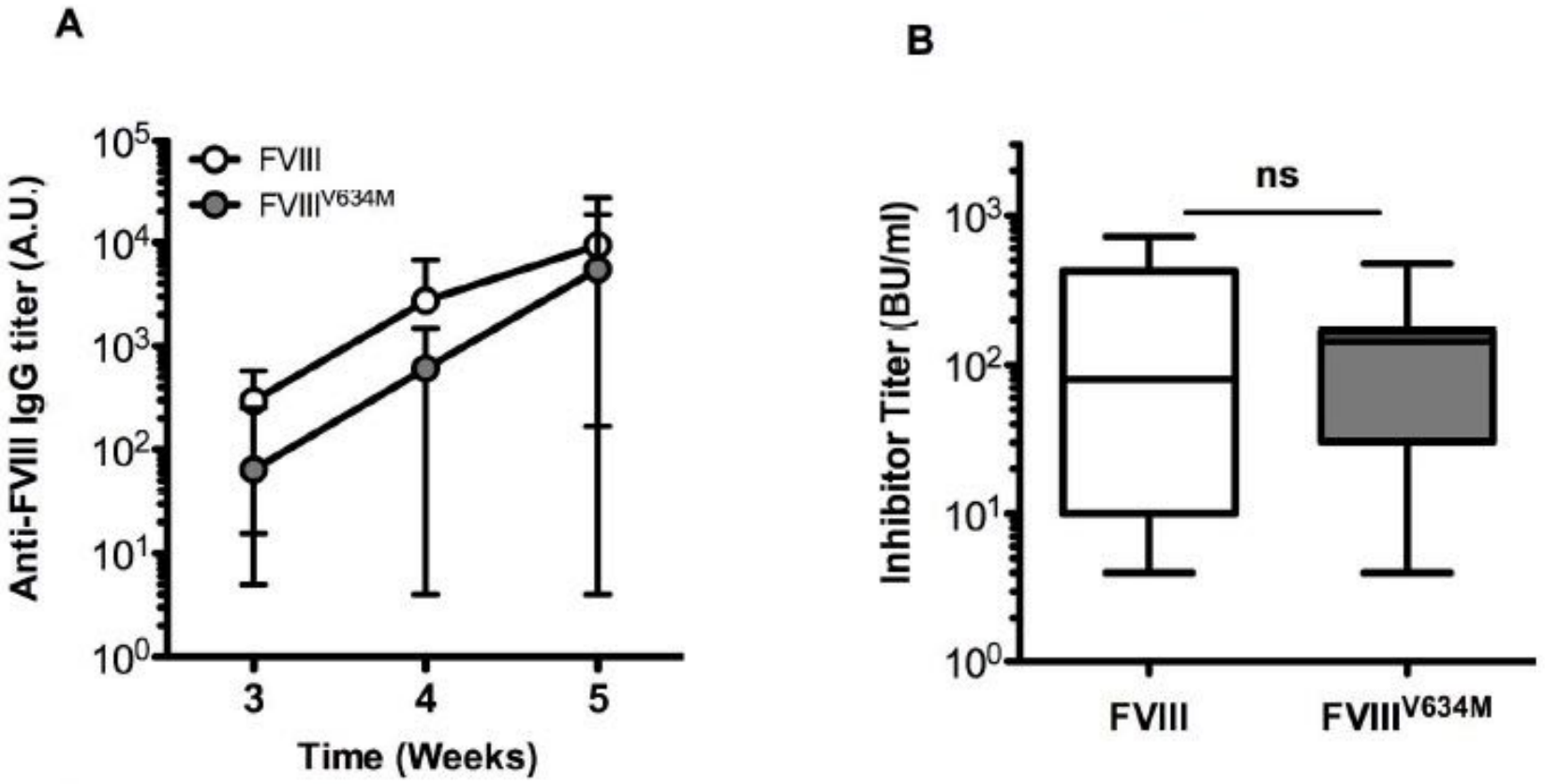
Blood 2009

Role of coagulation-associated processes on factor VIII immunogenicity in a mouse model of severe hemophilia A

B. GANGADHARAN,*†‡ S. DELIGNAT,*†‡ V. OLLIVIER,§ N. GUPTA,*†‡ N. MACKMAN,¶ S. V. KAVERI*†‡ and S. LACROIX-DESMAZES*†‡

JTH 2014

Pro-coagulant activity of FVIII 2/5



Gangadharan JTH 2014

FVIII antigen 3/5

Thromb Haemost. 2006 Sep;96(3):309-16.

Recombinant factor VIII and factor VIII-von Willebrand factor complex do not present danger signals for human dendritic cells.

Pfistershammer K[1], Stöckl J, Siekmann J, Turecek PL, Schwarz HP, Reipert BM.

Haemophilia (2012), 1–4 DOI: 10.1111/hae.12087

Therapeutic factor VIII does not trigger TLR1.2 and TLR2.6 signalling *in vitro*

M. TEYSSANDIER,*†‡ S. ANDRÉ,*†‡ N. GUPTA,*†‡ S. DASGUPTA,*†‡§ J. BAYRY,*†‡¶** S. V. KAVERI*†‡¶** and S. LACROIX-DESMAZES1*†‡¶** ON BEHALF OF THE ABIRISK CONSORTIUM

ABIRISK

Coagulation and Fibrinolysis

ABIRISK

Danger signal-dependent activation of human dendritic cells by plasma-derived factor VIII products

Lilija Miller[1]; Sabrina Weissmüller[1]; Eva Ringler[1]; Peter Crauwels[2]; Ger van Zandbergen[2]; Rainer Seitz[3]; Zoe Waibler[1]; on behalf of the ABIRISK consortium

[1]Junior Research Group "Novel Vaccination Strategies and Early Immune Responses", Paul-Ehrlich-Institut, Langen, Germany; [2]Division of Immunology, Paul-Ehrlich-Institut, Langen, Germany; [3]Division of Haematology / Transfusion Medicine, Paul-Ehrlich-Institut, Langen, Germany

FVIII antigen 3/5

Contents lists available at ScienceDirect

Cellular Immunology

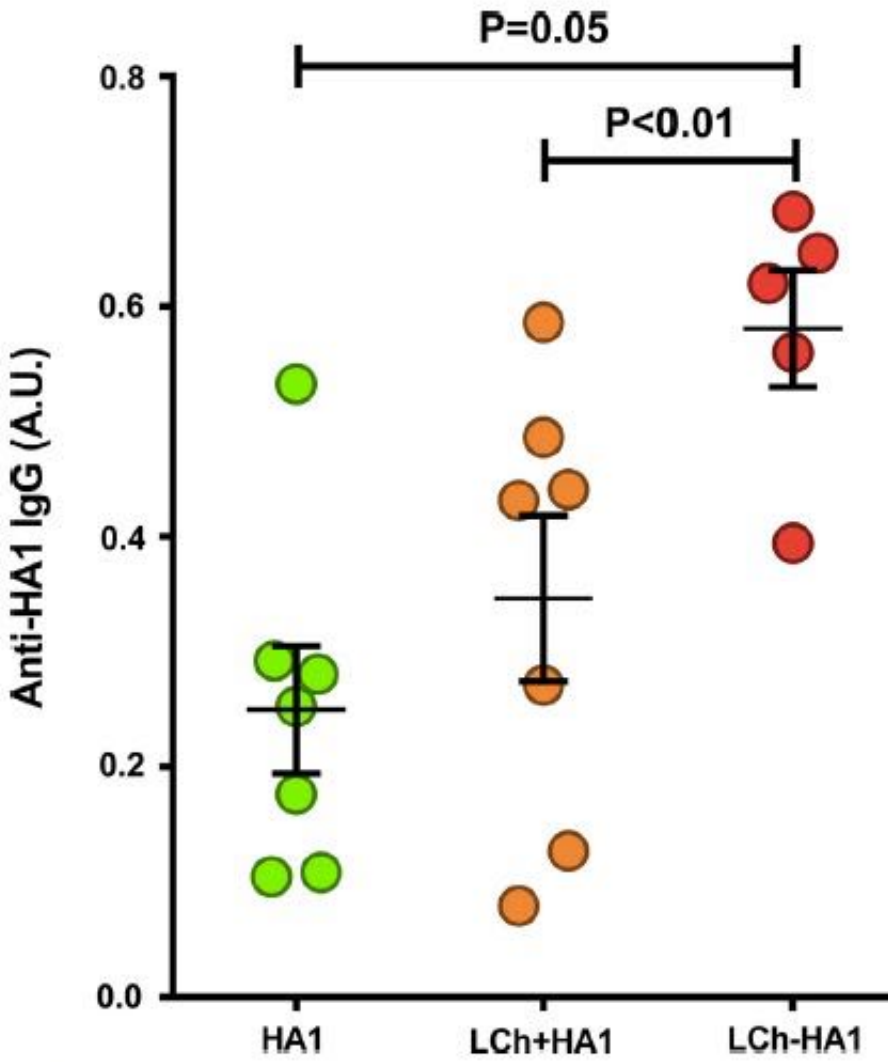
journal homepage: www.elsevier.com/locate/ycimm

Review article

Immunogenicity of long-lasting recombinant factor VIII products

Mathieu Ing[a,b,c], Nimesh Gupta[d], Maud Teyssandier[a,b,c], Bernard Maillère[e], Marc Pallardy[f], Sandrine Delignat[a,b,c], Sébastien Lacroix-Desmazes[a,b,c,*], on behalf of the ABIRISK consortium

[a] Sorbonne Universités, Université Pierre et Marie Curie, UMR_S 1138, Centre de Recherche des Cordeliers, F-75006 Paris, France
[b] INSERM, UMR_S 1138, Centre de Recherche des Cordeliers, F-75006 Paris, France
[c] Sorbonne Paris Cité, Université Paris Descartes, UMR_S 1138, Centre de Recherche des Cordeliers, F-75006 Paris, France
[d] National Institute of Immunology, New Delhi, India
[e] CEA-Saclay Institute of Biology and Technologies, Gif sur Yvette, France
[f] INSERM, UMR996, Faculté Pharmacie, Université Paris Sud, France



Vaccination 4/5

Regular Article

blood

THROMBOSIS AND HEMOSTASIS

Concurrent influenza vaccination reduces anti-FVIII antibody responses in murine hemophilia A

Jesse D. Lai,[1] Paul C. Moorehead,[2,3] Kate Sponagle,[1] Katharina N. Steinitz,[4] Birgit M. Reipert,[4] Christine Hough,[1] and David Lillicrap[1]

Key Points

- Vaccination against influenza, with and without the adjuvant MF59, decreases the risk of inhibitor development in HA mice.
- Decreased FVIII immunogenicity may be attributed to antigenic competition via T-cell chemotaxis toward the site of vaccination.

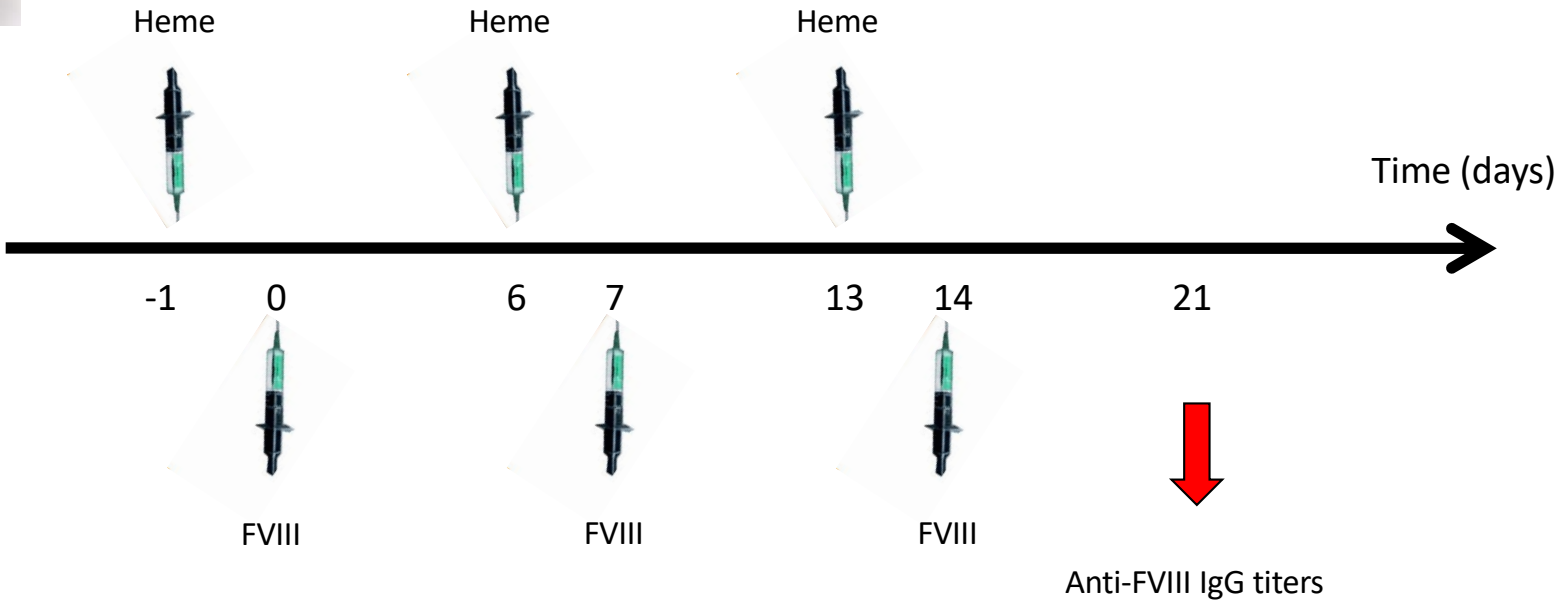
Pednet study:

Work submitted

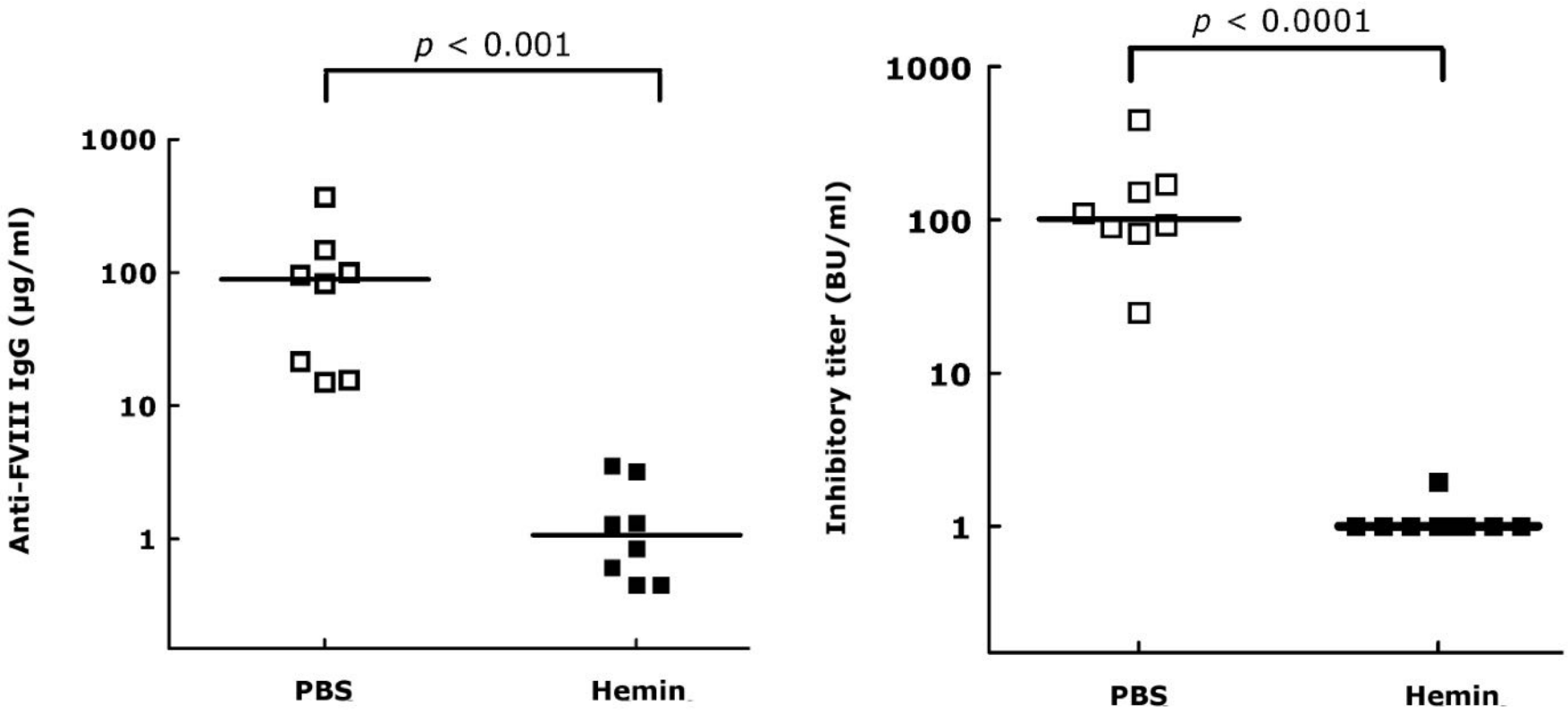
Confirms the findings in FVIII-KO mice

Hemolysis 5/5

FVIII KO mice



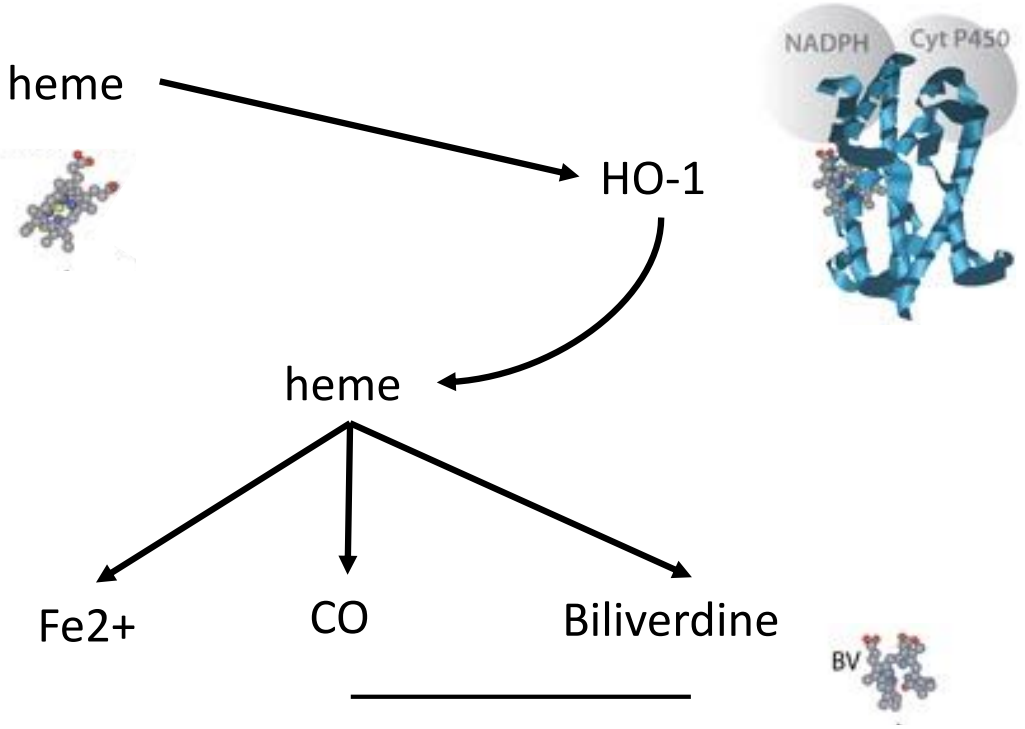
Hemolysis 5/5



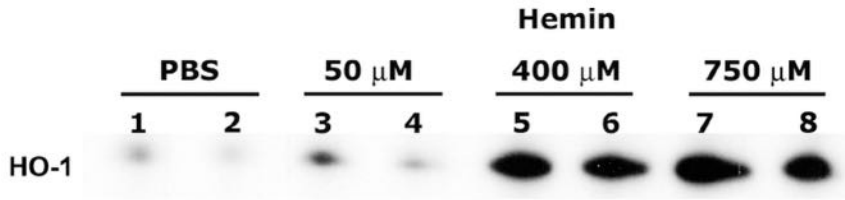
=> **Drastic reduction in the anti-FVIII IgG levels**

Dimitrov Blood 2010

Anti-inflammatory properties of heme oxygenase-1 (HO-1)



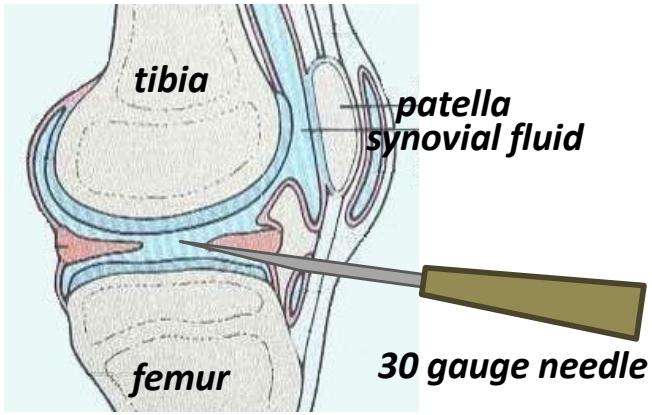
24 hr

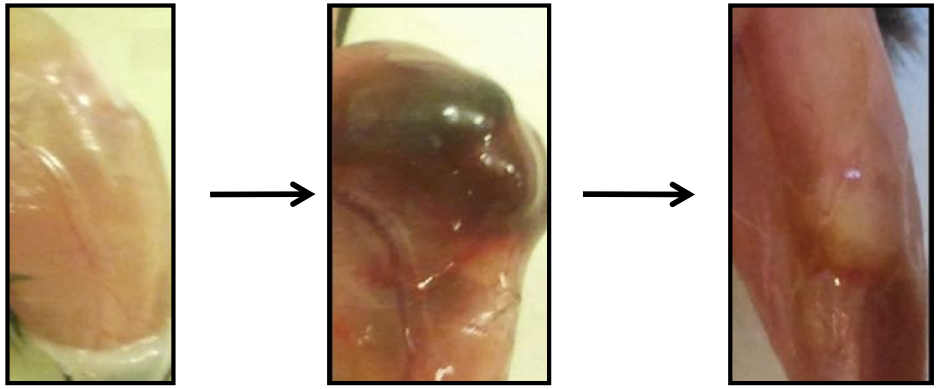


Gozzelino R et al 2010

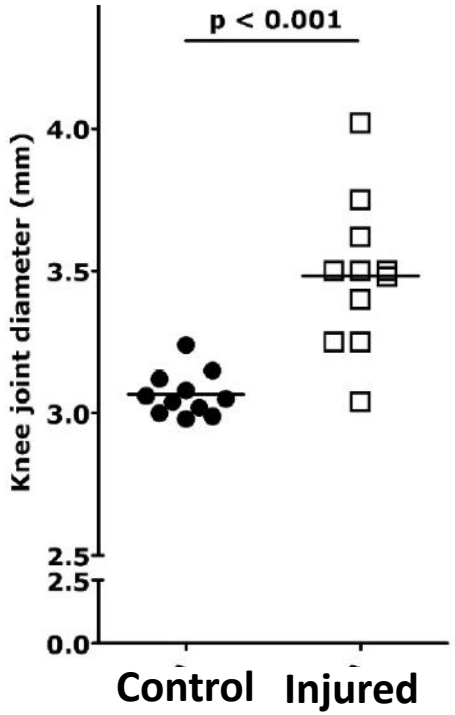
Dimitrov Blood 2010

Acute bleeding 5/5



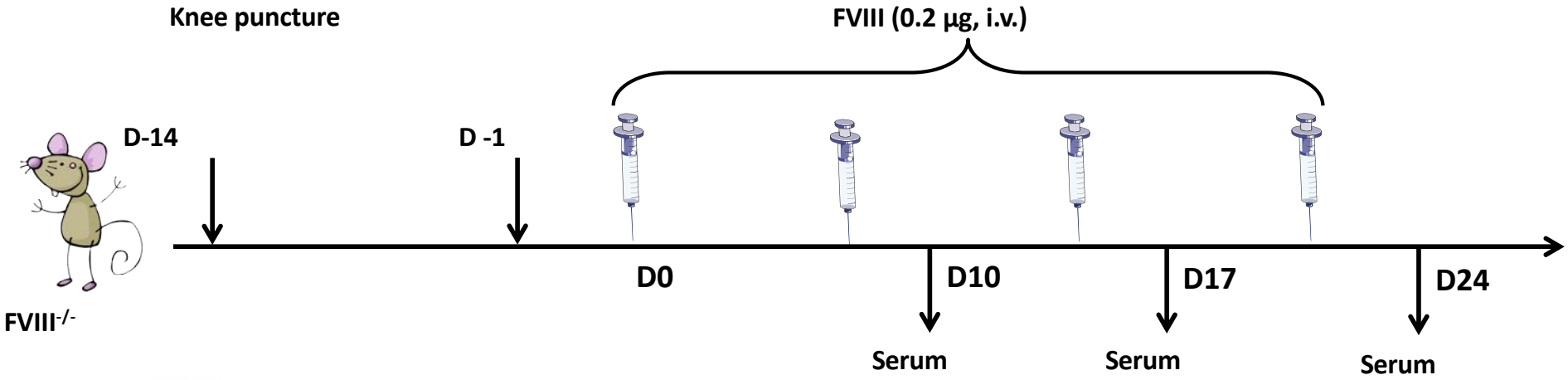


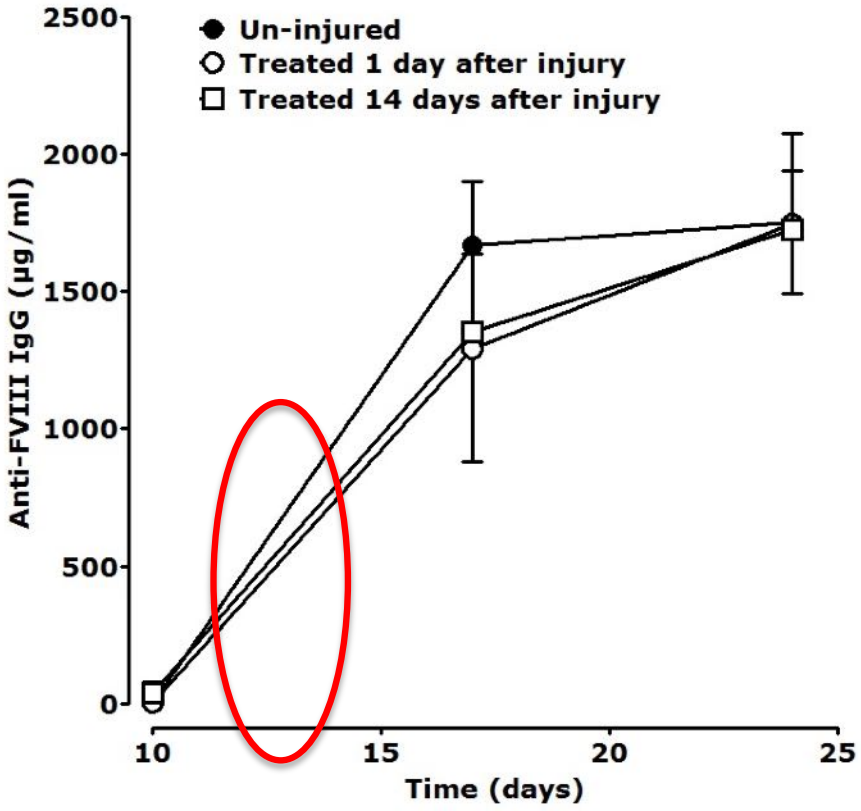
Control | D+1 Hemarthrosis | D+14 Arthropathy



Peyron Haemophilia 2014

Acute bleeding 5/5





Anti-FVIII IgG titer

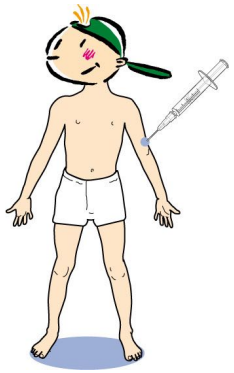
=> Hemarthrosis and arthropathy do not represent risk factors for the development of anti-FVIII IgG

! Induction of HMOX1

Peyron Haemophilia 2014

Controling inflammation

Polymorphisms in the promoter of the *hmox1* gene



Patients

ARTICLES

Disorders of Coagulation

Development of inhibitory antibodies to therapeutic factor VIII in severe hemophilia A is associated with microsatellite polymorphisms in the *HMOX1* promoter

Yohann Repessé,[1,2,3,8]* Ivan Peyron,[1,2,3]* Jordan D Dimitrov,[1,2,3] Suryasarathi Dasgupta,[5] Elika Farrokhi Moshai,[1,2,3] Catherine Costa,[6] Annie Borel-Derlon,[8] Benoit Guillet,[9] Roseline D'Oiron,[10] Achille Aouba,[11] Chantal Rothschild,[11] Johannes Oldenburg,[7] Anna Pavlova,[7] Srinivas V Kaveri,[1,2,3,4] and Sébastien Lacroix-Desmazes[1,2,3,4] on behalf of the ABIRISK consortium

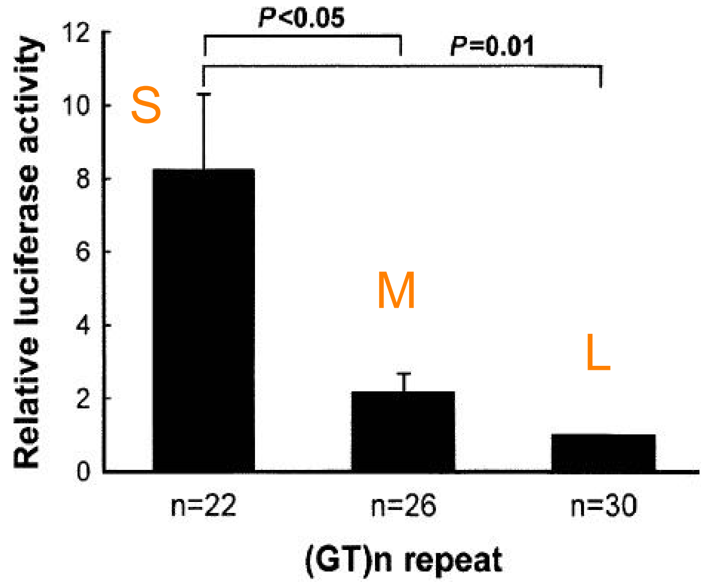
 doi:10.3324/haematol.2013.084665

Controling inflammation

Polymorphisms in the promoter of the *hmox1* gene

5'……….aaaggttttgtgtgtgtgtgtgtgtgtgtgtgtgtgtatgtgtgtgtgtgtgtgtgtgtgtgtgttt
tctctaaaagtcctatggccagactttgtttcccaagggtcatatgactgctcctctccaccccacactggccc
ggggcgggctgggcg………...3'

Microsatellite: GT repeats



Chen *et al.* 2002

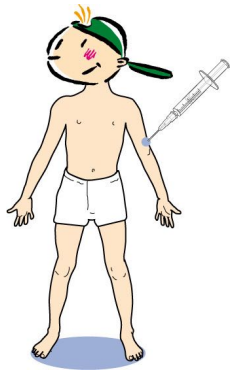
Controling inflammation

Polymorphisms in the promoter of the *hmox1* gene

Cohort of severe HA

. 76 INH+

. 203 INH- (>150 CED)



Patients

Controling inflammation

Polymorphisms in the promoter of the *hmox1* gene

Distribution of HO-1 microsatellites $(GT)_n$

	Severe hemophilia A patients		Odds ratio (95% CI) vs class			
Class	INH- (%)	INH+ (%)	other classes	S	M	L
S	67 (16.5%)	19 (12.5%)	0.72 (0.42-1.24)	1		
M	317 (78.1%)	117 (77.0%)	0.94 (0.6-1.47)	1.3 (0.75-2.26)	1	
L	22 (5.4%)	16 (10.5%)	2.05 (1.05-4.02)*	2.56 (1.13-8.82)*	1.97(1.01-3.88)*	1
Total	406	152				

*P<0.05

Controling inflammation

Polymorphisms in the promoter of the *hmox1* gene

Frequency of genotypes

	Severe hemophilia A patients		
	INH- (%)	INH+ (%)	OR (95% CI)
L/L+L/M+L/S	10.8%	19.7%	2.02 (0.99-4.14) p<0.05
S/S+M/S+M/M	89.2%	80.3%	

two-tailed Chi-square test

=> Capacity to control innate immune responses/inflammation

Capacity to induce tolerance
CpG-TLR9-IDO1-Treg axis

The Journal of Clinical Investigation

RESEARCH ARTICLE

IDO1 suppresses inhibitor development in hemophilia A treated with factor VIII

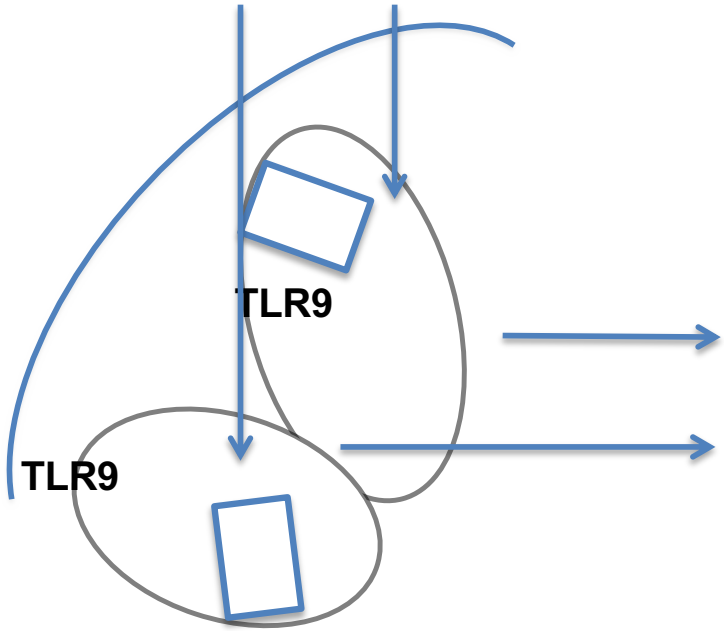
Davide Matino,[1] Marco Gargaro,[1] Elena Santagostino,[2] Matteo N.D. Di Minno,[3] Giancarlo Castaman,[4,5] Massimo Morfini,[5] Angiola Rocino,[6] Maria E. Mancuso,[2] Giovanni Di Minno,[3] Antonio Coppola,[3] Vincenzo N. Talesa,[1] Claudia Volpi,[1] Carmine Vacca,[1] Ciriana Orabona,[1] Rossana Iannitti,[1] Maria G. Mazzucconi,[7] Cristina Santoro,[7] Antonella Tosti,[8] Sara Chiappalupi,[1] Guglielmo Sorci,[1] Giuseppe Tagariello,[9] Donata Belvini,[9] Paolo Radossi,[9] Raffaele Landolfi,[10] Dietmar Fuchs,[11] Louis Boon,[12] Matteo Pirro,[13] Emanuela Marchesini,[13] Ursula Grohmann,[1] Paolo Puccetti,[1] Alfonso Iorio,[14] and Francesca Fallarino[1]

[1]Department of Experimental Medicine, University of Perugia, Perugia, Italy. [2]Angelo Bianchi Bonomi Hemophilia and Thrombosis Centre, Fondazione IRCCS Cà Granda, Ospedale Maggiore Policlinico, Milan, Italy. [3]Regional Reference Centre for Coagulation Disorders, Department of Clinical and Experimental Medicine, Federico II University, Naples, Italy. [4]Department of Cell Therapy and Hematology, San Bortolo Hospital, Vicenza, Italy. [5]Centro Emofilia, Azienda Ospedaliera Careggi, Florence, Italy. [6]Hemophilia and Thrombosis Centre, San Giovanni Bosco Hospital, Naples, Italy. [7]Department of Cellular Biotechnology and Hematology, La Sapienza University, Rome, Italy. [8]Department of Medicine, University of Perugia, Perugia, Italy. [9]Transfusion Service, Hemophilia and Regional Blood Disease Centre, Castelfranco Veneto, Italy. [10]Institute of Internal Medicine and Geriatrics, Hemostasis Research Center, Catholic University, Rome, Italy. [11]Division of Biological Chemistry, Biocenter, Innsbruck Medical University, Innsbruck, Austria. [12]Bioceros, Utrecht, Netherlands. [13]Department of Medicine, Perugia, Italy. [14]Departments of Clinical Epidemiology and Biostatistics and Medicine, McMaster University, Hamilton, Ontario, Canada.

Capacity to induce tolerance

CpG-TLR9-IDO1-Treg axis

CpG-rich oligodenucleotides
(CpG-ODNs)



Indoleamine 2,3-dioxygenase 1
(IDO1)

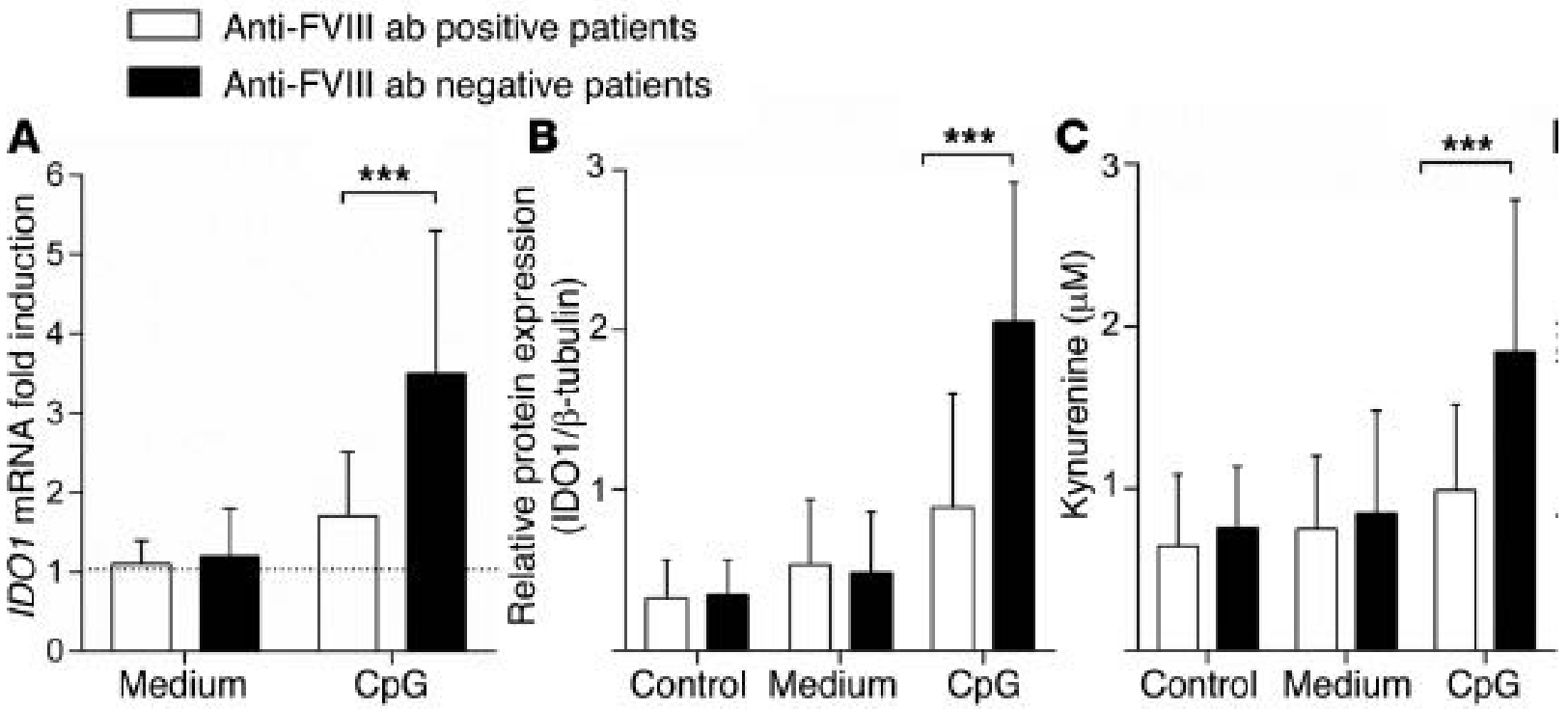
Tryptophan
degradation → Kynurenine

CD4+ CD25- T cells → CD4+CD25+ FoxP3+ T cells

Capacity to induce tolerance

CpG-TLR9-IDO1-Treg axis

CpG-rich oligodenucleotides (CpG-ODNs) + PBMCs from HA patients with or without inhibitors

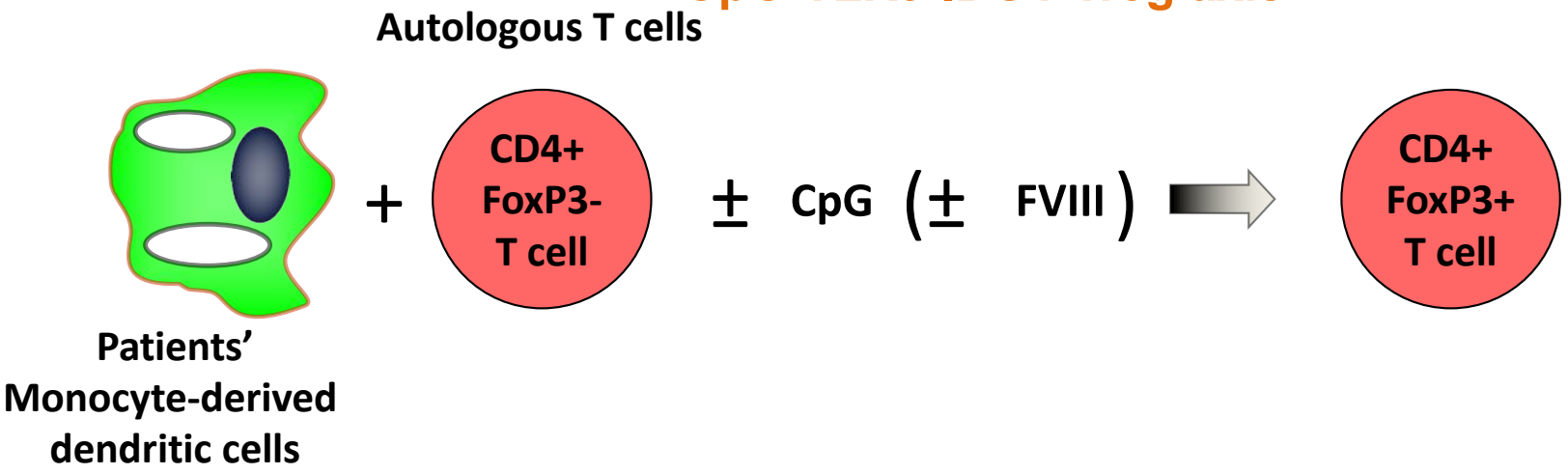


=> Increase in TGFß in supernatant
Mostly dendritic cells
Only in inhibitor-negative patients

Matino JCI 2015

Capacity to induce tolerance

CpG-TLR9-IDO1-Treg axis

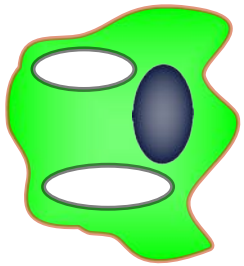


Matino JCI 2015

Capacity to induce tolerance

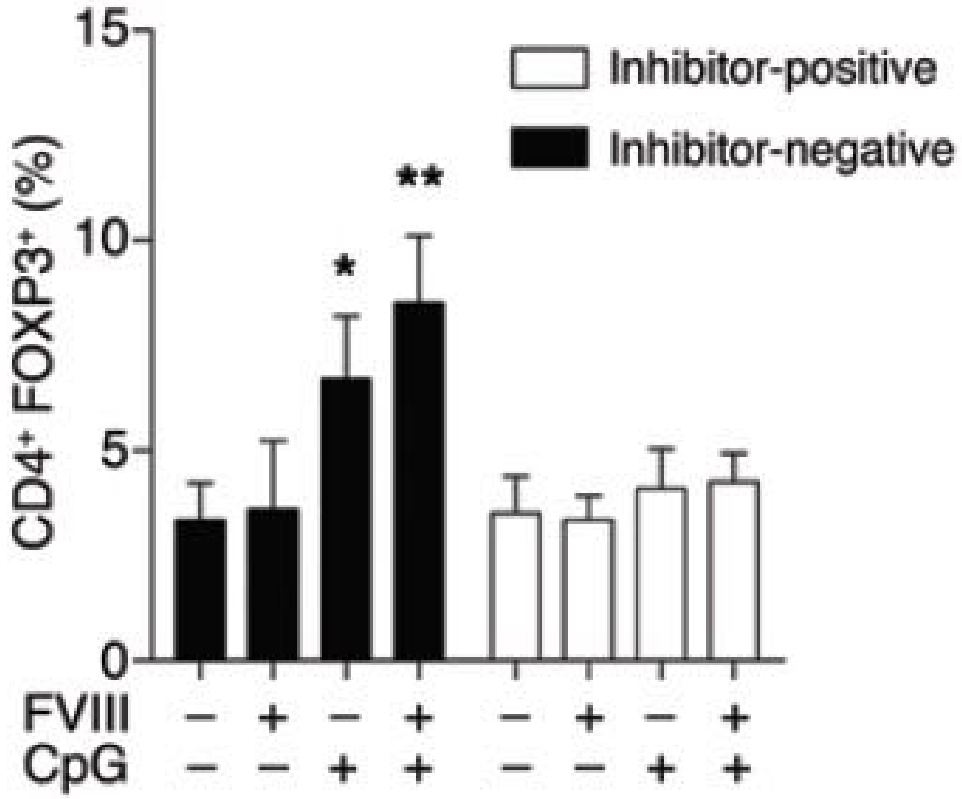
CpG-TLR9-IDO1-Treg axis

Autologous T cells



Patients' Monocyte-derived dendritic cells

\+ CD4+ FoxP3- T cell ± CpG (± FVIII) → CD4+ FoxP3+ T cell

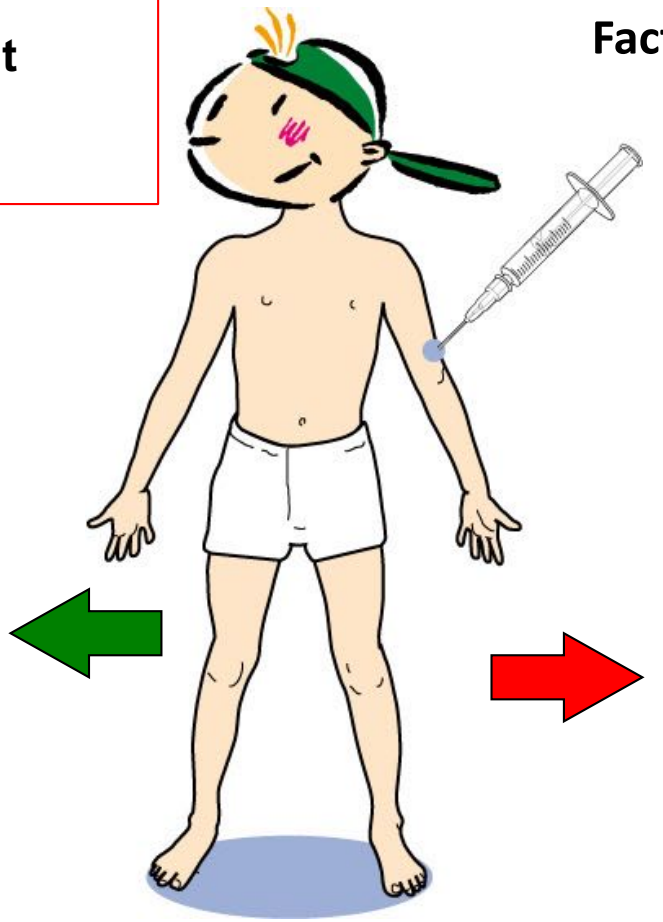


Matino JCI 2015

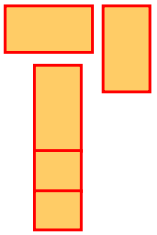
A conceptual change in our understanding of inhibitor development

. Induction of Immune Tolerance

. SIPPET study: 27% of transient inhibitors

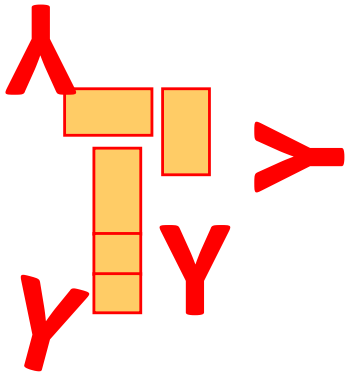


Factor VIII



70–95% of the patients

5-30% of the patients



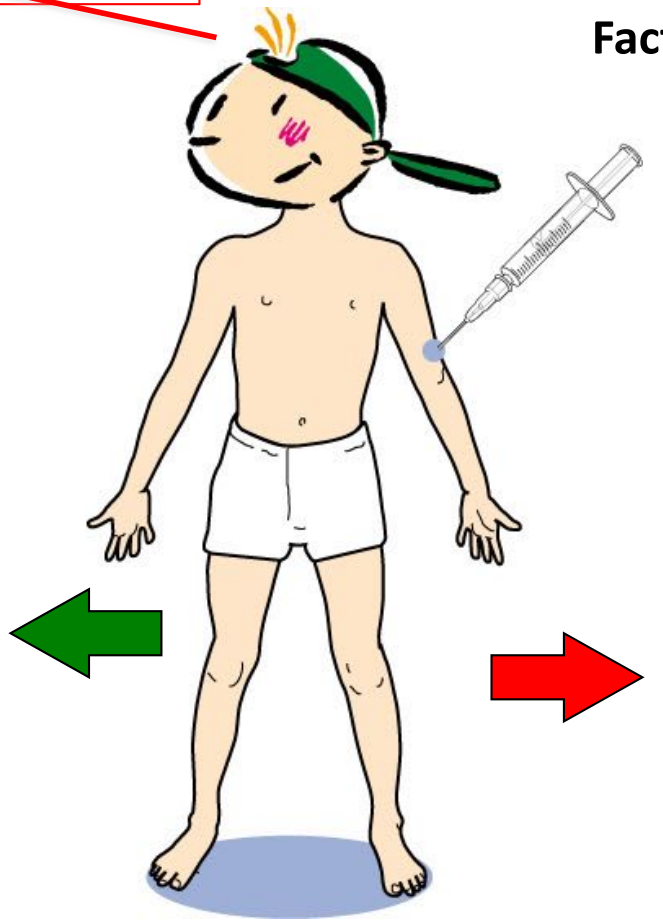
FVIII inhibitors

Peyvandi NEJM 2016

A conceptual change in our understanding of inhibitor development

~~Why do 5 to 30% of the patients develop an immune response to FVIII?~~

Factor VIII



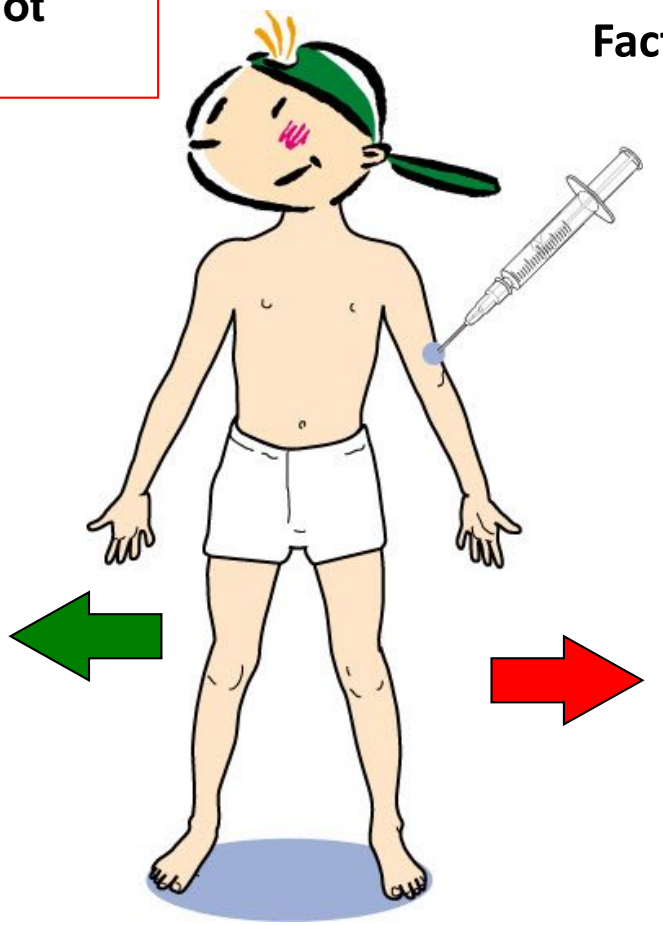
70–95% of the patients

5-30% of the patients

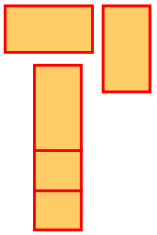
FVIII inhibitors

A conceptual change in our understanding of inhibitor development

All patients develop an immune response to FVIII
Why are 5-30% of the patients not able to control it?

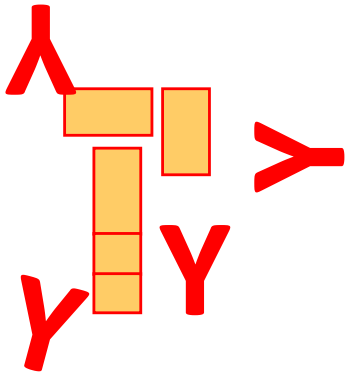


Factor VIII



70–95% of the patients

5-30% of the patients



FVIII inhibitors

Consequences

- **Consequence for immunosuppression**

  Different mechanisms of action of different immunosuppressive drugs

- **Consequence for patient management**

  No need to avoid vaccination period or bleedings, need to monitor dose

- **Consequence for research**

  Make FVIII invisible = ok but no tolerance
  Induce active tolerance

Conclusions

- **FVIII recognition is part of physiology**

  With a price to pay

- **Poor central tolerance to endogenous FVIII**

  Relies mainly on peripheral tolerance?

- **In HA patients: all identified danger signals may just be normal assessment of exogenous FVIII by the immune system**

- **Inhibitory response results merely from inability of some patients' organism to develop peripheral tolerance, rather than from exacerbated capacity of some patients to mount immune responses**