ARE RECOMBINANT PRODUCTS MORE LIKELY TO ENGENDER INHIBITORS?

ARE PLASMA DERIVED PRODUCTS MORE EFFECTIVE FOR INDUCING IMMUNE TOLERANCE ?

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INHIBITORS in HEMOPHILIA

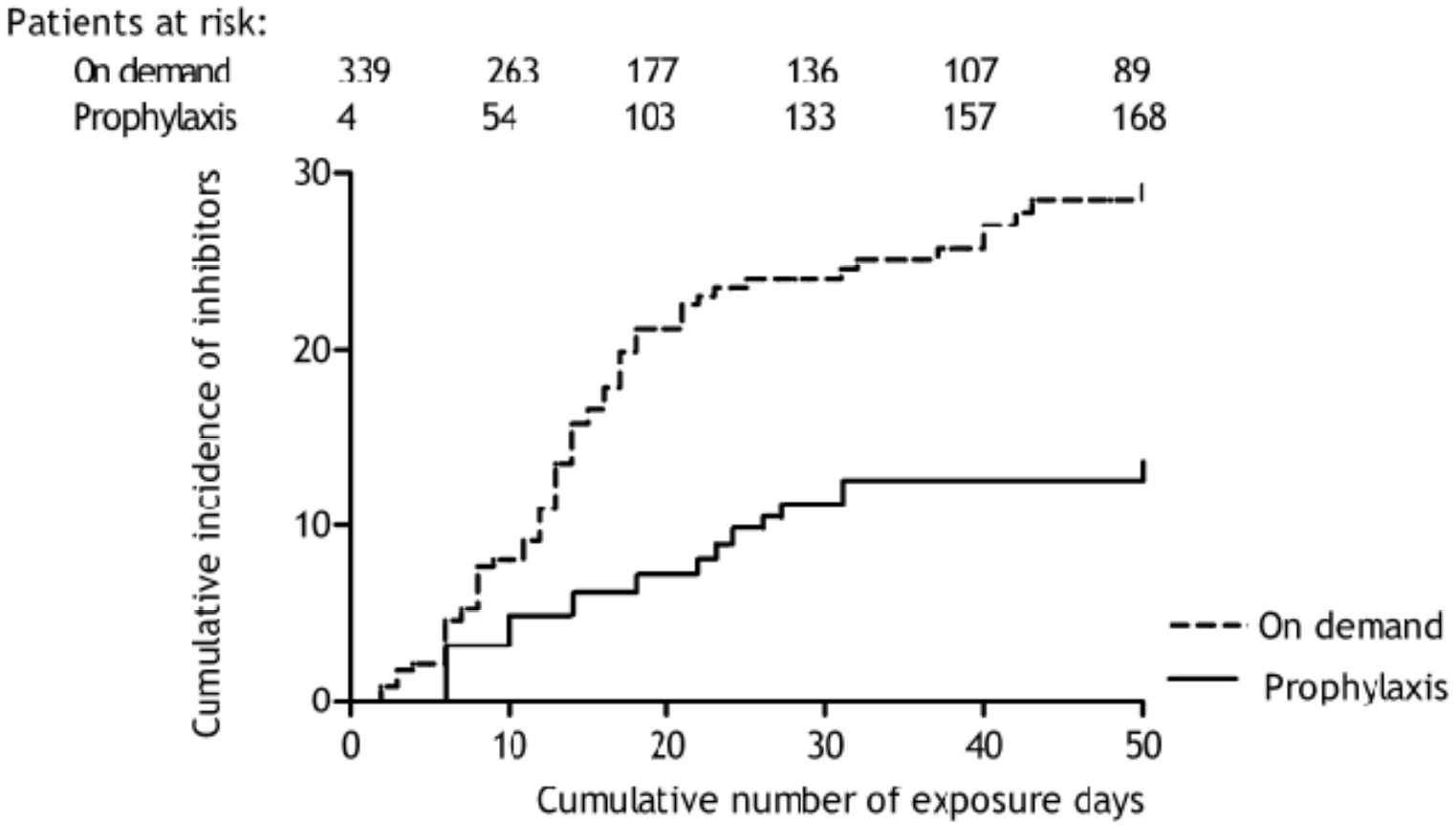
- Antihemophilic factors are now efficient
- Antihemophilic factors are now safe
- Antihemophilic factors are still immunogenic

- **When Antihemophilic factors are in sufficient amount to treat patients, inhibitor is the greatest fight and the most difficult problem to manage in hemophiliacs treatment**

INHIBITORS in HAEMOPHILIA

- Established Risk Factors
- Influence of drug
- Works in progress

INHIBITORS PREVALENCE: On demand vs prophylaxis



Gown et al, Blood 2007

INHIBITORS IN HAEMOPHILIA: Influence of drugs

- Clinical data
- Biological data

INFLUENCE of TREATMENT on the PREVALENCE of INHIBITORS

- **34 patients with inhibitors among 148 patients**
  - 16 patients (13 treated by rFVIII): > 5 UB
  - 23 patients (19 treated by rFVIII): > 5 UB and/or ITI
- **Date of diagnosis**
  - < 10 ED in 9 patients
  - 10 to 20 ED in 17 patients
  - 21 to 50 ED in 5 patients
  - > 50 ED in 3 patients
- **7/62 (11%) treated by plasma derived F VIII (pFVIII)**
- **27/86 (30%) treated by recombinant F VIII (rFVIII)**

Goudemand et al, Blood 2006

INHIBITORS IN HAEMOPHILIA: Influence of drugs

AHF	Inhibitors(total)			High responders		
	Incidence	RR	IC95	Incidence	RR	IC95
FVIII-LFB	10,3	1,0		5,2	1	
Recombinant	32,3	2,4	1,0-5,8	15,o	2	0,7 - 9,6

Goudemand et al., Blood 2006

INHIBITORS in HEMOPHILIA A PATIENTS: CANAL STUDY

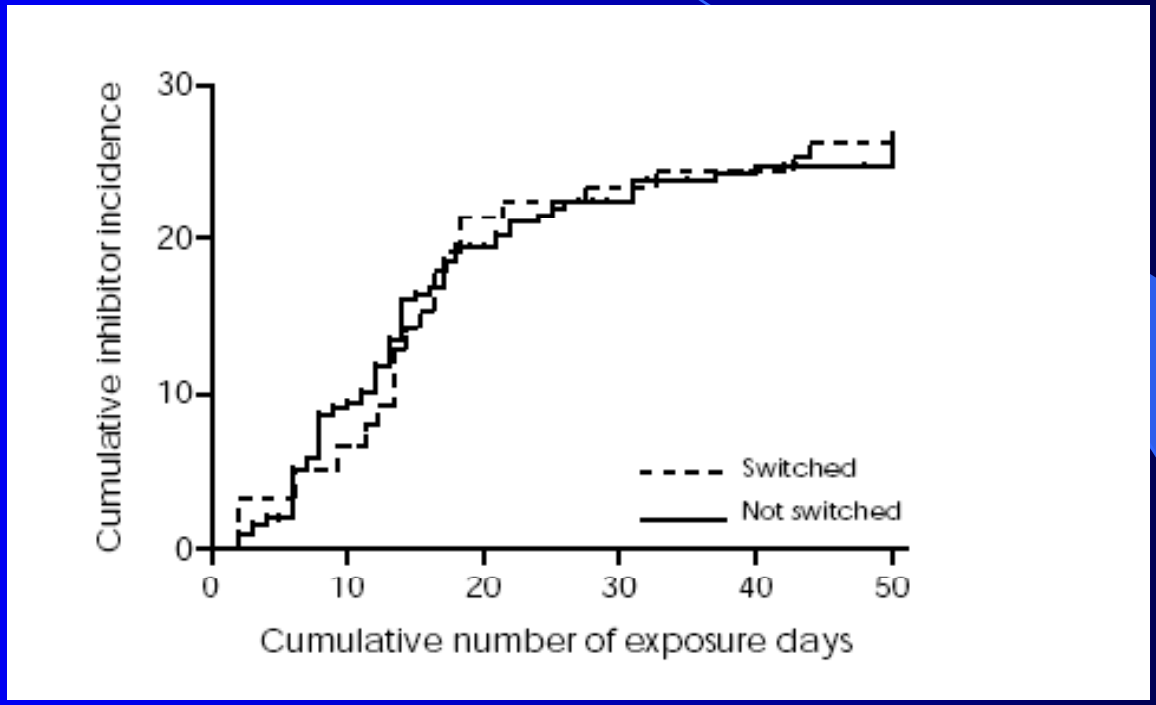
- Retrospective study on 316 patients

Type of F VII	ALL: Crude RR (CI)	ALL: Adjusted RR (CI)	High Titre: Crude RR (CI)	Adjusted RR (CI)
Recombinant	1.0	1.0	1.0	1.0
pdF	0.8 (0.5 - 1.3) P = 0.34	0.7 (0.4 - 1.1) P = 0.14	0.9 (0.5 – 1.2) P = 0.72	0.8 (0.4 – 1.3) P = 0.33

Gouw et al, Blood 2007

INHIBITORS: Canal Study and the role of switch pFVIII/rFVIII

376 patients
13 in Europe
1 centre canada



Switch rFVIII/pFVIII

No difference pFVIII / rFVIII
Switch: no incidence on inhibitor incidence

Gouw et al, Blood 2007

INHIBITORS IN HAEMOPHILIA: Influence of drugs

- Number and percentages of inhibitors in different clinical studies

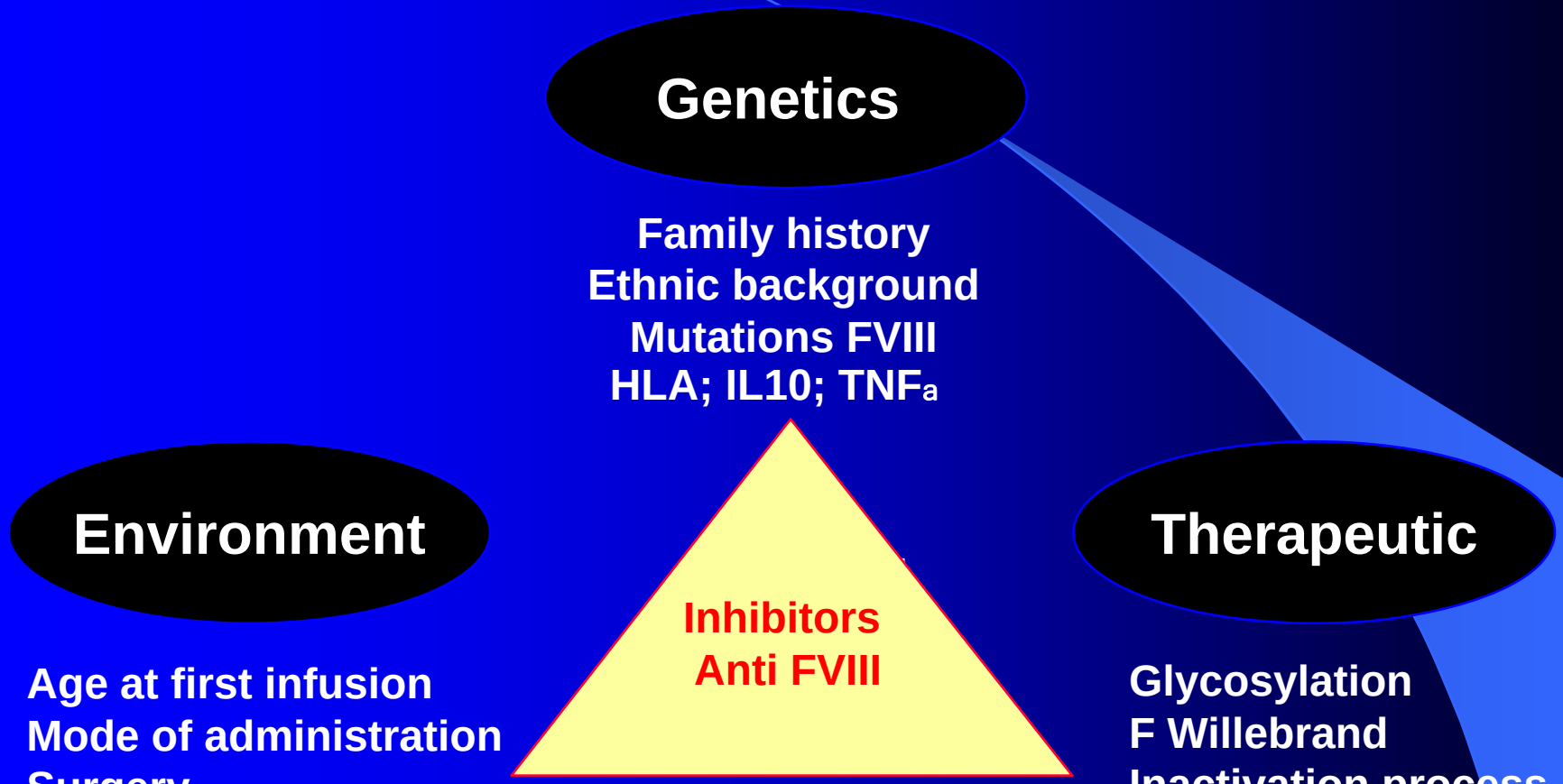
pdF	N	Inhib	%Inhib
Brown	74	3	4,00
Glomstein	19	2	11,00
Lusher 1990	25	6	24,00
Addiego 1992	23	2	9,00
Ehrenforth 1992	27	14	52,00
Ljung 1992	77	16	21,00
Addiego 1993	89	25	28,00
de Biasi 1994	48	11	23,00
Munlean 1997	21	9	43,00
RokickaMilewska 1999	19	1	5,00
Gringeri 2006	71	7	10,00
Goudemand 2006	62	7	11,00
Escuriola 2006	57	12	21,00
Gouw 2007	135	29	22,00
Chalmers 2007	132	18	14,00

Recombinant	N	Inhibitors	% Inhibitors
Bray 1994	71	17	24,00
Gringeri 1998	29	6	21,00
Lusher 1998	97	26	27,00
Gruppo 1998	72	22	31,00
Rotschild 1998	50	14	28,00
Lusher 2003	101	32	32,00
Yoshioka 2003	31	13	42,00
Lusher 2004	65	19	29,00
Kreuz 2005	37	5	14,00
Goudemand 2006	86	27	31,00
Escuriola 2006	47	17	36,00
Gouw 2007	181	53	29,00
Chalmers 2007	172	47	27,00
Gouw 2007	236	67	28,00

INHIBITORS IN HAEMOPHILIA: Influence of drugs

- What are we comparing?
  - Immunogenicity versus inhibitor development
  - Incidence versus prevalence
  - Type of inhibitors
    - Low titre versus high titre

RISK FACTORS for INHIBITORS



J.Astermark, 2005
J.Goudemand,2006

Wight, 2003; Kreuz, 2004;
Escuriola, 2006

INHIBITORS IN HAEMOPHILIA: Influence of drugs

- Which population?
  - Role of ethnicity
  - Prophylaxis versus on-demand
  - Age at the first infusion

INFLUENCE of ETHNIC BACKGROUND on the PREVALENCE of INHIBITORS

Group	Inhibitors (total)			High response		
	Incidence	RR	IC95	Incidence	RR	IC95
Caucasians	15,0	1,0		7,8	1	
Autres	62,8	6,7	2,9-15,3	26,8	3,5	1,2-10,3

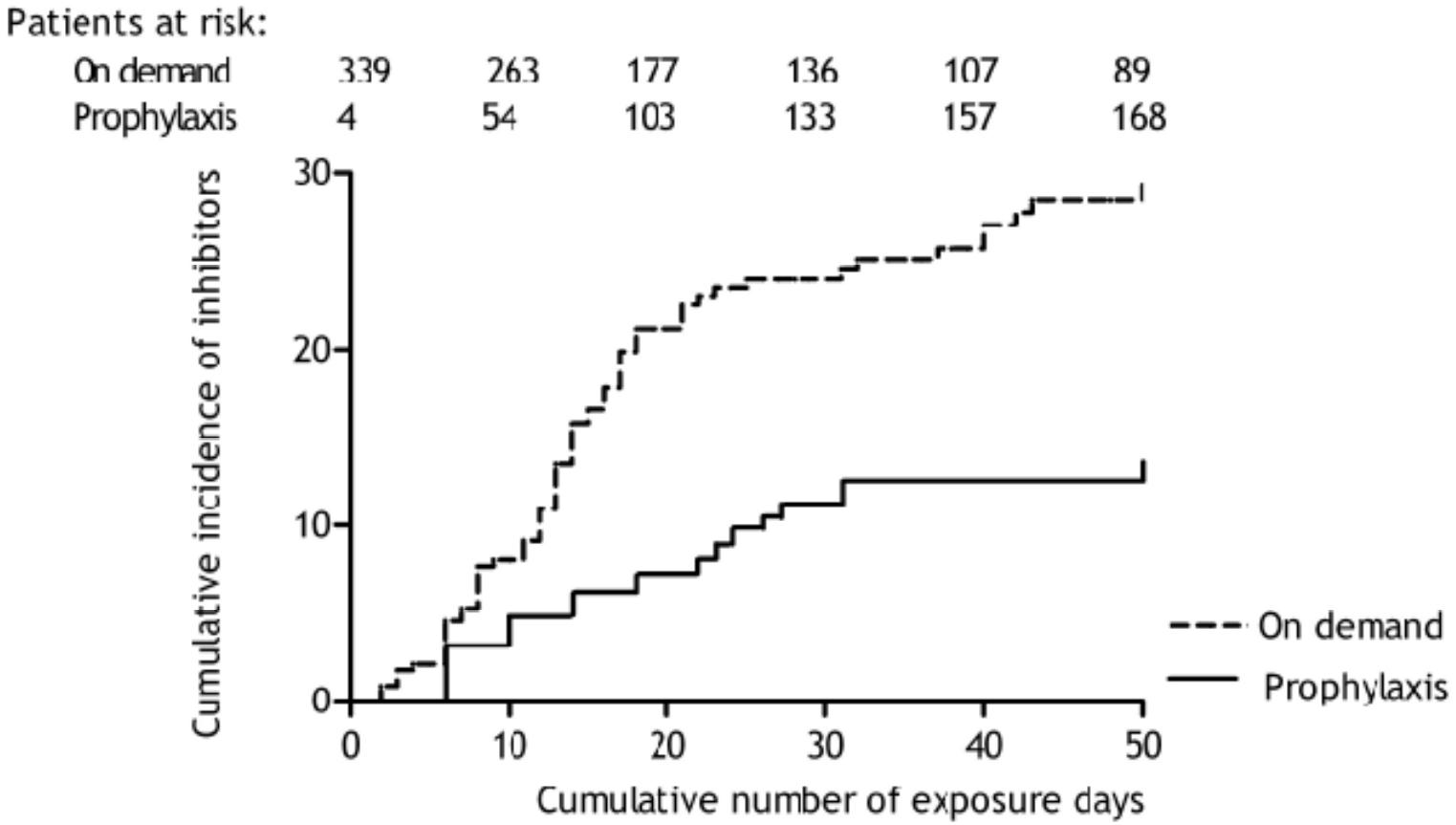
Goudemand et al., Blood 2006

INFLUENCE of AGE at FIRST INFUSION on the PREVALENCE of INHIBITORS

Age at 1st inf	Inhibitors (total)			High Responders		
	Incidence	RR	IC95	Incidence	RR	IC95
< 6 monthss	38,1	1,0		16,0	1	
6 to 11 months	21,3	0,5	0,2-1,3	10,6	0,8	0,2-2,8
> 12 months	15,7	0,3	0,1-0,7	8,3	0,5	0,1- 1,8

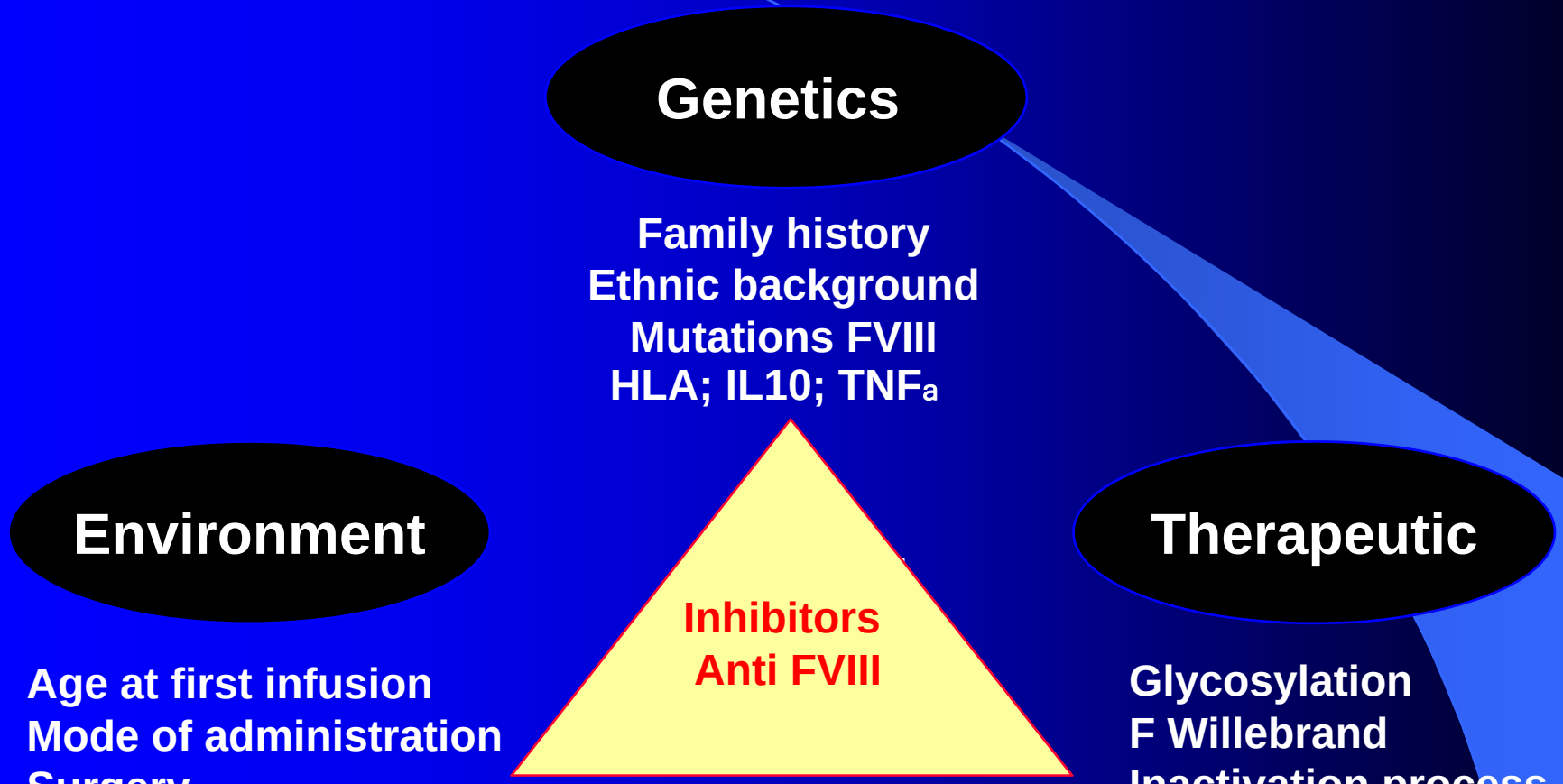
Goudemand et al., Blood 2006

INHIBITORS PREVALENCE: On demand vs prophylaxis



Gown et al, Blood 2007

RISK FACTORS for INHIBITORS



J.Astermark, 2005
J.Goudemand,2006

Wight, 2003; Kreuz, 2004;
Escuriola, 2006

INHIBITORS IN HAEMOPHILIA: Influence of drugs

- Which drug?
  - Plasma derived
    - Intermediate versus highly purified
    - Amount of Willebrand factor
  - Recombinant
    - BHK versus CHO derived
    - B-deleted
    - Fisrt, second and third generation

INHIBITORS in HEMOPHILIA A PATIENTS: CANAL STUDY

Type of F VII	ALL: Crude RR *(CI)*	ALL: Adjusted RR *(CI)*	High Titre: Crude RR *(CI)*	Adjusted RR *(CI)*
Recombinant	1.0	1.0	1.0	1.0
pdF, *low vWF*	**0.3** *(0.1 - 1.1)* P = 0.7	**0.4** *(0.1 - 1.1)* P = 0.8	**0.3** *(0.1 – 1.2)* P = 0.9	**0.3** *(0.1 – 1.3)* P = 0.11
pdF, *high vWF*	**1.0** *(0.6 - 1.6)* P = 0.91	**0.8** *(0.5 - 1.4)* P = 0.45	**1.1** *(0.7 – 2.0)* P = 0.61	**0.9** *(0.5 – 1.6)* P = 0.79
Kogenate *(BHK)*	1.0	1.0	1.0	1.0
Kogenate Bayer *(BHK, APF)*	**1.1** *(0.2 – 4.5)* P = 0.94	**1.2** *(0.3 – 5.4)* P = 0.79	**1.5** *(0.3 – 6.5)* P = 0.60	**1.6** *(0.3 – 7.3)* P = 0.55
Recombinate *(CHO)*	**1.1** *(0.5 – 2.3)* P = 0.75	**1.0** *(0.5 – 2.1)* P = 1.0	**1.4** *(0.6 – 3.1)* P = 0.39	**1.2** *(0.5 – 2.7)* P = 0.7
Refacto *(CHO, B-deleted)*	**1.4** *(0.8 – 2.6)* P = 0.24	**1.6** *(0.9 – 3.2)* P = 0.14	**1.5** *(0.7 – 3.0)* P = 0.30	**1.4** *(0.6 – 3.1)* P = 0.38

INHIBITORS IN HAEMOPHILIA: Influence of drugs

- Can biology be helpful?
  - Role of vWF in inhibitor development

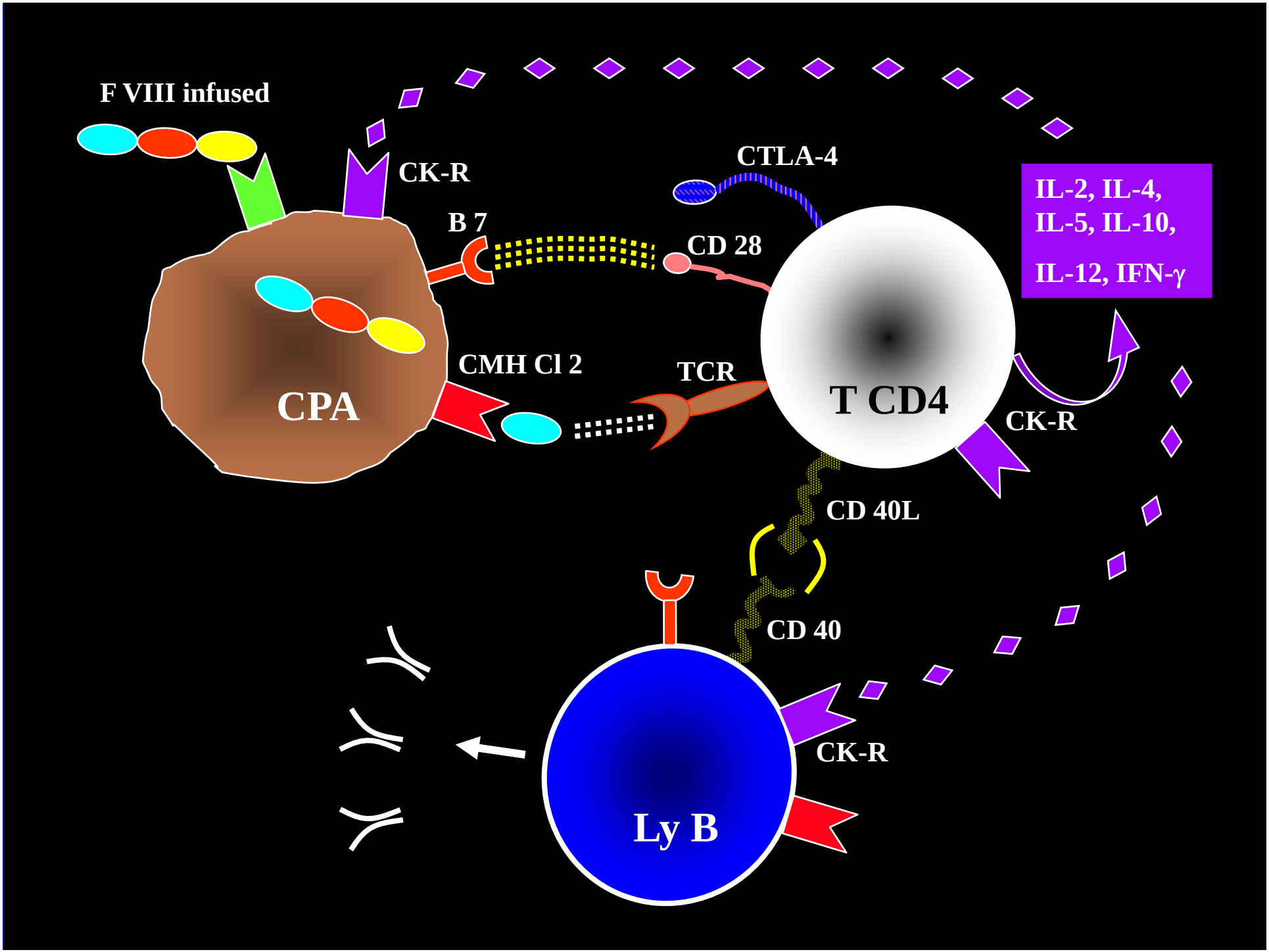
Von WILLEBRAND FACTOR and anti FVIII ANTIBODIES

- Epitopes corresponding to vWF-FVIII binding sites are masked by vWF (especially C2 domain)

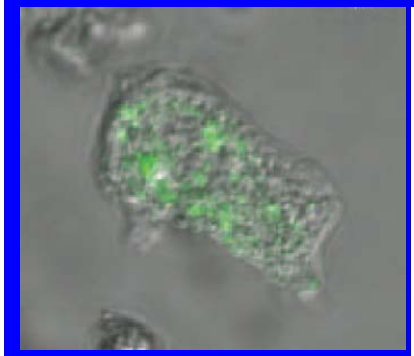
- But VWF decreases also the Anti-A2 reactivity

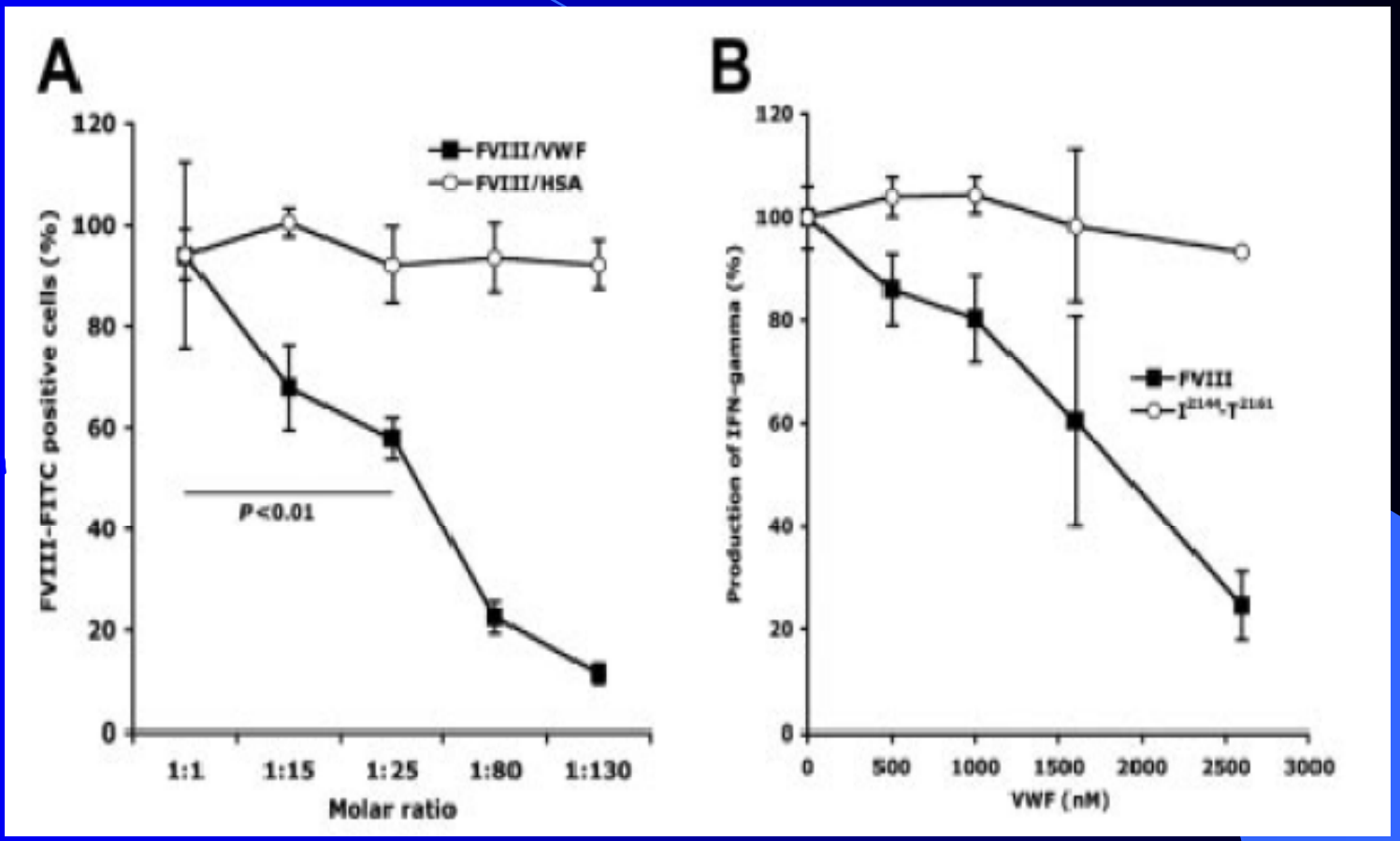
(less than anti-C2)

Hypothesis : 3D modification of FVIII complexed with vWF


F VIII infused
CK-R
B 7
CTLA-4
CD 28
IL-2, IL-4,
IL-5, IL-10,
IL-12, IFN-γ
CMH Cl 2
TCR
CPA
T CD4
CK-R
CD 40L
CD 40
CK-R
Ly B

INHIBITORS IN HAEMOPHILIA: Influence of drugs





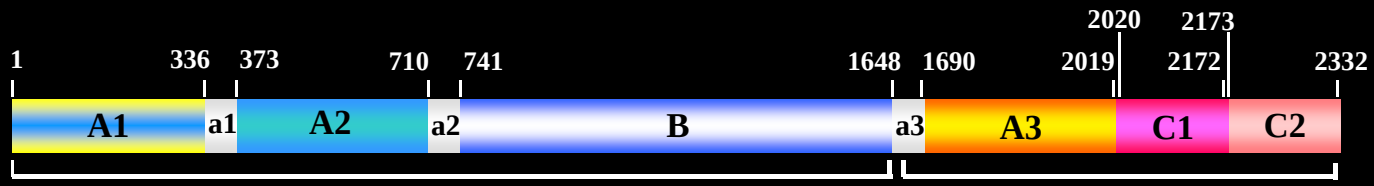
vWF reduces in vitro FVIII endocytosis by Dendritic cells and the consequent presentation to T-cells

(Dasgupta et al. Blood 2007;91:610-2)

INHIBITORS IN HAEMOPHILIA: Influence of drugs

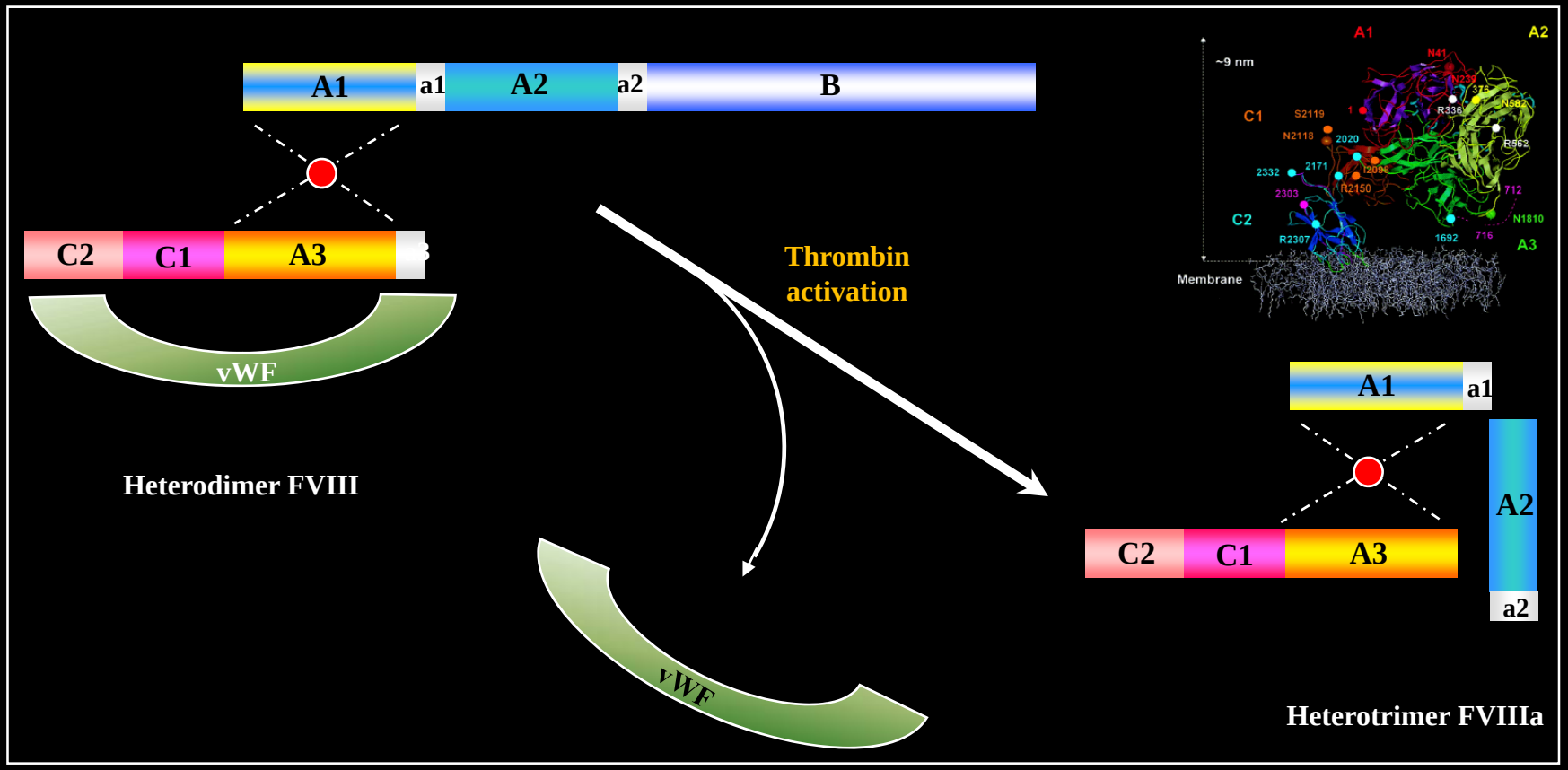
- Can biology be helpful?
  - Inhibitor represent the apparent immune response to F VIII
  - We need to better understand this immune response to F VIII in all its components:
    - Antibodies (inhibiting and non inhibiting)
    - Cells
  - New tools
    - Epitope mapping
    - Elispot

FACTOR VIII: STRUCTURE and ACTIVATION



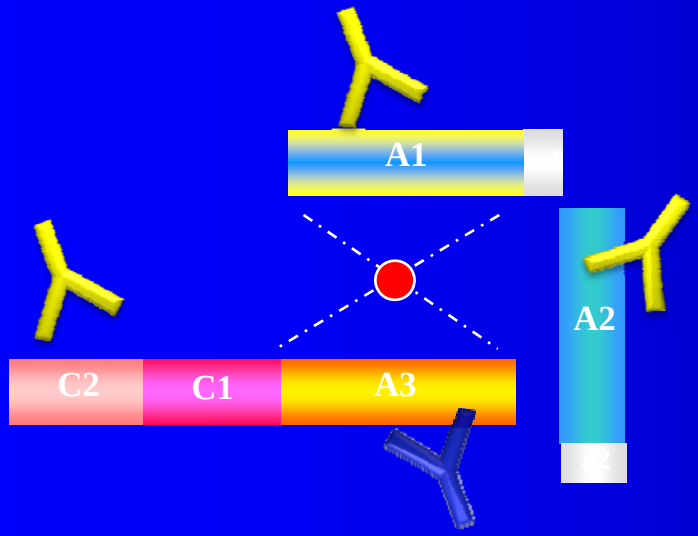
Chaine lourde

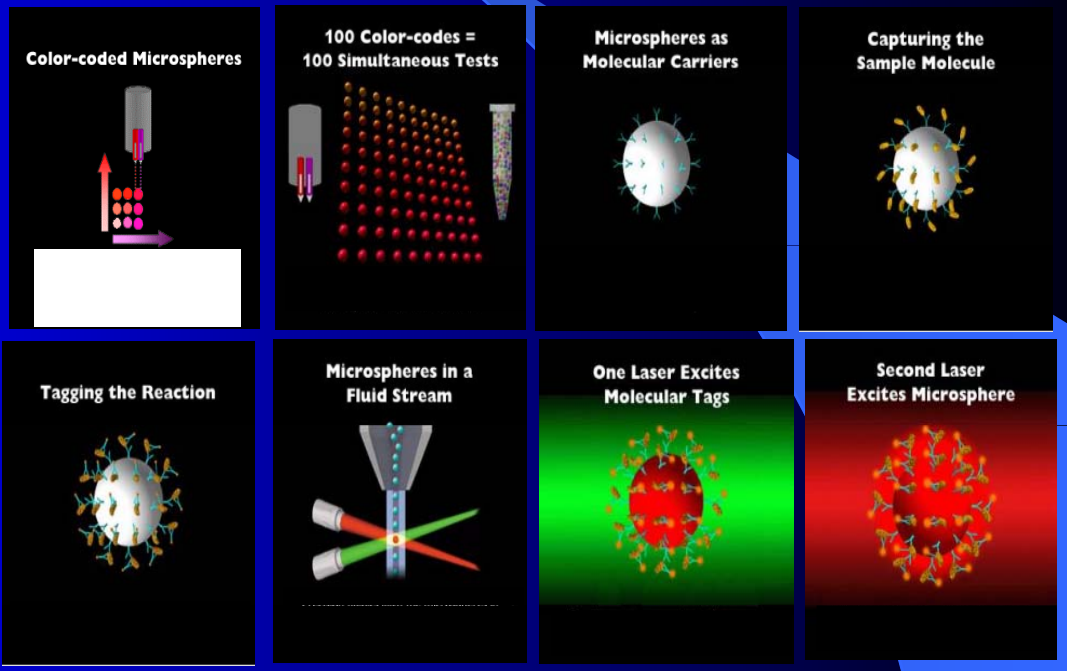
Chaine légère



EPITOPE MAPPING

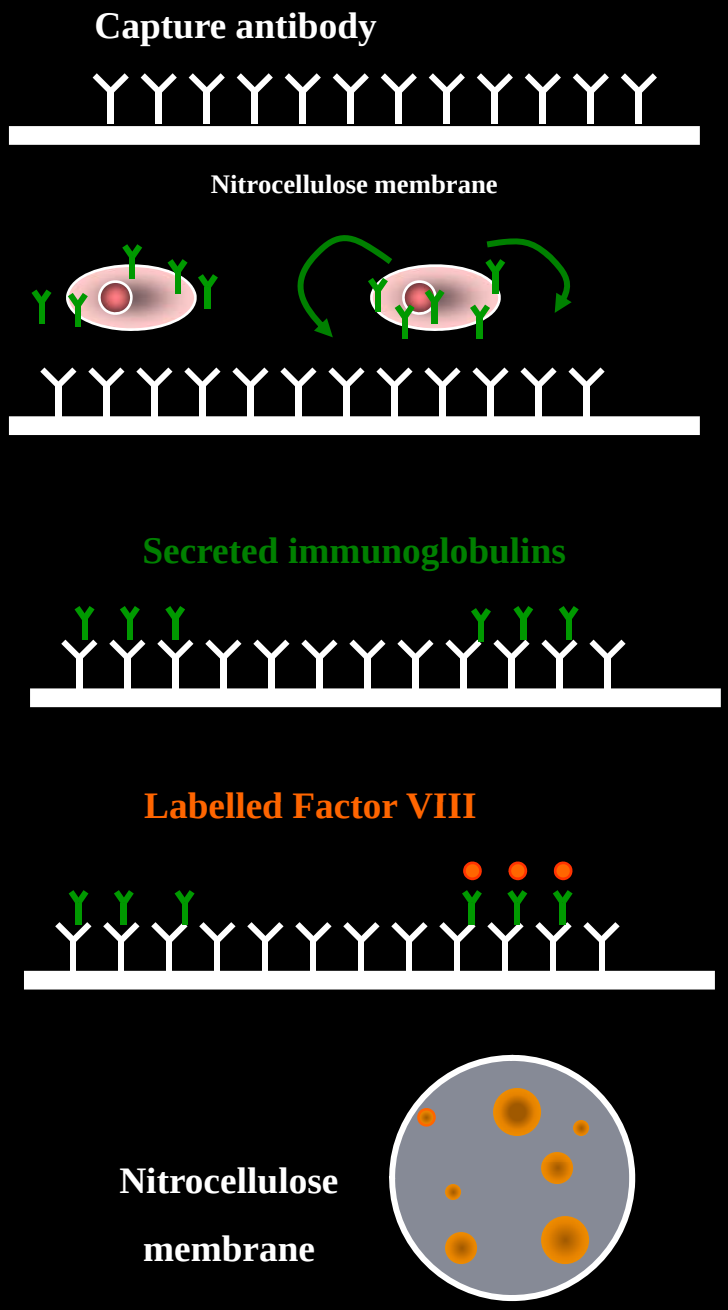
. a1 3%
. A1 2,9%
. A2 and/or C2 68%
. A3 46%





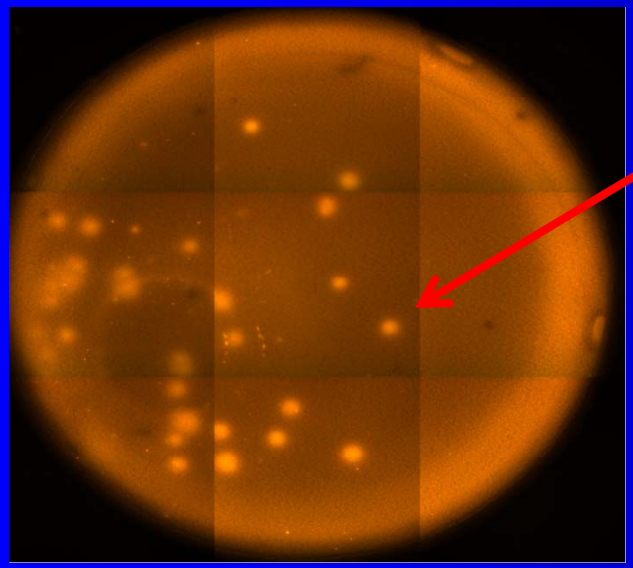
Luminex technology

ELISpot Method



ELISpot on anti FV VIII ab secreting B Lymphocytes

1 Spot = 1 B lymphocyte secreting Ig anti F VIII



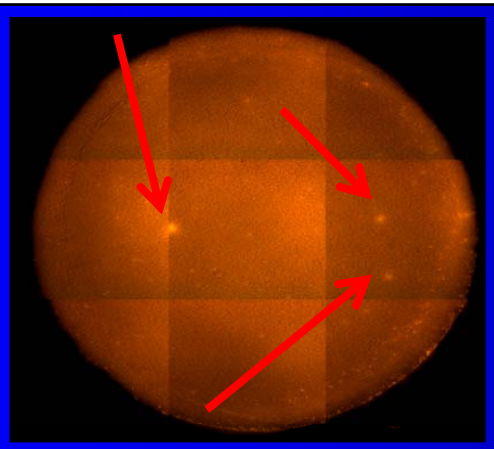
***Coating* : anti-IgG**
***Révélation* : FVIII labelled with a fluorochrom**

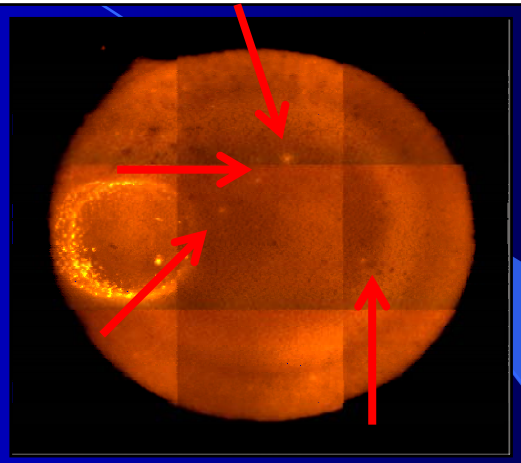
***Photo* : Obtained with mice hybridom(Birgit Reipert, Baxter, Vienne) secreting anti F VIII IgG anti-facteur VIII**

ELISpot on anti FV VIII ab secreting B Lymphocytes

Patient 3: with inhibitor

3 spots IgA

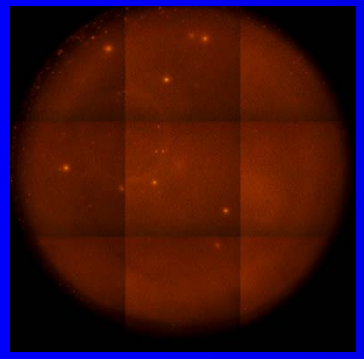




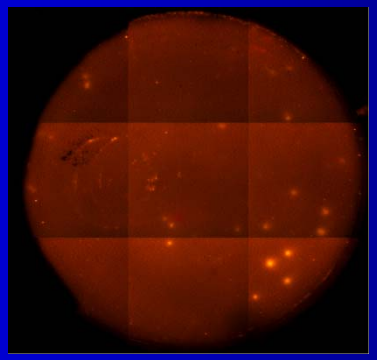
4 spots IgG

Patient 2 : after successful ITI

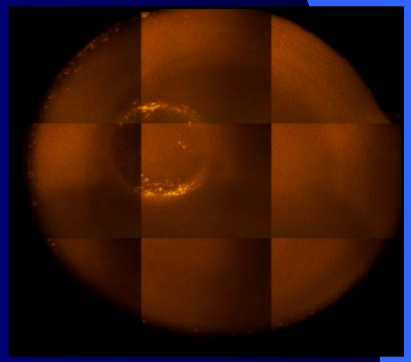
Spots IgA



Spots IgM



No IgG spot



INHIBITORS in HAEMOPHILA: Conclusions

- There are some arguments to suspect a more frequent development of inhibitors with recombinant as compared to plasma derived factors
- Role of vWF has to be considered both in ab generation and ITI
- New tools are required to better understand the immunological response to F VIII
- Only a prospective randomized clinical study is able to compare the incidence of inhibitors between according to the drug used