

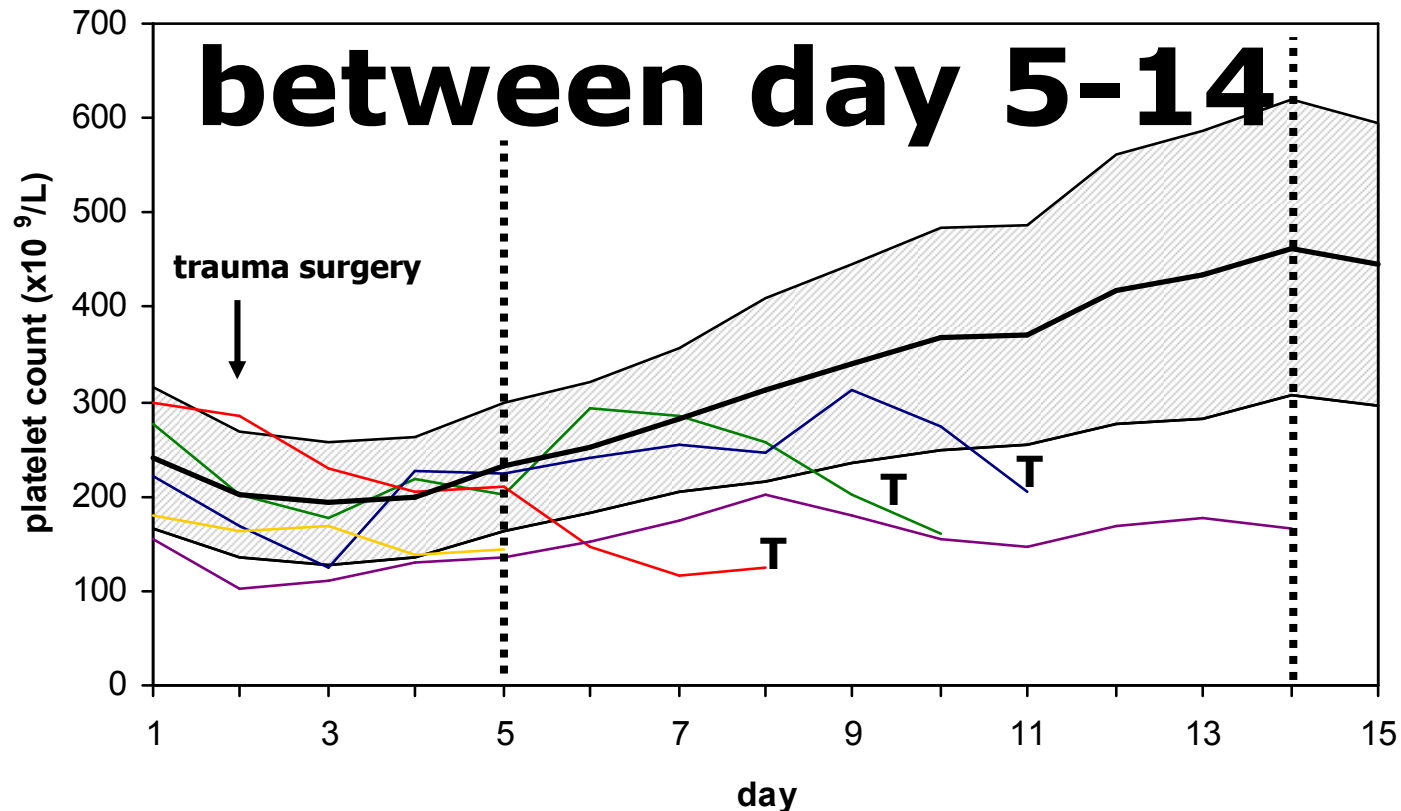
Heparin-induced Thrombocytopenia the most frequent drug induced immune response

Andreas Greinacher

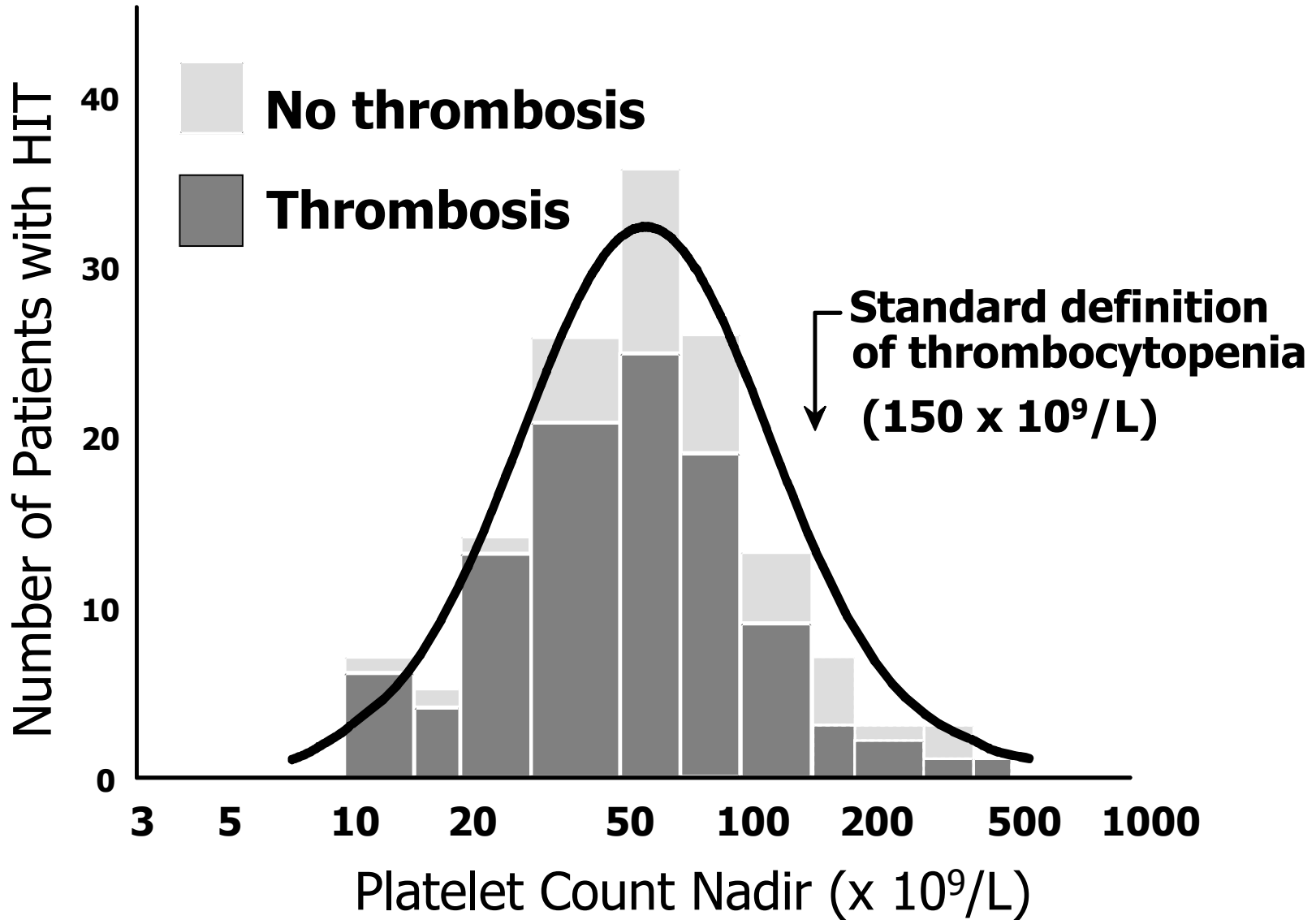
Institut für Immunologie und Transfusionsmedizin
Universität Greifswald
Germany



Platelet count decrease $> 50\%$ and/or new thrombotic complications between day 5-14



Platelet Count Nadir



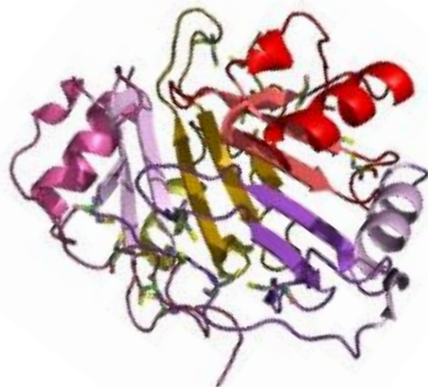
Problems in recognizing HIT

**Moderate thrombocytopenia is
very frequent in sick patients**

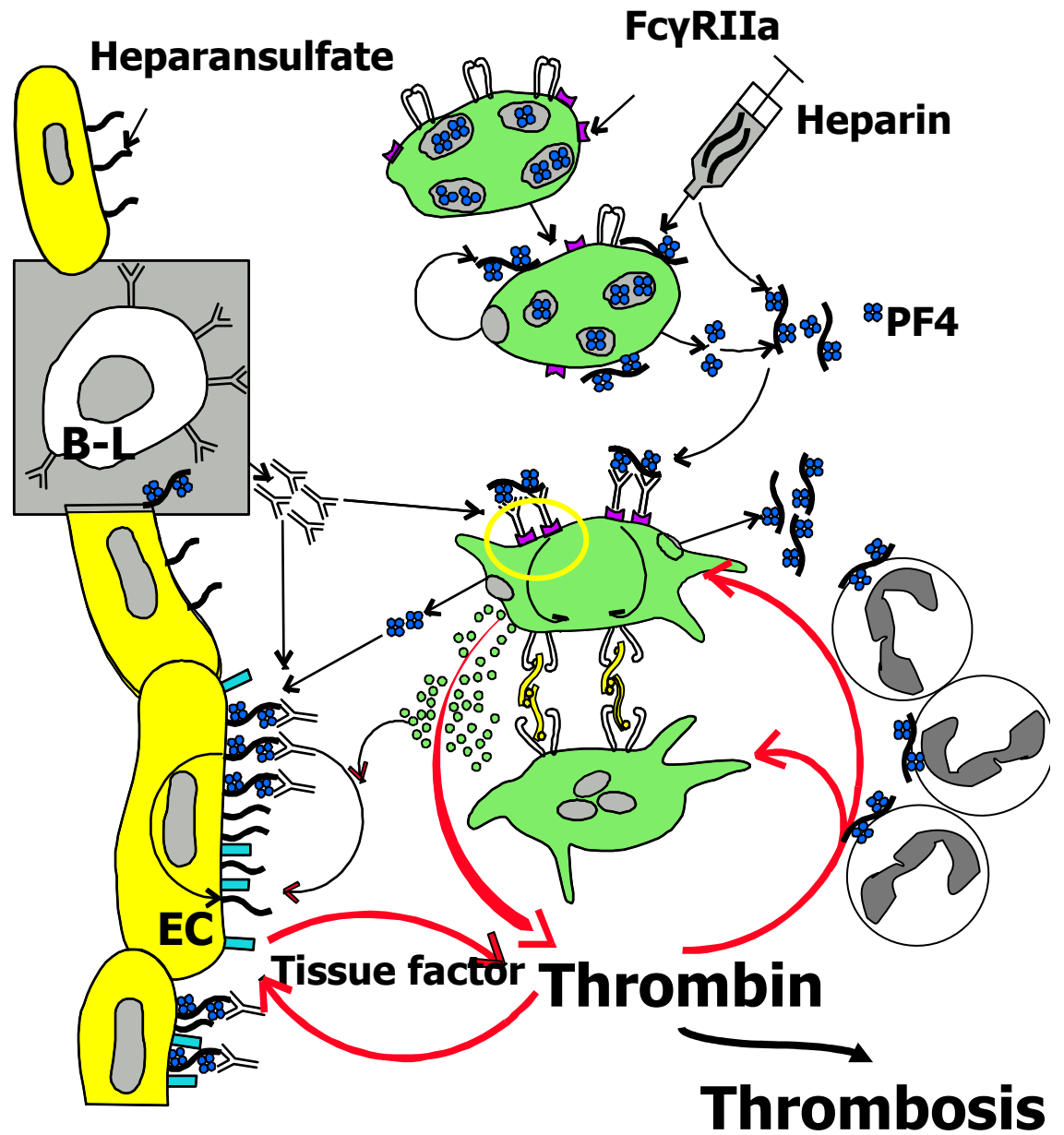
Thrombosis despite heparin

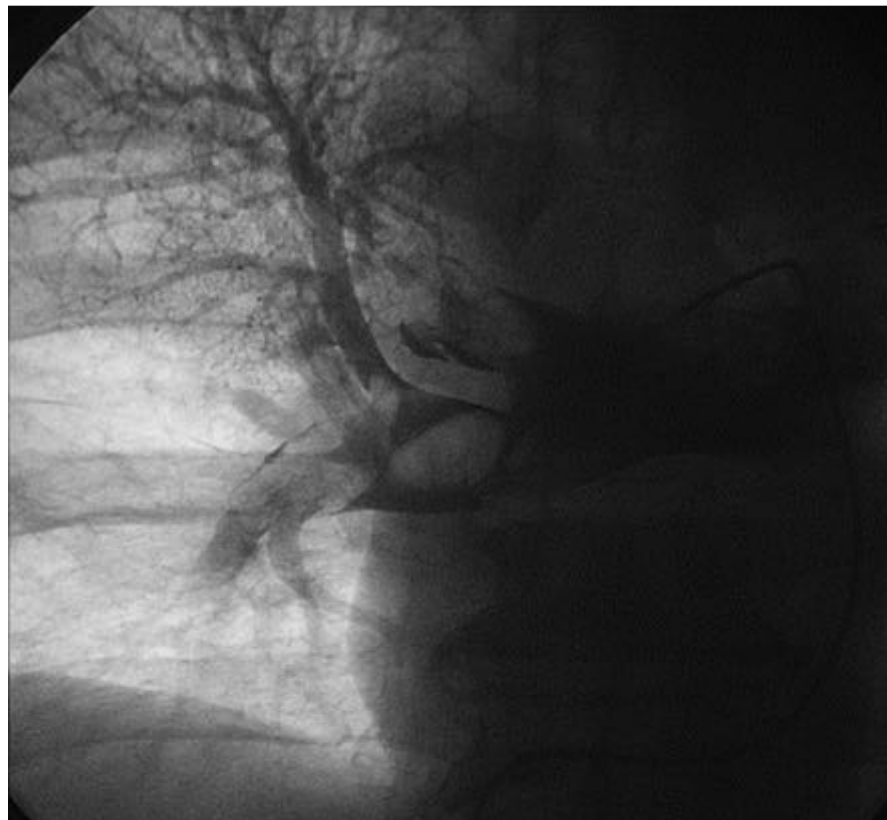
vs

thrombosis caused by heparin

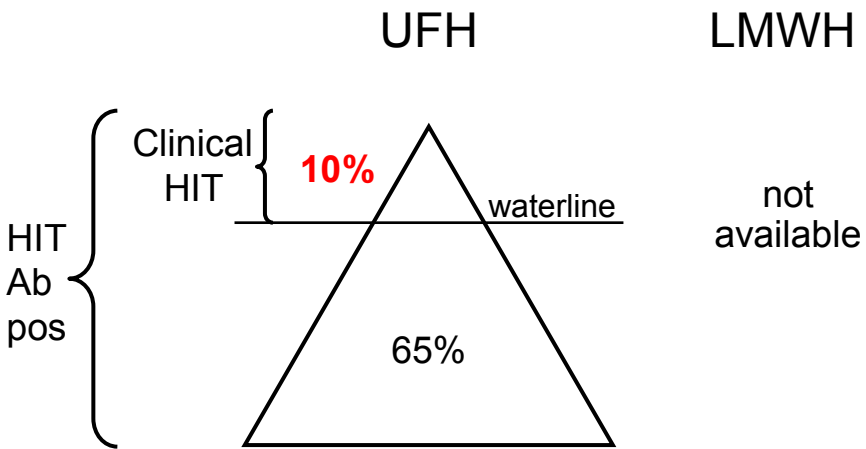


PF4

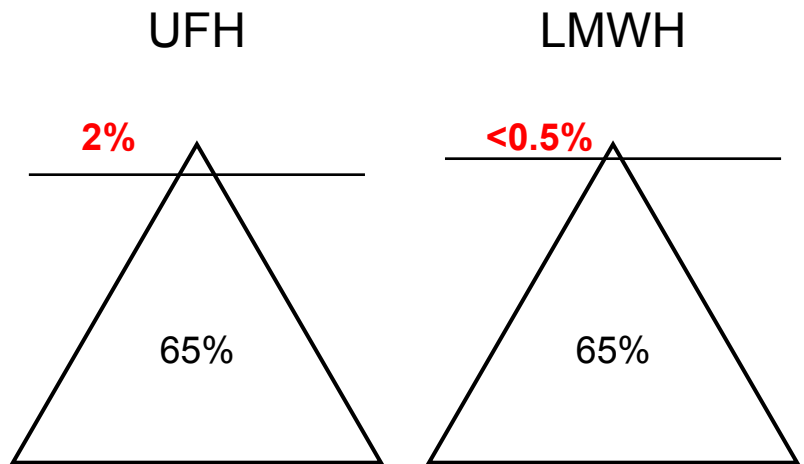




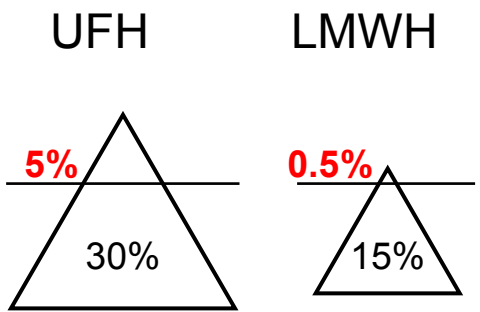
Mechanical Cardiac Support (MCS)



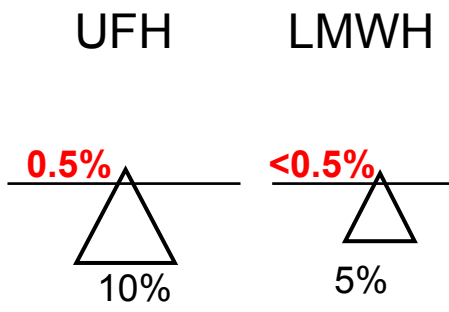
Cardiac Surgery (Non-MCS)



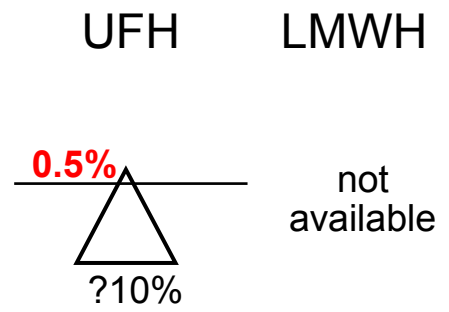
Orthopedic Surgery



Medical Patients



ICU Patients

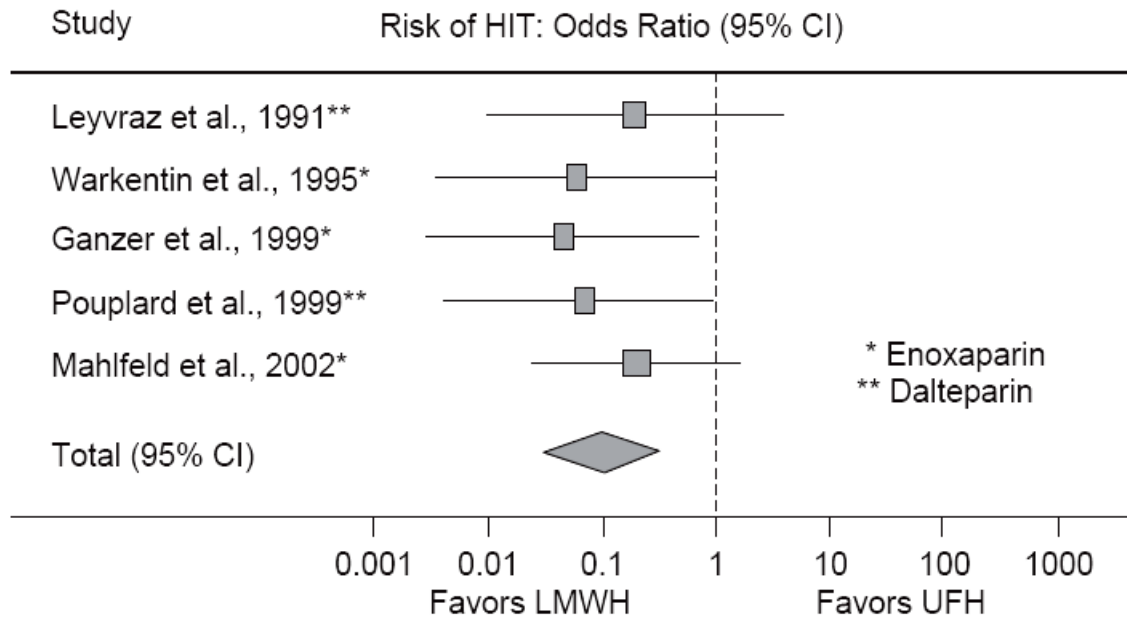


HIT Risk Groups

Why does the risk of HIT
depend on the patient group?

UFH vs LMWH?

Reduced risk of HIT with LMWH:
OR = 0.10 (0.03-0.33); p=0.0002



Studies comparing the frequency of HIT between UFH and LMWH

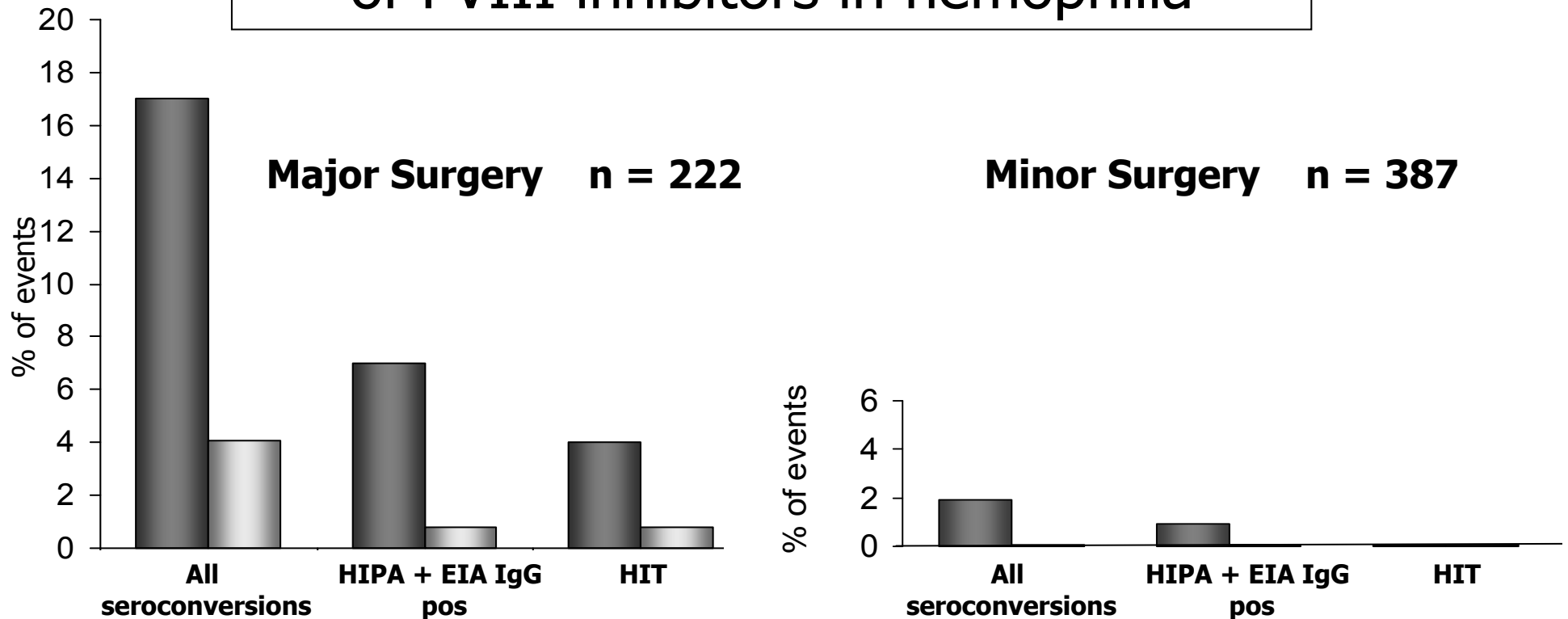
Frequency of HIT (patients with HIT/patients exposed)

Study and Method	Setting	LMWH	Female, UFH	Male, UFH	Female, LMWH	Male, LMWH
Primary analysis						
RCT ²⁸	Surgery	Enoxaparin	13/173 (7.5%)	3/159 (1.9%)	1/187 (0.5%)	1/146 (0.7%)
PCS (B/A) ³¹	Surgery	Enoxaparin	10/131 (7.6%)	2/100 (2.0%)	0/171 (0.0%)	0/100 (0.0%)
PCS (B/A) ³²	Surgery	Enoxaparin	5/182 (2.7%)	0/ 70 (0.0%)	1/171 (0.6%)	0/ 81 (0.0%)
PCS ³³	Surgery	Dalteparin	4/ 55 (7.3%)	2/102 (2.0%)	0/ 39 (0.0%)	0/132 (0.0%)
PCS (B/A) ³⁴	Medical	Nadroparin	4/ 93 (4.3%)	1/107 (0.9%)	0/ 75 (0.0%)	0/ 36 (0.0%)
RCT ³⁵	Medical	Reviparin	1/169 (0.6%)	0/206 (0.0%)	0/347 (0.0%)	0/415 (0.0%)
PCS ⁴²	Medical	NA (UFH)	4/332 (1.2%)	1/266 (0.4%)	---	---
PCS ⁴³	Medical	Several*	---	---	5/830 (0.6%)	9/935 (1.0%)

Overall: female vs male OR 2.37 (95%CI 1.37 – 4.09) p=0.0015
UFH: female vs male OR 4.53 (95%CI 2.15 – 9.56) p<0.0001

Anti-PF4/heparin Immune Response in Trauma Patients

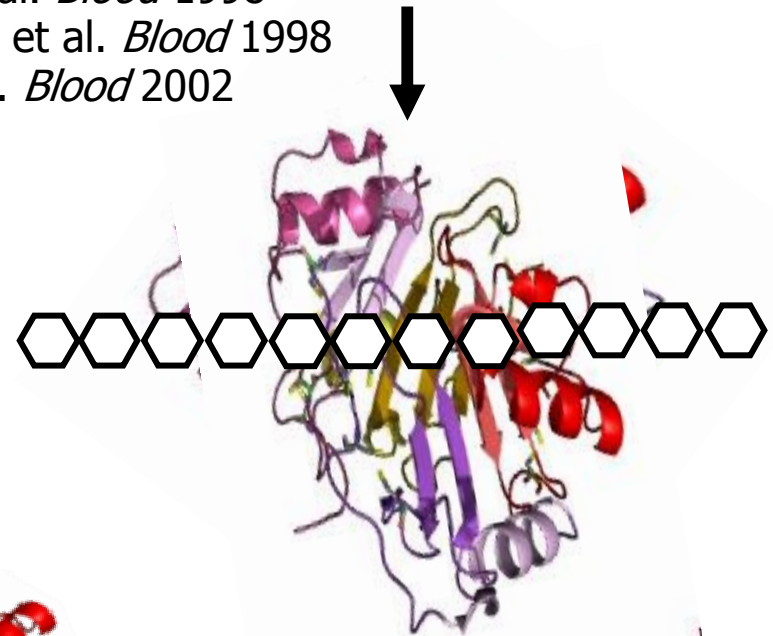
This parallels the risk for development of FVIII inhibitors in hemophilia



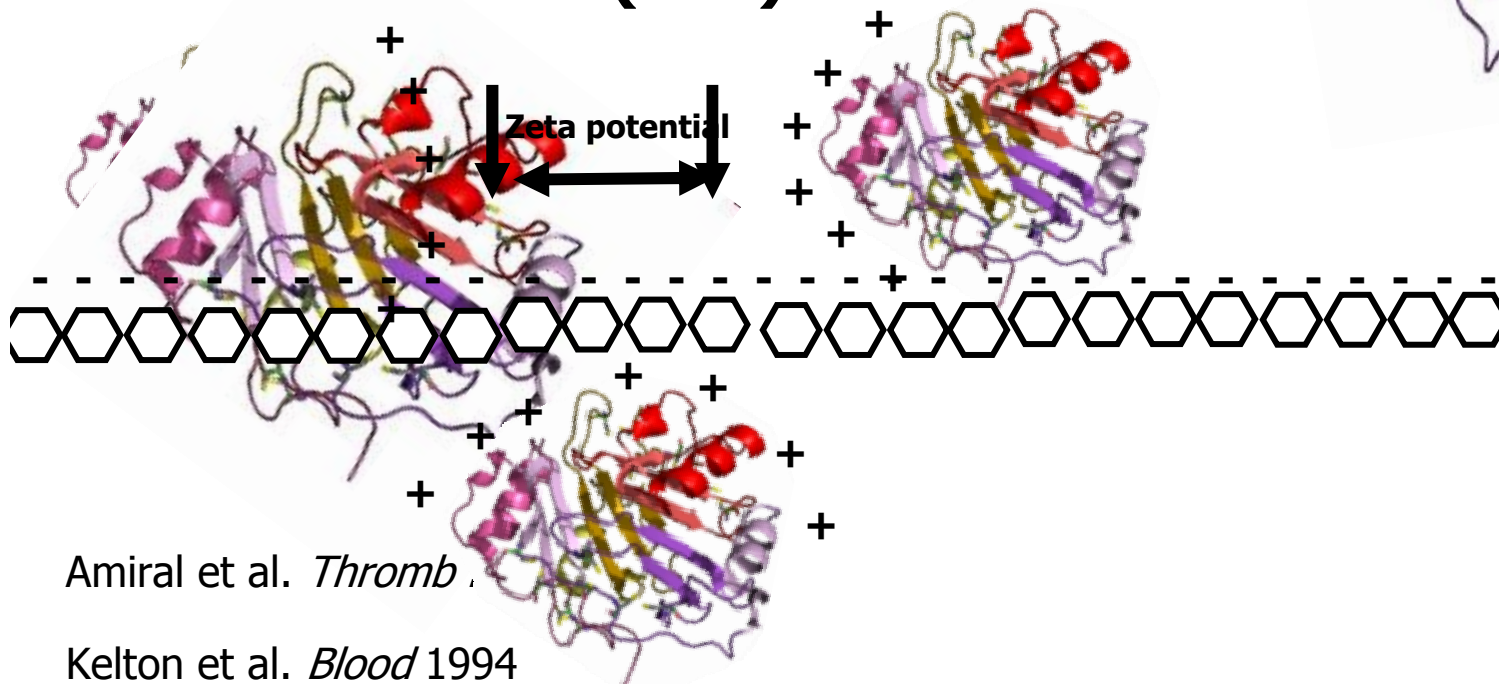
HIT Immunology

What is the antigen?

Suh et al. *Blood* 1998
Ziporen et al. *Blood* 1998
Li et al. *Blood* 2002



Platelet Factor 4 (PF4)



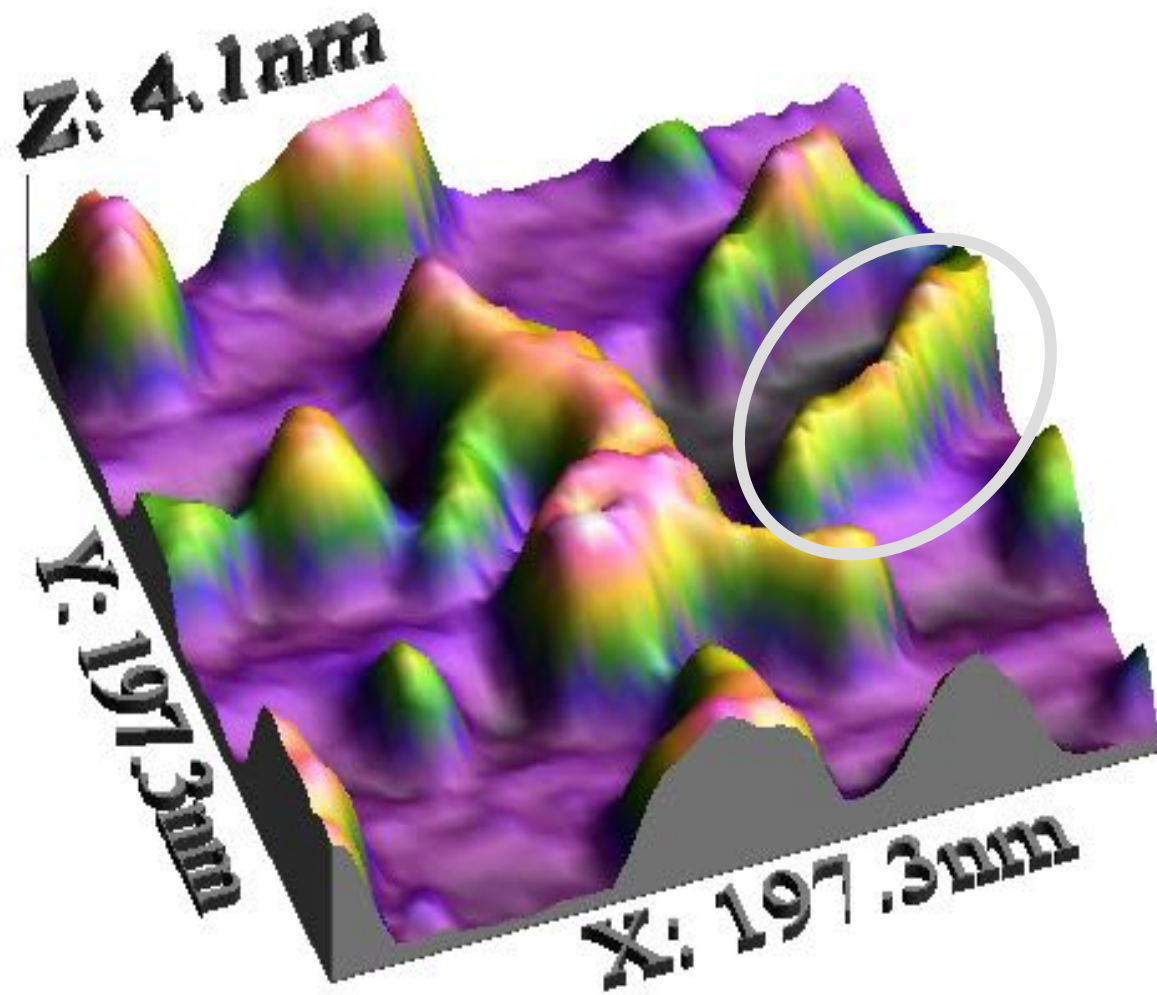
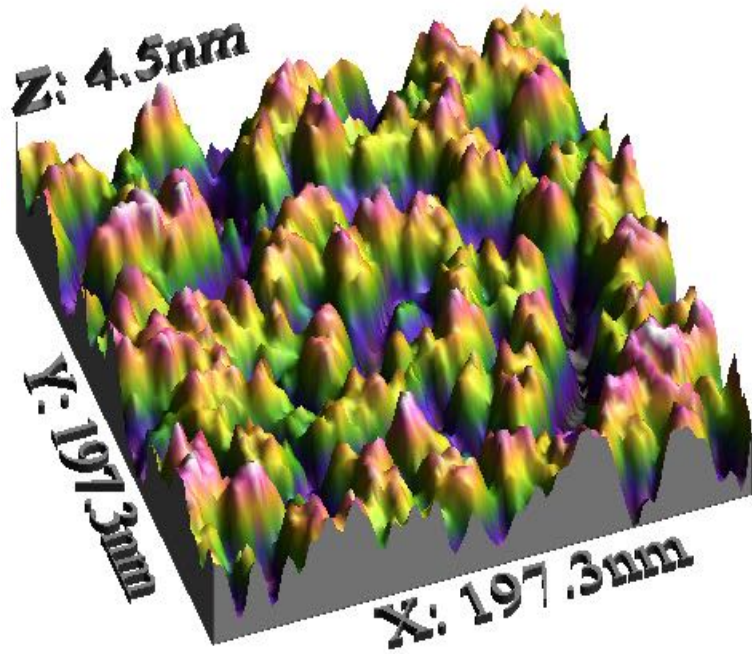
Amiral et al. *Thromb* .

Kelton et al. *Blood* 1994

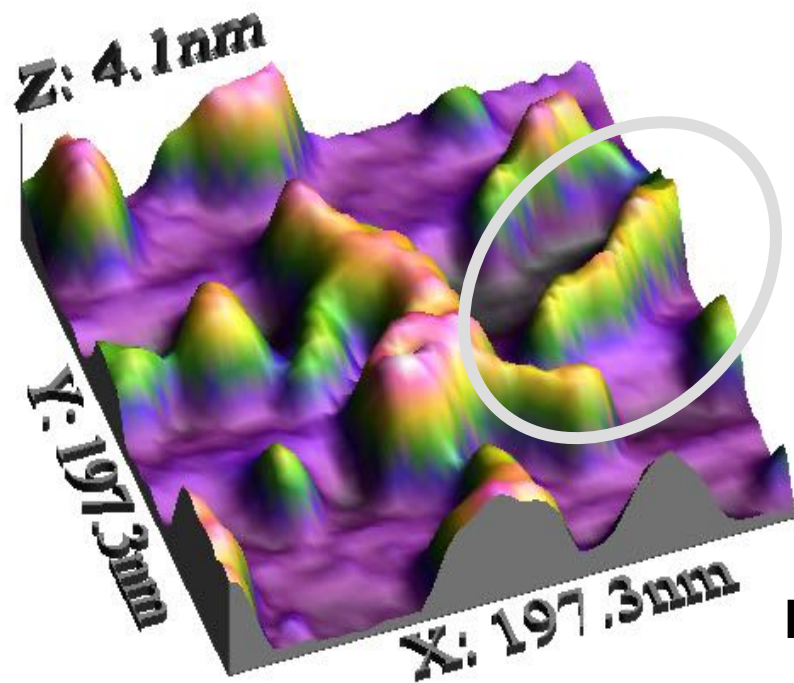
Visentin et al. *J Clin Invest* 1994

Greinacher et al. *Thromb Haemost* 1994

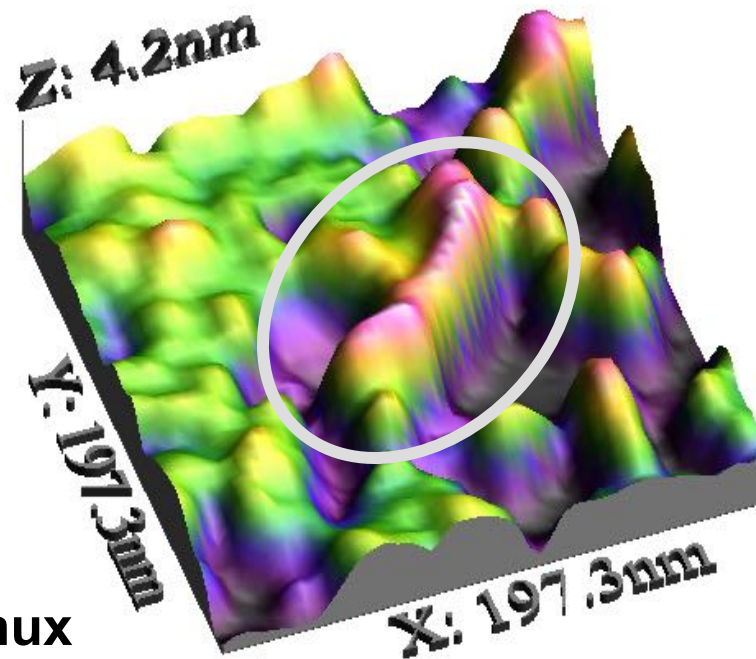
Greinacher et al. *Arterioscler Thromb Vasc Biol* 2006;26:2386-93



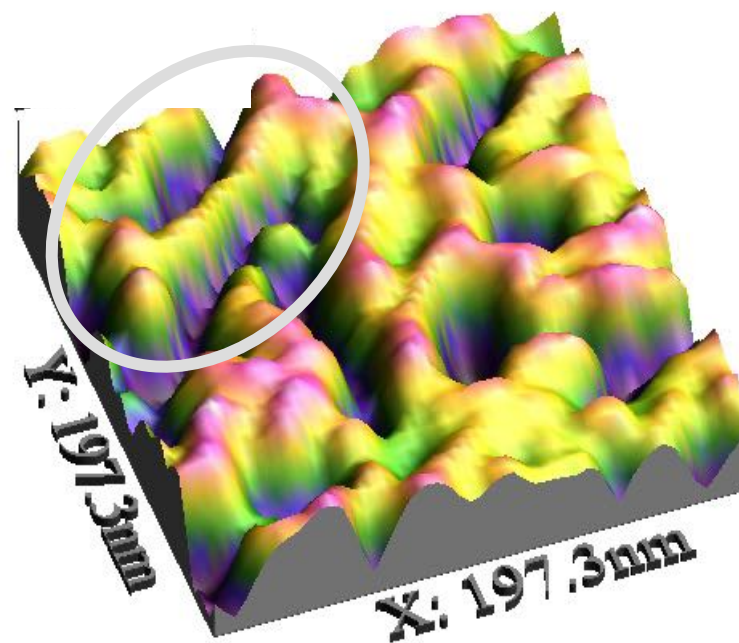
PF4/UFH



PF4/LMWH

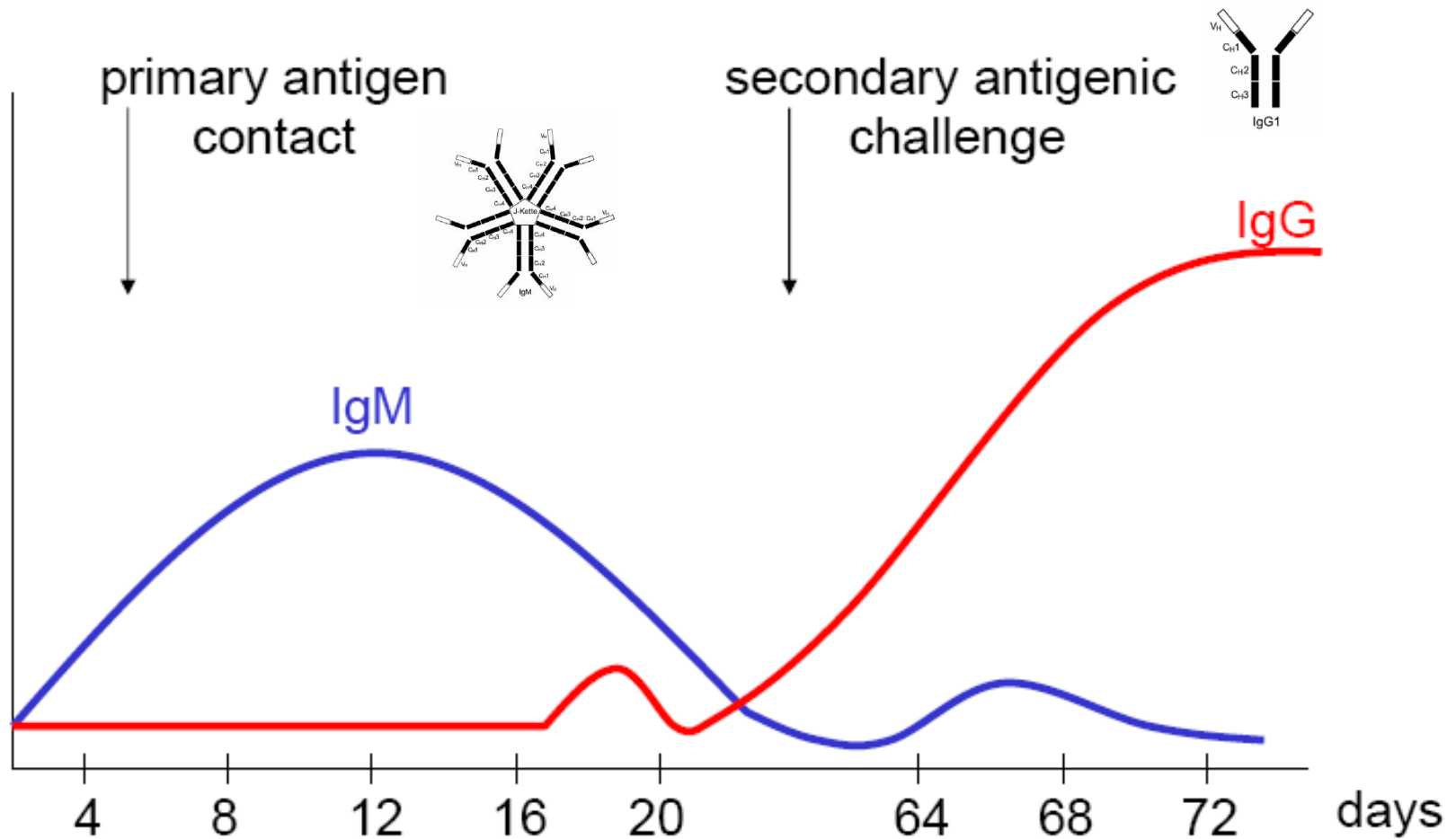


PF4/fondaparinux

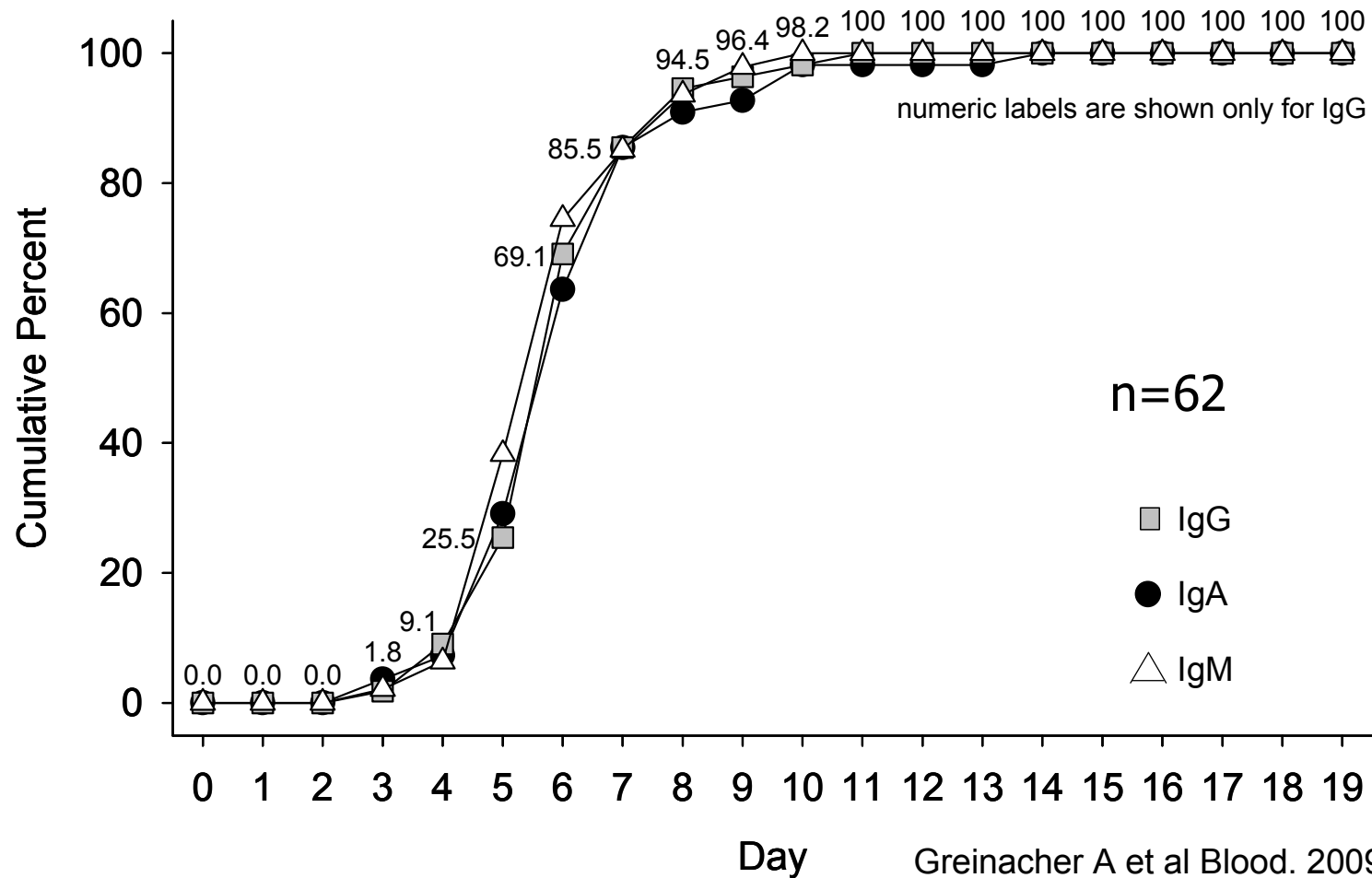


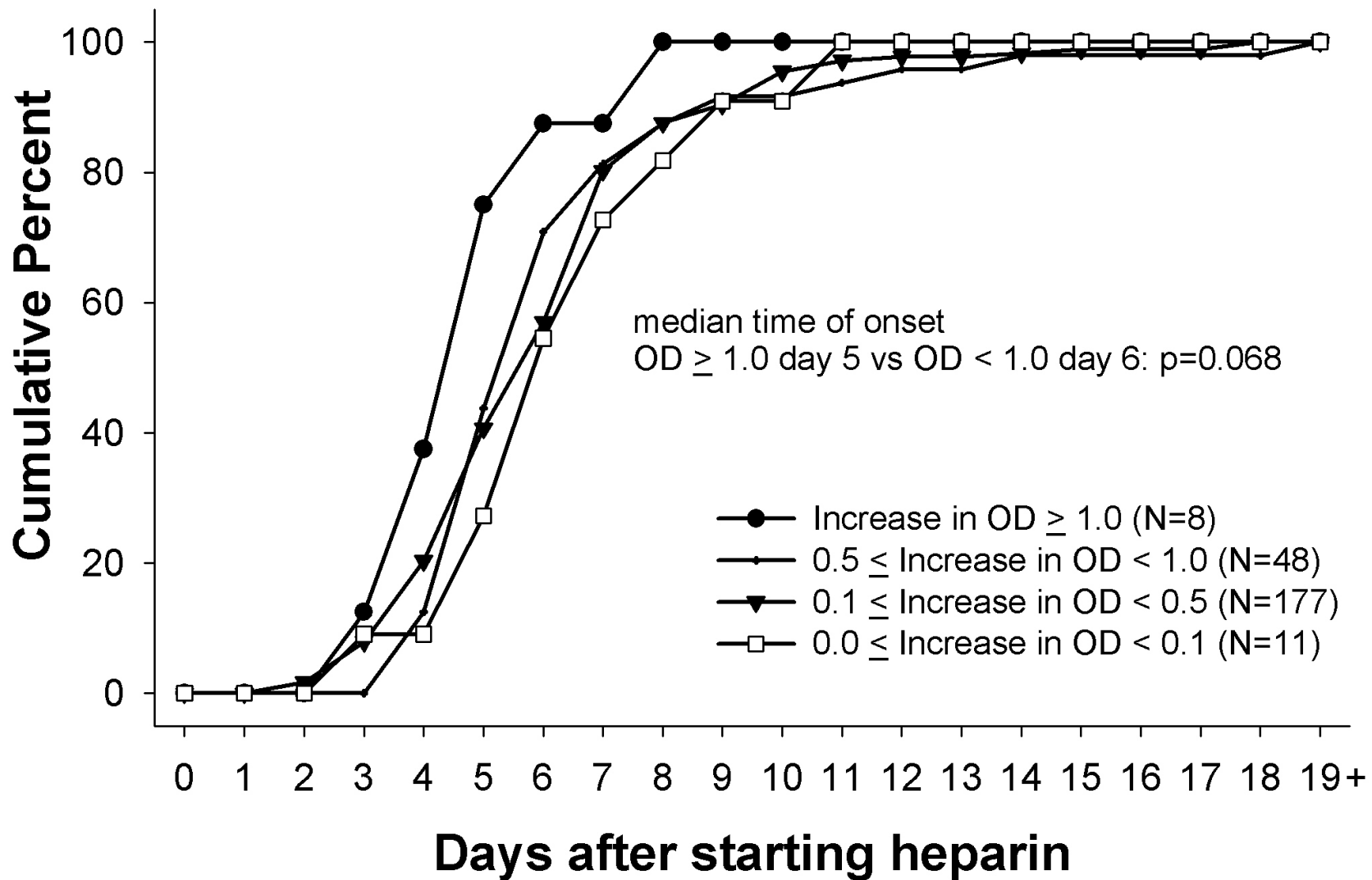
Classical Antibody Response

Class switching

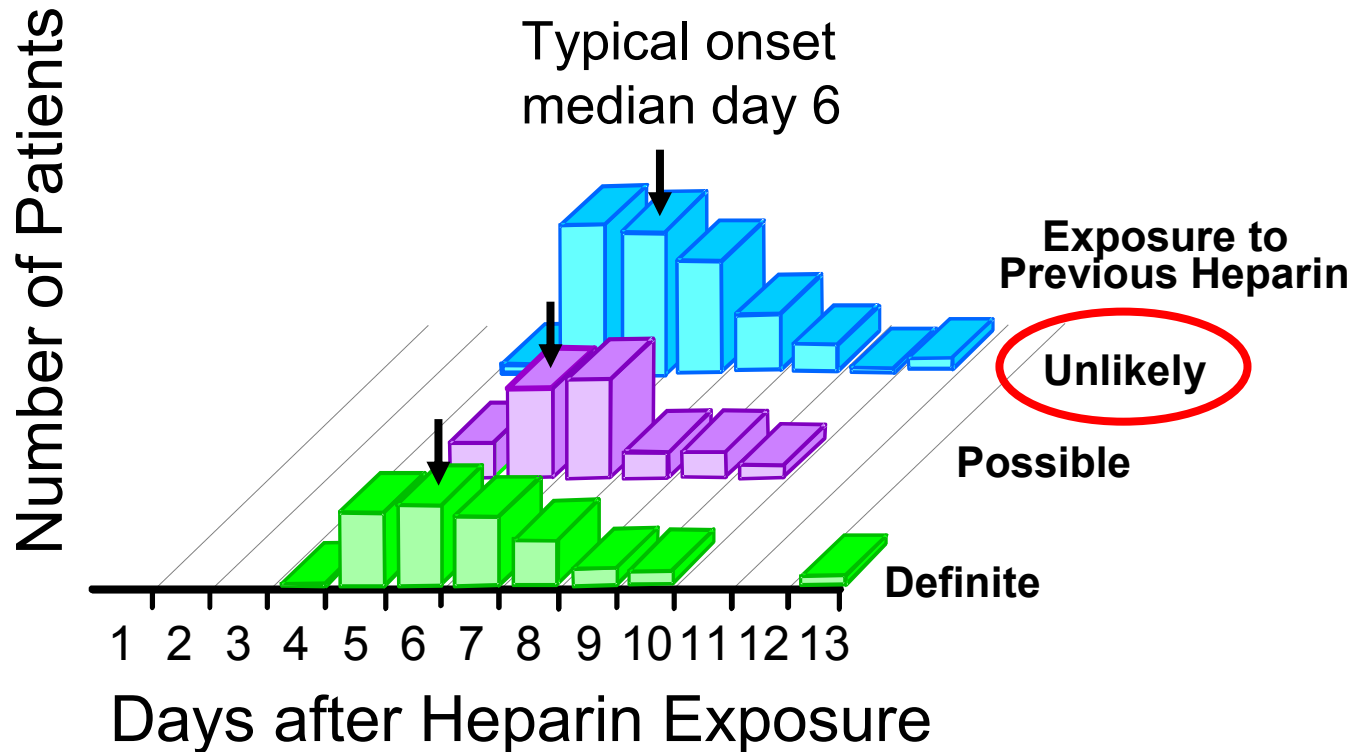


IgG and IgM Antibodies Occur with the Same Timing



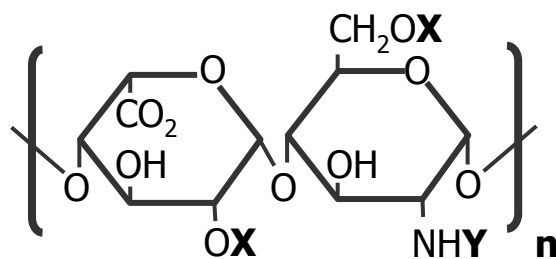


Influence of Prior Heparin on Timing of Platelet Fall

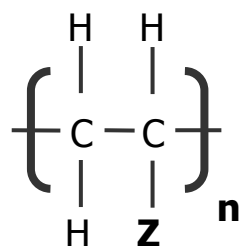


Substitutes for Heparin in the PF4/heparin EIA

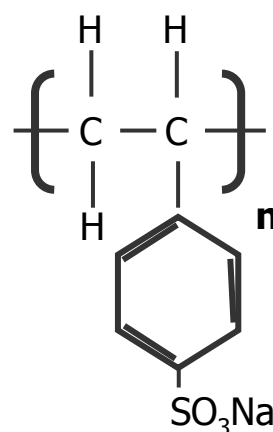
Heparin



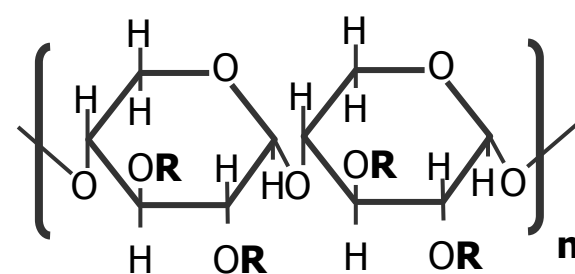
Polyvinyl



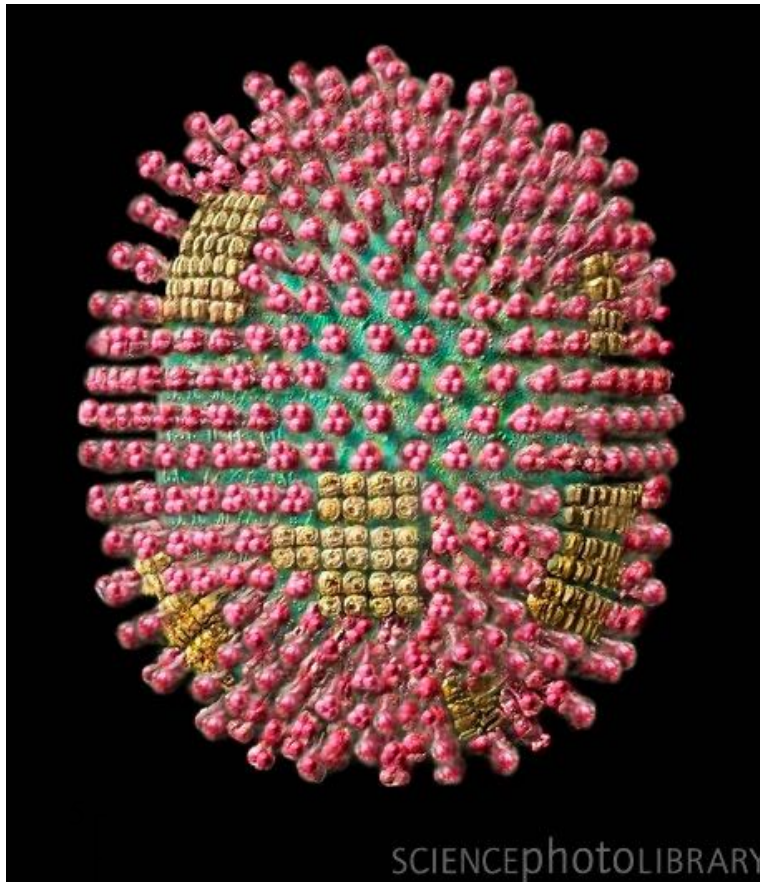
Polystyrene-4 sodium-sulfonate



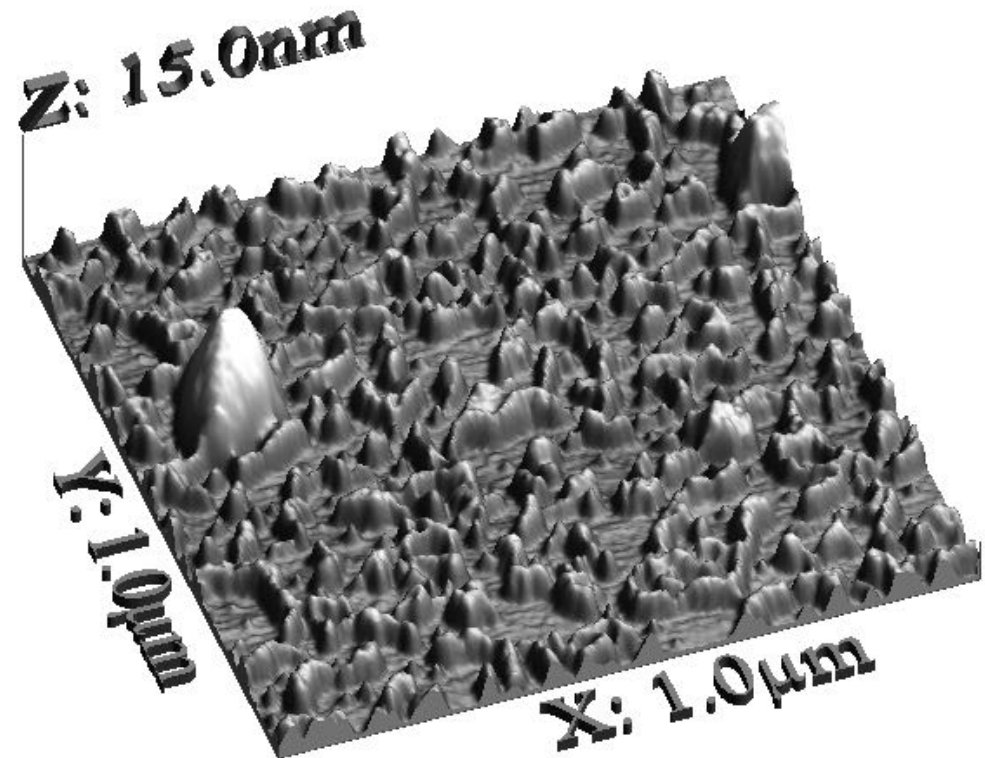
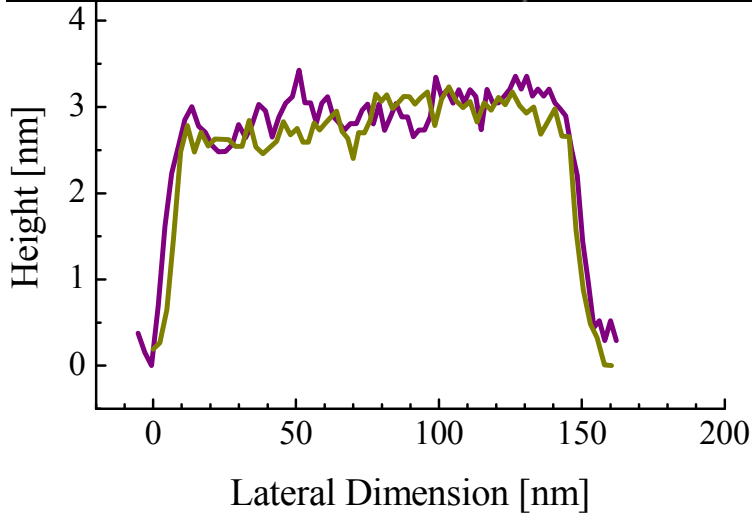
Pentosan polysulfate sodium



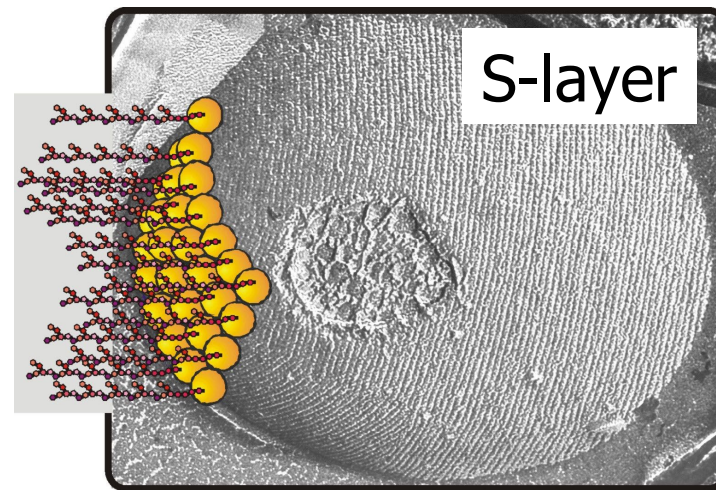
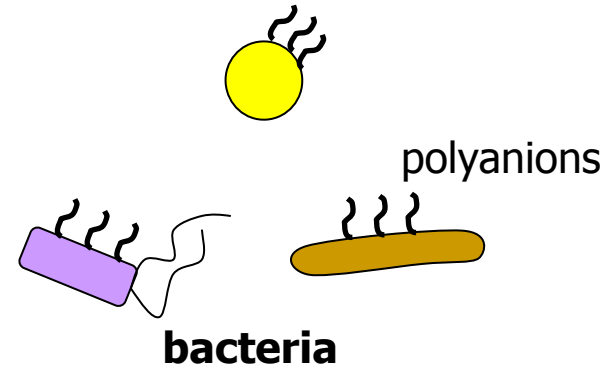
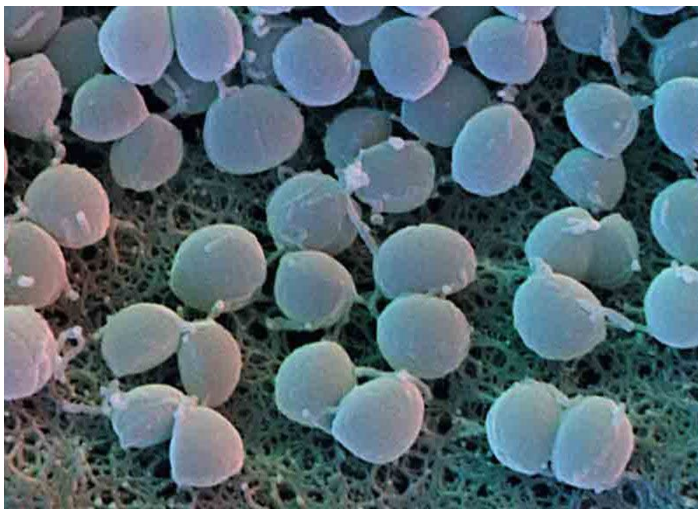
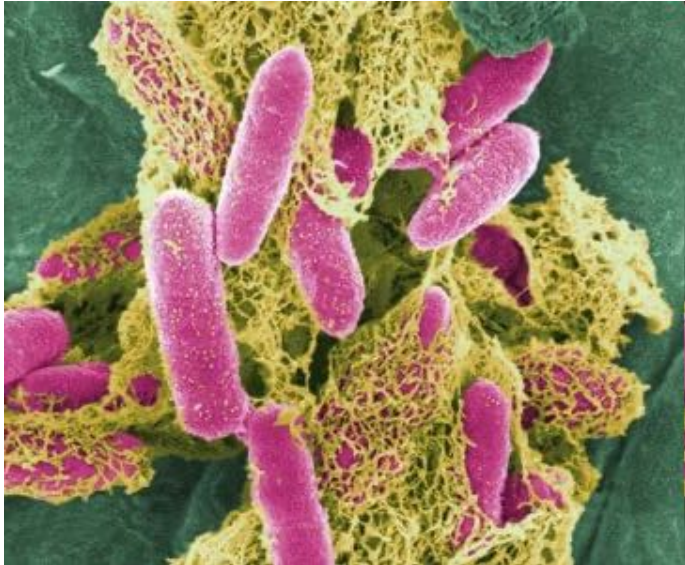
Heparin-associated thrombocytopenia in a patient treated with polysulphated chondroitin sulphate. Greinacher A et al. Br J Haematol 1992;81:252-4.

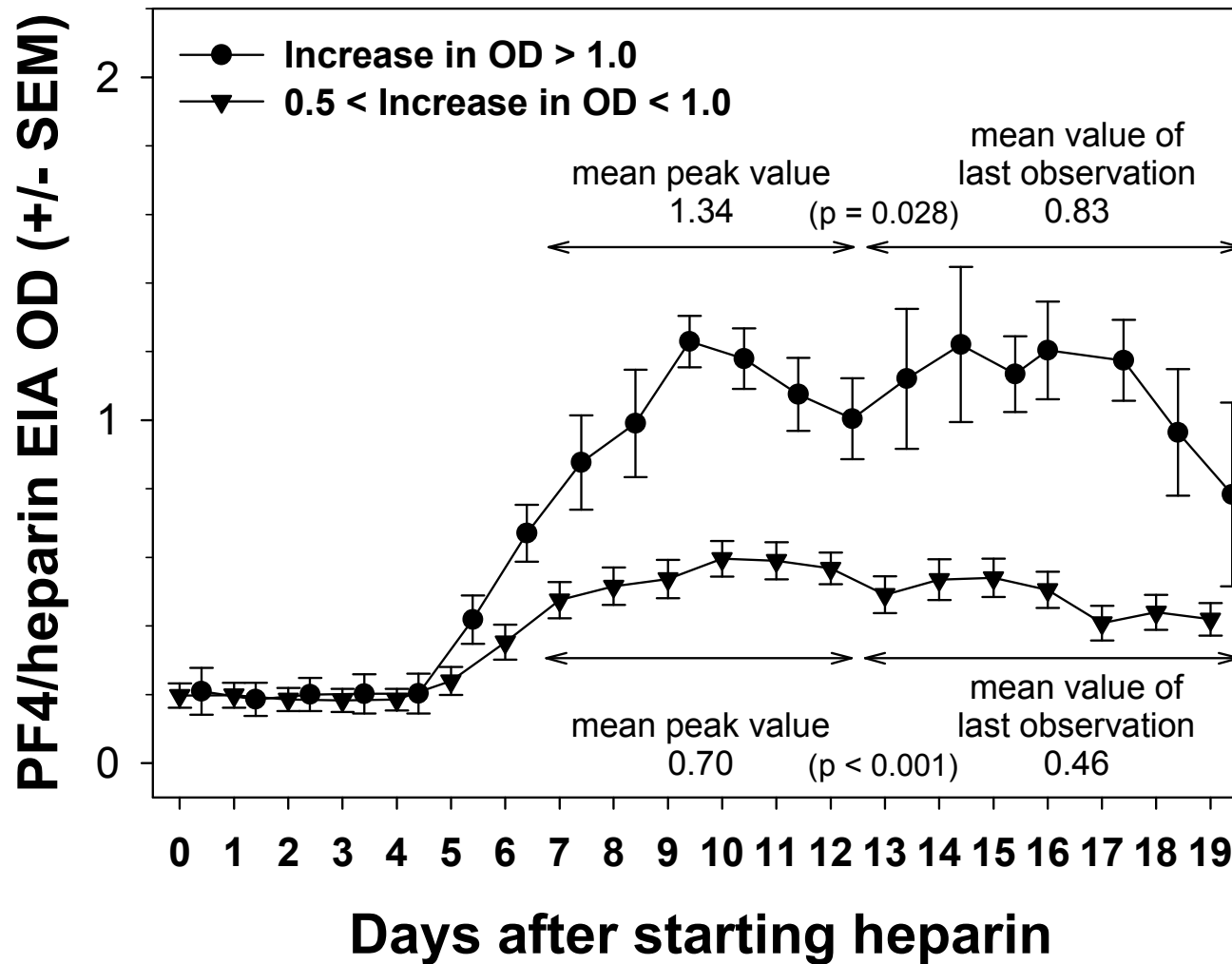


HIV	100 nm
Influenza Virus	150 nm
Herpesviren	200 nm



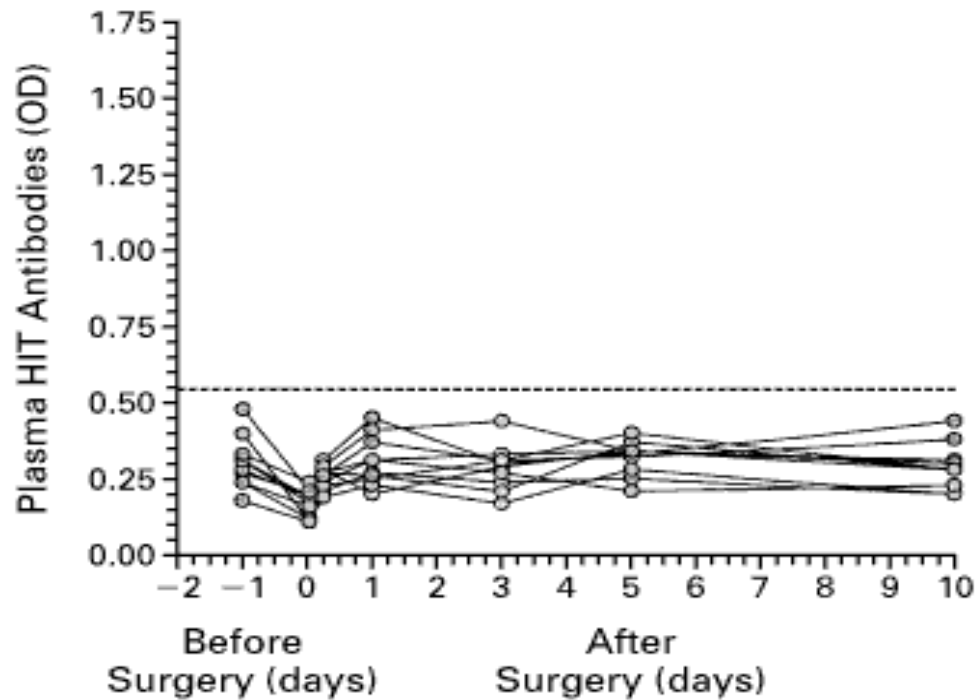
Does PF4 bind to bacteria?





Number of patients																				
●	8	8	8	8	8	8	8	8	8	8	8	8	7	6	5	5	4	4	4	4
▼	39	39	39	39	39	39	39	39	39	39	39	39	37	31	29	27	23	18	14	13

Use of Heparin during Cardiopulmonary Bypass in Patients with a History of Heparin-Induced Thrombocytopenia



Pötzsch et al. N Engl J Med, 2000:343; 515

No evidence for memory B-cells
in patients developing
PF4/heparin IgG antibodies
within 10 days

**seroconversion to PF4/H-
IgG 30 patients**

**positive ELISPOT for anti-
PF4/H: 2/30**

**positive ELISPOT for anti T-
toxin: 12/24**

Selleng K et al. Transfusion 2009

Greifswald

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