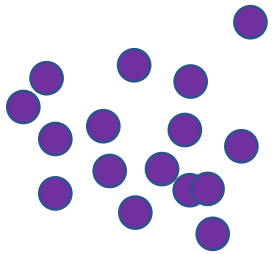
The coagulation system in *Staphylococcus aureus* endovascular infections

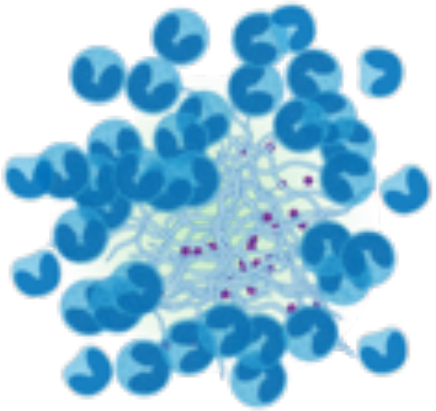
Thomas Vanassche
Leuven, Belgium

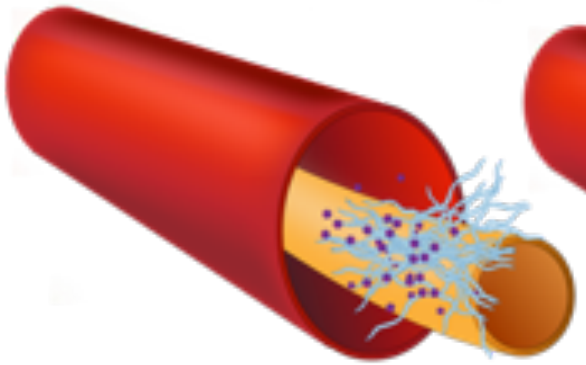
Staphylococcus aureus

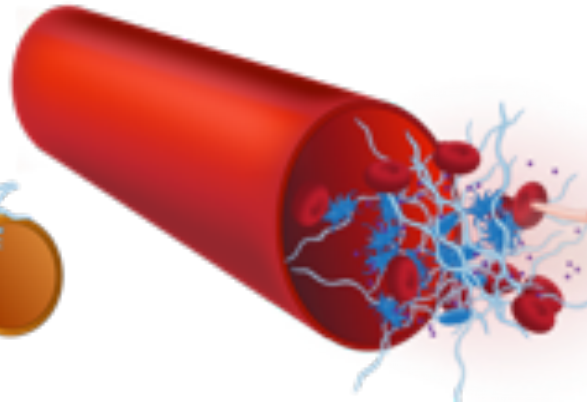
S. aureus disease spectrum

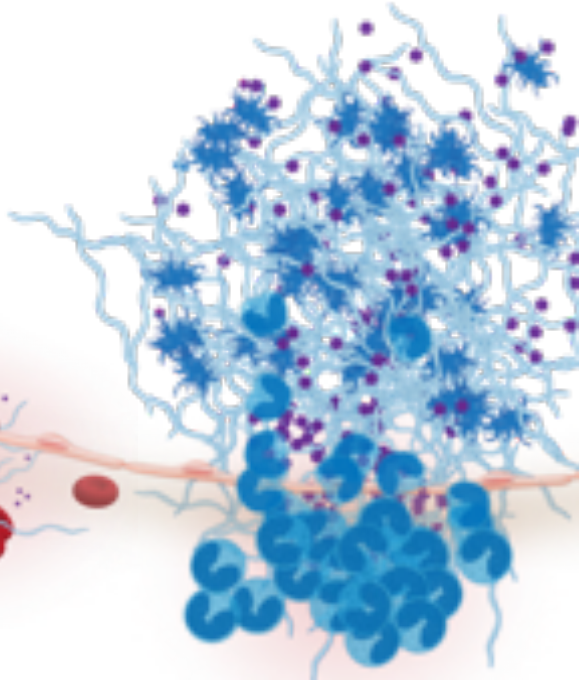
1/5











COLONISATION

COMMENSAL

INVASION

ABCESS

PERSISTENCE

CATHETER- AND DEVICE-RELATED INFECTIONS

DISSEMINATION

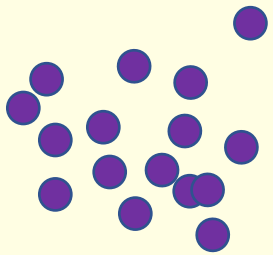
SEPSIS

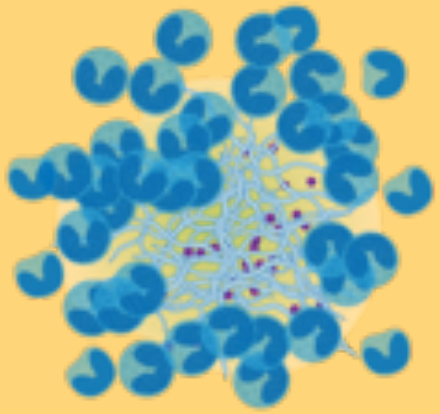
ENDOVASCULAR ADHESION

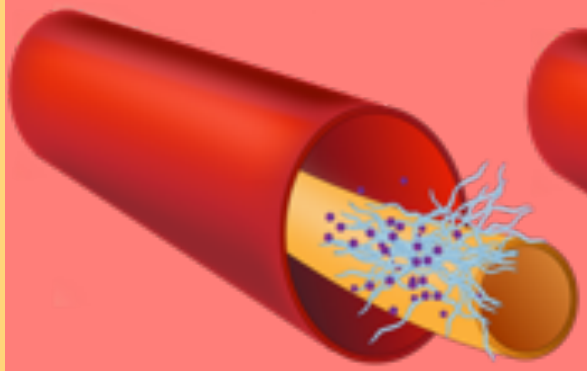
INFECTIVE ENDOCARDITIS

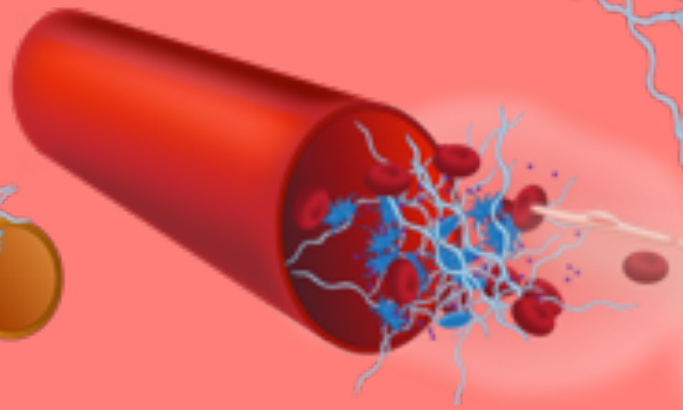
SEVERITY

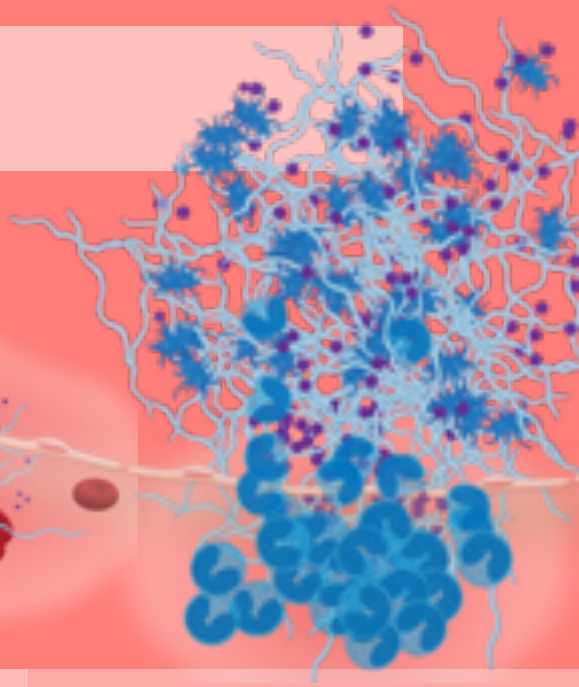
S. aureus disease spectrum







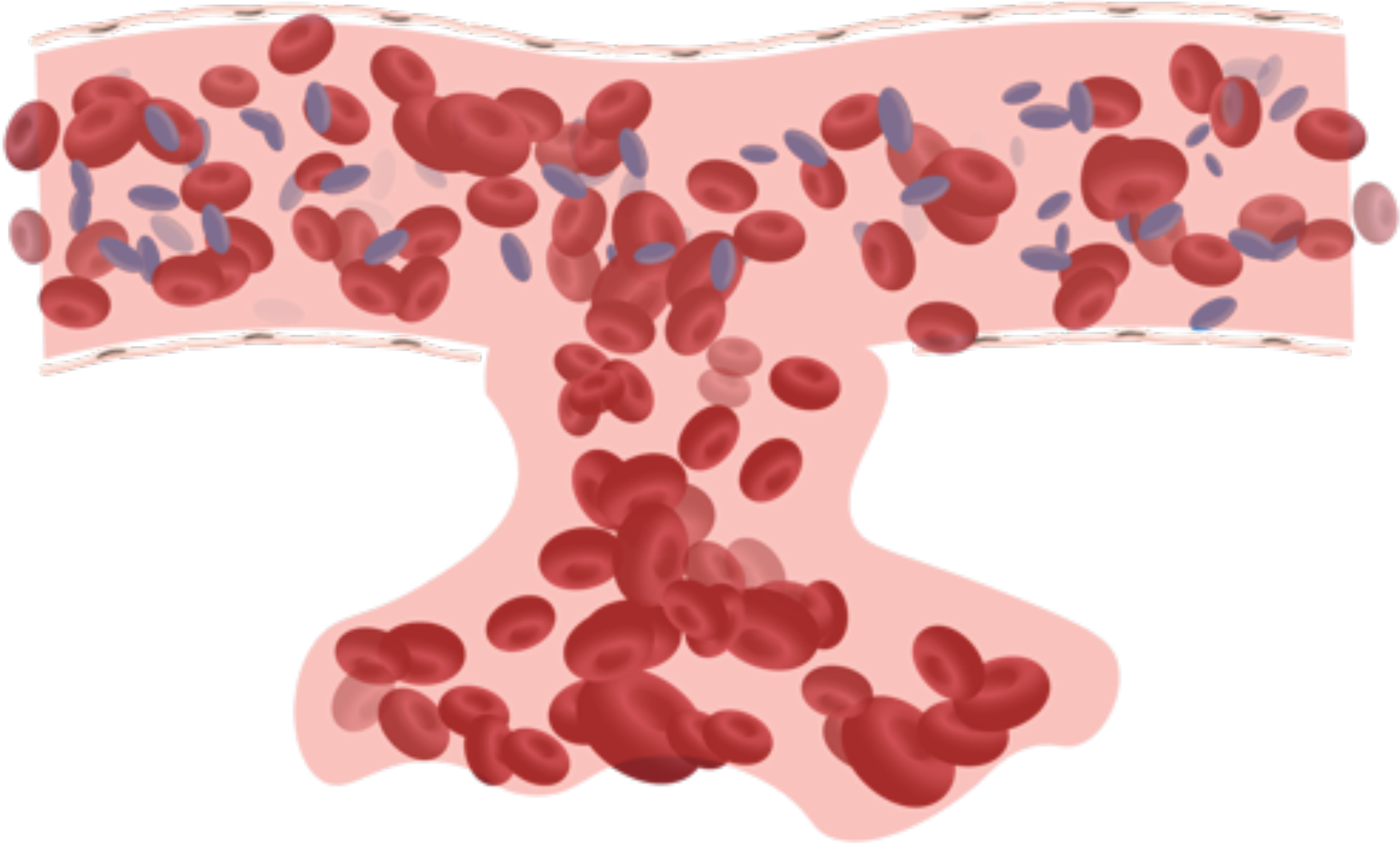


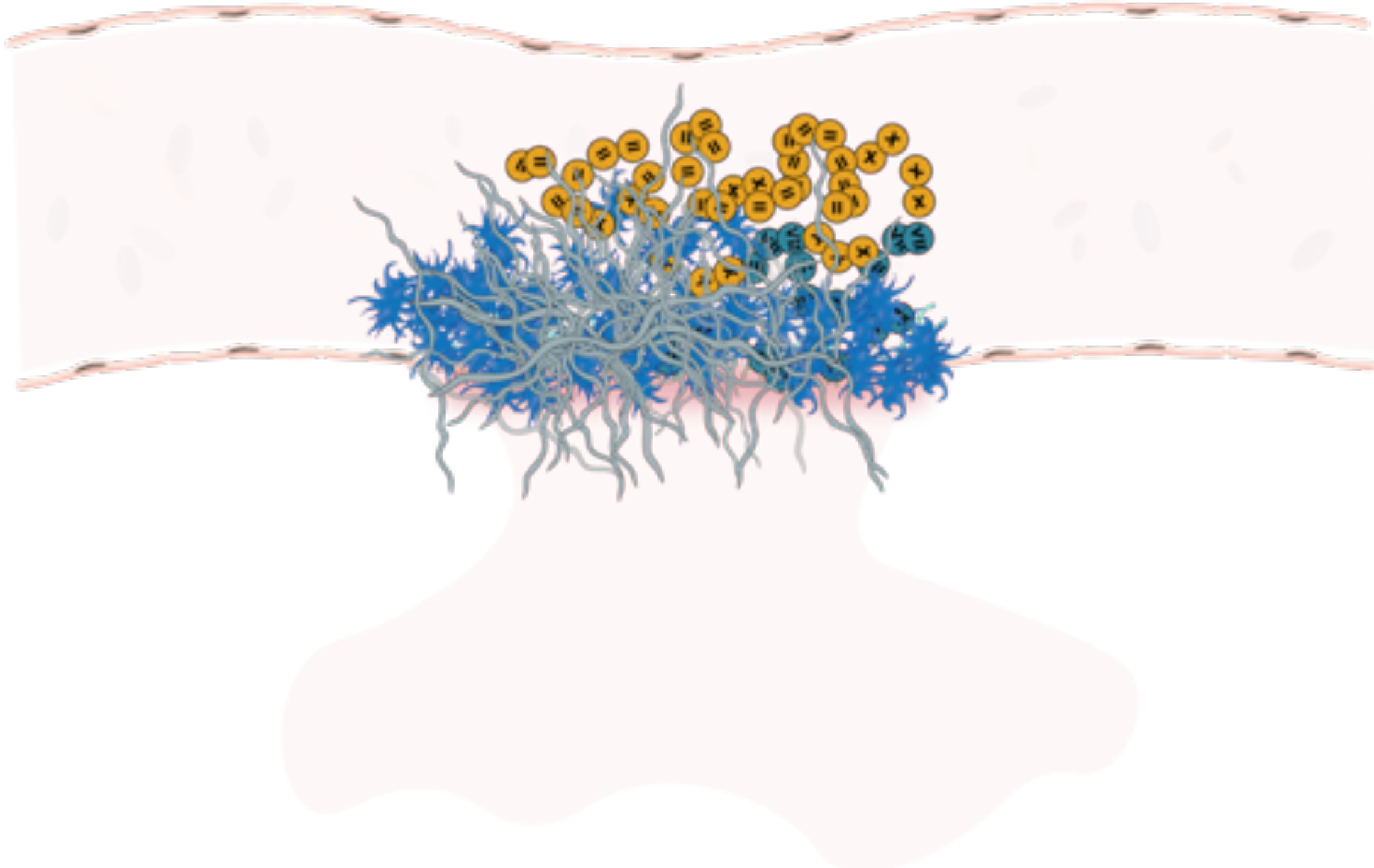


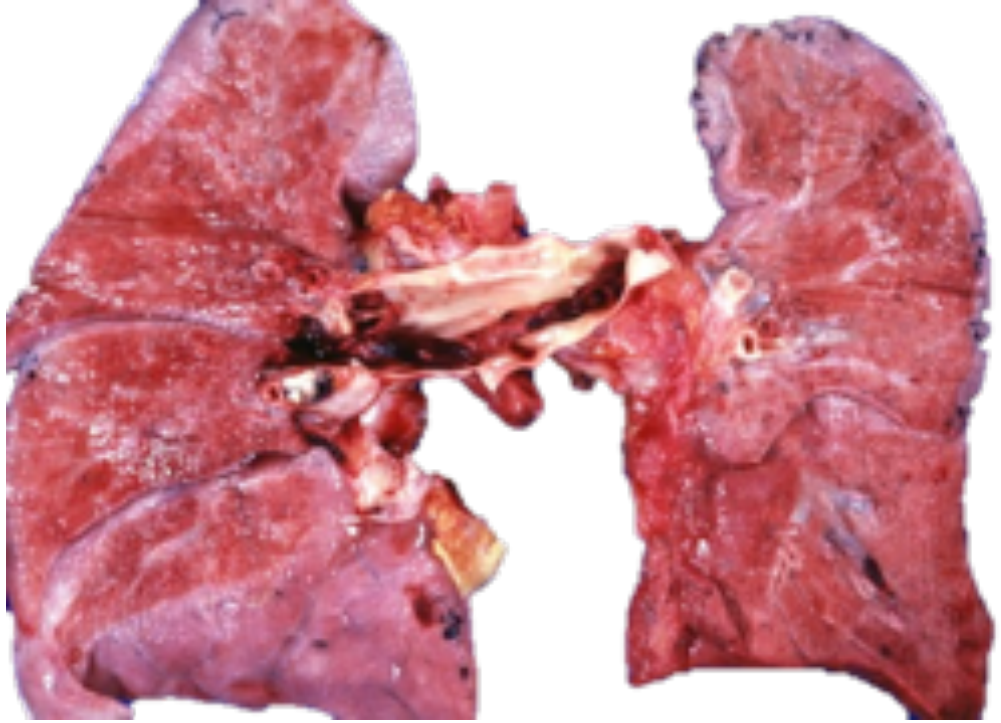
COLONISATION	INVASION	PERSISTENCE	DISSEMINATION	ENDOVASCULAR ADHESION
COMMENSAL	ABCESS	CATHETER- AND DEVICE-RELATED INFECTIONS	SEPSIS	INFECTIVE ENDOCARDITIS

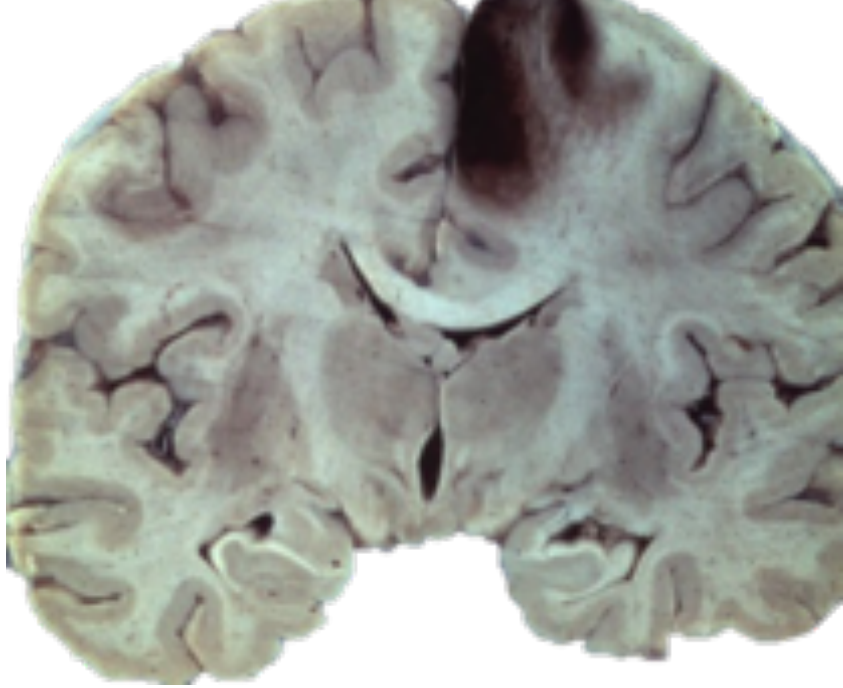
SURFACE **SKIN** **BLOOD**

THE COAGULATION SYSTEM PROTECTS AGAINST LIFE-THREATENING BLEEDING







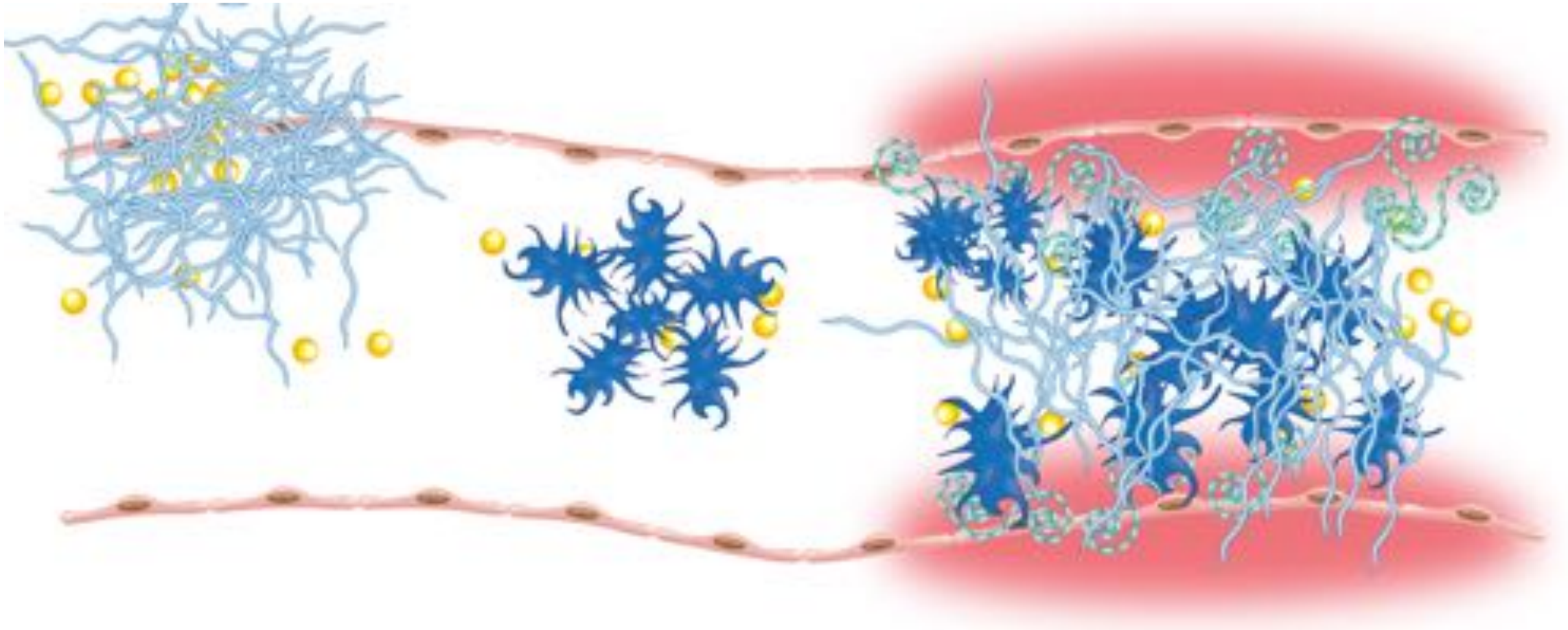


1/3

THE COAGULATION SYSTEM PROTECTS AGAINST LIFE-THREATENING BLEEDING

BUT UNREGULATED ACTIVATION IS OUR N°1 KILLER

THE COAGULATION SYSTEM PROTECTS AGAINST LIFE-THREATENING INFECTIONS

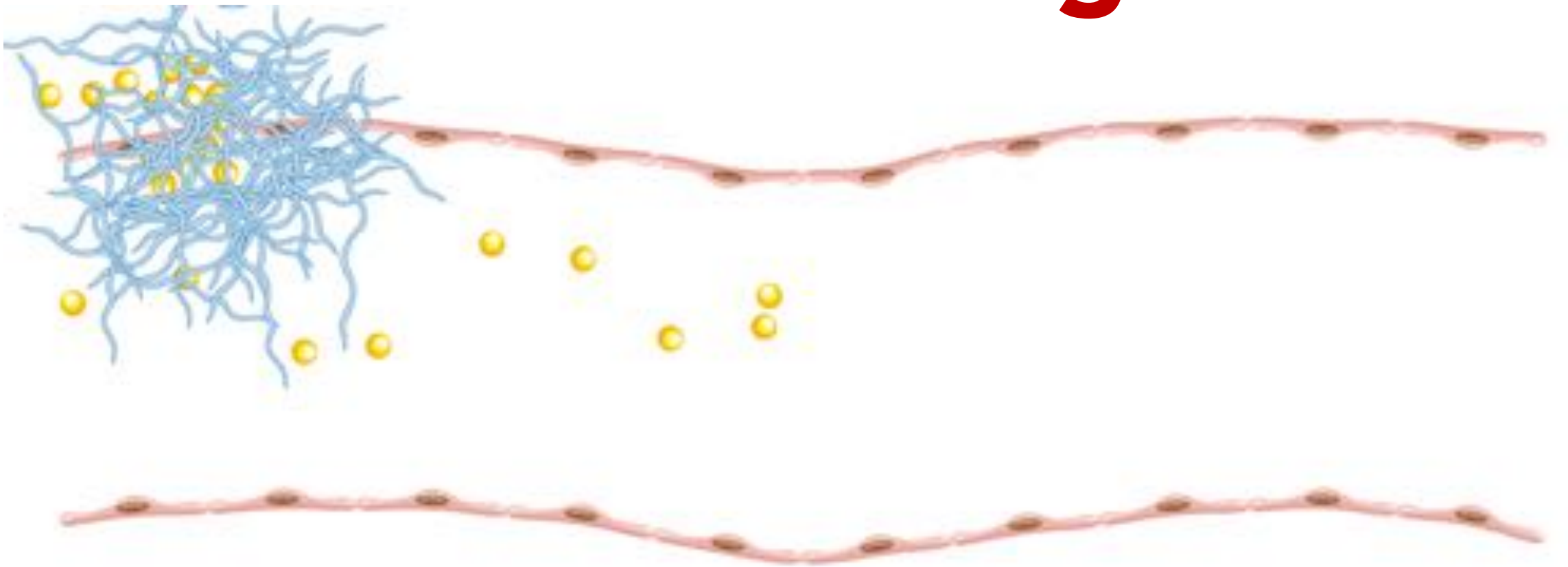


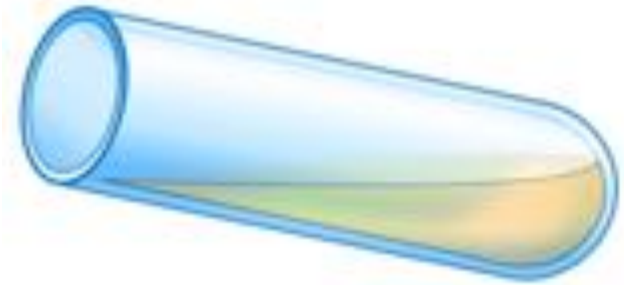
THE COAGULATION SYSTEM PROTECTS AGAINST LIFE-THREATENING INFECTIONS BUT INADEQUATE RESPONSE INCREASES MORTALITY

S. AUREUS HAS EVOLVED TO *ESCAPE* THE COAGULATION SYSTEM

S. AUREUS HAS EVOLVED TO *USE* THE COAGULATION SYSTEM TO ITS *OWN* ADVANTAGE TO *PROMOTE* INFECTION

S.aureus and coagulation





coagulase test negative =
coagulase-negative staphylococ (CNS)

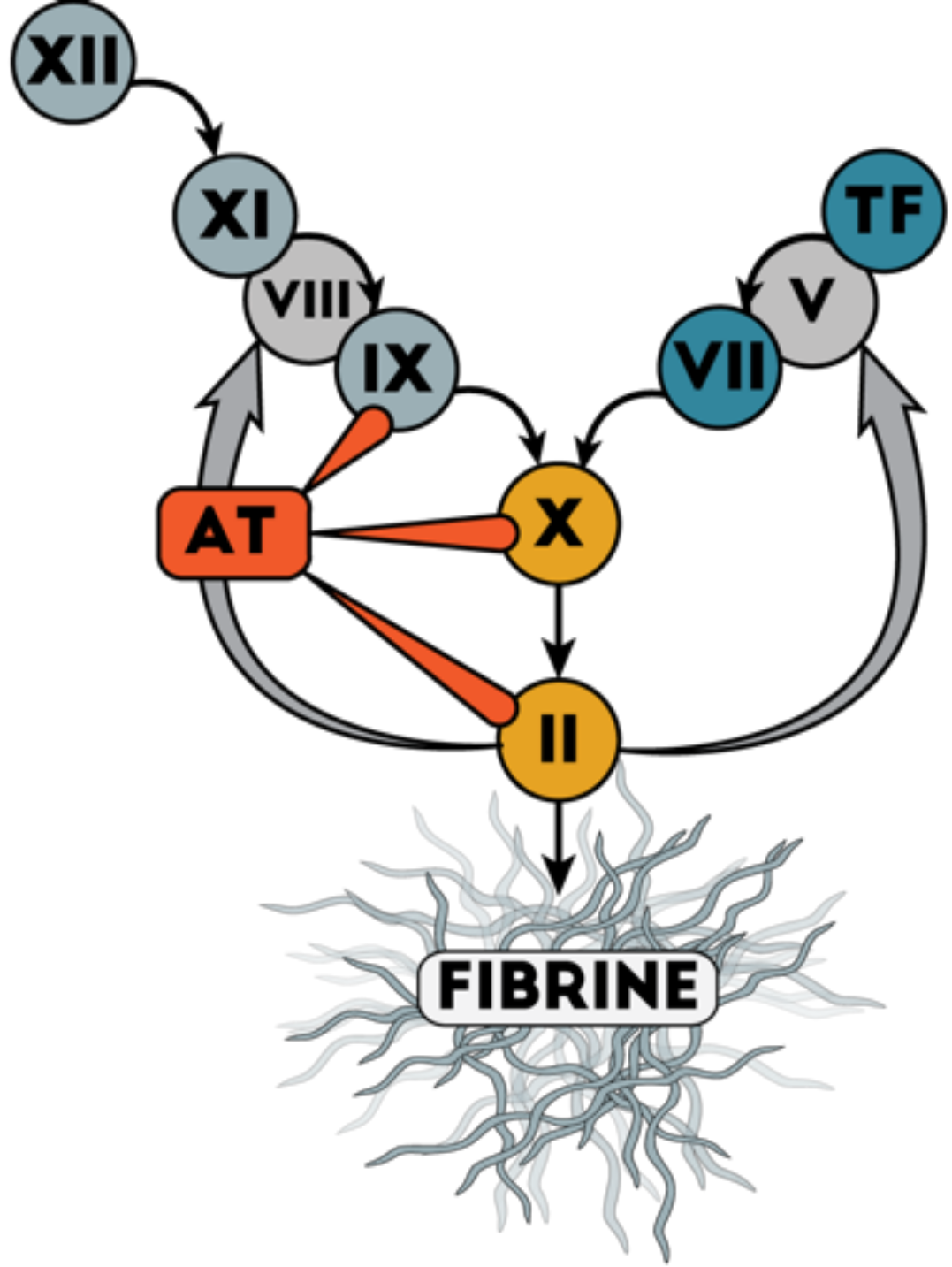
coagulase test positive =
Staphylococcus aureus (S. aureus)

COAGULASE AND HEMOLYSIN TESTS AS MEASURES OF THE PATHOGENICITY OF STAPHYLOCOCCI

GEORGE H. CHAPMAN, CONRAD BERENS, ADELINE PETERS AND LILIAN CURCIO
Clinical Research Laboratory and laboratory of the Lighthouse Eye Clinic of the New York Association for the Blind, New York, N.Y.

Received for publication April 18, 1934

"The determination of the coagulase is important because, regardless of its color, a coagulating strain is probably pathogenic"


XII
XI
VIII
IX
TF
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VII
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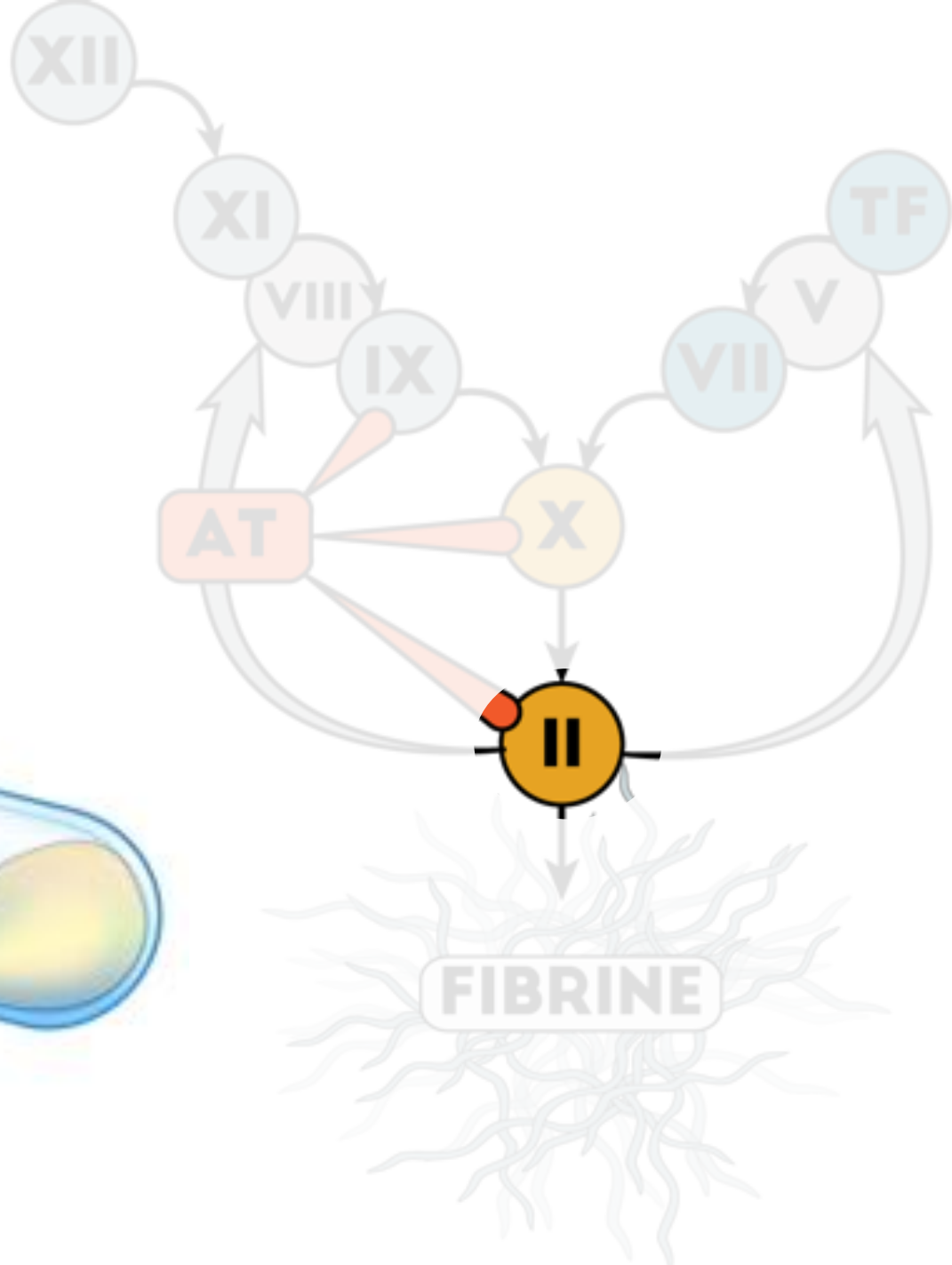
II
FIBRINE


XII
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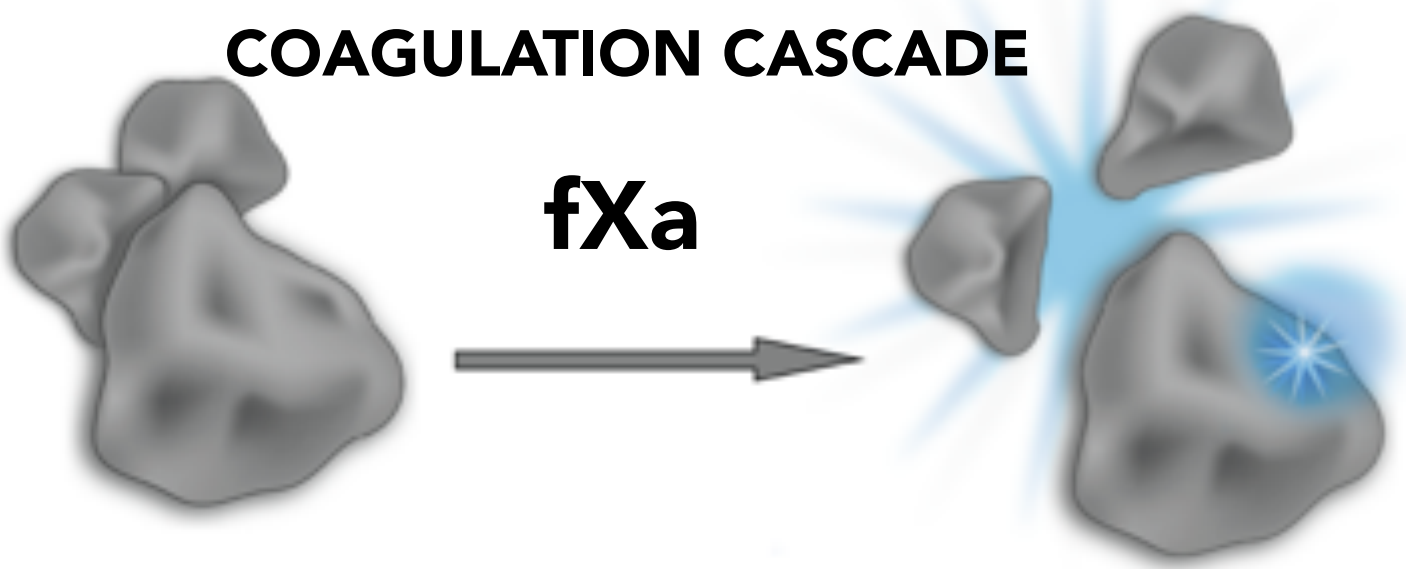
FIBRINE

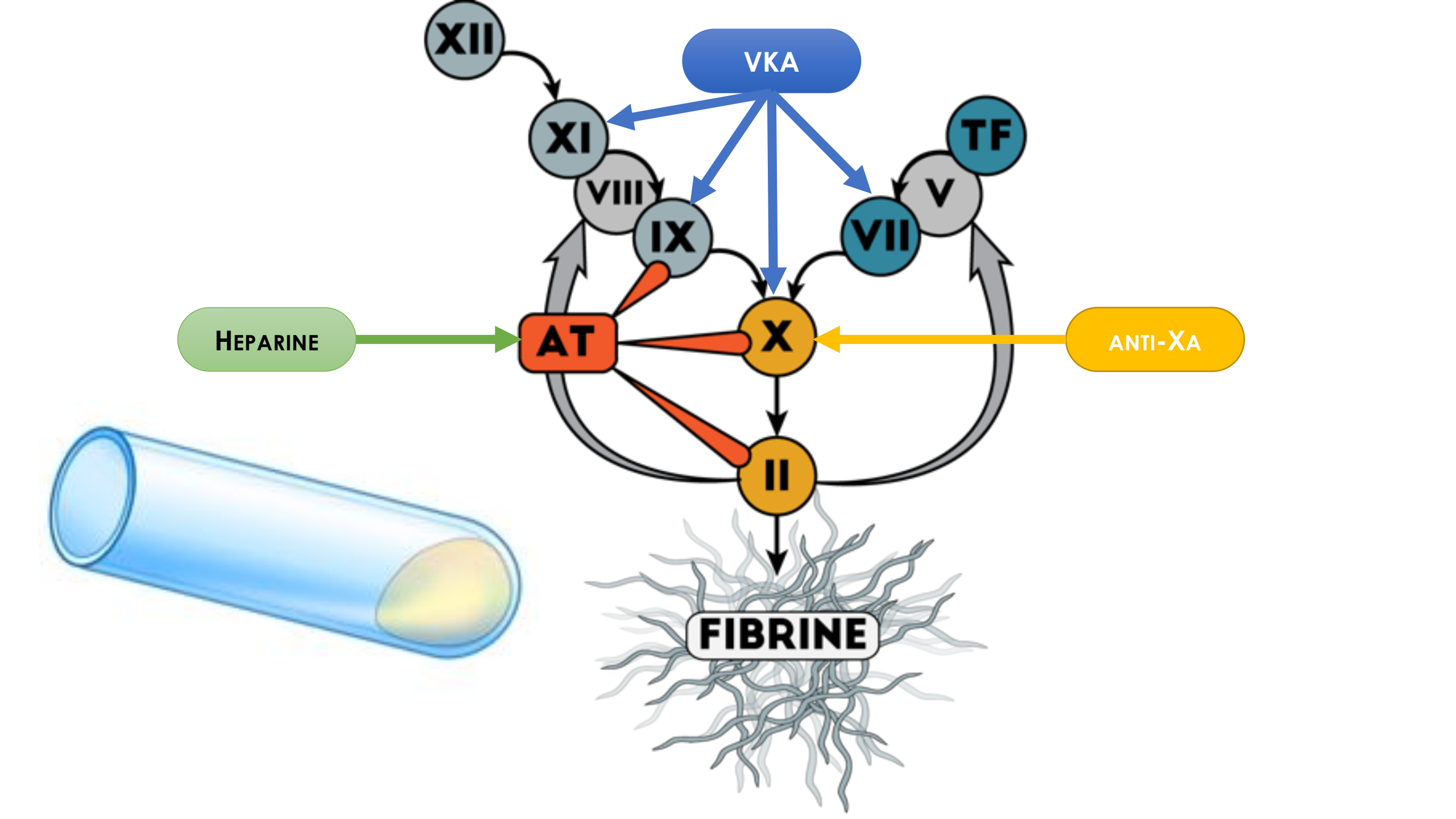
COAGULATION CASCADE



S. AUREUS COAGULASES:

- **STAPHYLOCOAGULASE**
- **VWBP**

'STAPHYLOTHROMBIN'


XII
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HEPARINE
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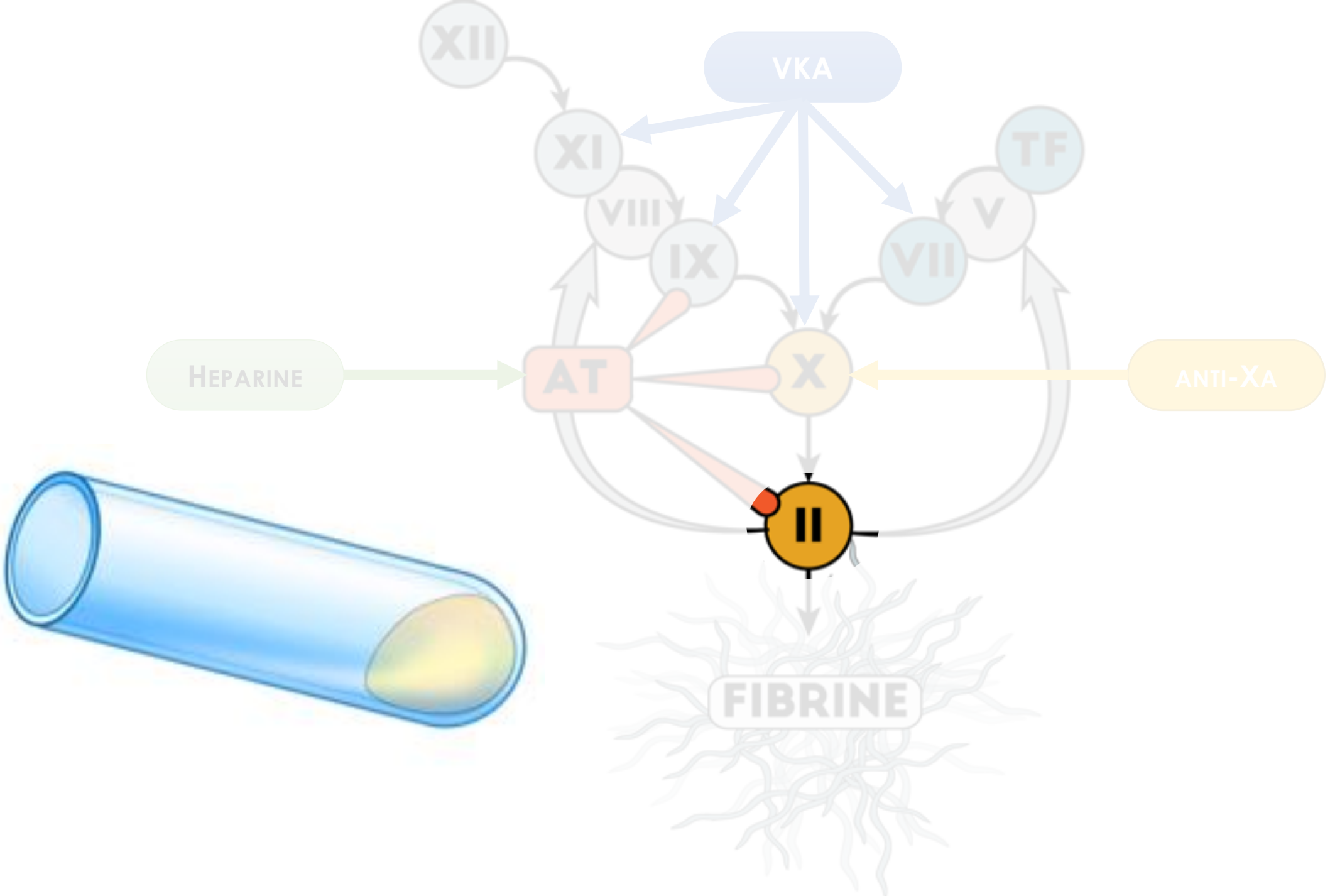
ANTI-XA
II
FIBRINE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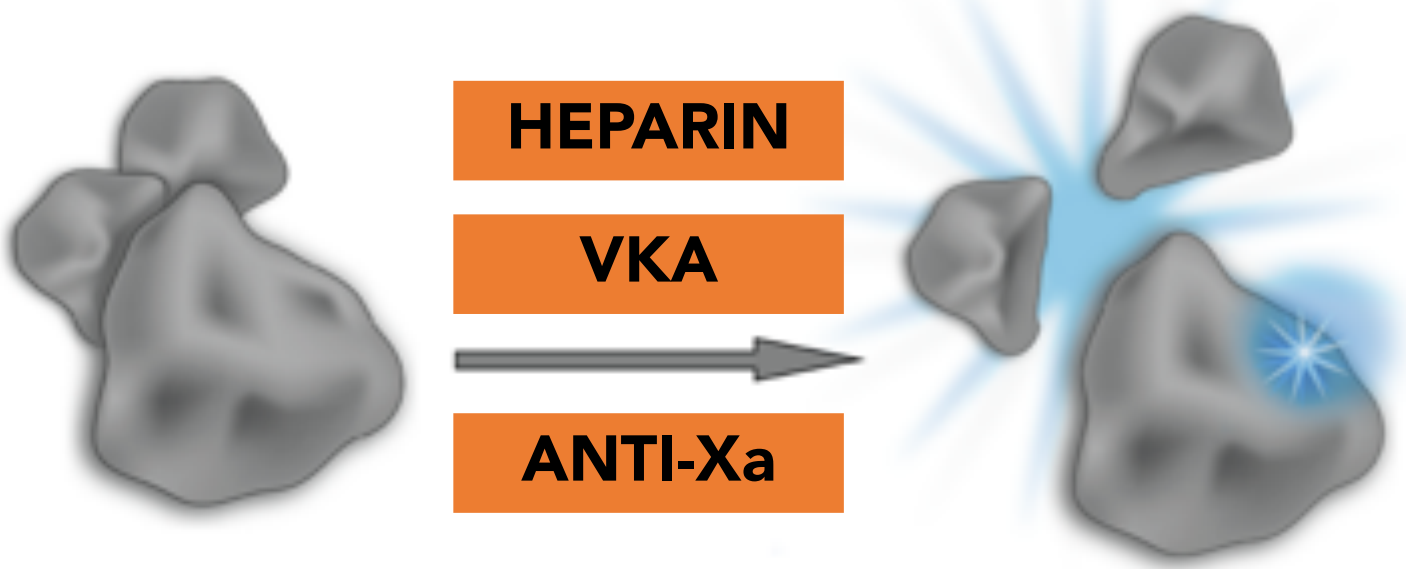
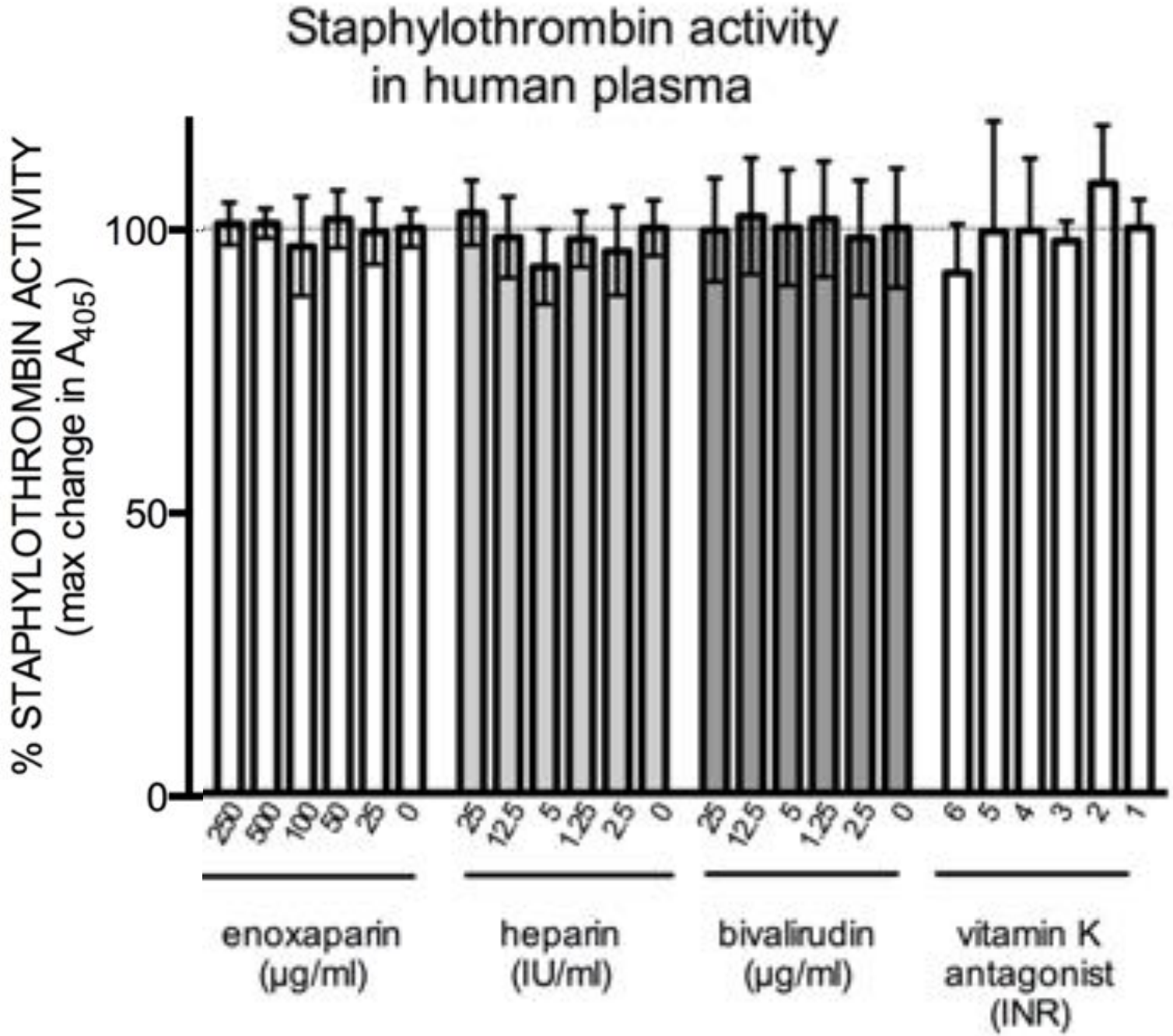


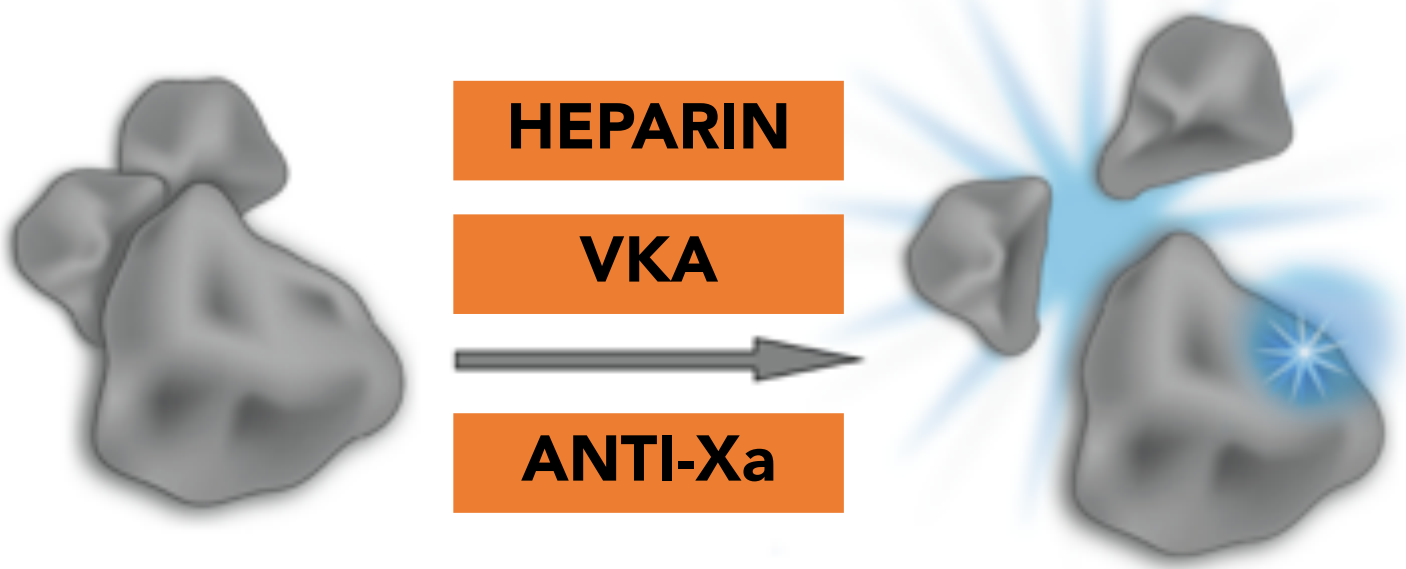
S. AUREUS COAGULASES:

- STAPHYLOCOAGULASE
- VWBP

'STAPHYLOTHROMBIN'

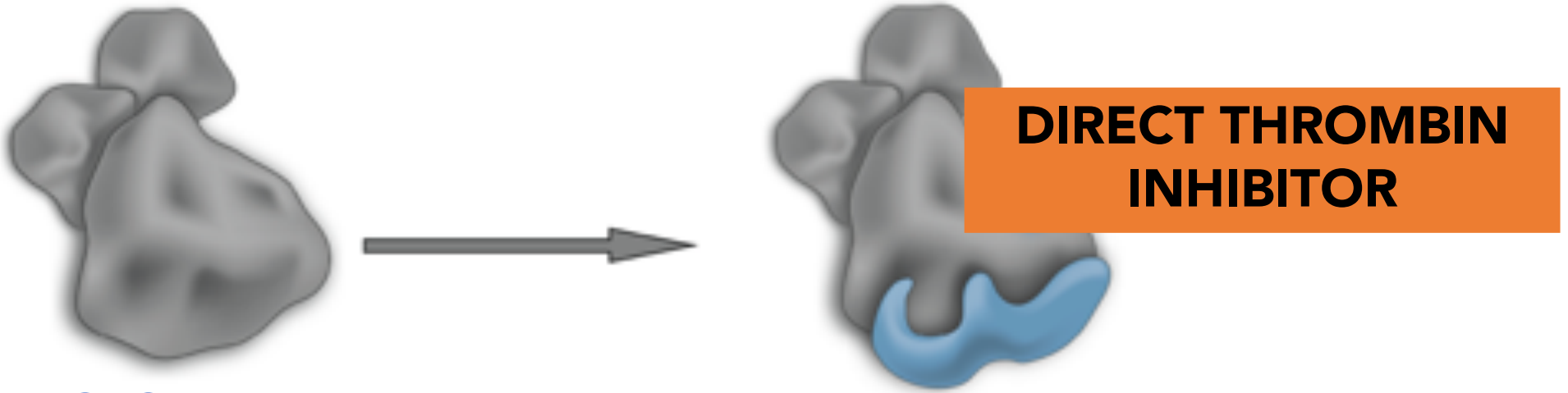


Vanassche et al, J Clin Microbiol 2010



PROTHROMBIN

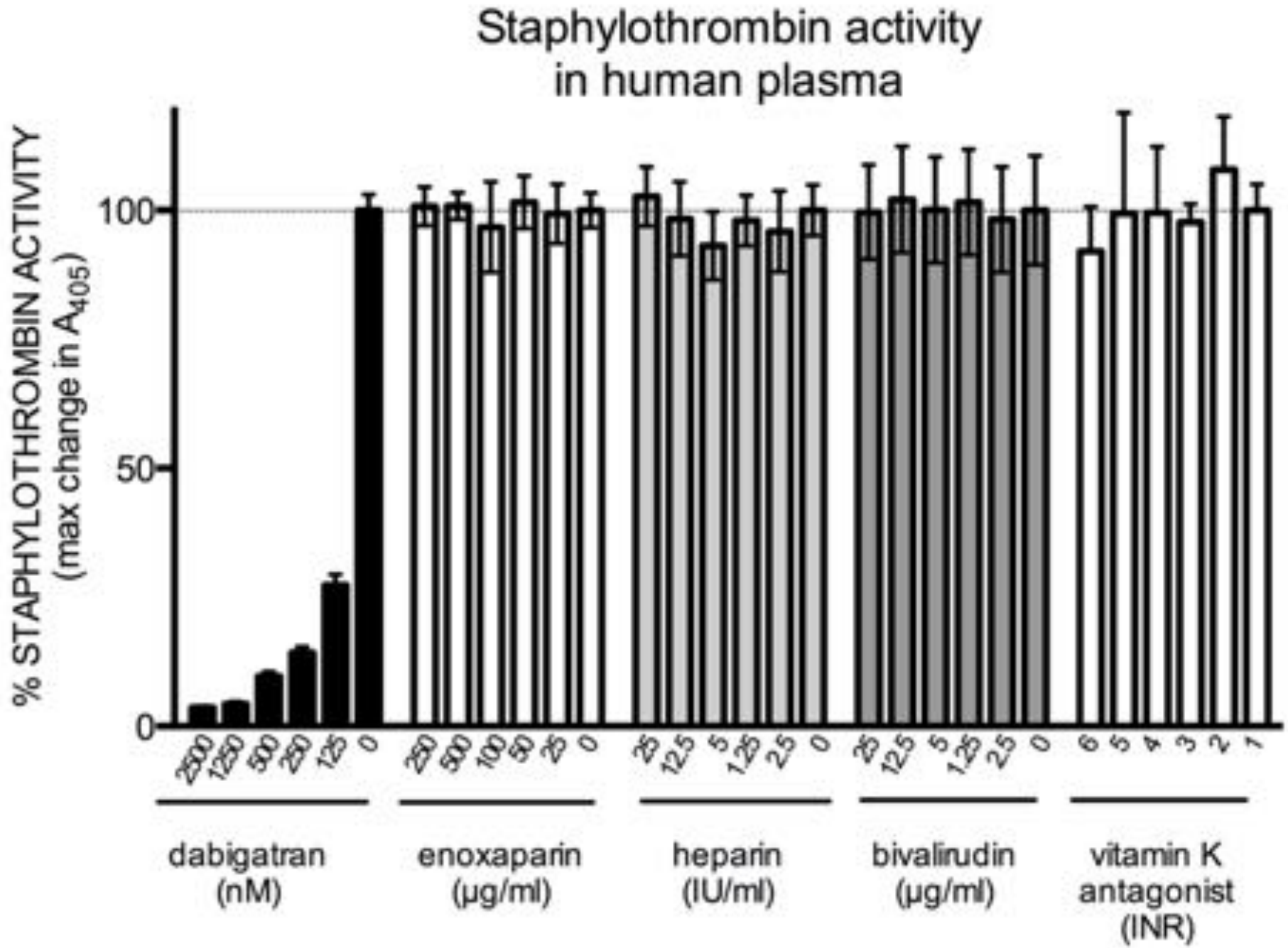
THROMBIN



S. AUREUS COAGULASES:

- STAPHYLOCOAGULASE
- VWBP

'STAPHYLOTHROMBIN'

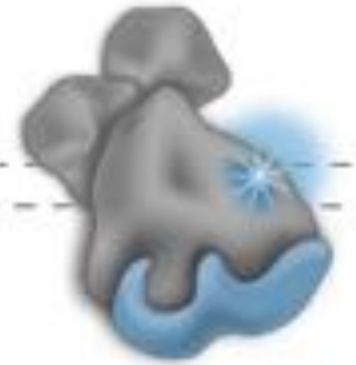


Vanassche et al, J Clin Microbiol 2010

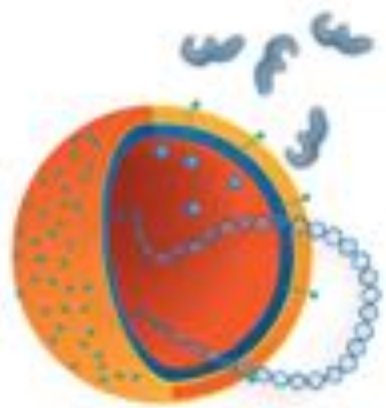
PHARMACOLOGICAL STRATEGY

CONTROL
(ENOXAPARIN,
HIRUDIN)

INHIBITION
DABIGATRAN

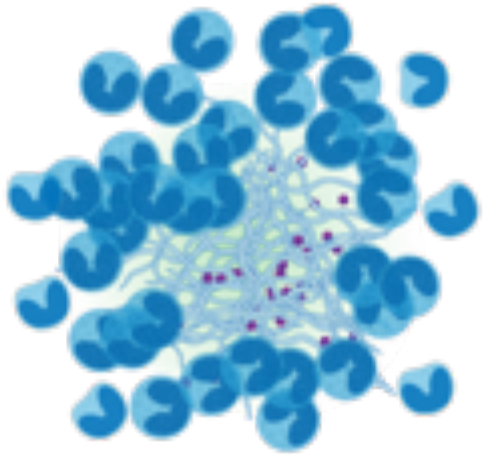


CONTROL
S. AUREUS
NEWMAN



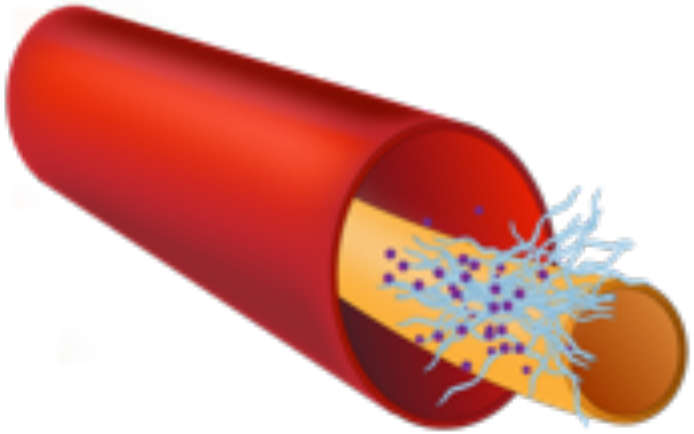
MUTANT
S. AUREUS
Δcoa,vwbp

GENETIC STRATEGY

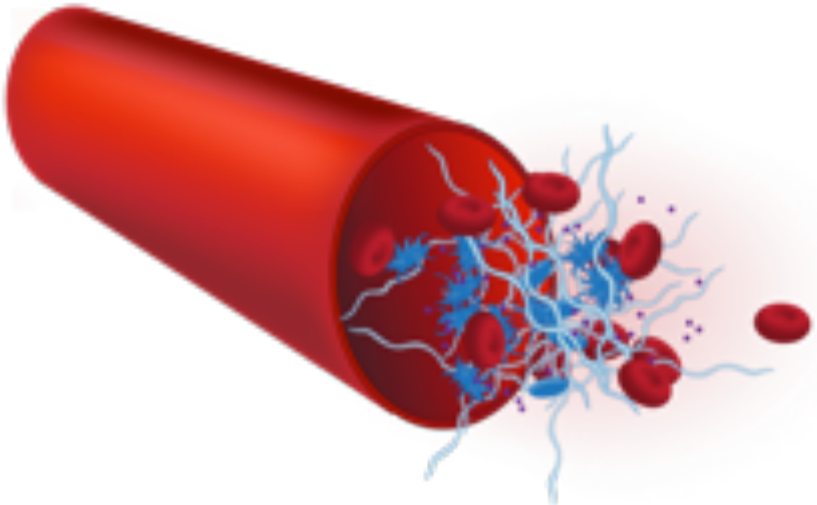


abscess formation

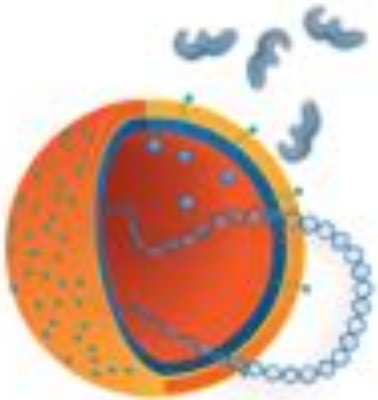
PHARMACOLOGICAL STRATEGY



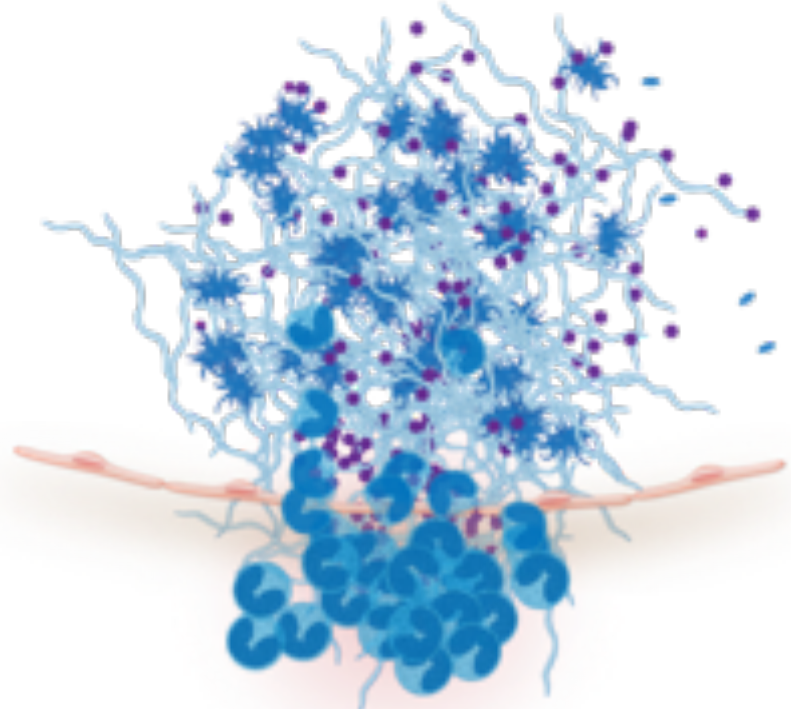
device-related infections



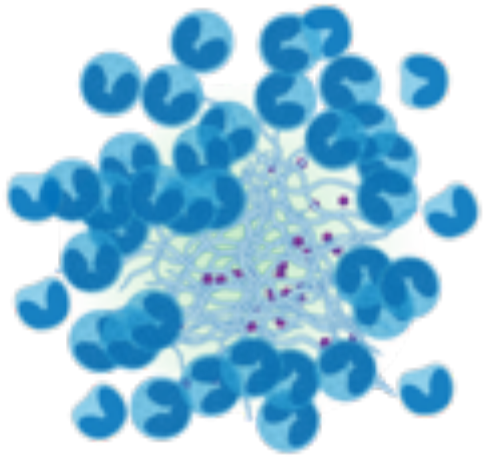
bloodstream infection and sepsis



GENETIC STRATEGY

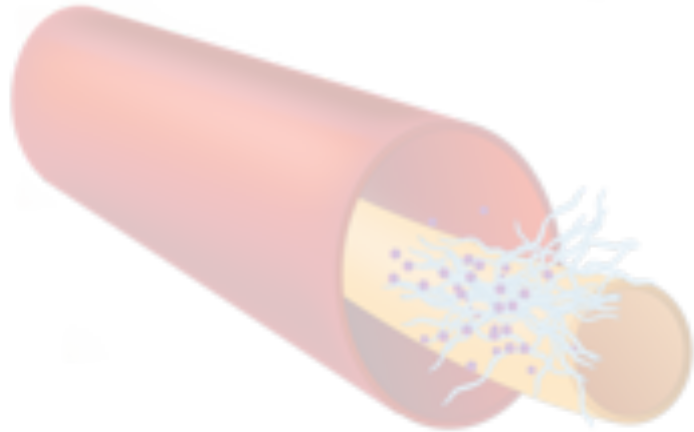


infective endocarditis

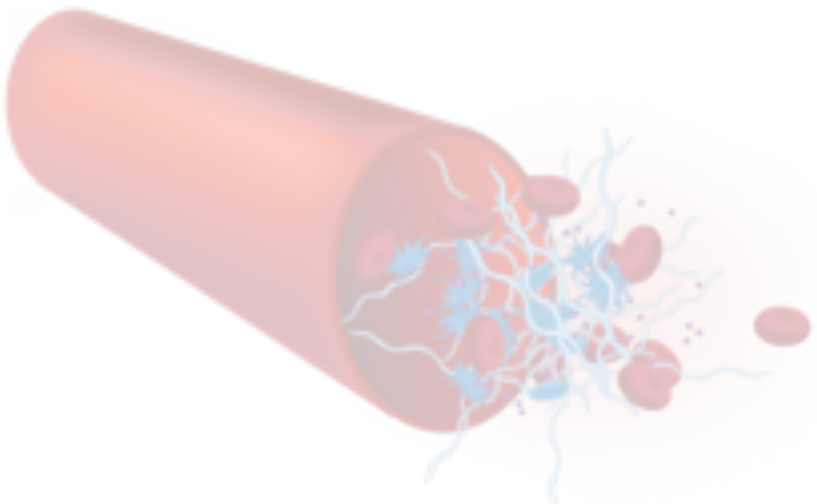


abscess formation

PHARMACOLOGICAL STRATEGY



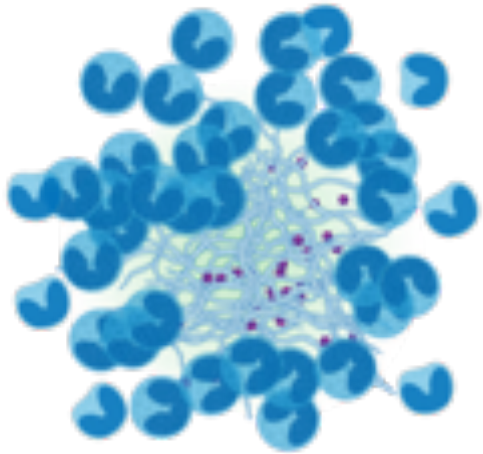
device-related infections



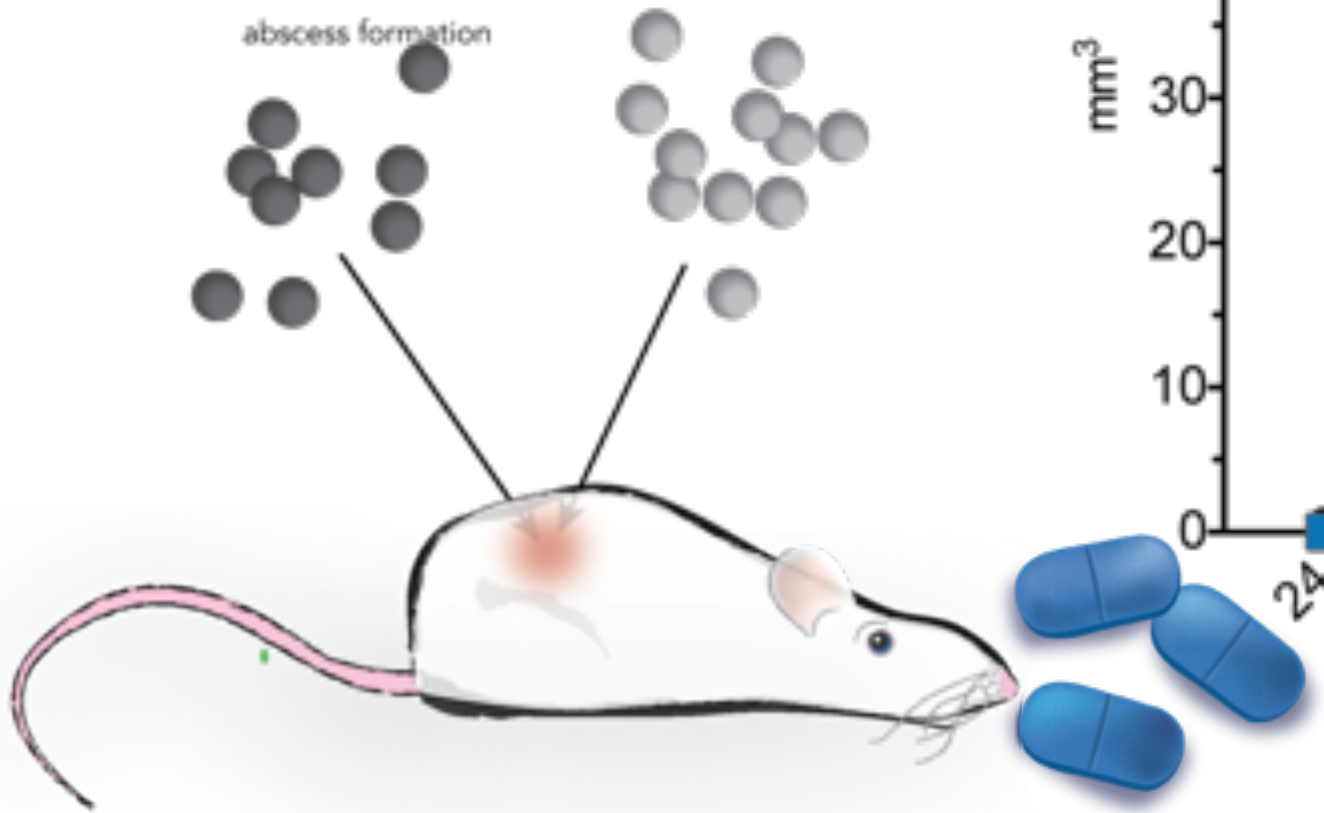
bloodstream infection and sepsis

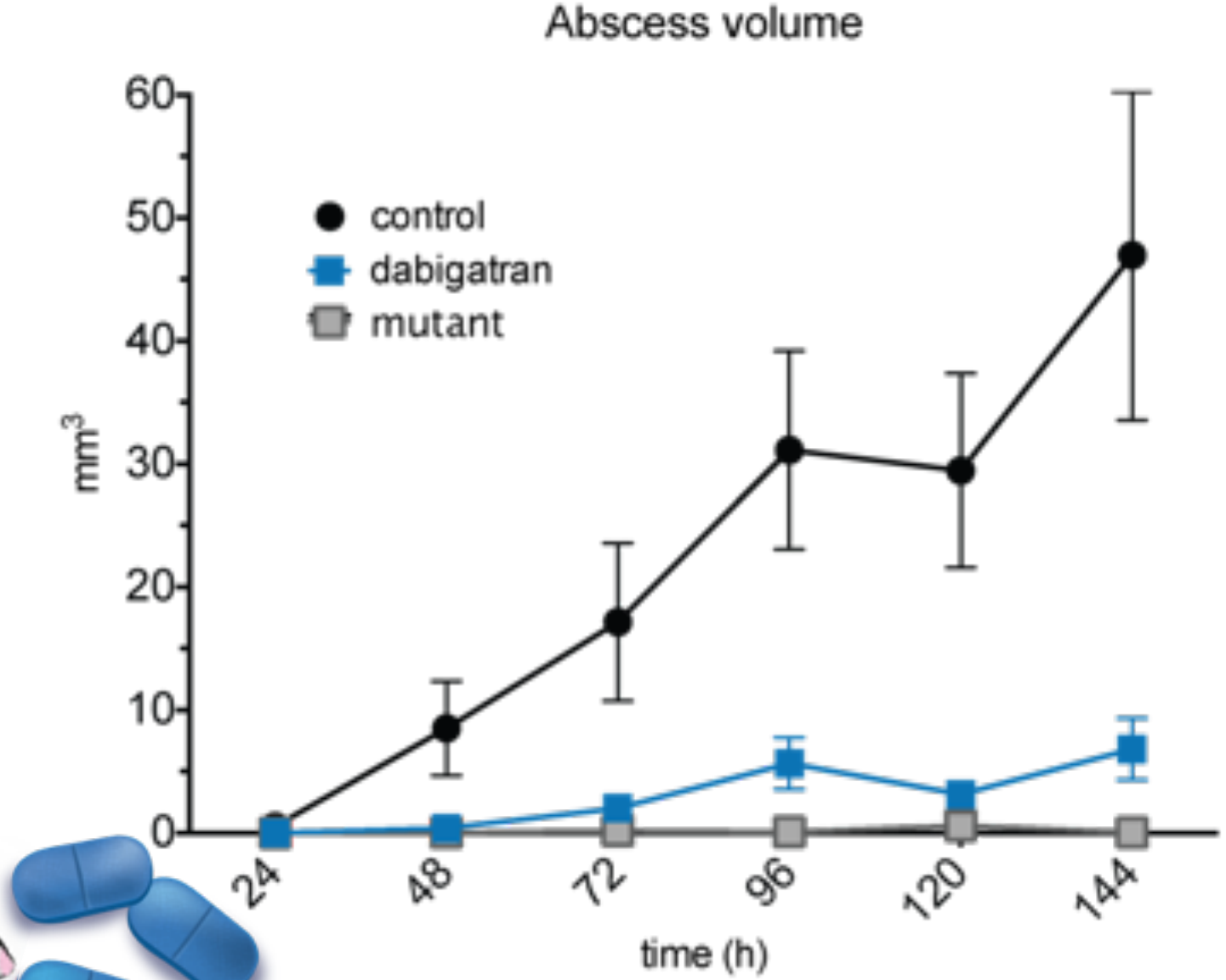
GENETIC STRATEGY

infective endocarditis



abscess formation

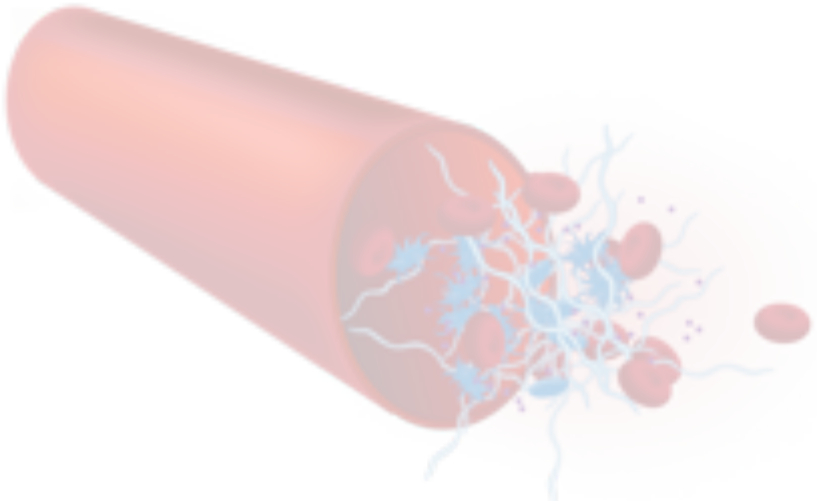




Vanassche et al, JTH 2011

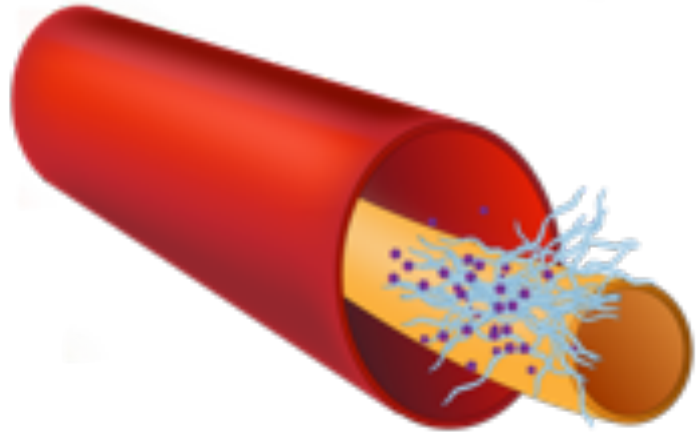
abscess formation

PHARMACOLOGICAL STRATEGY



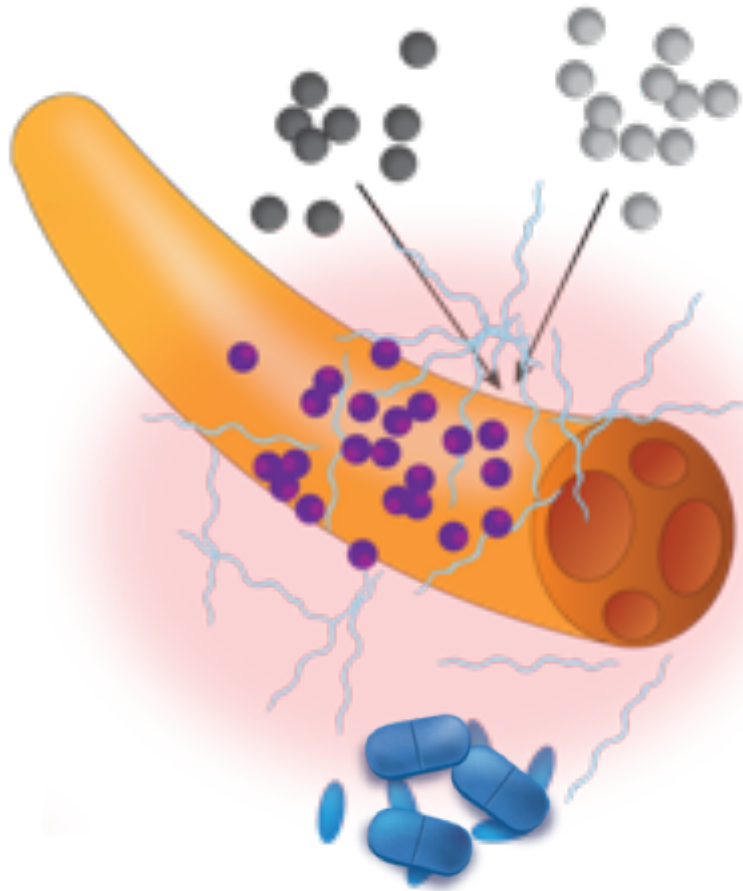
bloodstream infection and sepsis

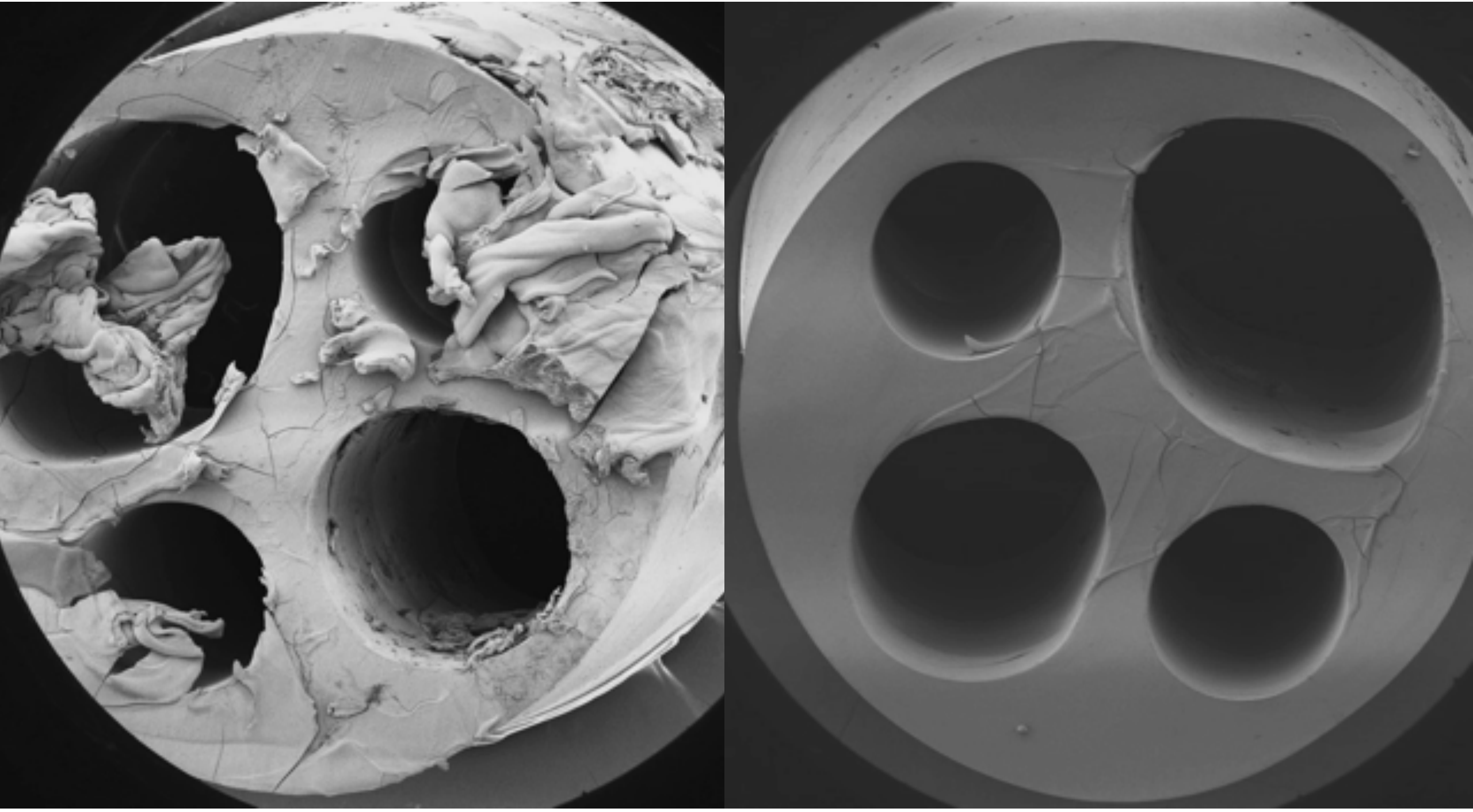
GENETIC STRATEGY

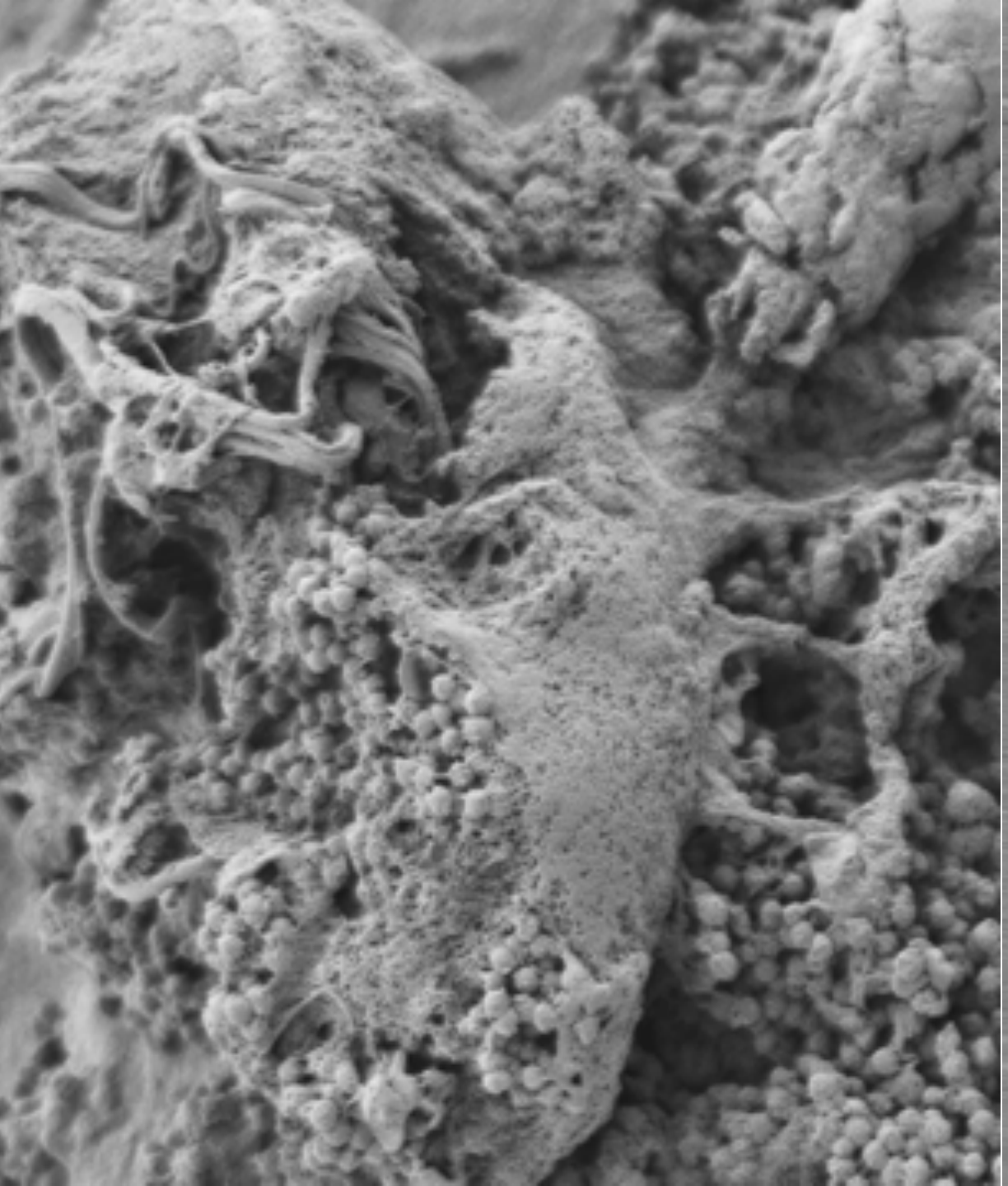


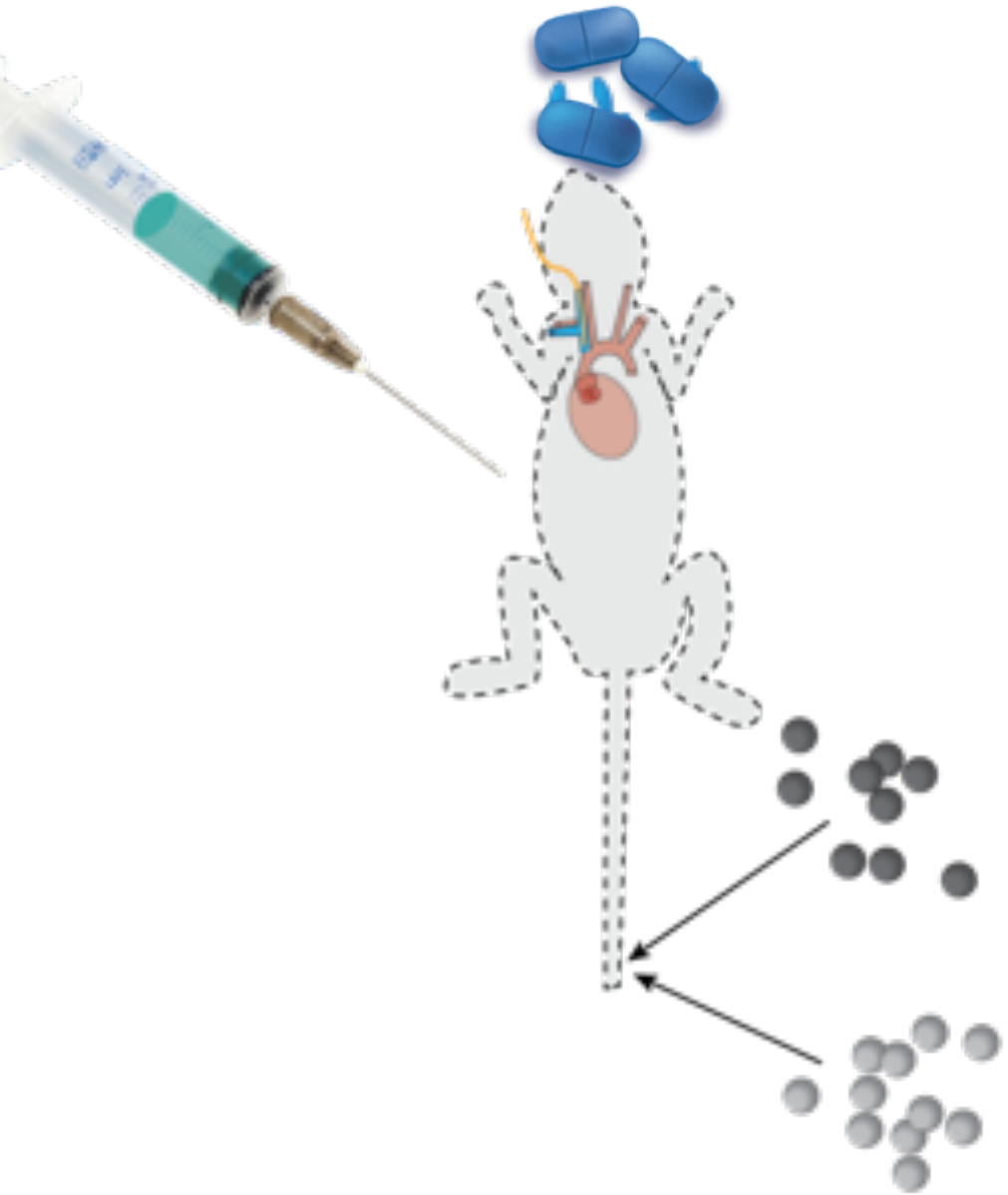
device-related infections

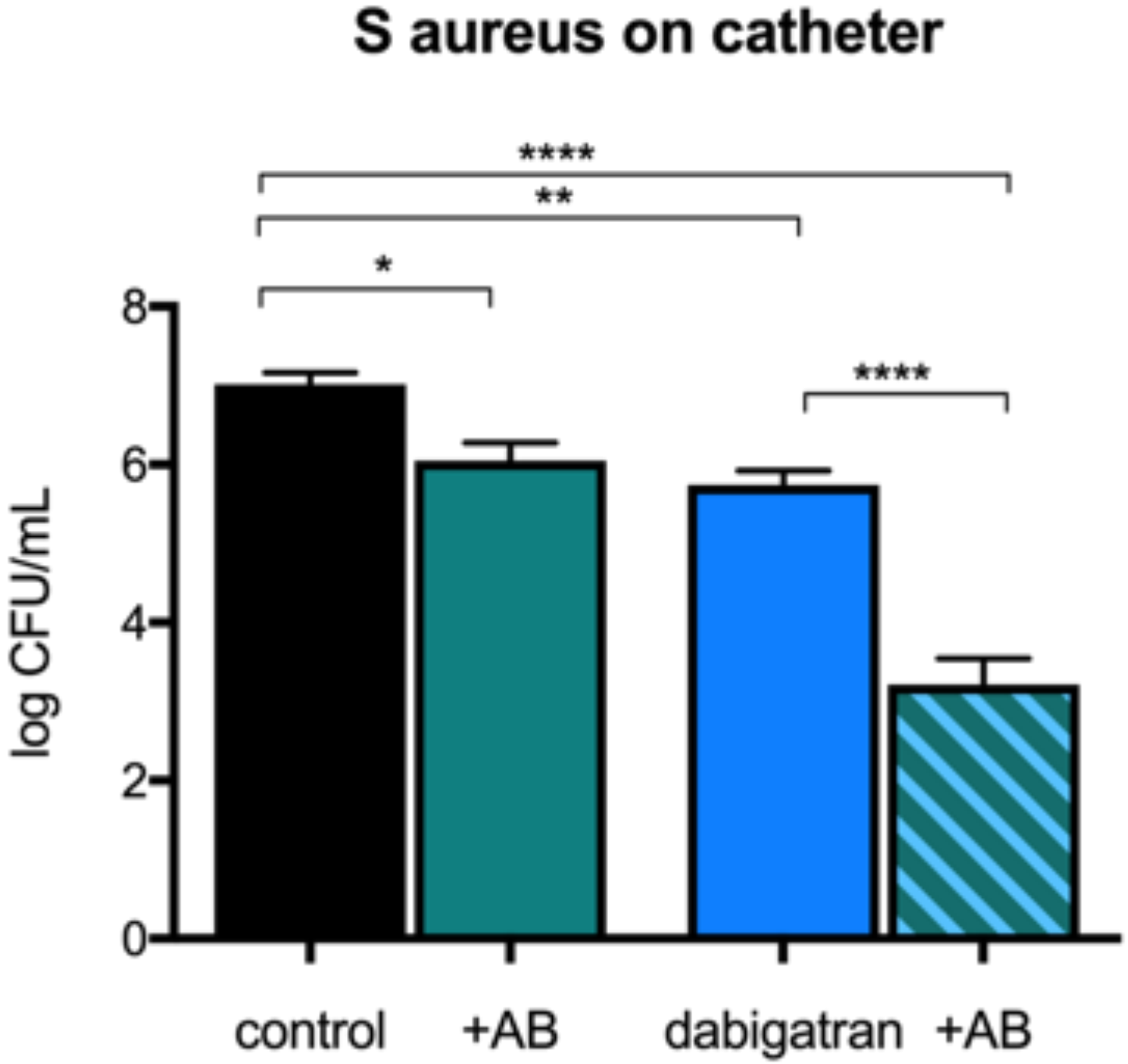
infective endocarditis







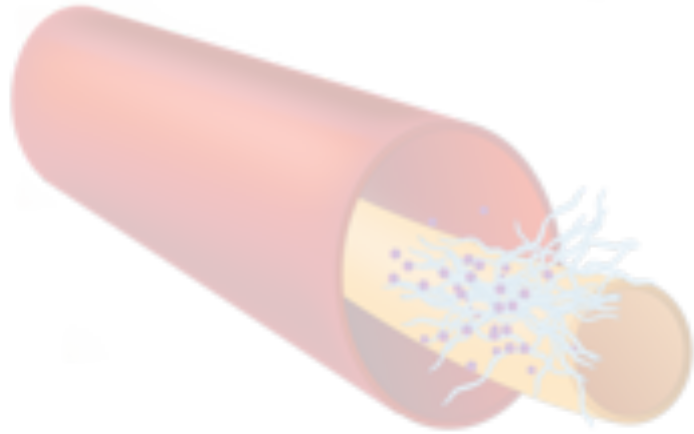




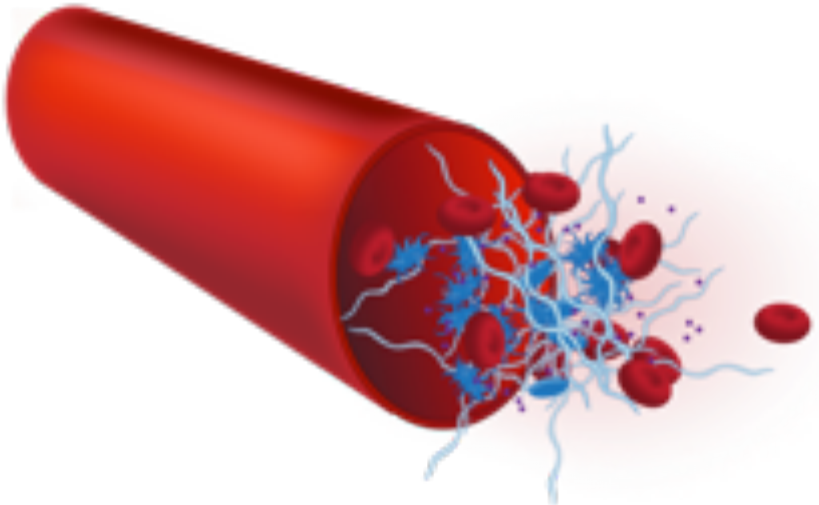
Vanassche et al, J Inf Dis 2013

abscess formation

PHARMACOLOGICAL STRATEGY



device-related infections



bloodstream infection and sepsis

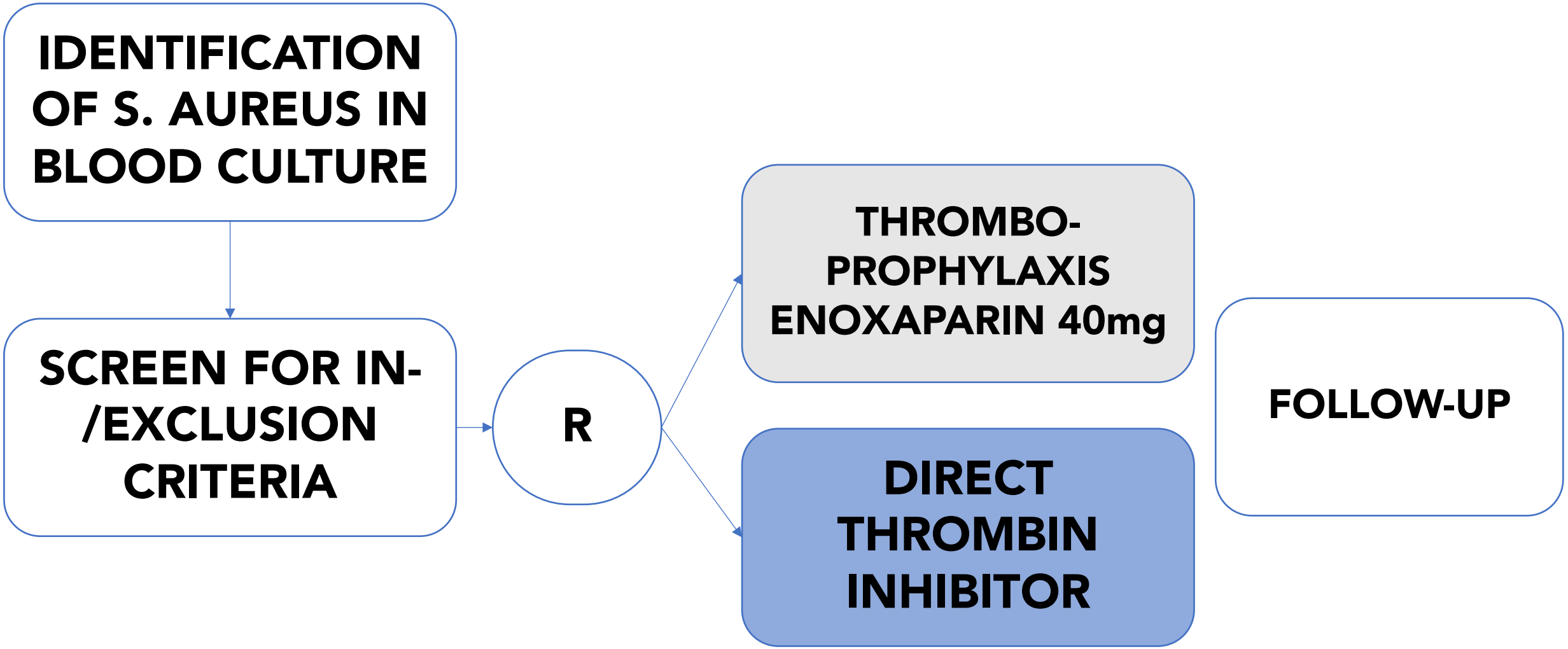
GENETIC STRATEGY

infective endocarditis

Direct thrombin inhibitors in patients with *S. aureus* bacteremia:

A randomized clinial trial

CLINICALTRIALS N° NTCC 0191162
MARCH 2013 --> APRIL 2016



PRIMARY ENDPOINT

FEASIBILITY

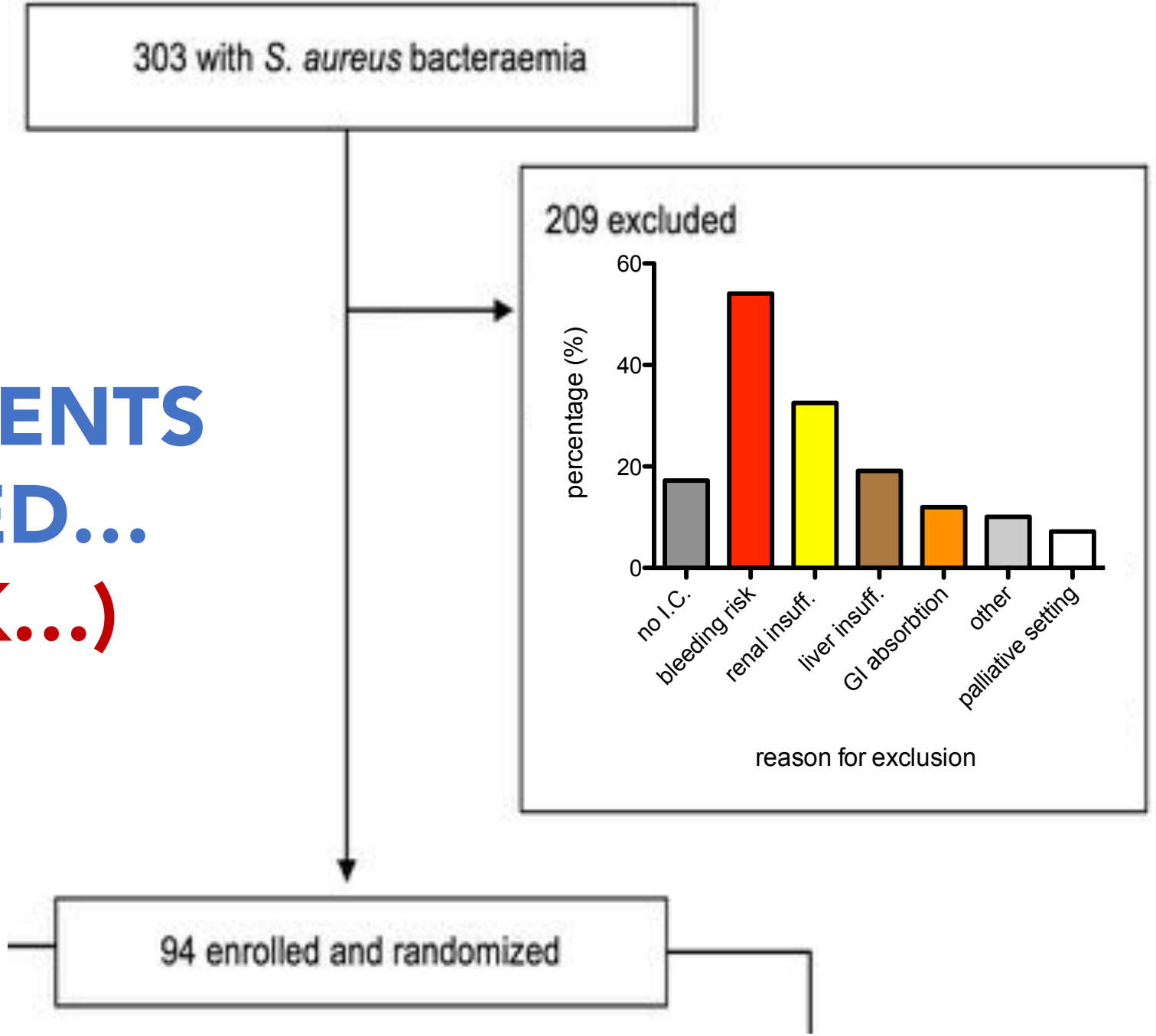
- RECRUITMENT OF PATIENTS
- ANTI-STAPHYLOTHROMBIN ACTIVITY

SAFETY

- MAJOR BLEEDING

FEASIBILITY?

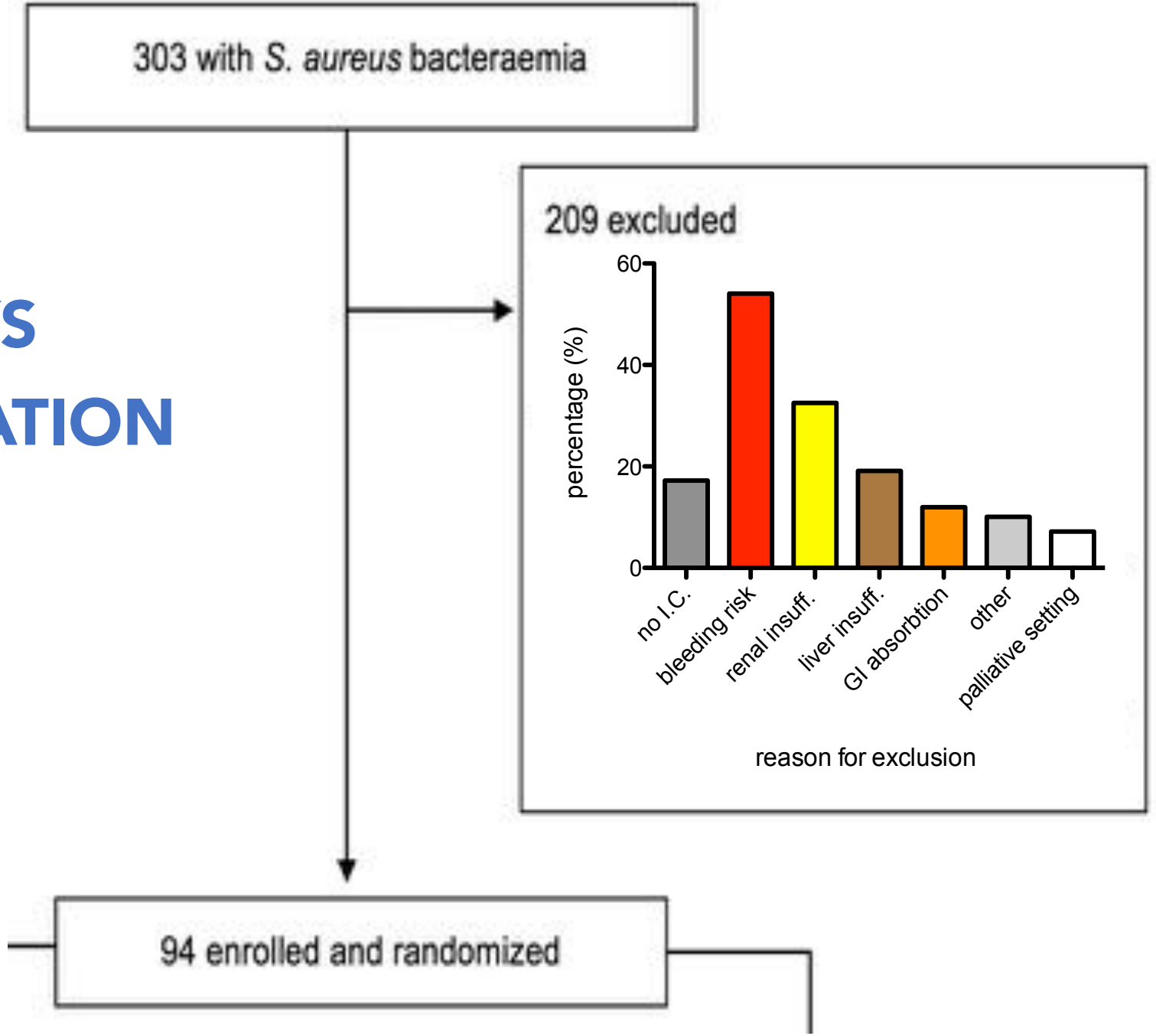
2 OUT OF 3 SCREENED PATIENTS WERE EXCLUDED… (BLEEDING RISK…)



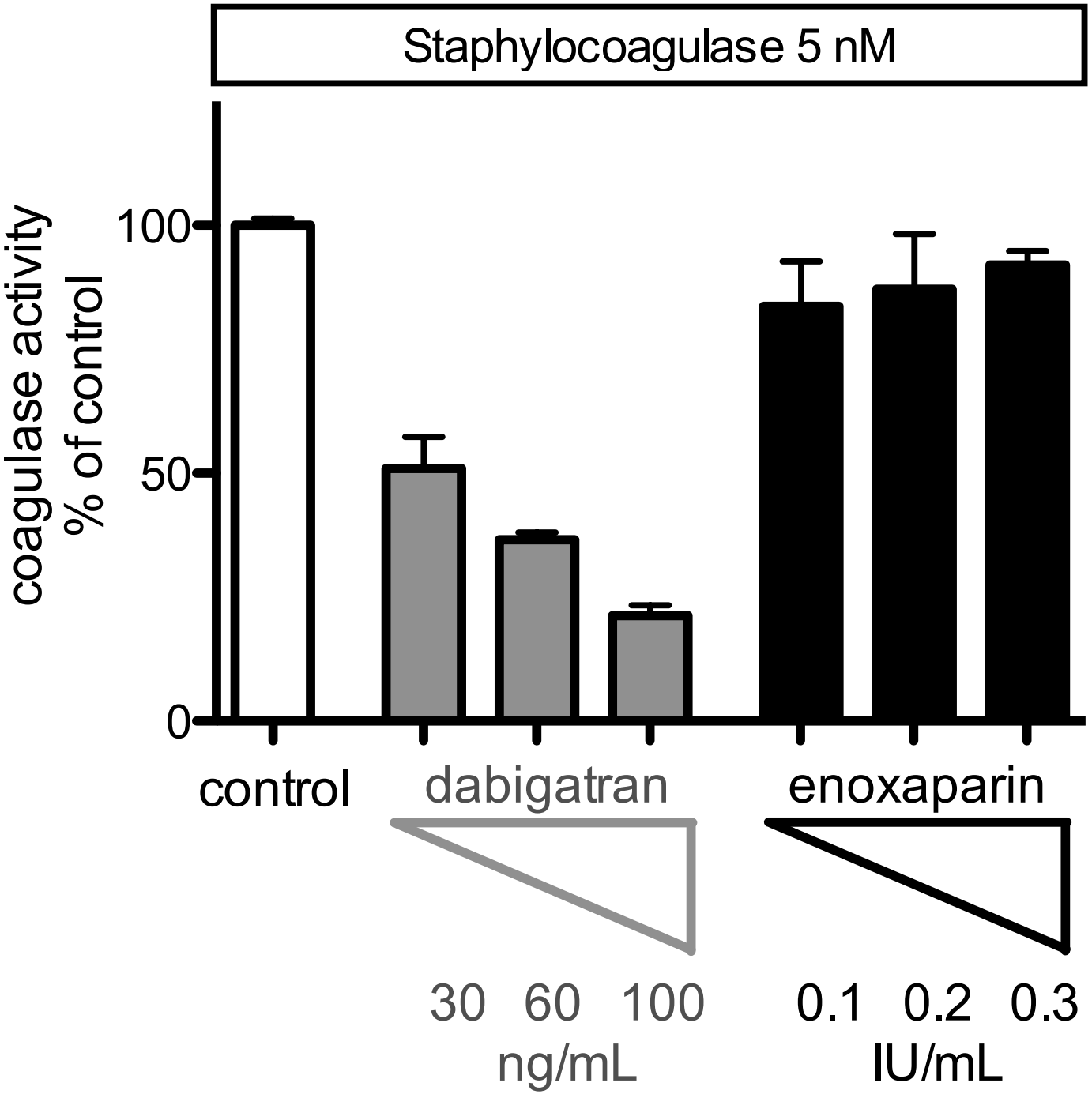
Peetermans et al, TH 2018

FEASIBILITY?

MEDIAN OF 2 DAYS BEFORE IDENTIFICATION OF PATHOGEN -> LATE START OF INTERVENTION



FEASIBILITY?



Peetermans et al, TH 2018

SAFETY?

CLINICALLY RELEVANT BLEEDING:
5 DABIGATRAN VS 5 LMWH

THROMBOTIC EVENTS:
7 DABIGATRAN VS 7 LMWH

SECONDARY ENDPOINTS

CHANGE IN D-DIMERS

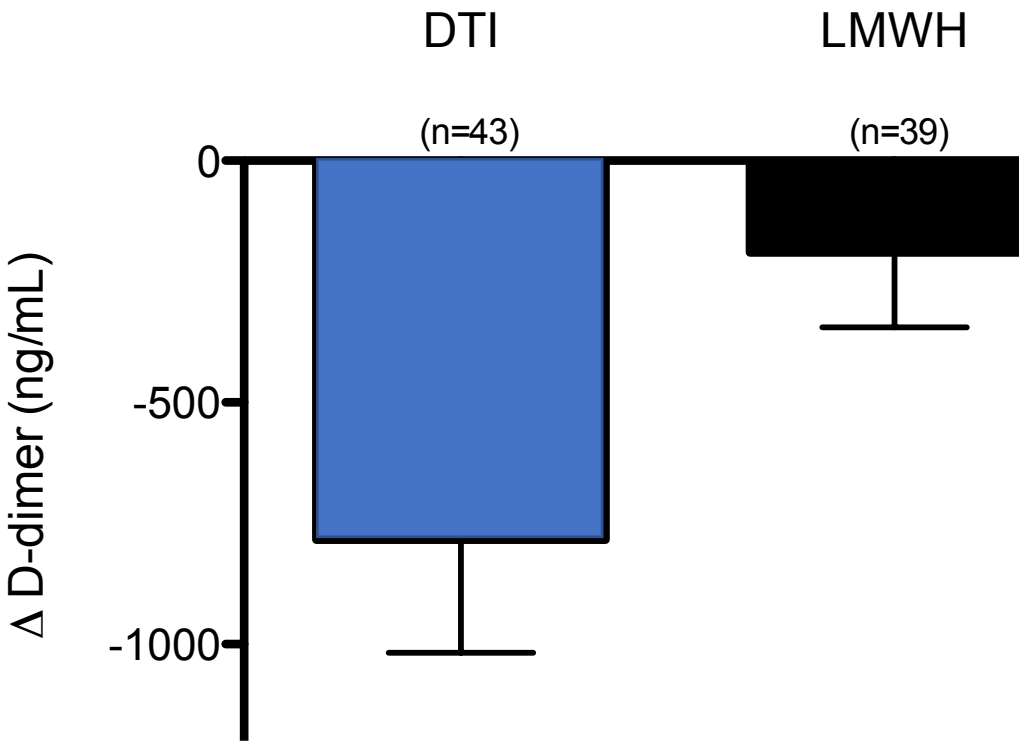
CHANGE IN INFLAMMATORY PARAMETERS

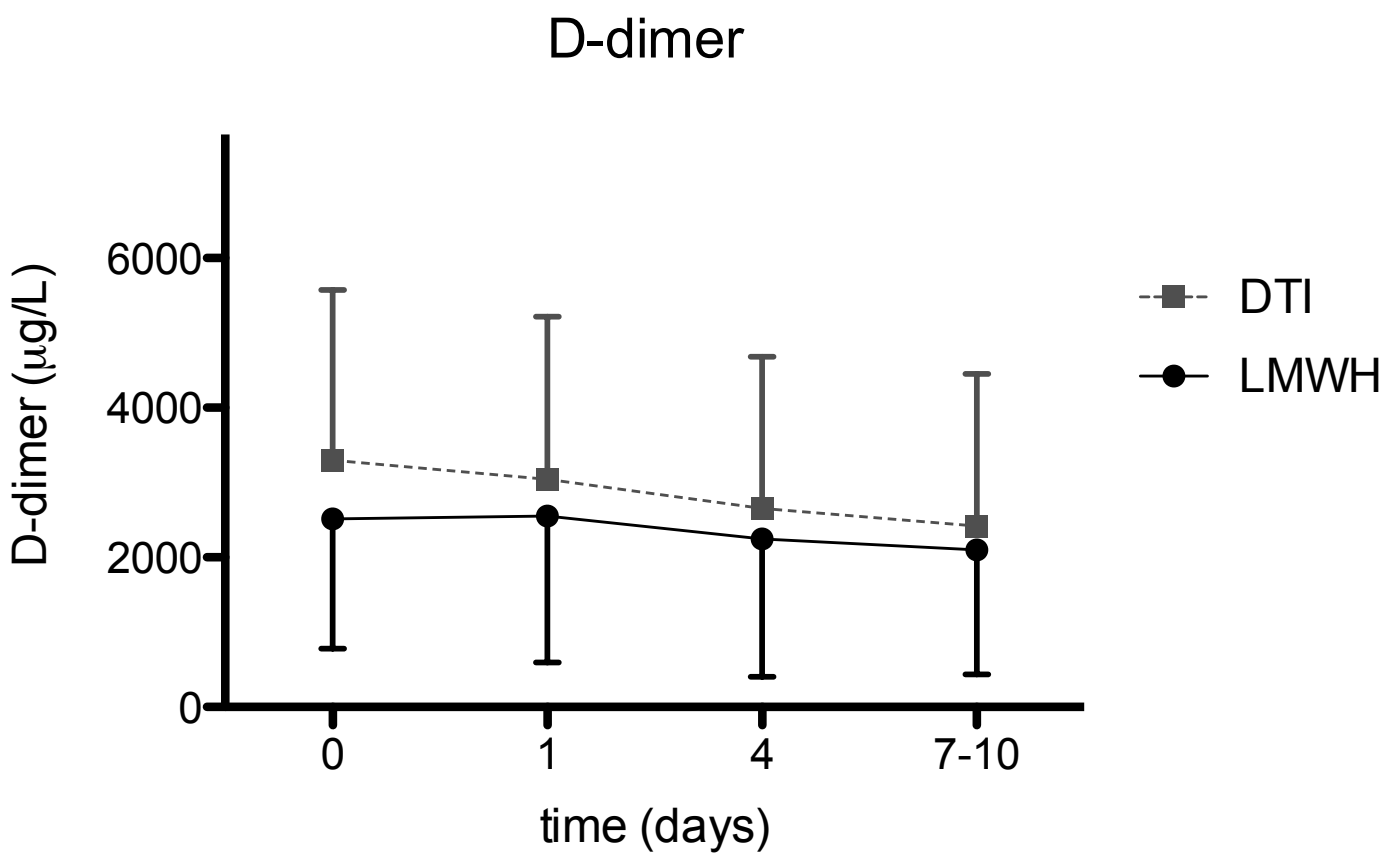
CHANGE IN BLOOD CULTURES

CLINICAL OUTCOMES

METASTATIC INFECTIONS DETECTED BY PET/CT

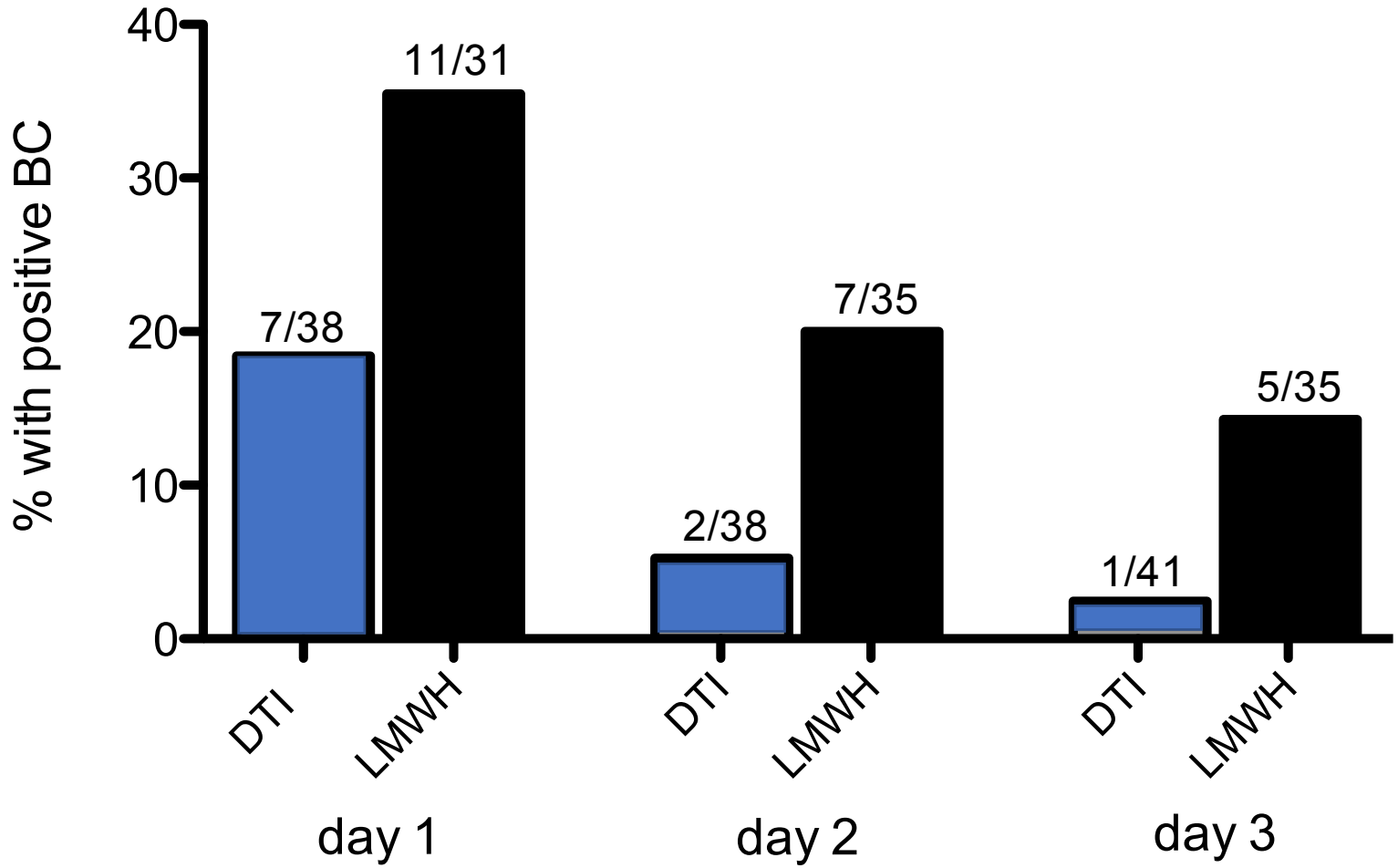
CHANGE IN D-DIMERS





Peetermans et al, TH 2018

POSITIVE BLOOD CULTURES



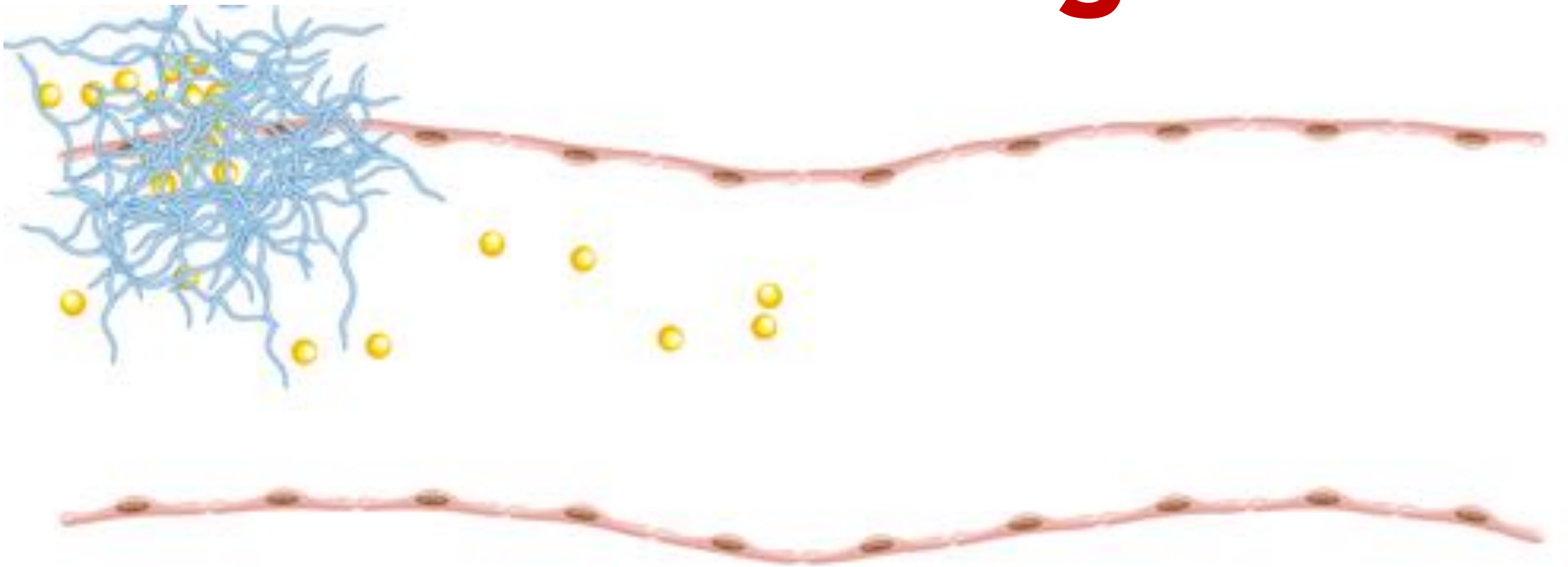
Peetermans et al, TH 2018

CLINICAL PARAMETERS

	DTI	LMWH
HOSPITAL STAY	19 (13-39)	16 (12-30)
DEFERVESCENCE (h)	26 (0-58)	12 (0-50)
ENDOCARDITIS	2	3
METASTATIC INFECTION	2/30 (6.7%)	6/26 (23%)
90 day MORTALITY	10	9
Of which infection-related	1/10	4/9

Peetermans et al, TH 2018

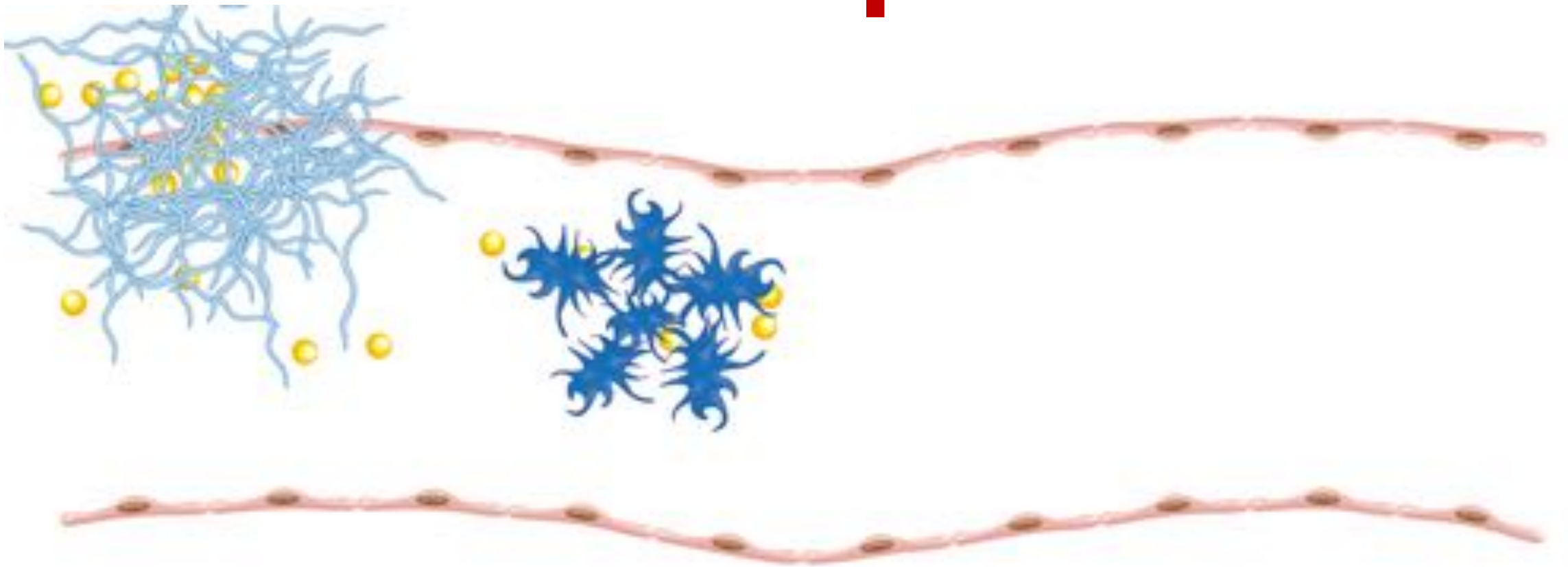
S.aureus and coagulation



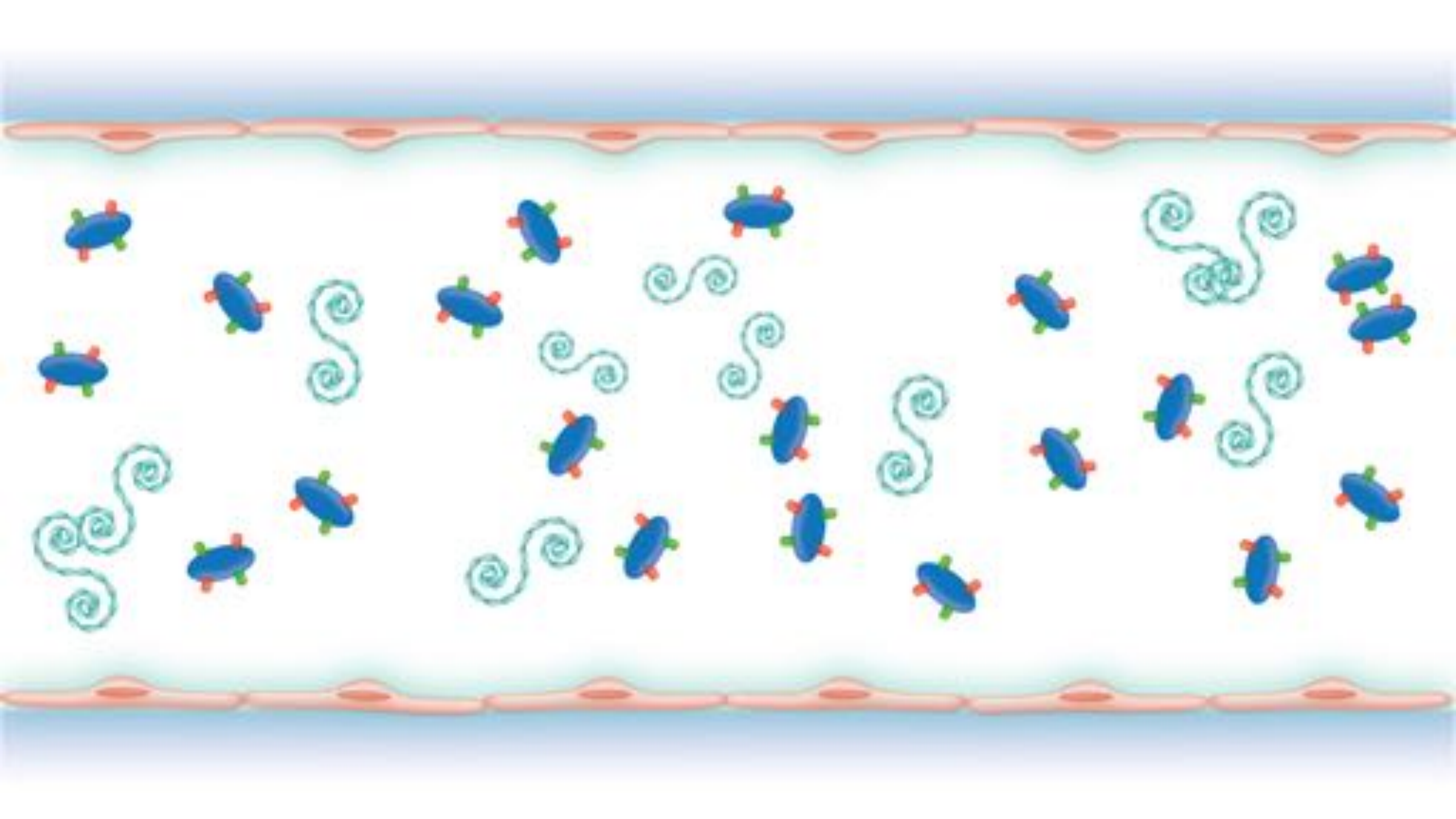
S.AUREUS TARGETS SPECIFIC THROMBIN EXOSITES TO FORM FIBRIN CLOTS THAT INCREASE INFECTIVITY AND ADHESION *IN VIVO*

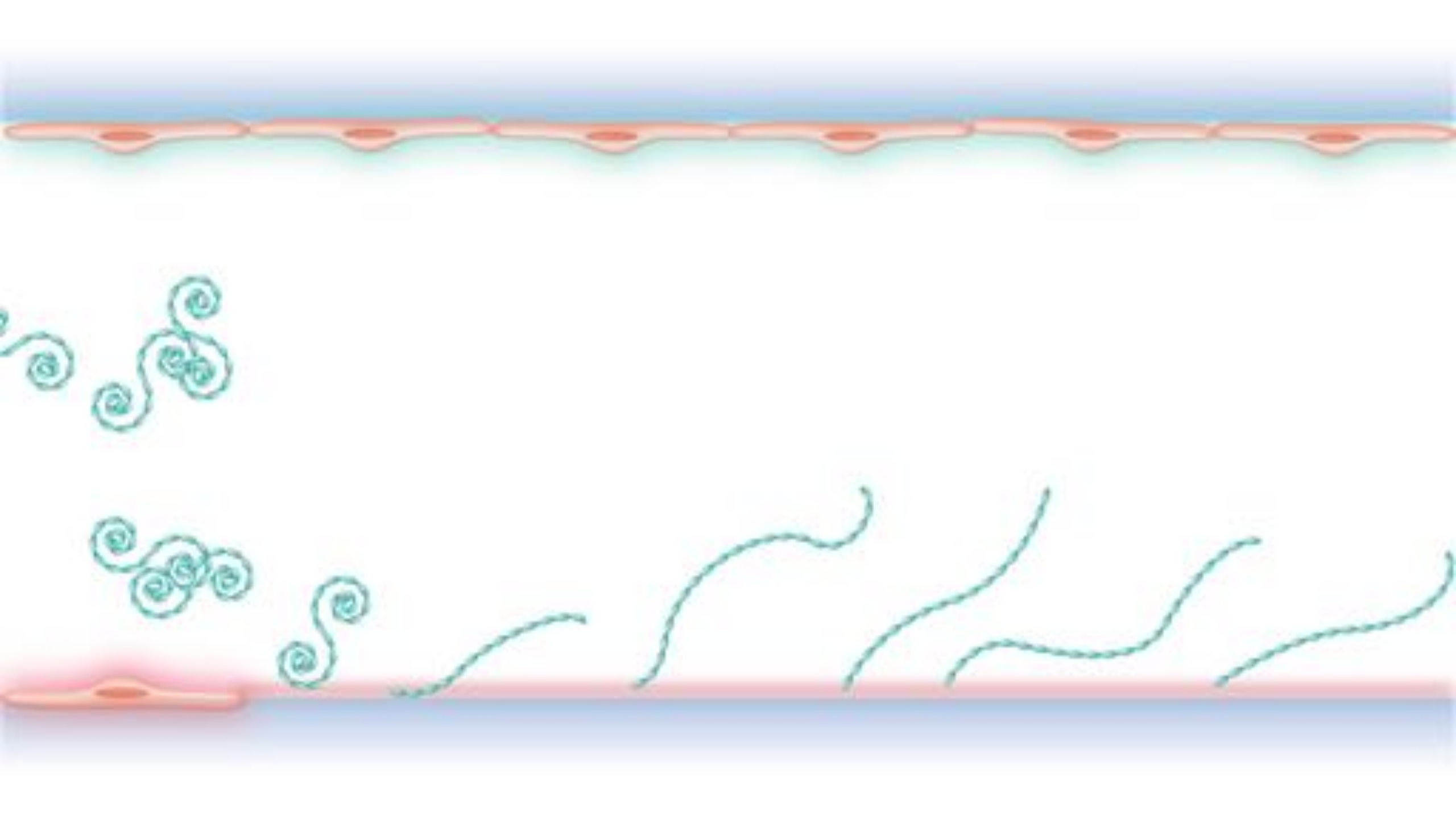
TARGETING COAGULASE ACTIVITY HAS POTENTIAL TO MODULATE PATIENT OUTCOMES

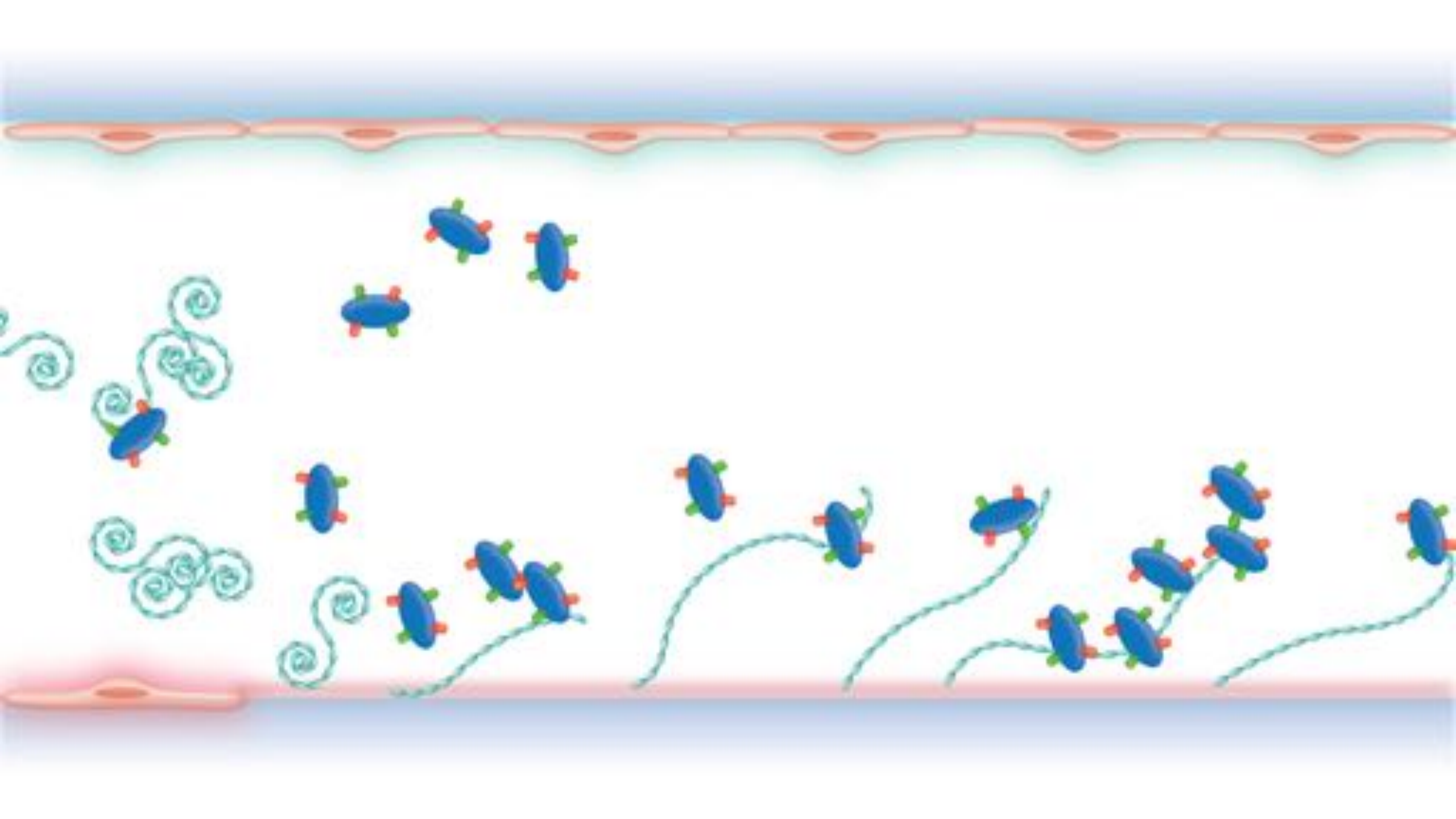
S.aureus and platelets

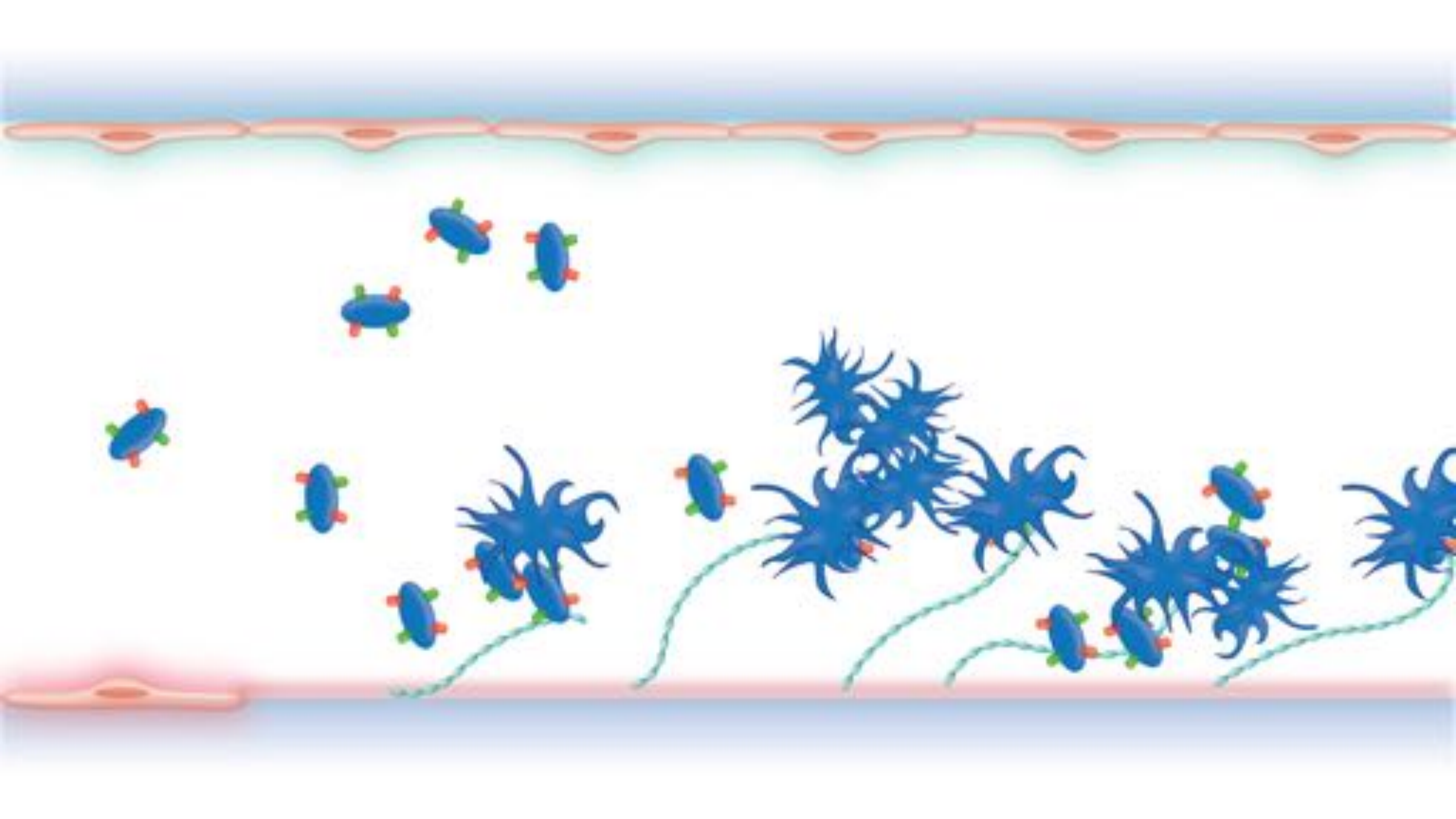


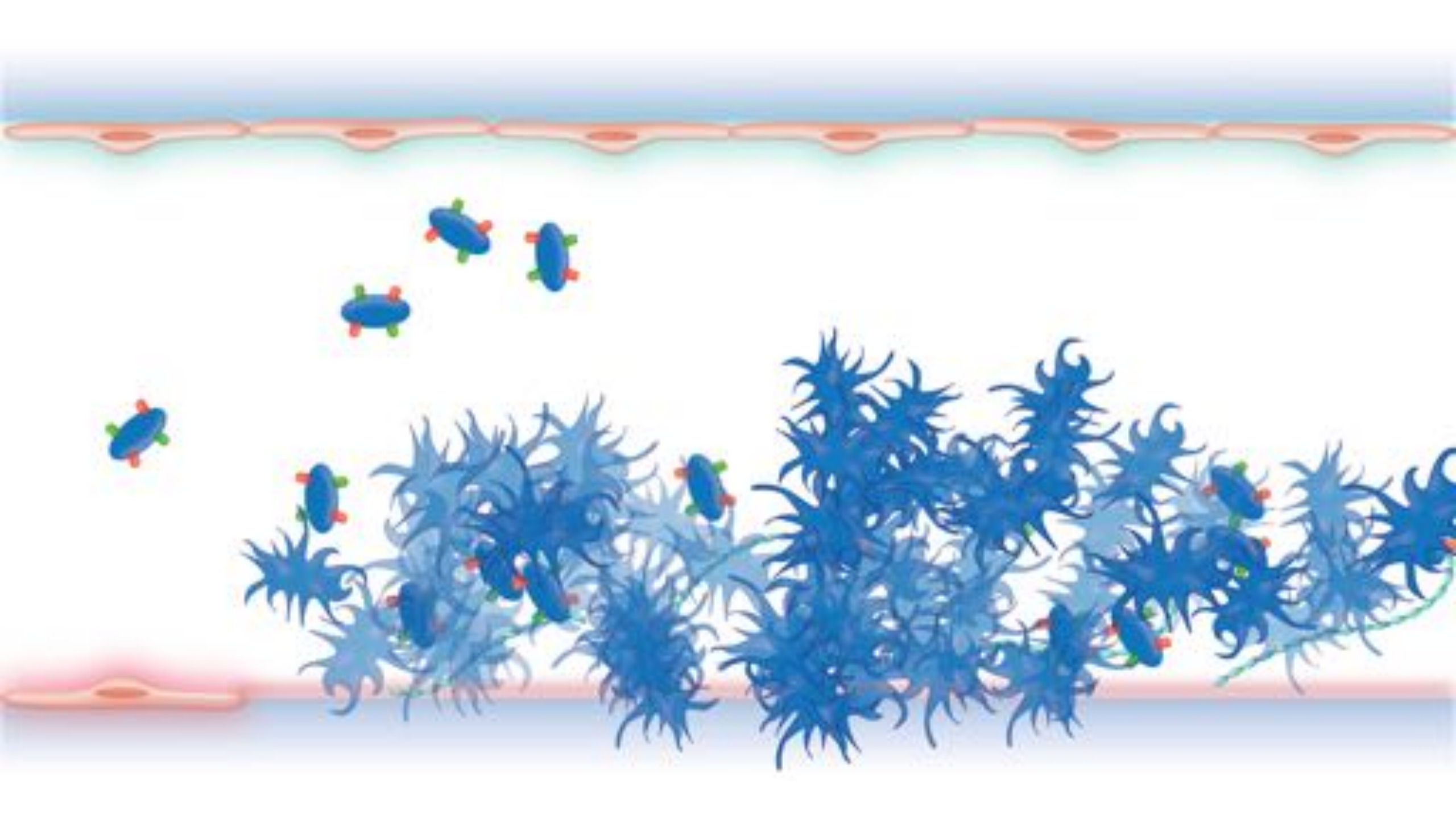
Faculteit, departement, dienst …

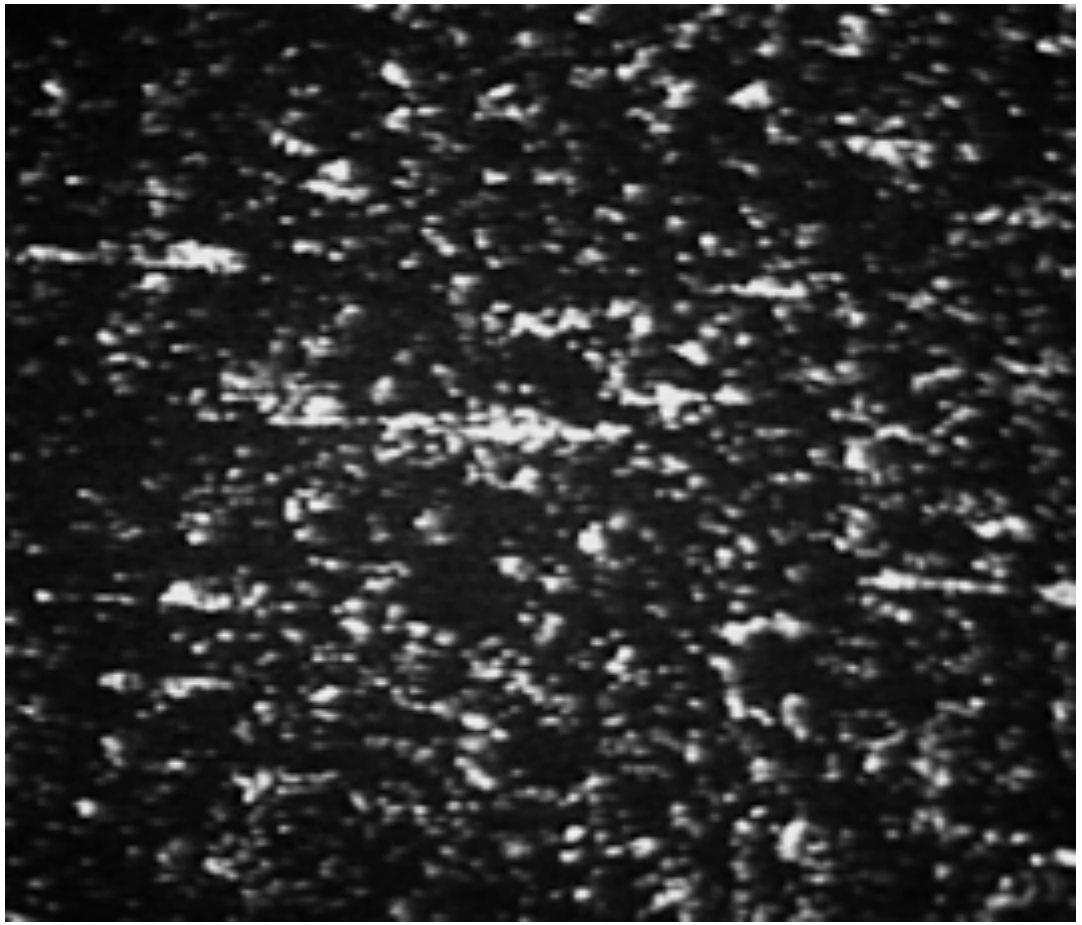


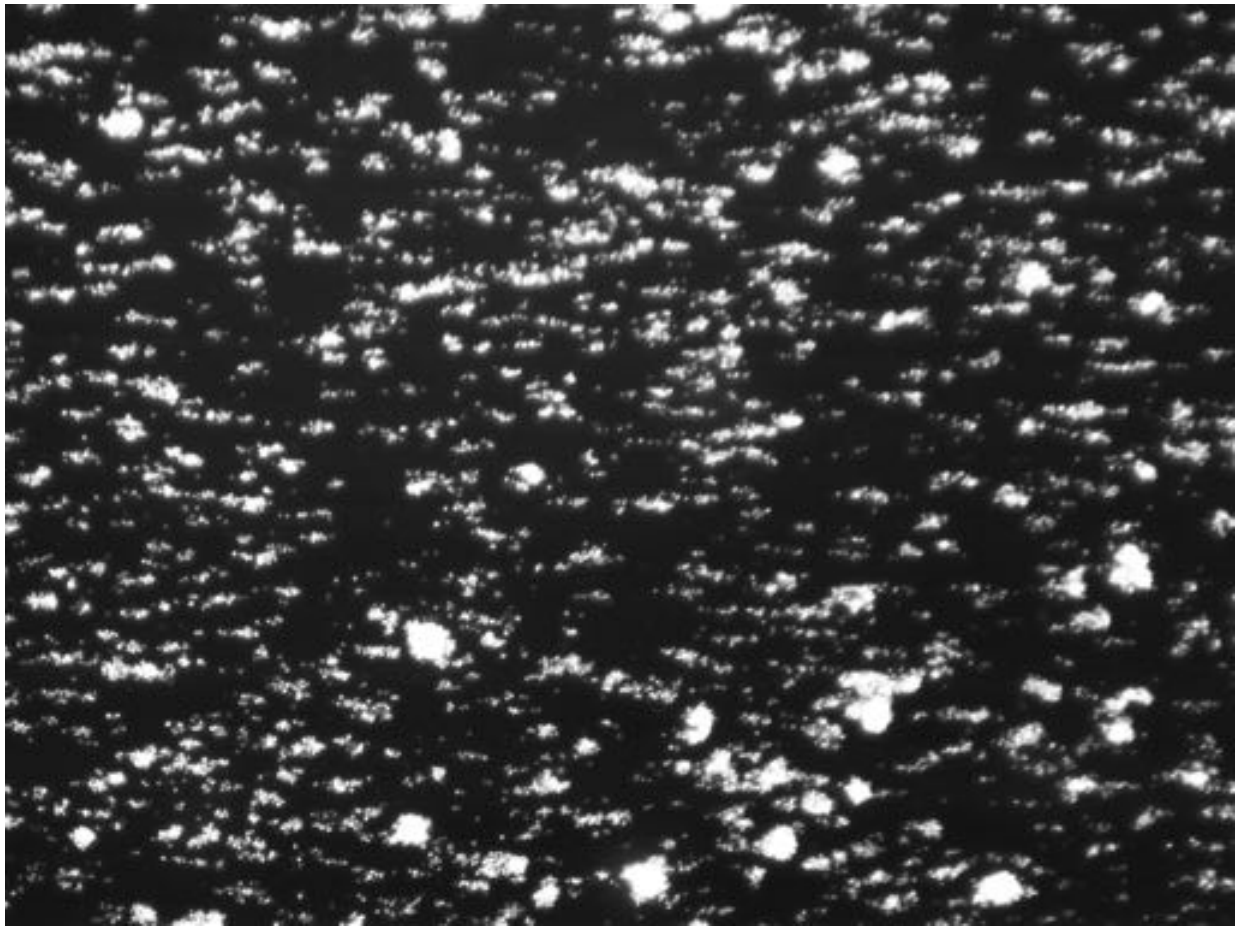


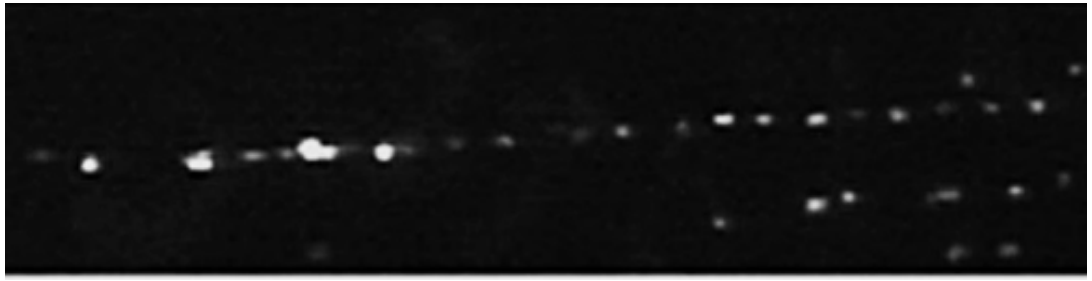


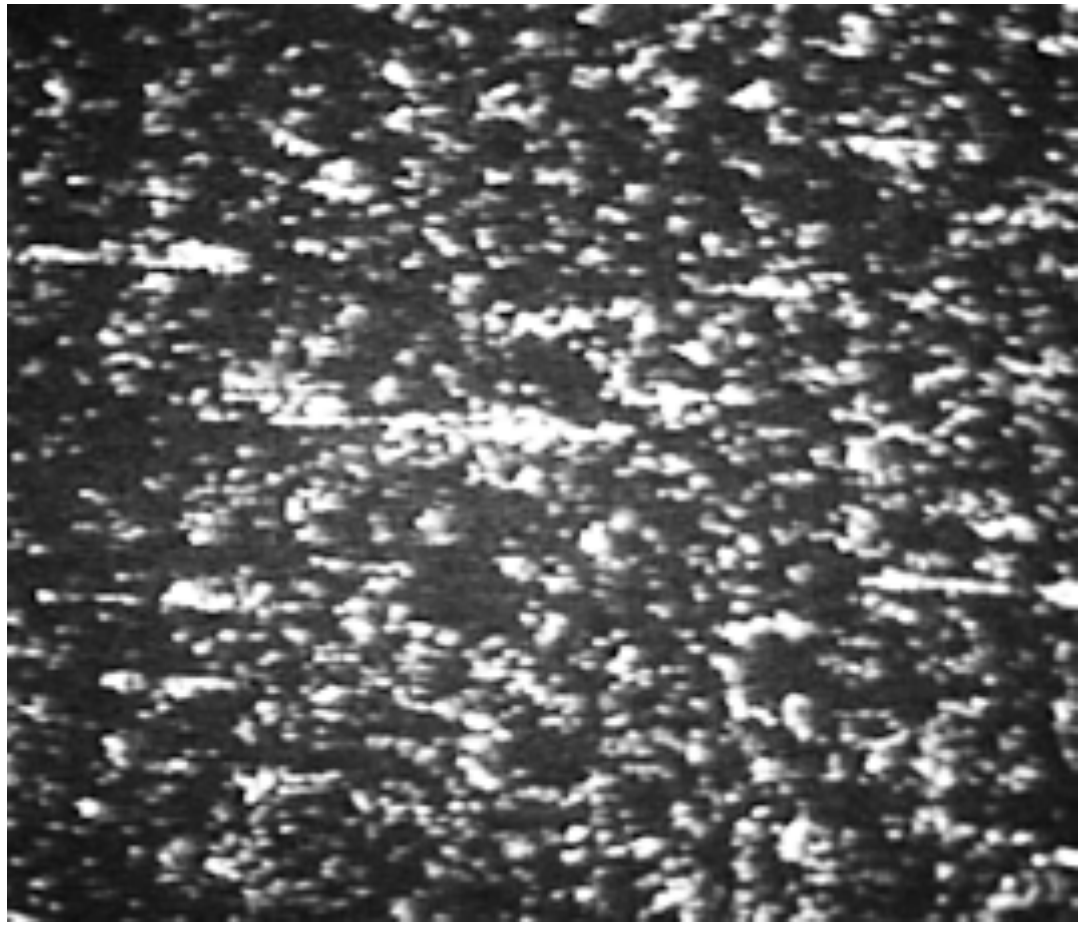


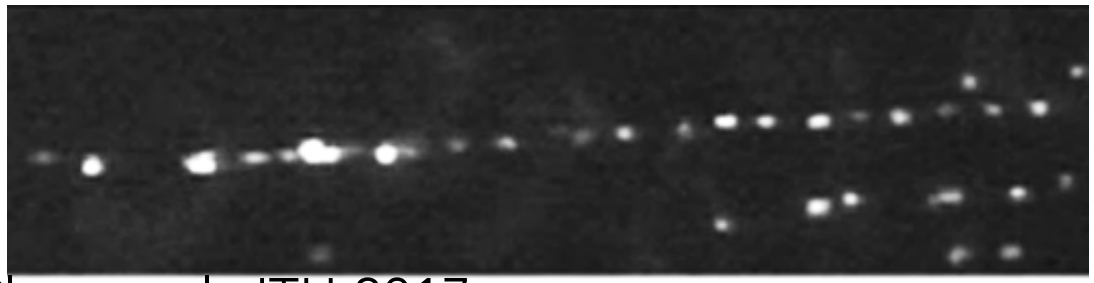


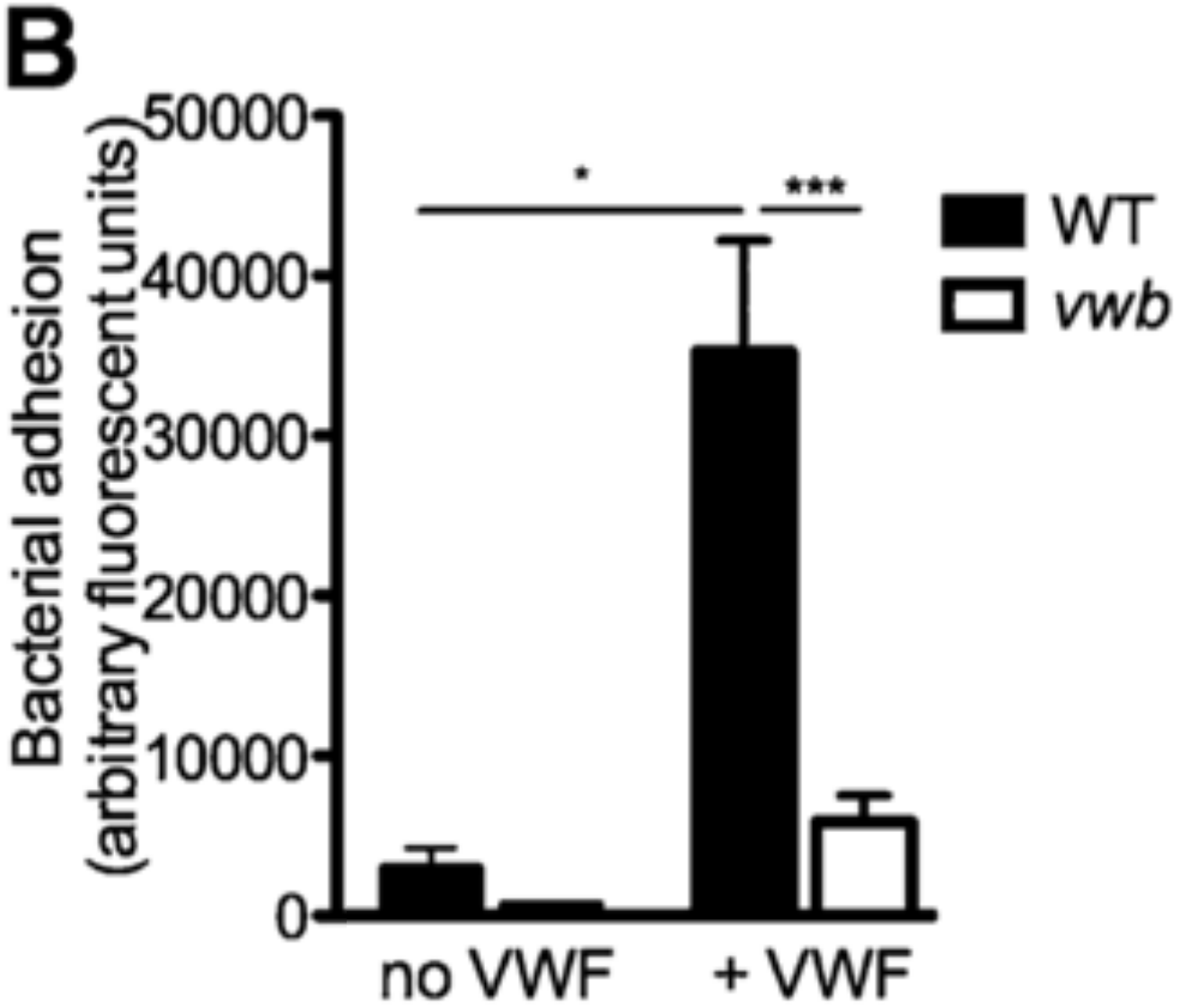




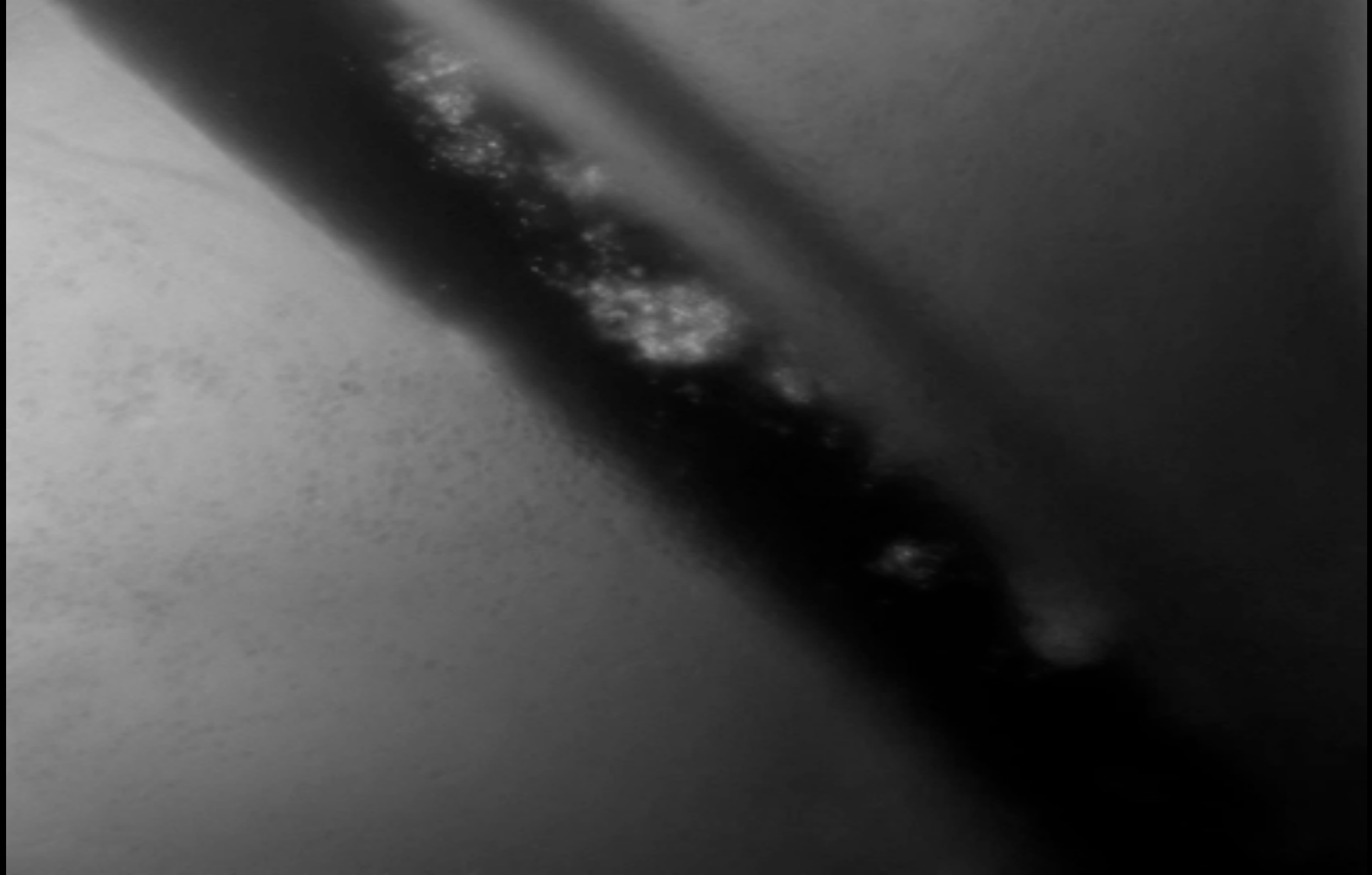


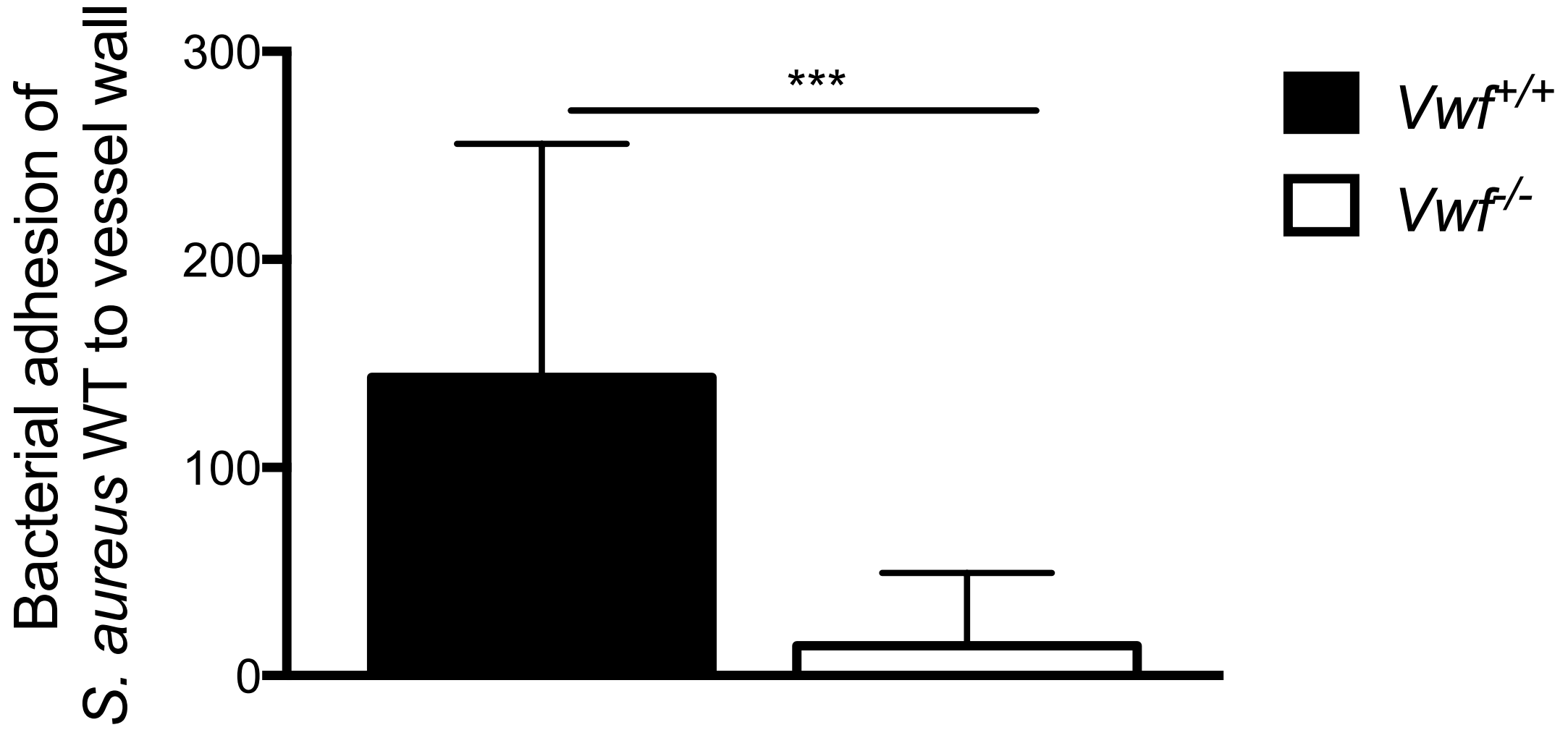




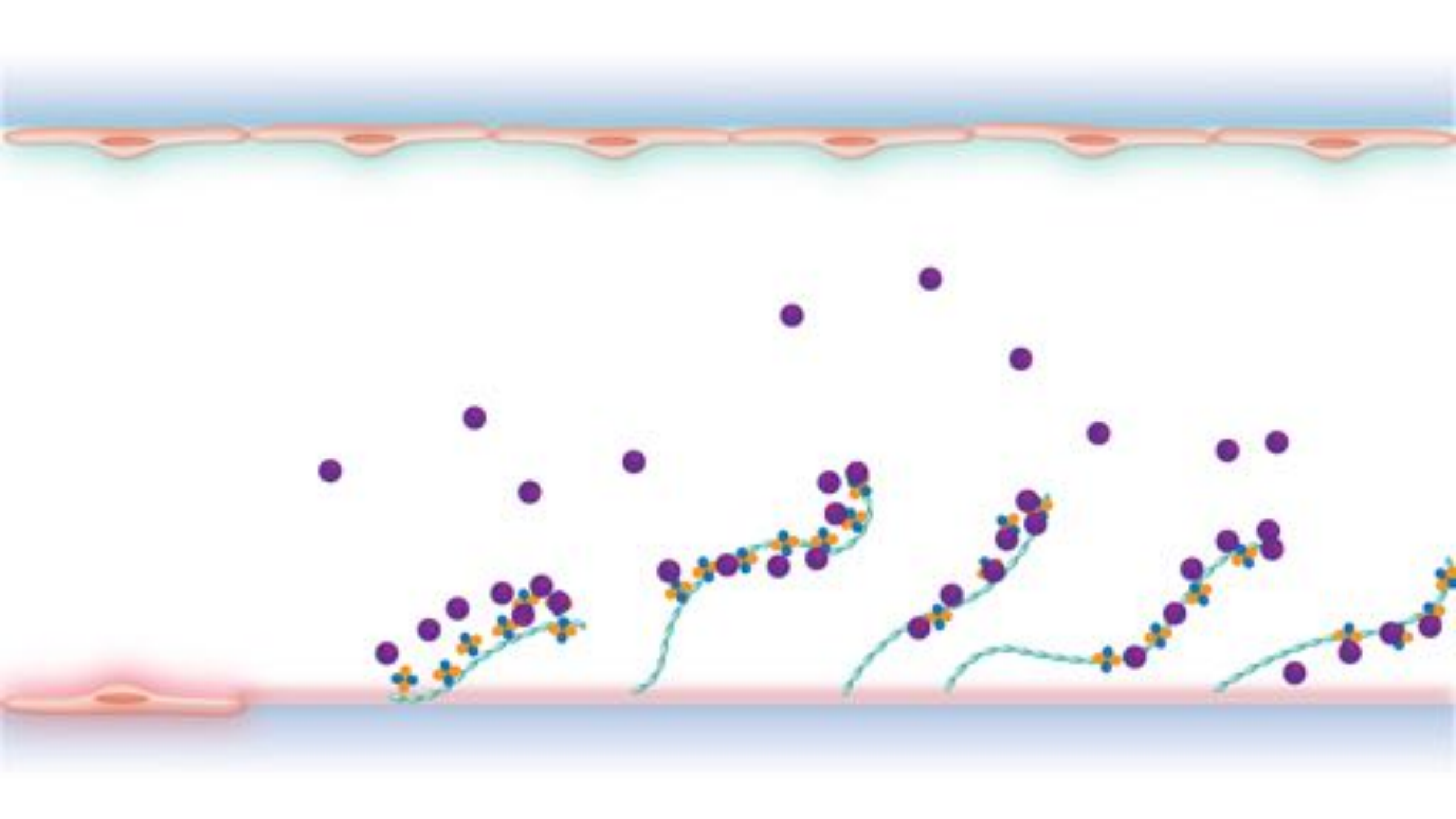


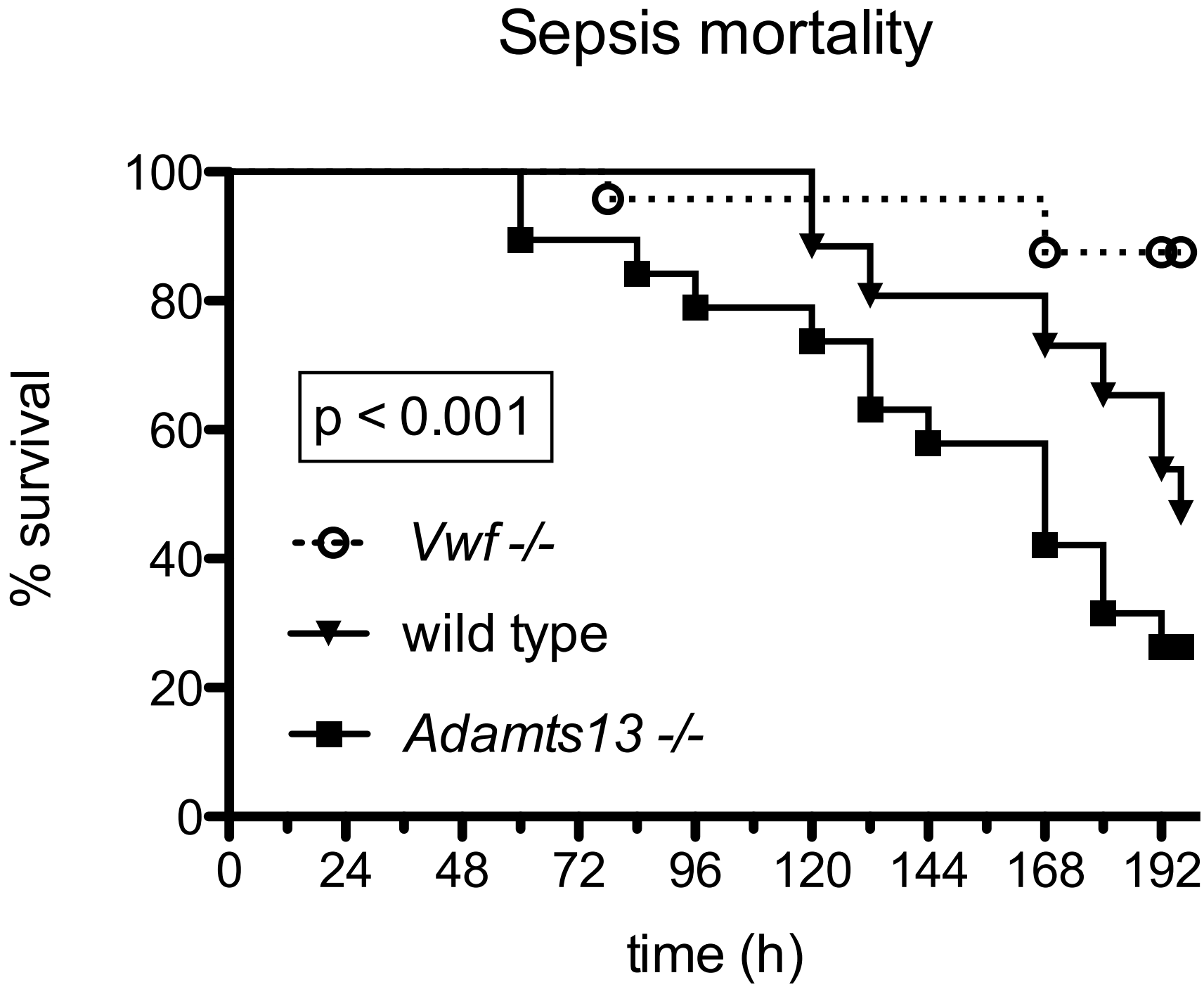
Claes et al, JTH 2017





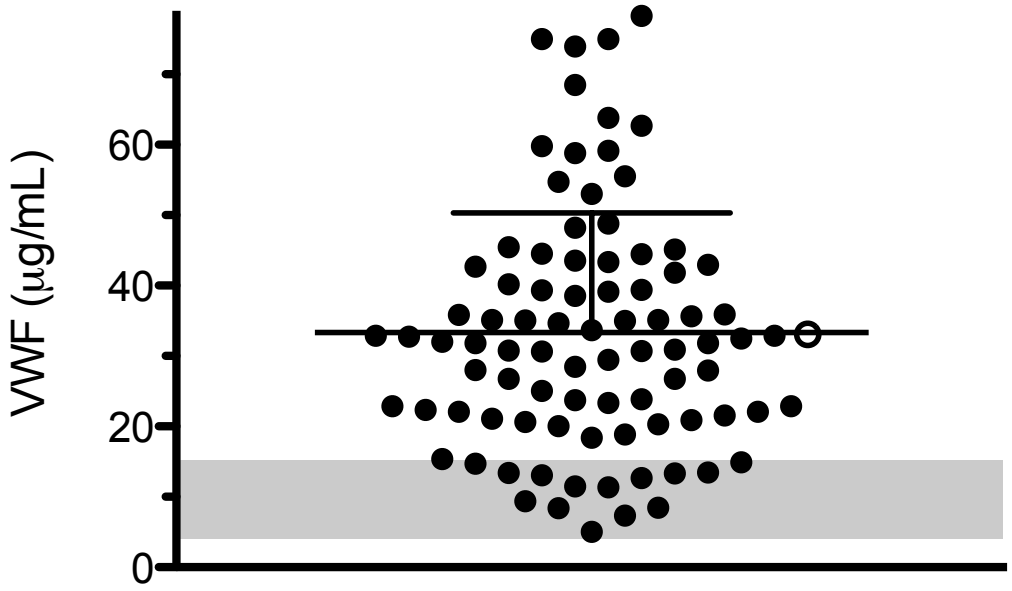
Claes et al, Blood 2014



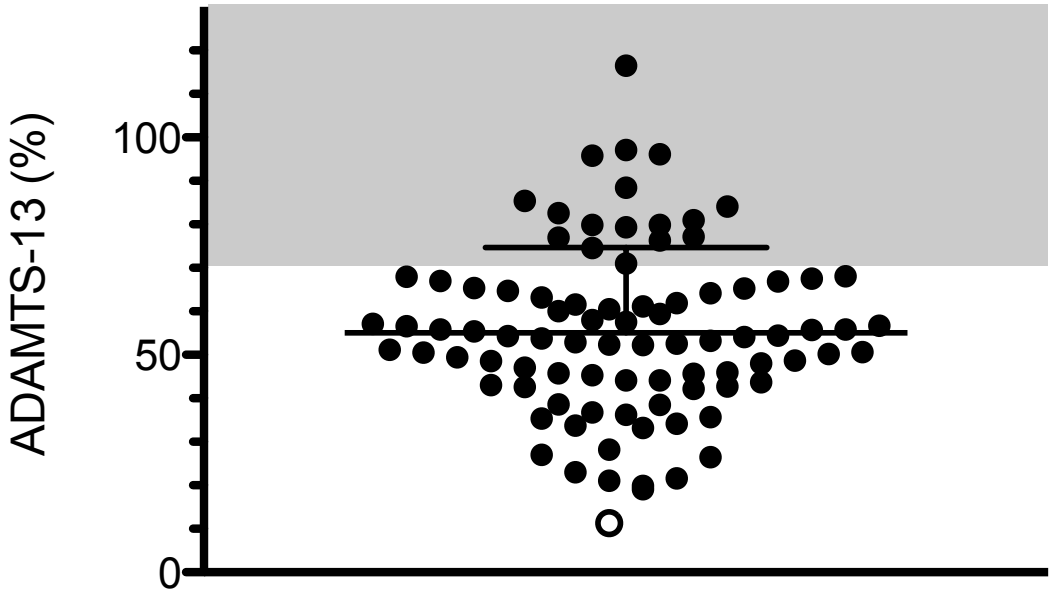

Sepsis mortality
100
80
60
40
20
0
% survival
p < 0.001
Vwf -/-
wild type
Adamts13 -/-
0
24
48
72
96
120
144
168
192
time (h)

IN PATIENTS WITH *S. AUREUS* SEPSIS

von Willebrand factor (VWF)

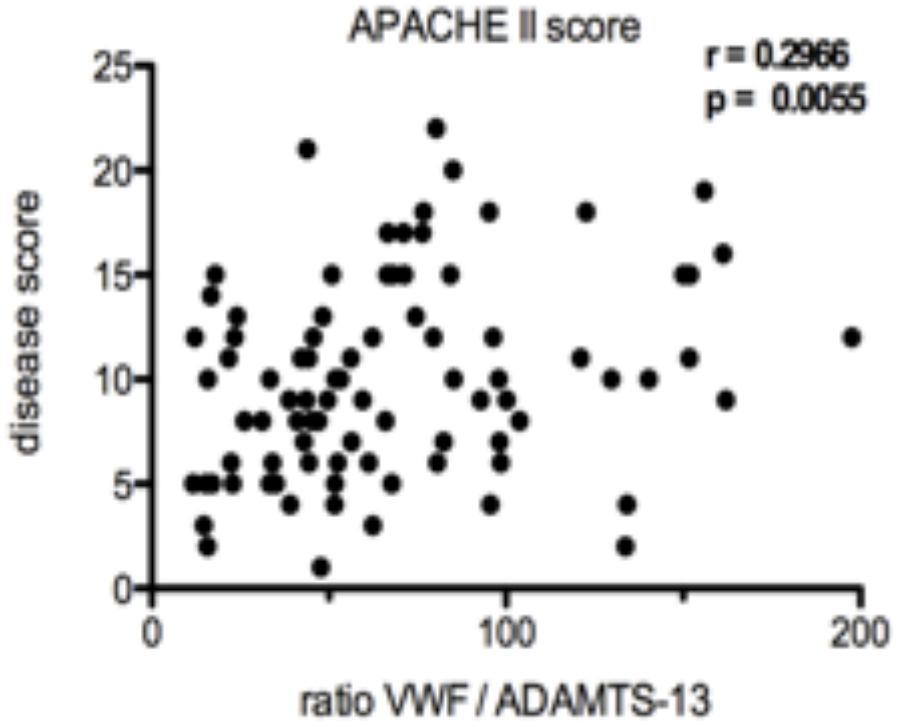


ADAMTS-13



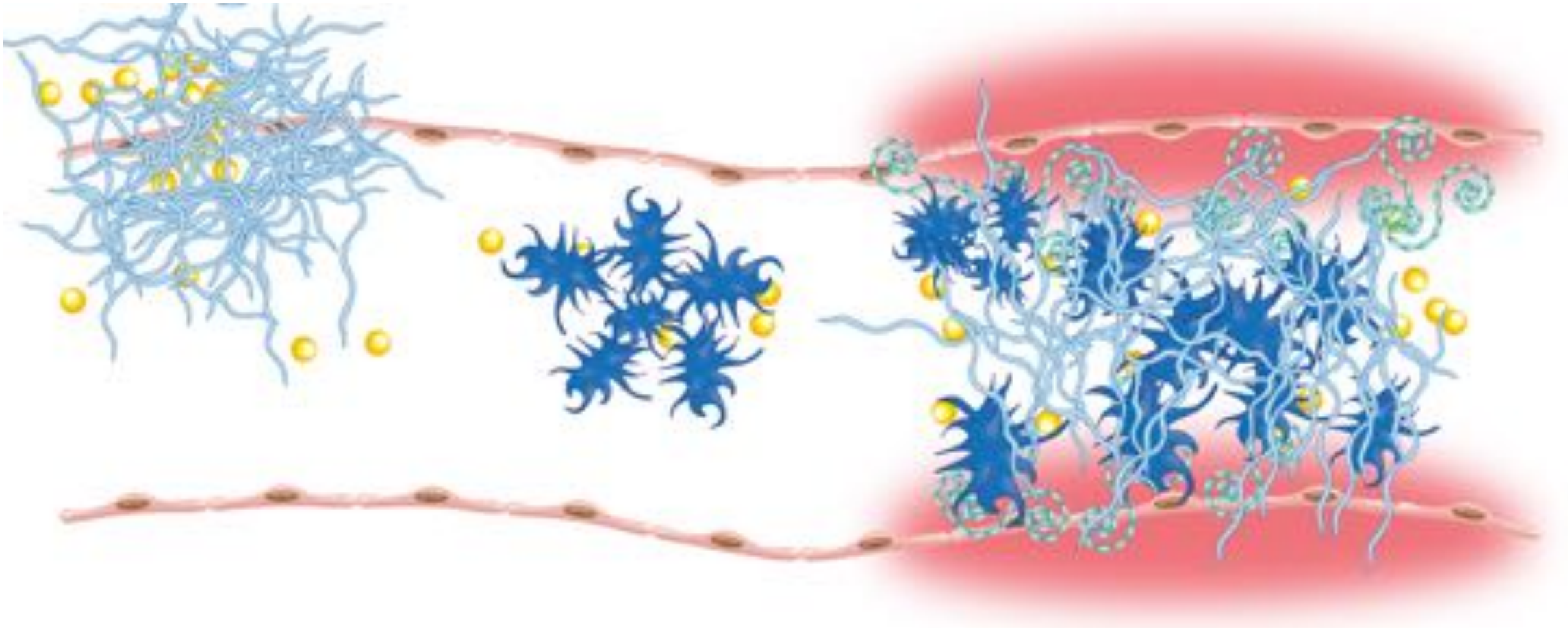
VWF LEVELS ARE HIGH AND ADAMTS-13 LEVELS ARE LOW

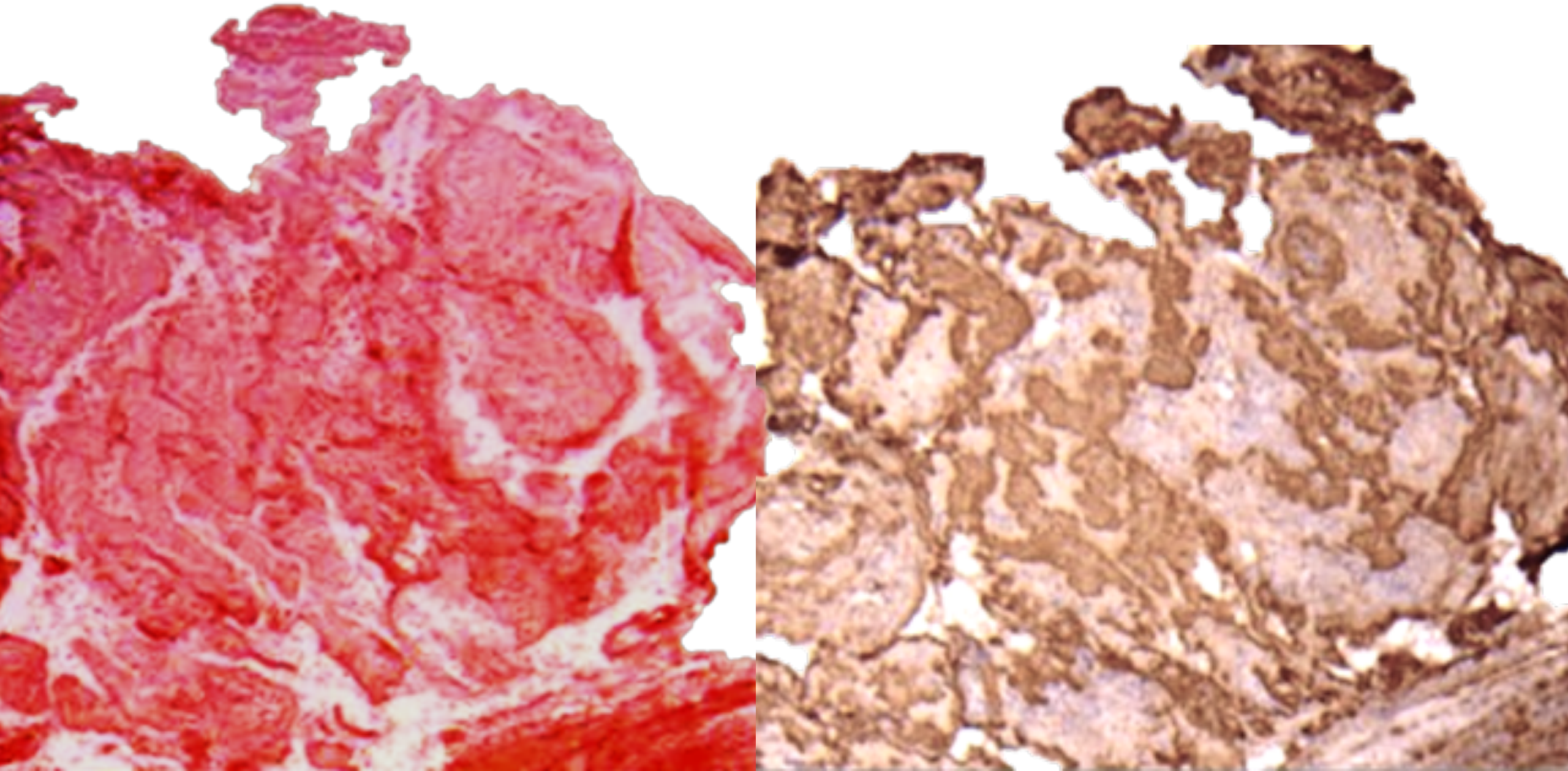
IN PATIENTS WITH S. AUREUS SEPSIS



VWF/ADAMTS-13
CORRELATES WITH DISEASE SEVERITY

S.aureus and endocarditis





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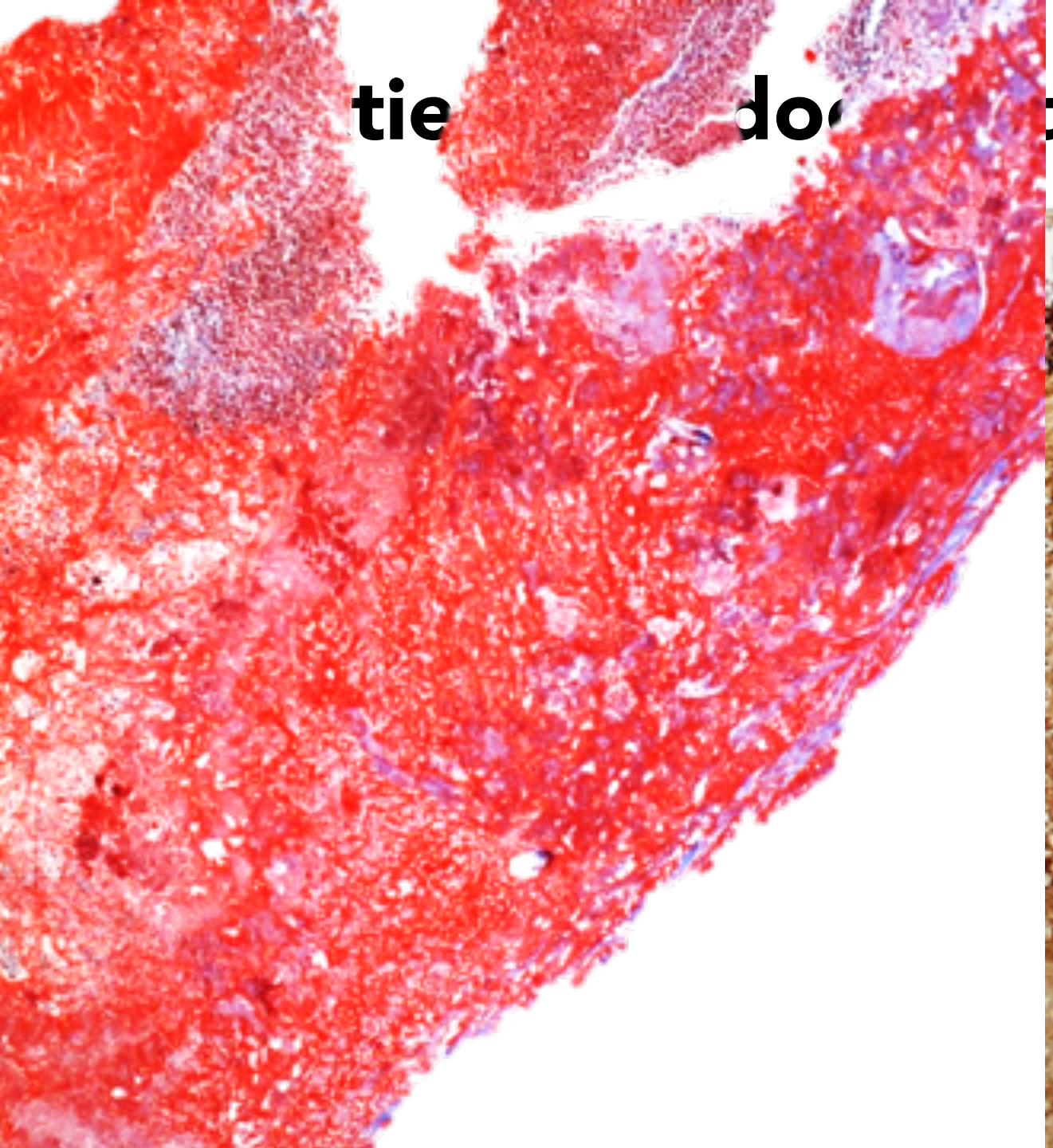
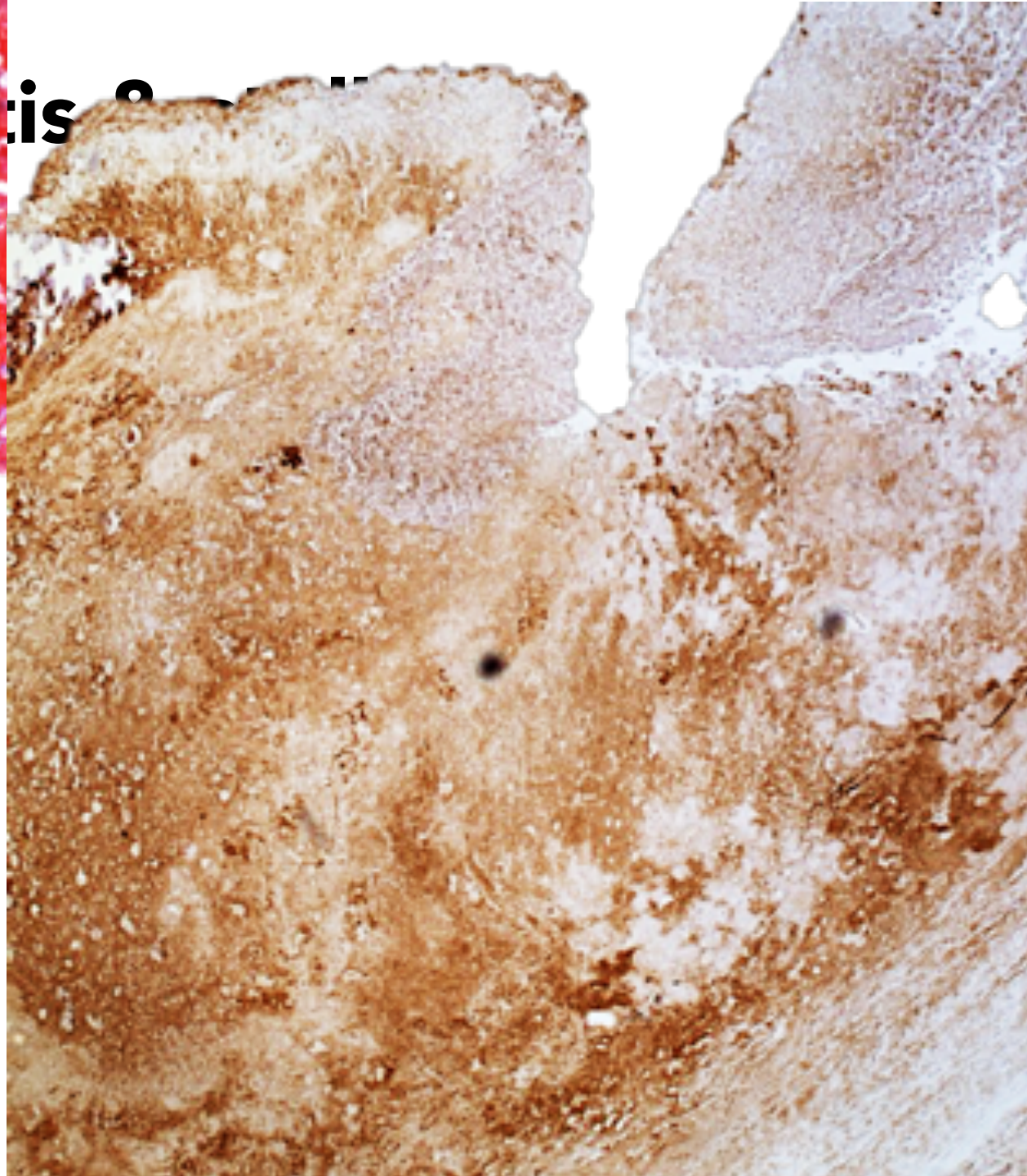
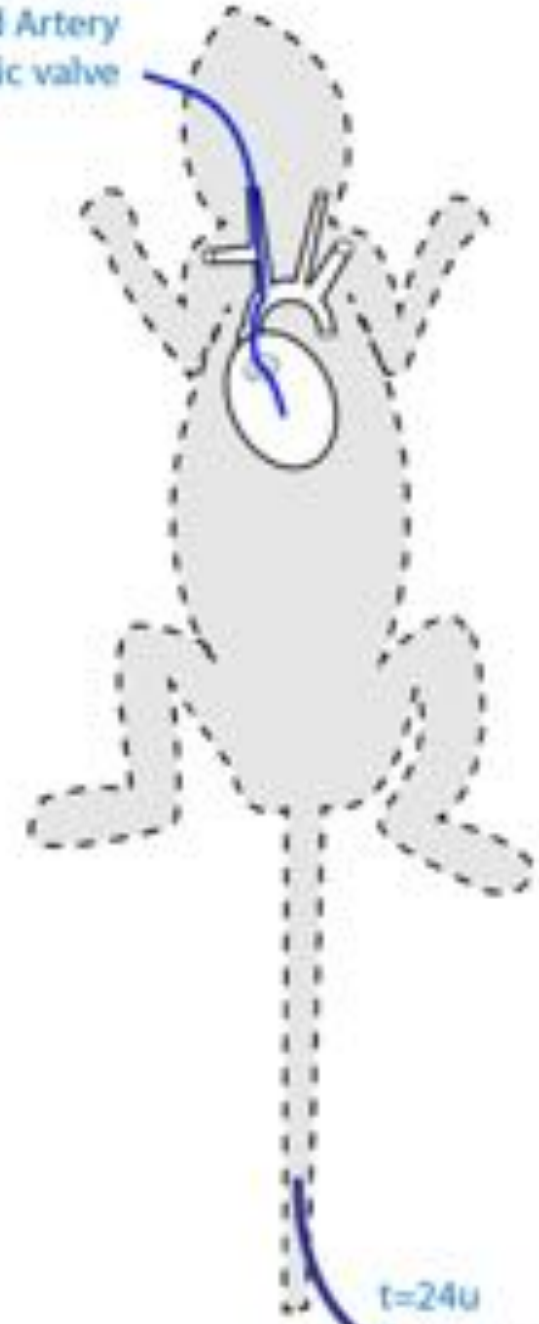
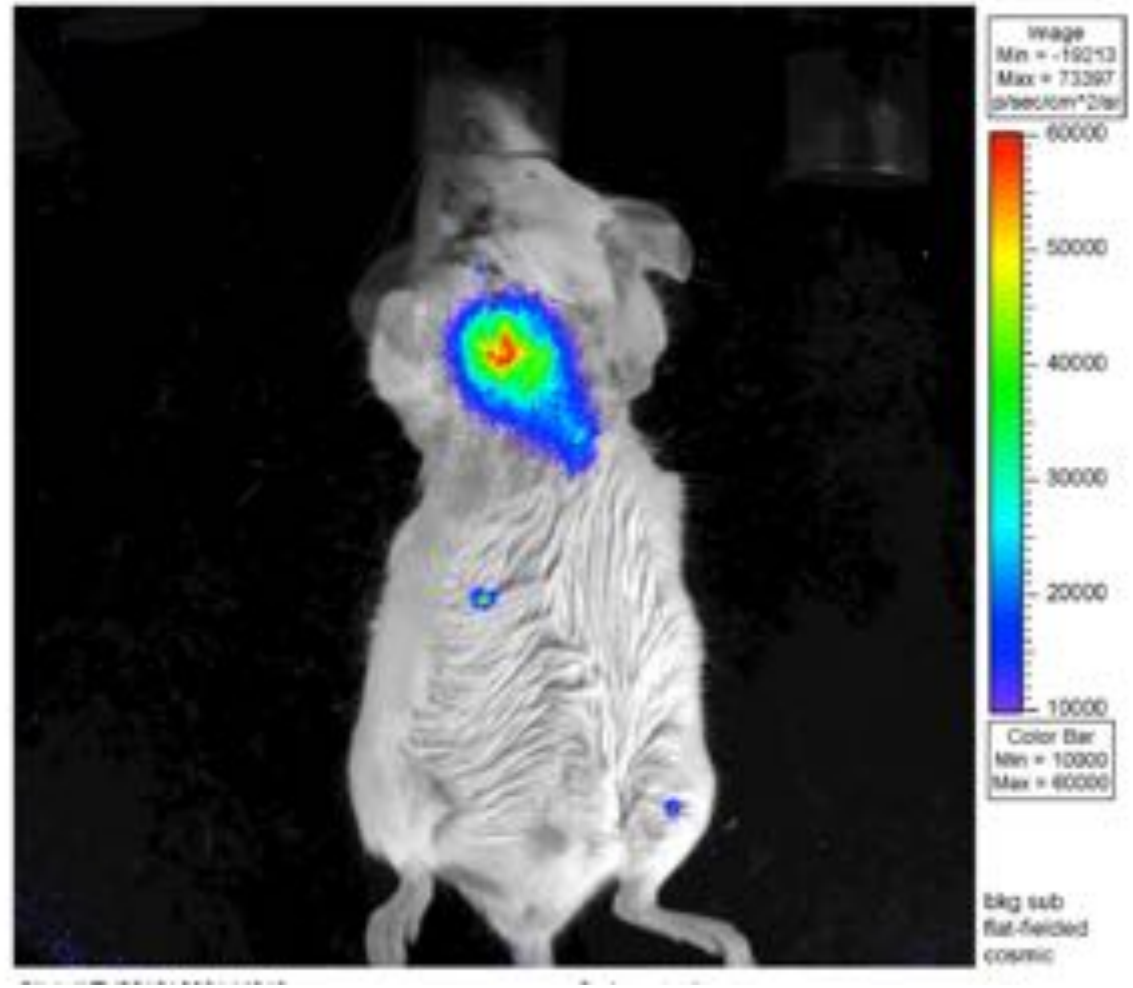


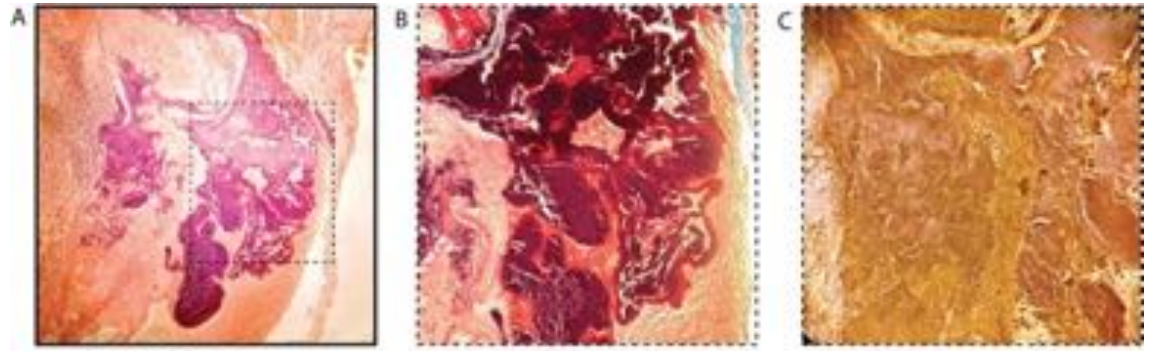


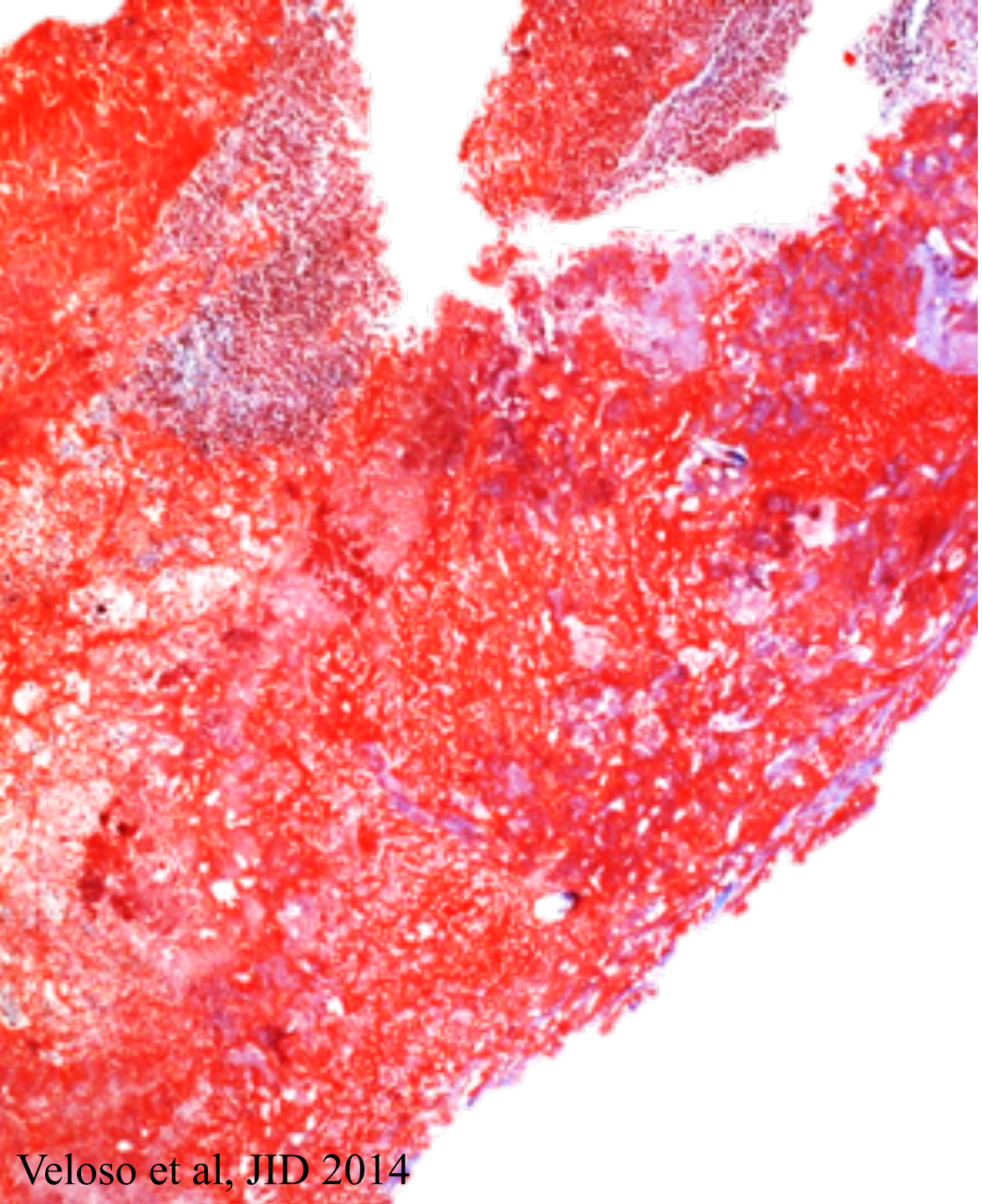
t=0
Ethylon wire
in right Carotid Artery
advanced until aortic valve

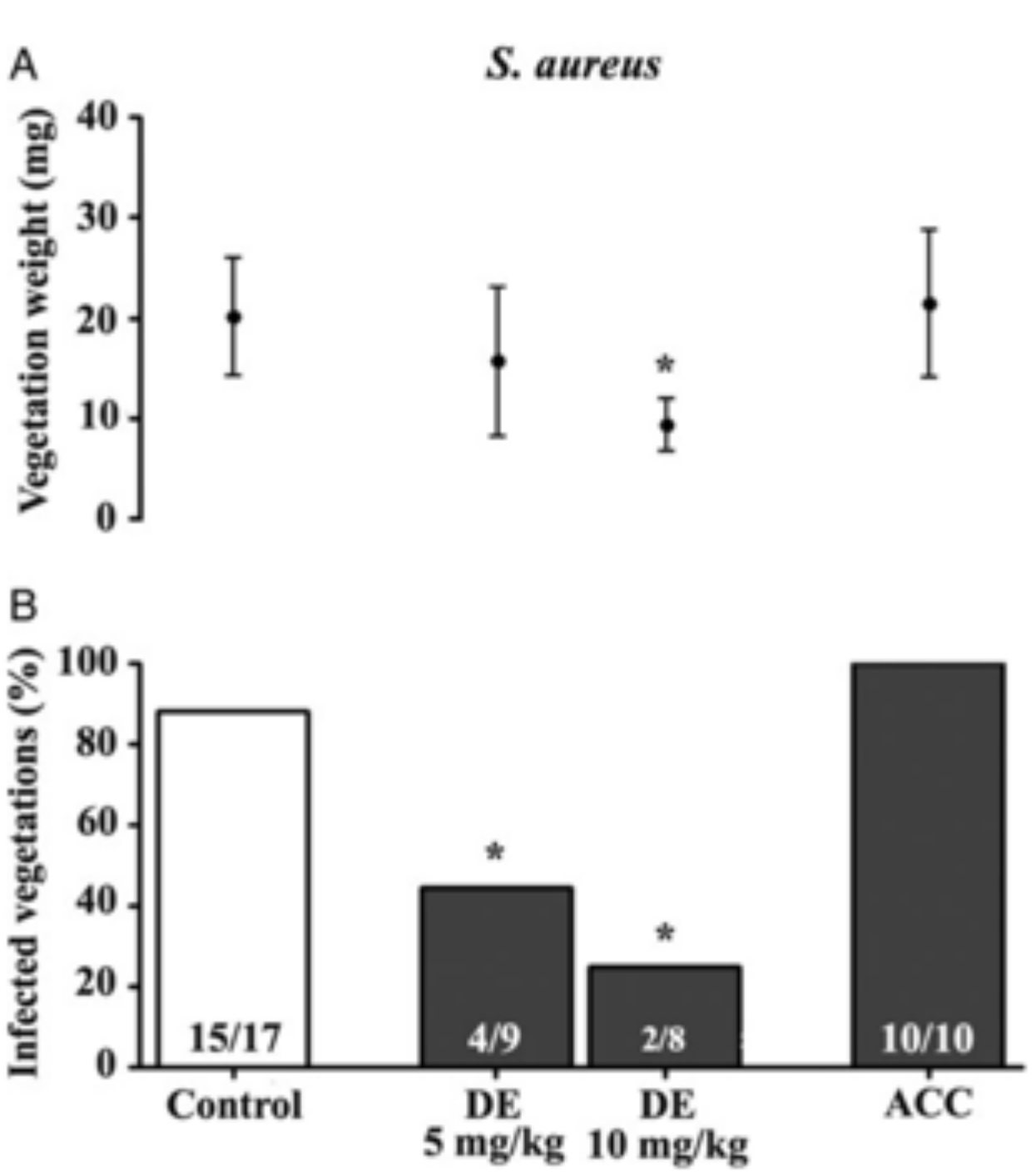


t=24u
S. aureus iv







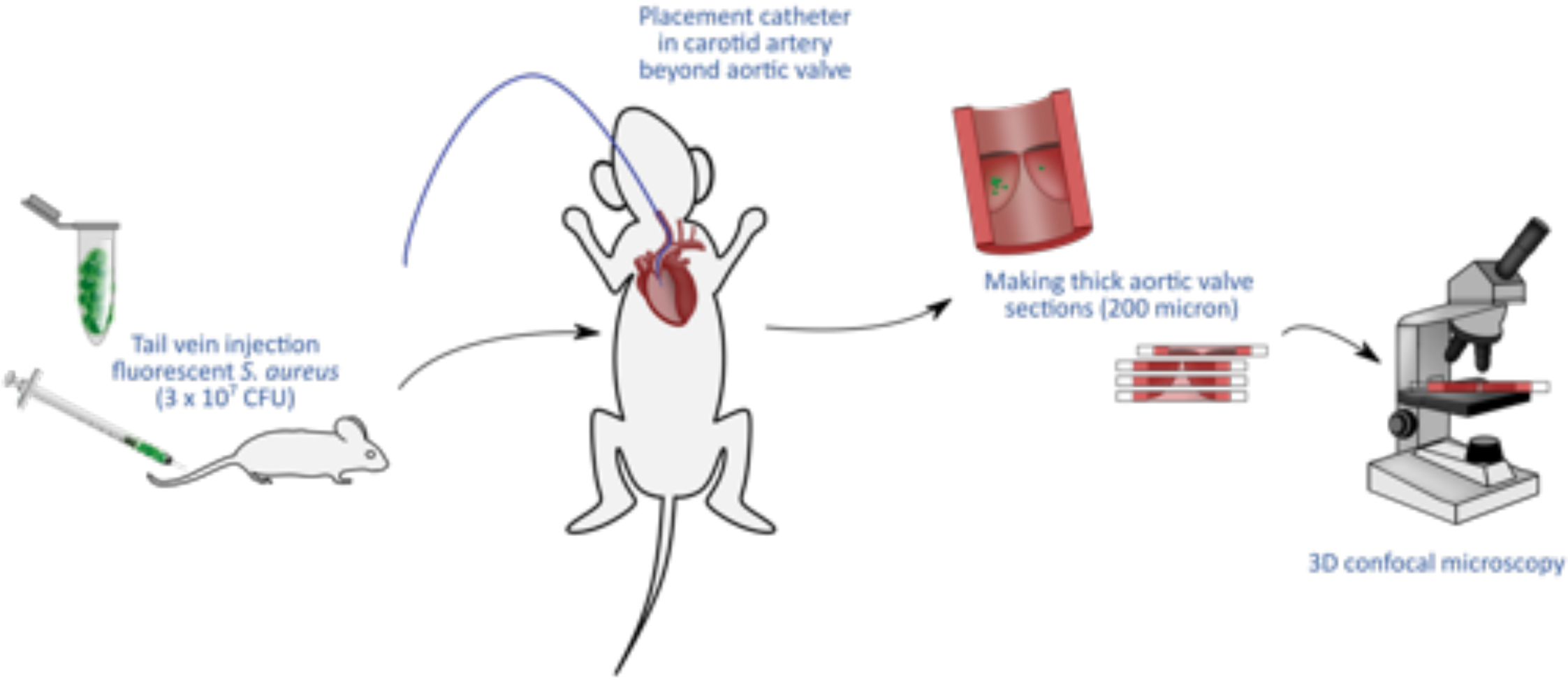


Veloso et al, JID 2014

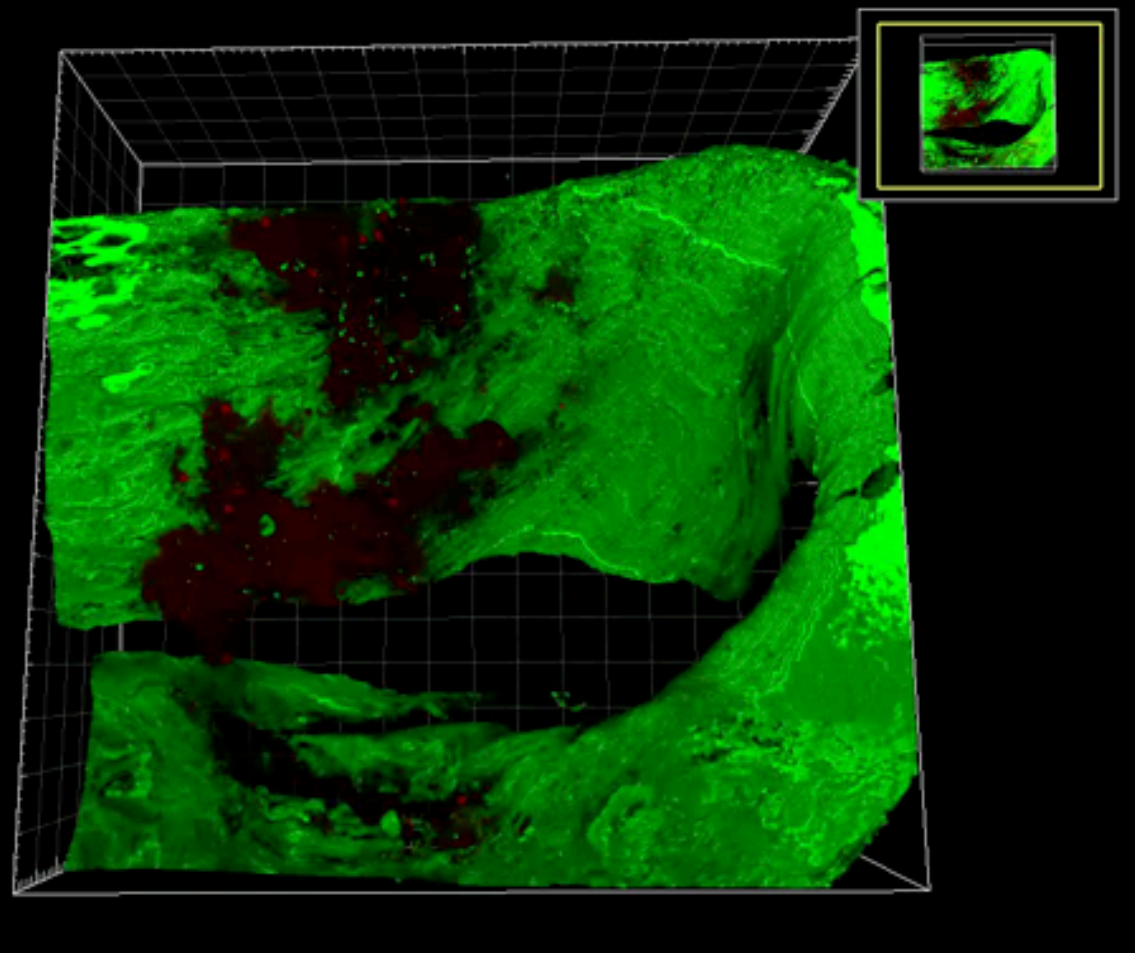
S. aureus uses VWF to attach to damaged valvular endothelium in vivo

More refined endocarditis animal models allow more detailed study of EARLY adhesion

A new model to study early bacterial adhesion



Liesenborghs et al. Eur Heart J. 2019



Endothelium

S. aureus

Liesenborghs et al. Eur Heart J. 2019

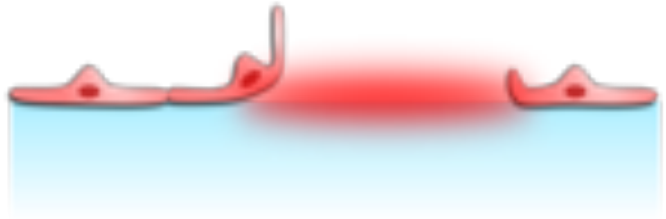
A new model to study early bacterial adhesion

No catheter

normal valve

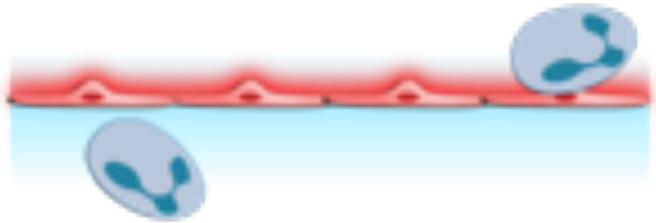
Catheter
no histamine

damaged valve



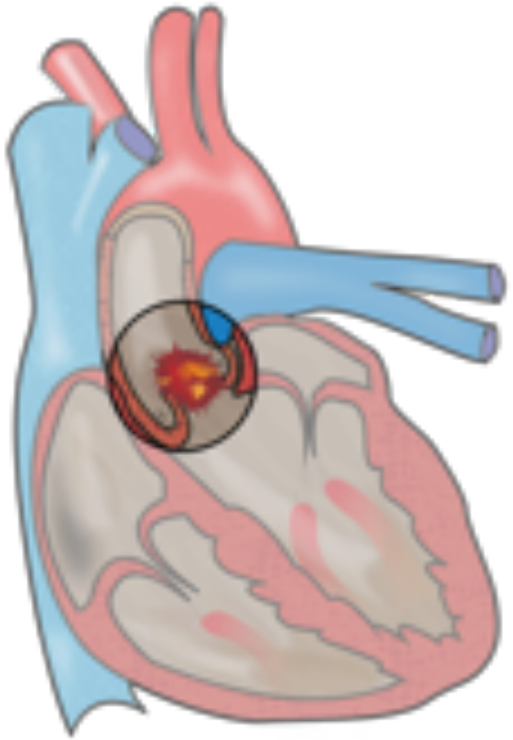
Catheter
histamine infusion

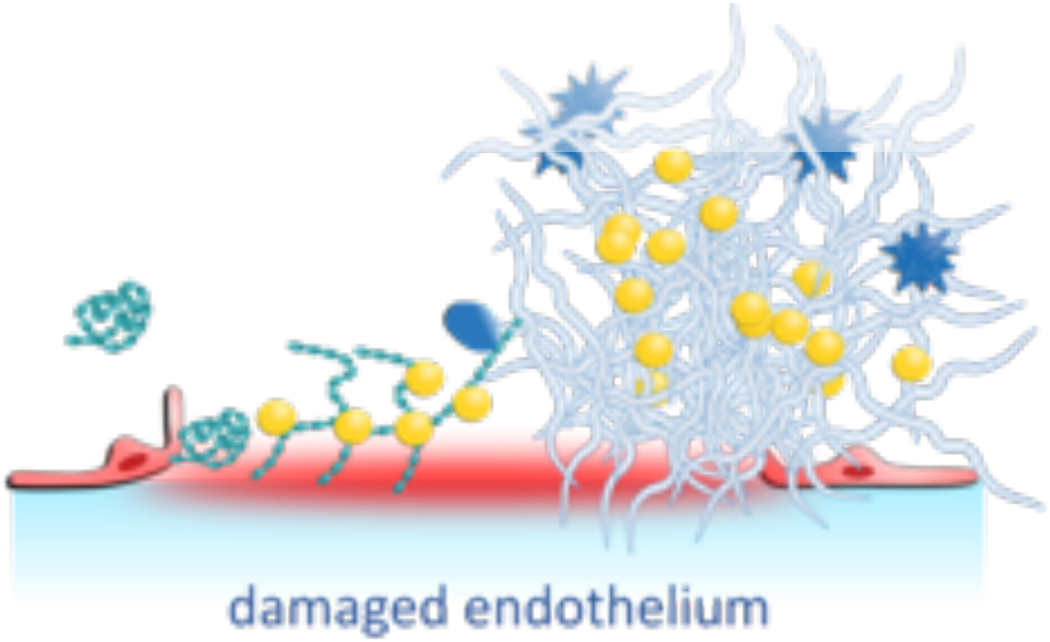
(damaged) +
inflamed valve



Liesenborghs et al. Eur Heart J. 2019

Mechanisms of adhesion





Liesenborghs et al. Eur Heart J. 2019

Damaged cardiac valve

Endothelium

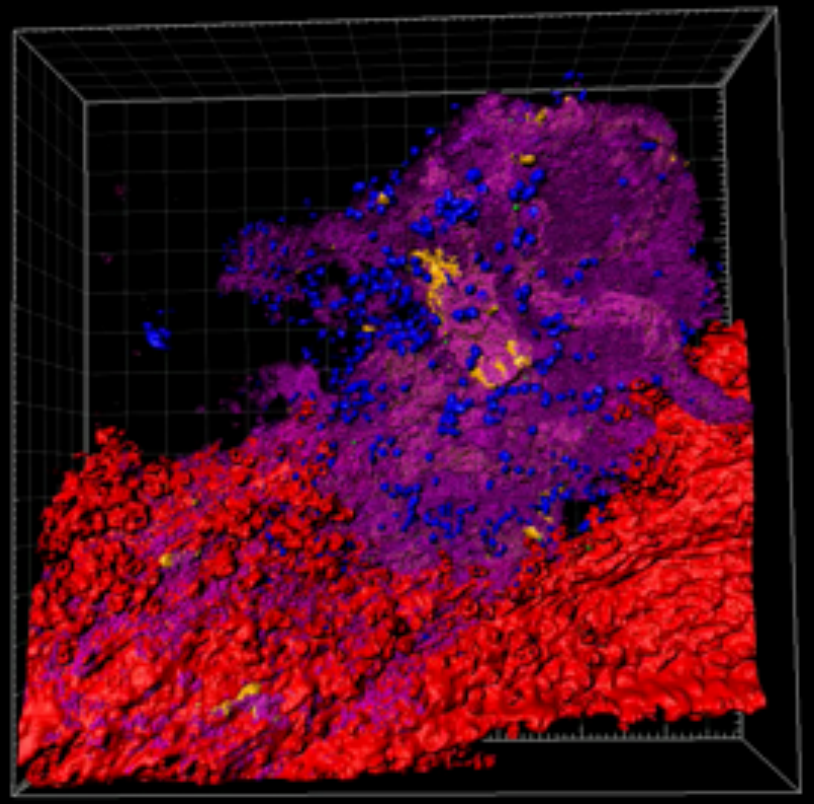
Platelets

Fibrin

S. aureus

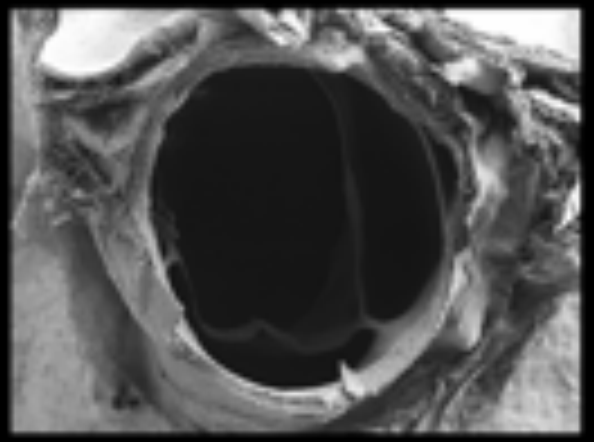
Dapi

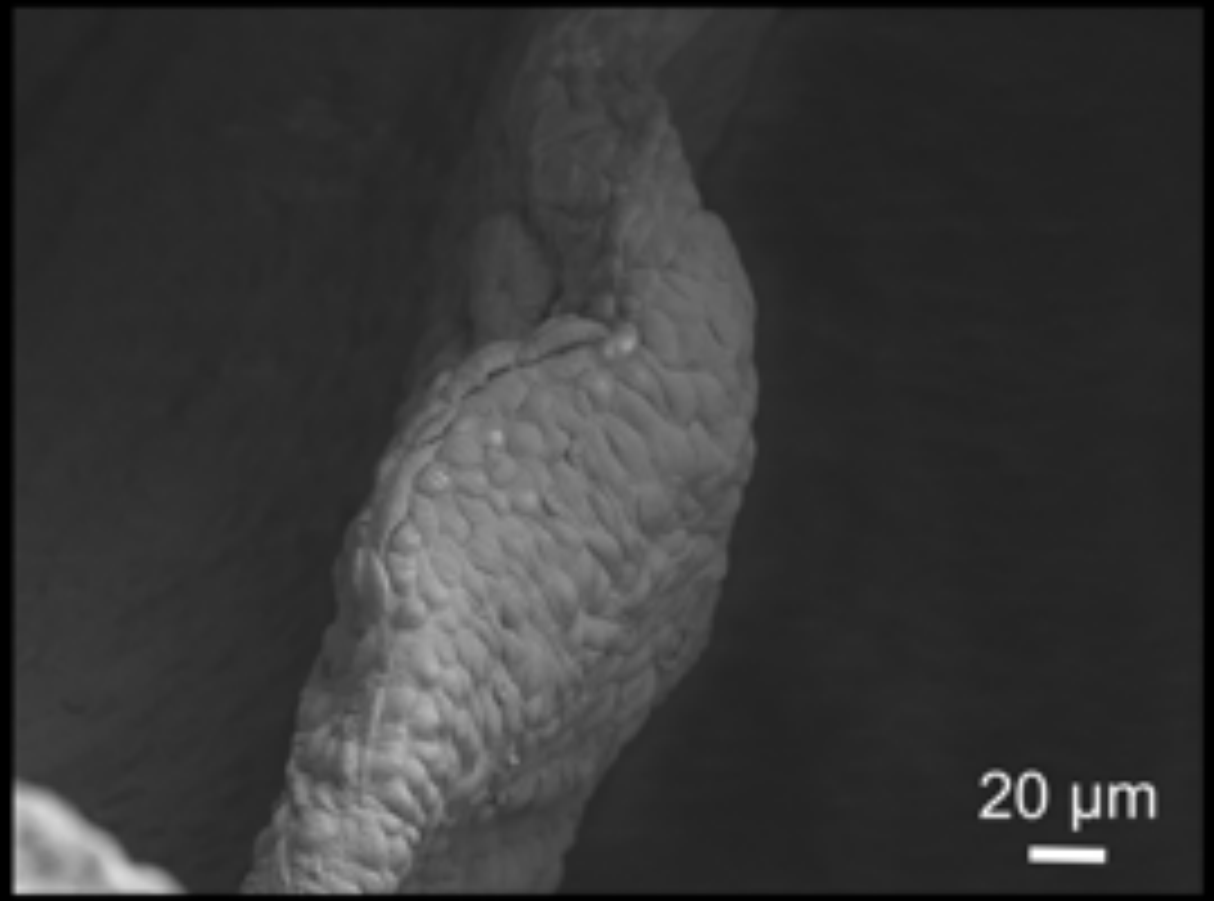
White blood cells



Liesenborghs et al. Eur Heart J. 2019

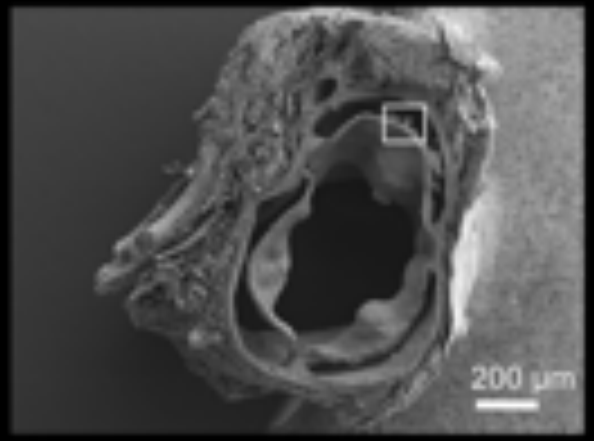
normal valve

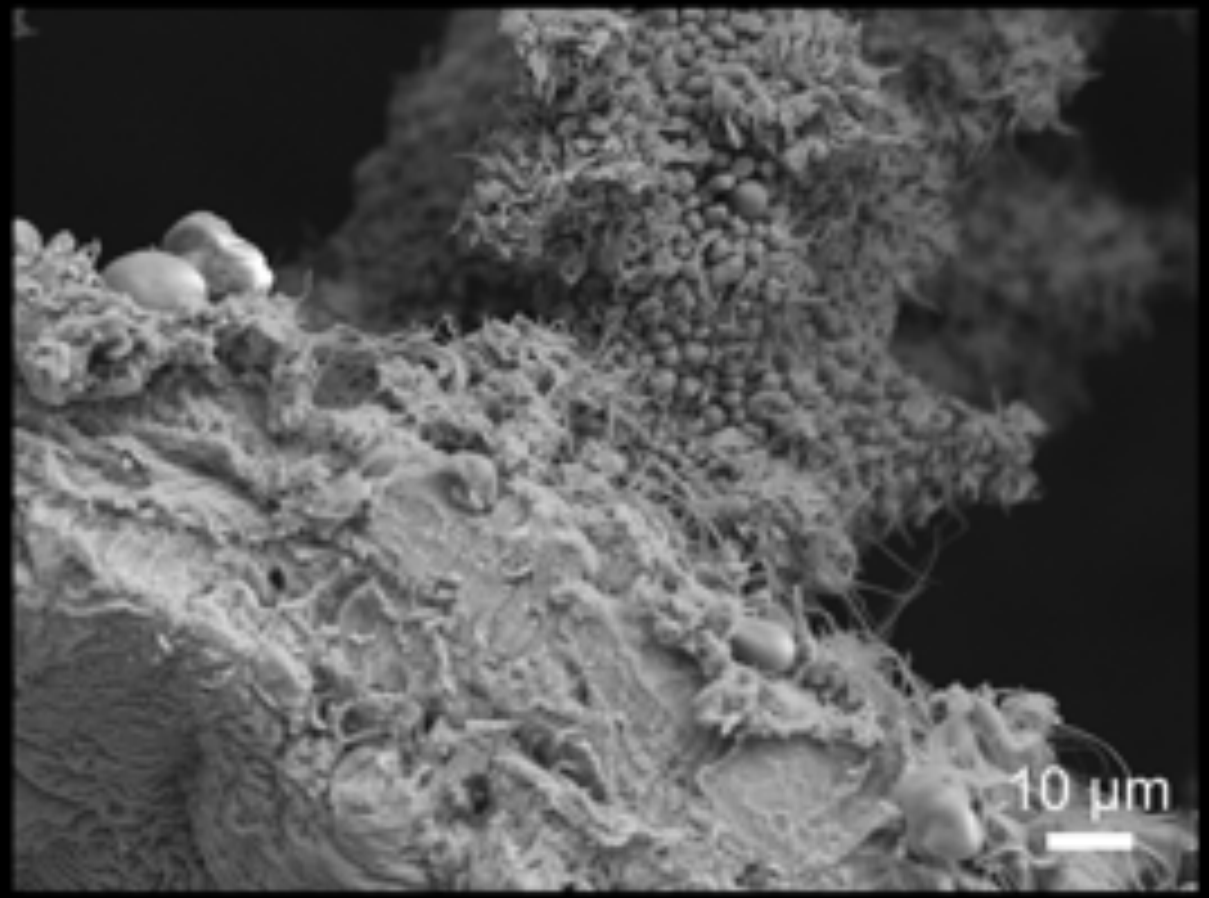




Liesenborghs et al. Eur Heart J. 2019

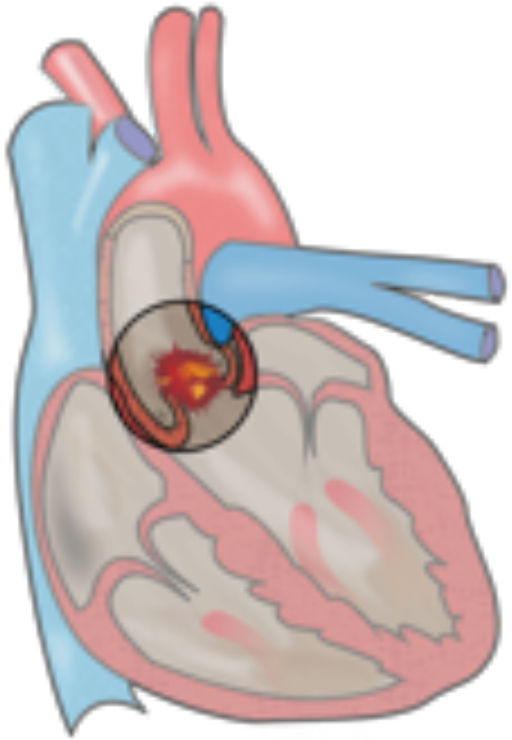
damaged valve

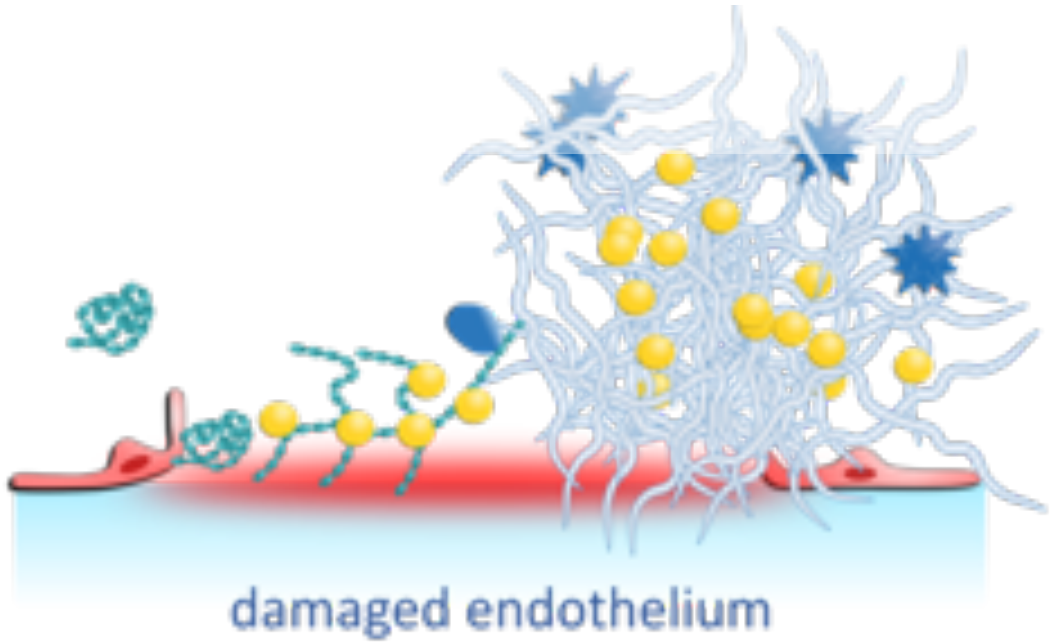


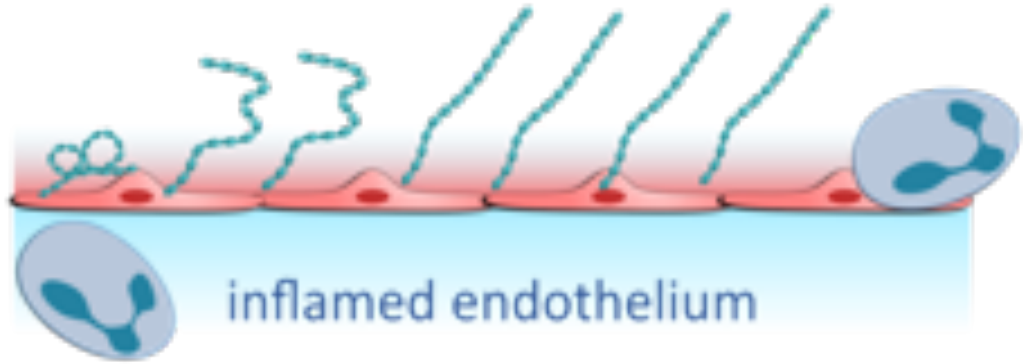


Liesenborghs et al. Eur Heart J. 2019

Mechanisms of adhesion

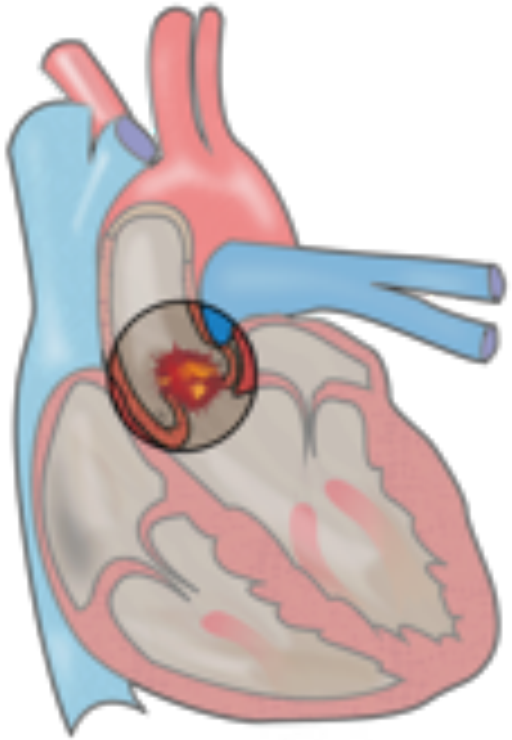


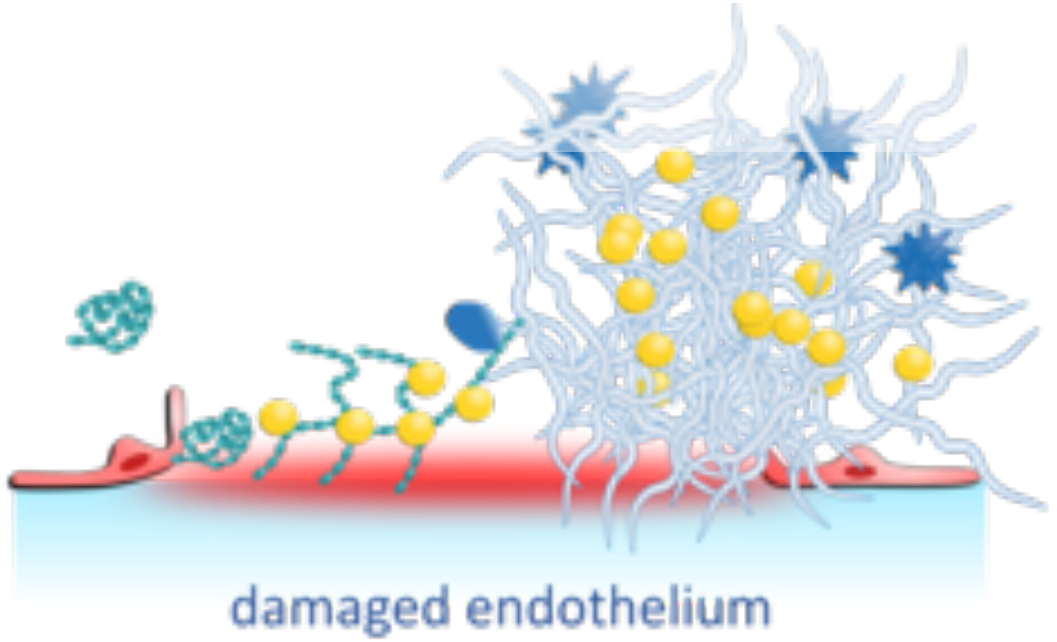


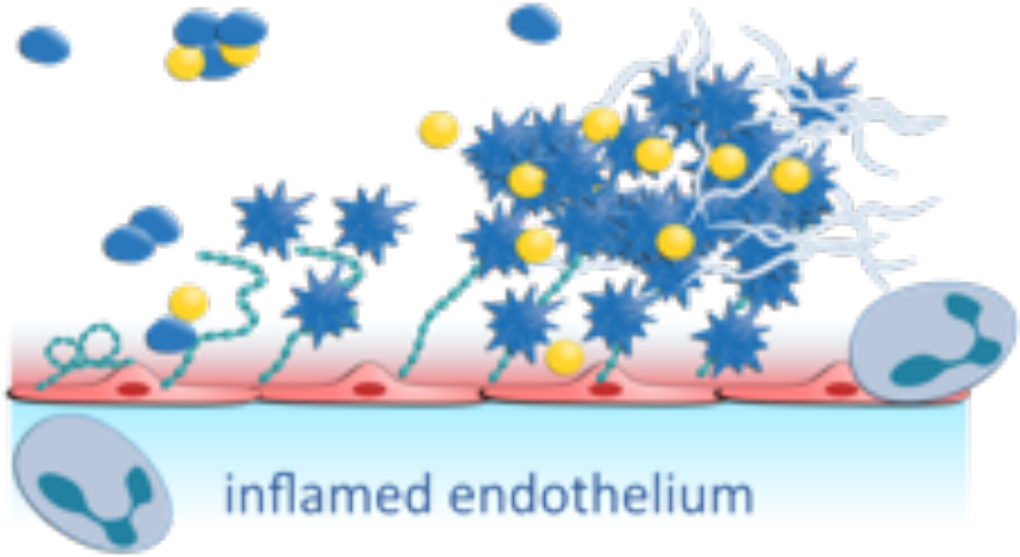


Liesenborghs et al. Eur Heart J. 2019

Mechanisms of adhesion







Liesenborghs et al. Eur Heart J. 2019

Inflamed cardiac valve

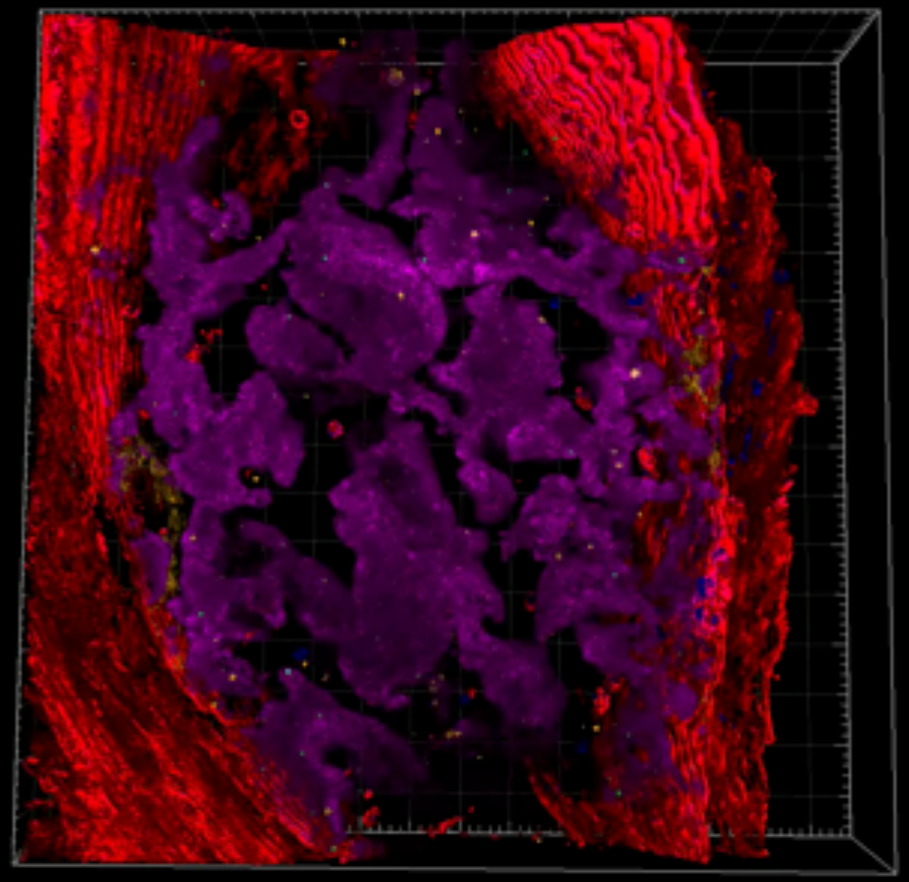
Endothelium

Platelets

Fibrin

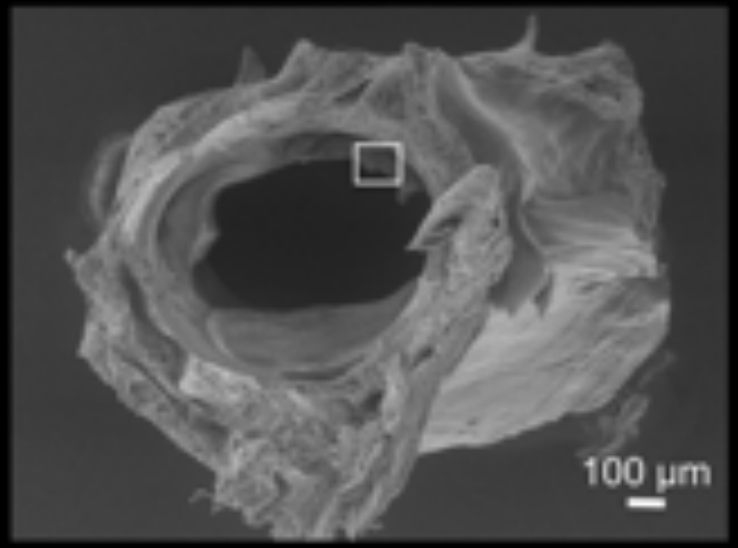
S. aureus

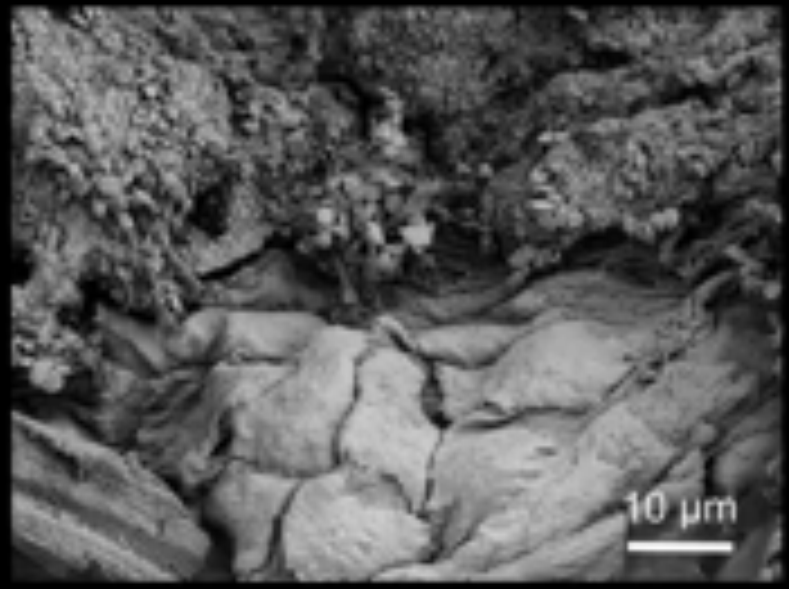
Dapi



Liesenborghs et al. Eur Heart J. 2019

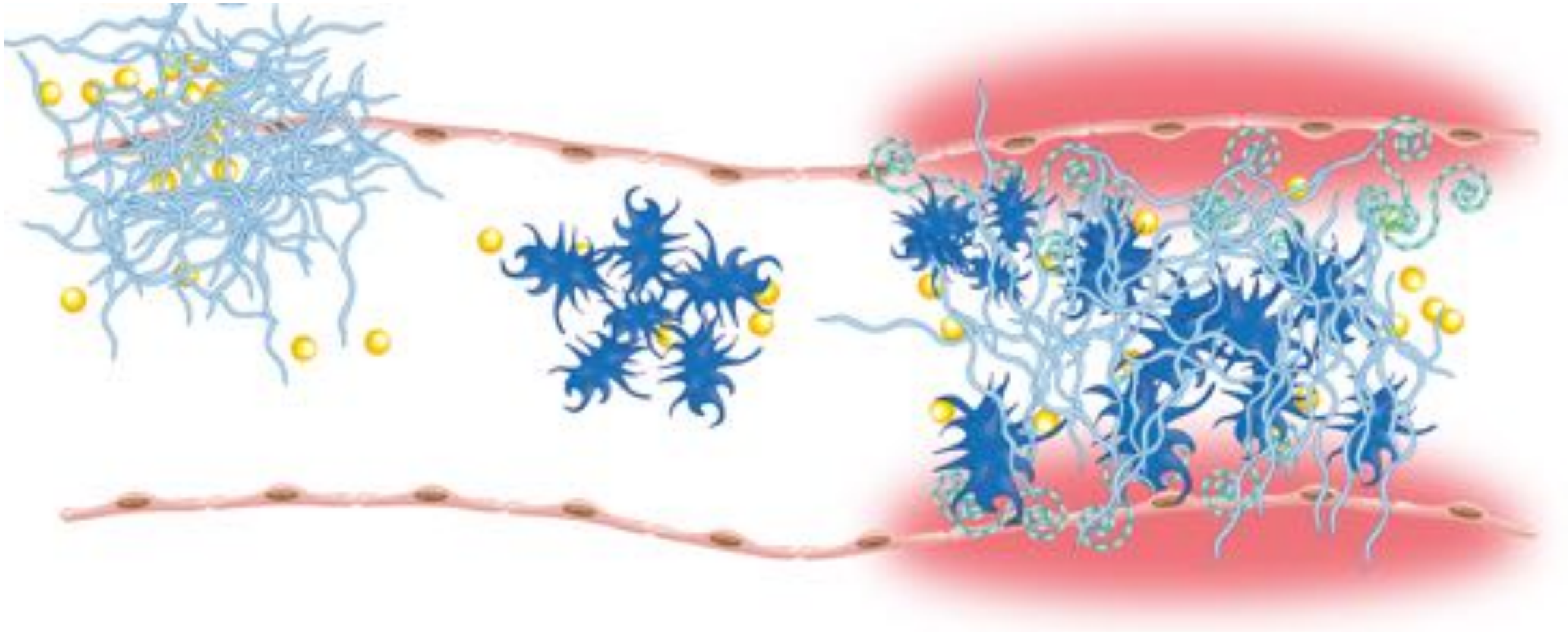
inflamed valve





Liesenborghs et al. Eur Heart J. 2019

S.aureus



S.aureus

coagulase
DTI?

platelet
recruitment
anti-VWF?

infective
endocarditis
anti-VWF?
anti-PLT?
anti-ClfA?

TARGETED VIRULENCE FACTOR INHIBITION