Future applications of recombinant human C1 esterase inhibitor (conestat alfa) in the setting of ischemia/reperfusion injury

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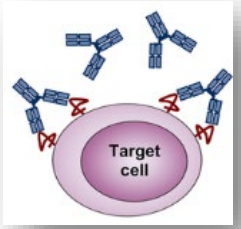
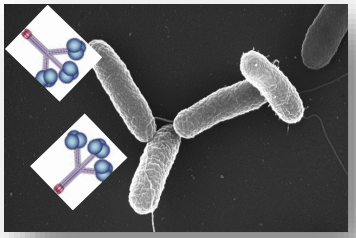
Disclosures

- **Research grants:** Pharming Biotechnologies B.V., Fondation Machaon, University Basel
- **Travel grants:** MSD, Gilead, Pfizer, Pharming Biotechnologies B.V.
- **Lecture fee:** MSD, Mundipharma
- **Consultation fee:** Pharming Biotechnologies B.V.

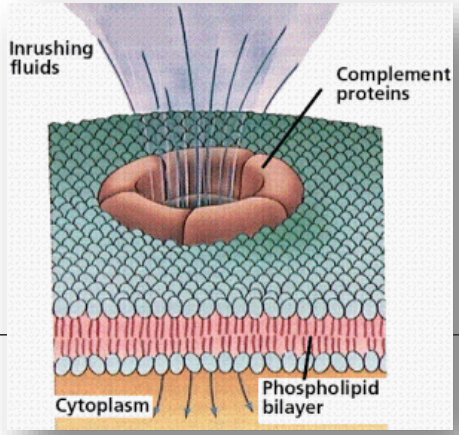
The complement system and cascade

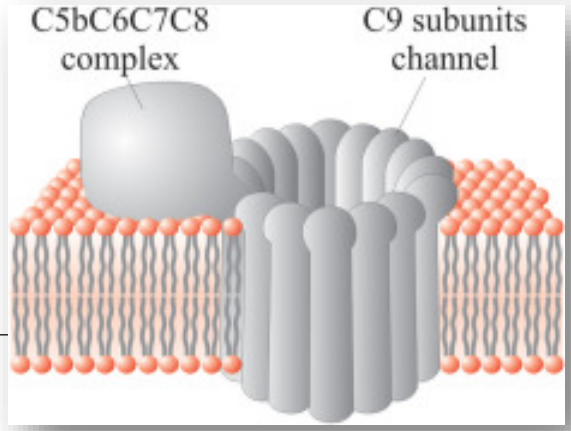
- Group of approximately 20 plasma proteins
- Essential part of the innate immune/defense system
- Many complement proteins are produced in the liver
- Activation
  - Antibodies
  - Bacteria/viruses
  - Sugars on dying cells or microorganisms
  - ….



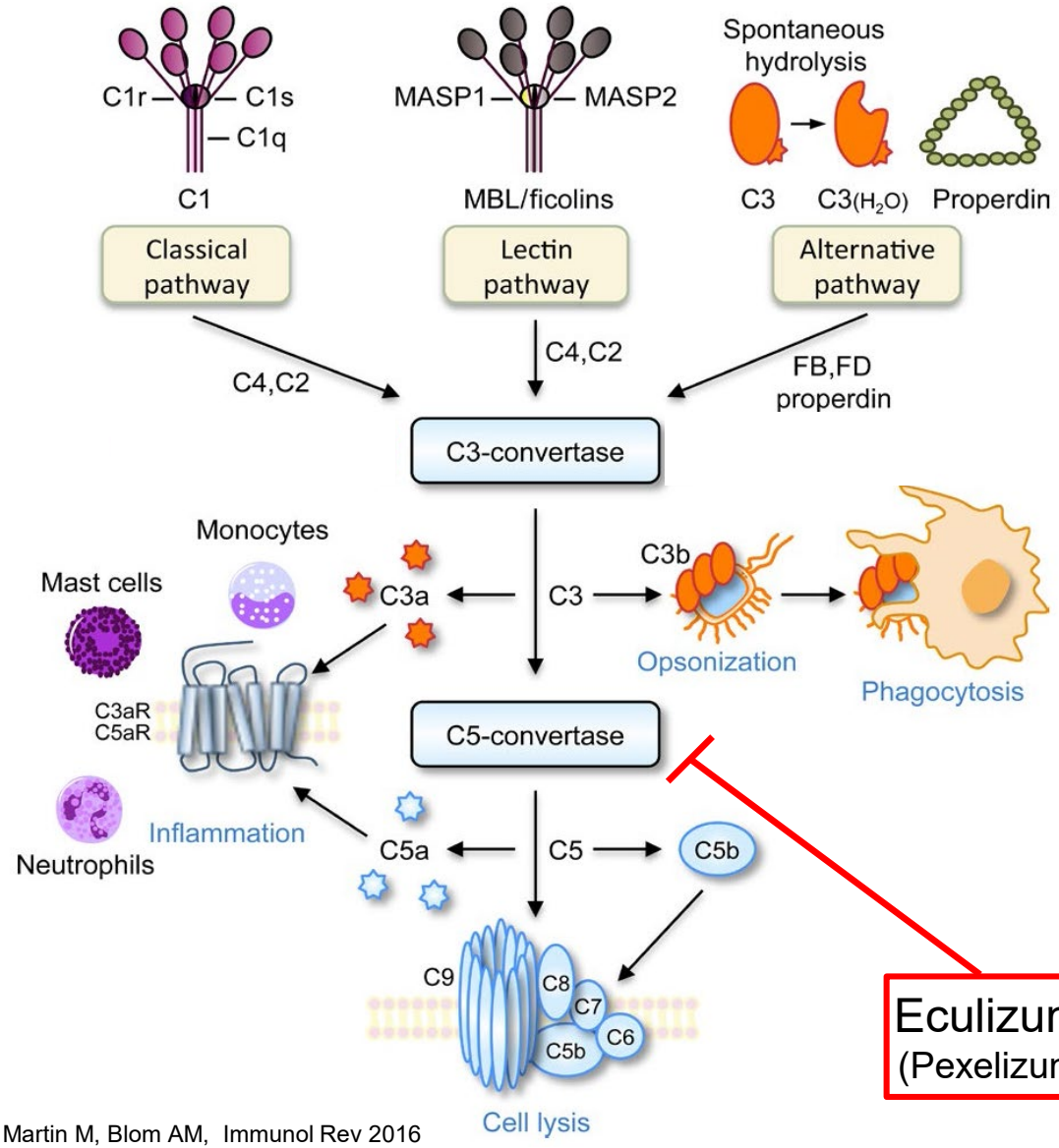


- Common terminal pathway: membrane attack complex





The complement system and cascade



Martin M, Blom AM, Immunol Rev 2016

Role of complement in many diseases

Dysregulation

PNH
aHUS and TTP
Transplant rejection
….

Autoimmune

Lupus nephritis
Guillain-Barré Syndrome
IgA nephropathy
- ….

Inflammatory

Macular degeneration
ANCA-associated vasculitis
Atherosclerosis
Sepsis
….

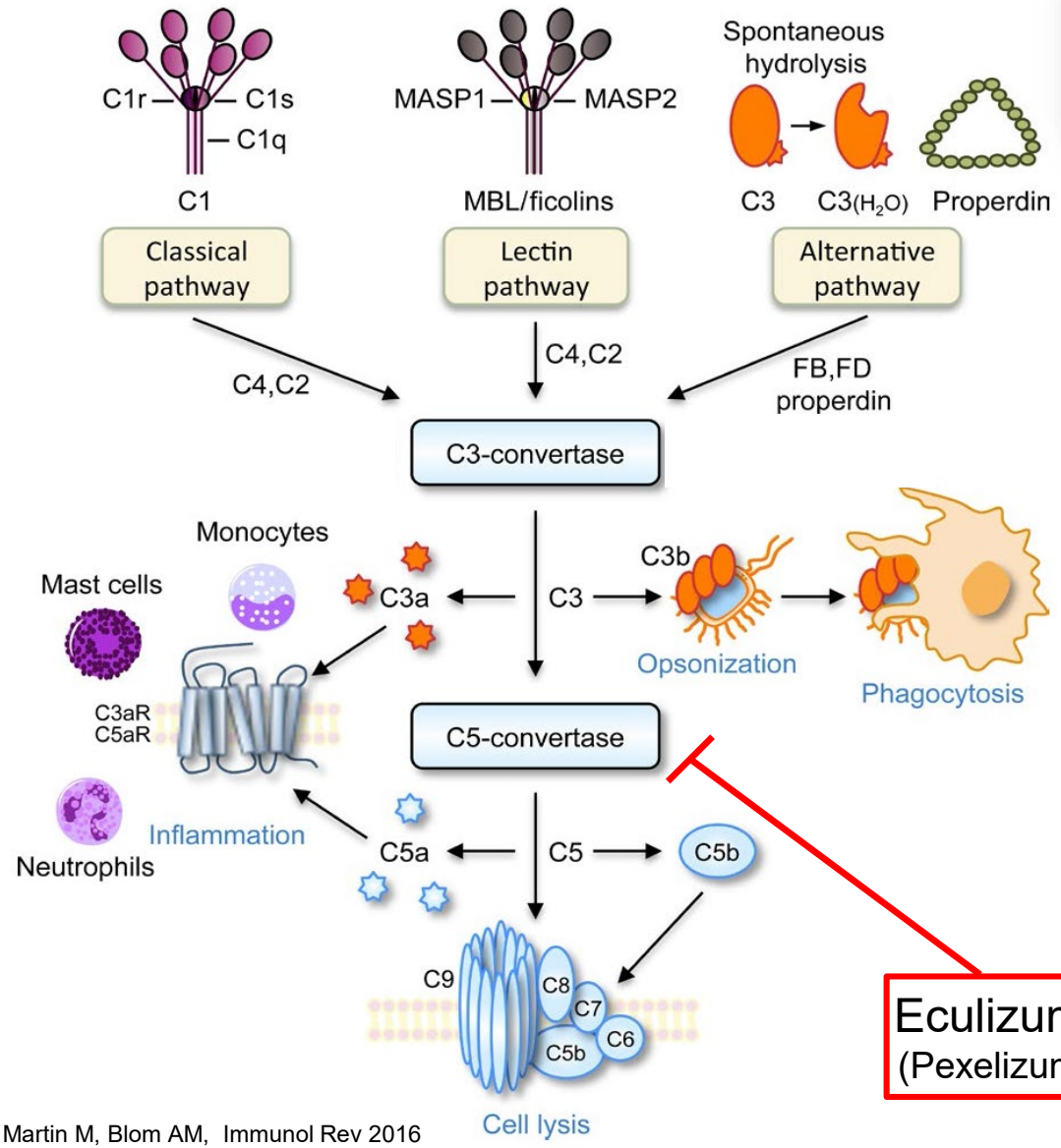
Ischemia-reperfusion

Myocardial infarction
Stroke
….

Acute injuries

Trauma
Hemodialysis
…..

The complement system and cascade



Martin M, Blom AM, Immunol Rev 2016

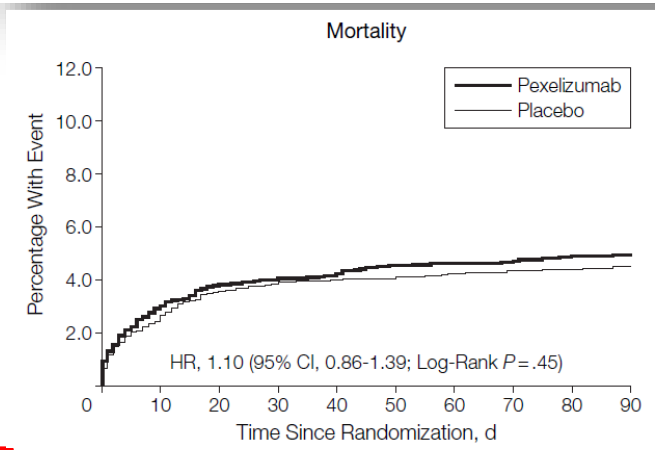
Alexion Provides Update On Phase 2 Clinical Trial With Eculizumab In Antibody Mediated Rejection (AMR) In Living-Donor Kidney Transplant Recipients

"…., we are disappointed that this trial did not meet its primary composite endpoint,"….

ORIGINAL CONTRIBUTION

Pexelizumab for Acute ST-Elevation Myocardial Infarction in Patients Undergoing Primary Percutaneous Coronary Intervention

A Randomized Controlled Trial



JAMA 2007

Eculizumab (Pexelizumab)

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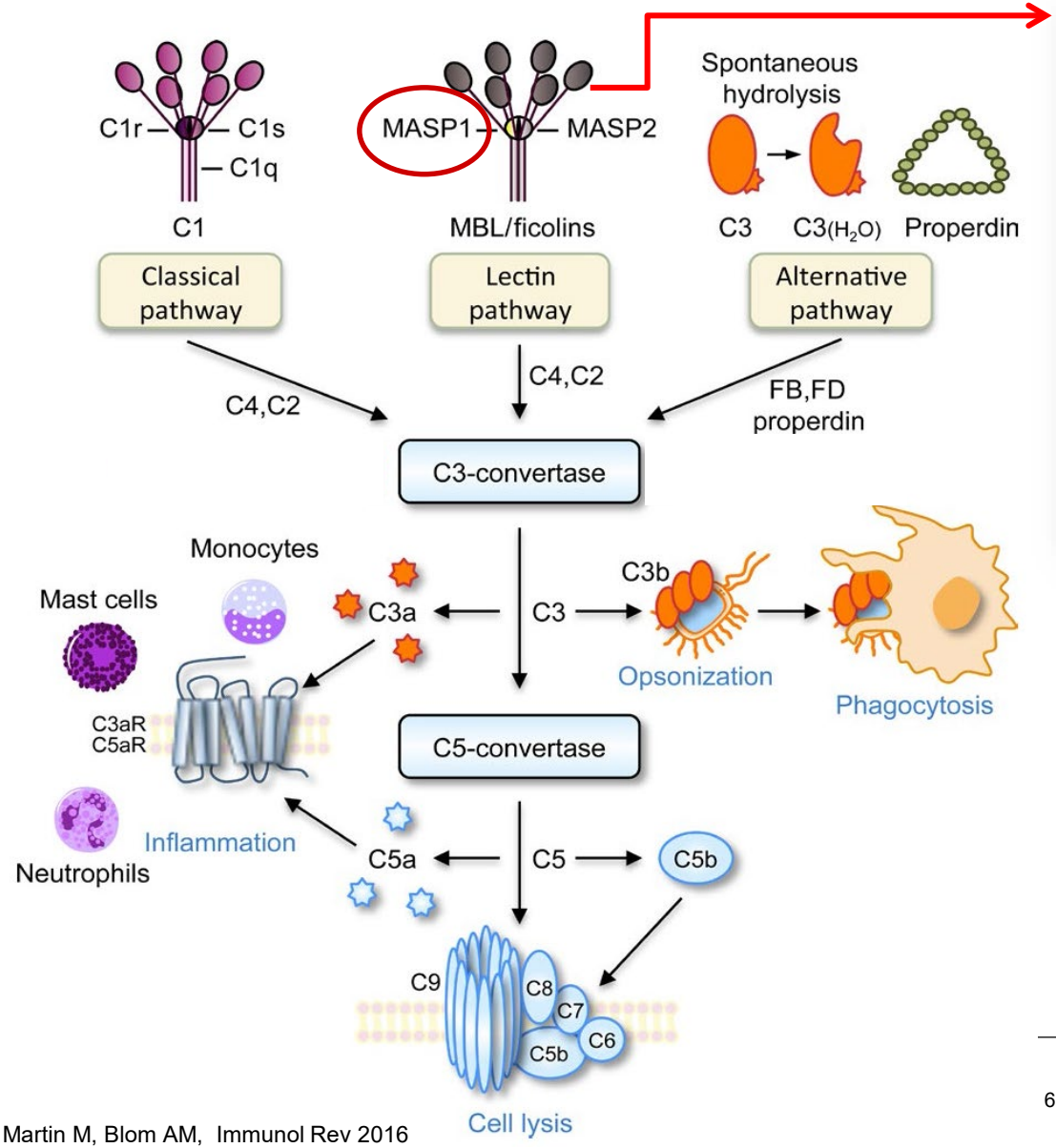
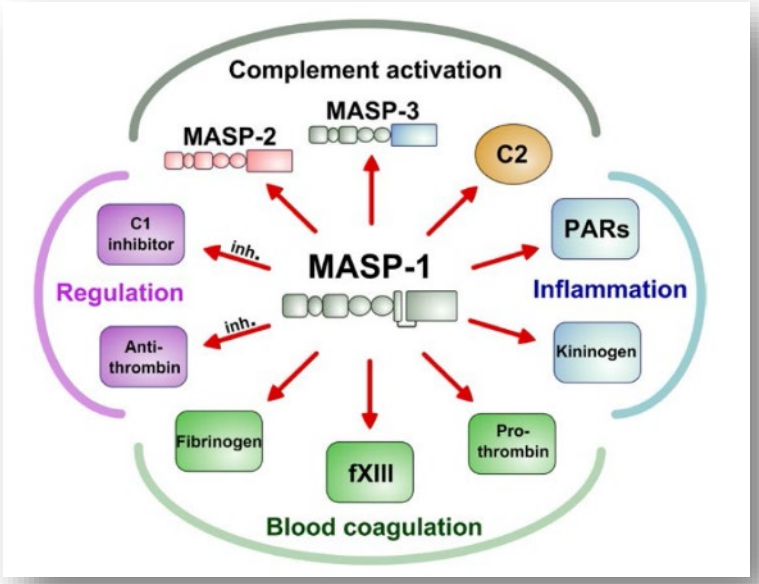
The complement system and cascade



Martin M, Blom AM, Immunol Rev 2016

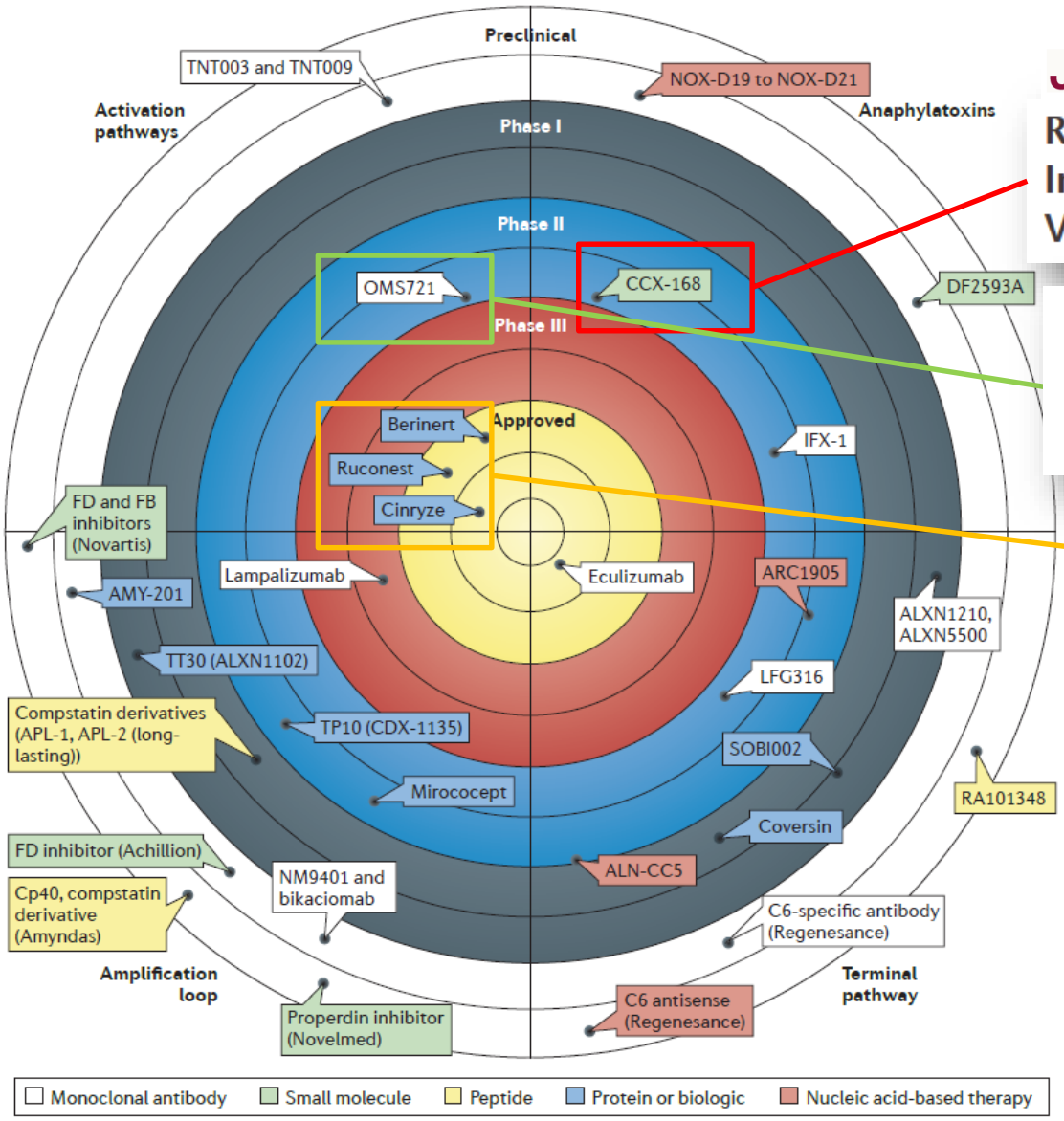


- Platelet activation
- Inflammation
- Vascular permeability
- Clot formation
- Complement activation

Dobo J et al., Immunol Rev 2016

Universitätsspital Basel

The complement system – a hot topic



JASN JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

Randomized Trial of C5a Receptor Inhibitor Avacopan in ANCA–Associated Vasculitis

FP201 **INTERIM RESULTS FROM AN ONGOING PHASE 2 STUDY EVALUATING THE USE OF A MASP-2 INHIBITOR FOR THE TREATMENT OF IGA NEPHROPATHY (IGAN)**

Jonathan Barratt[1], Eckhard Leifke[2], Steve Whitaker[2], Louis DeTulleo[2], Richard Lafayette[3]

ERA-EDTA 2019

C1 esterase inhibitor (C1INH)

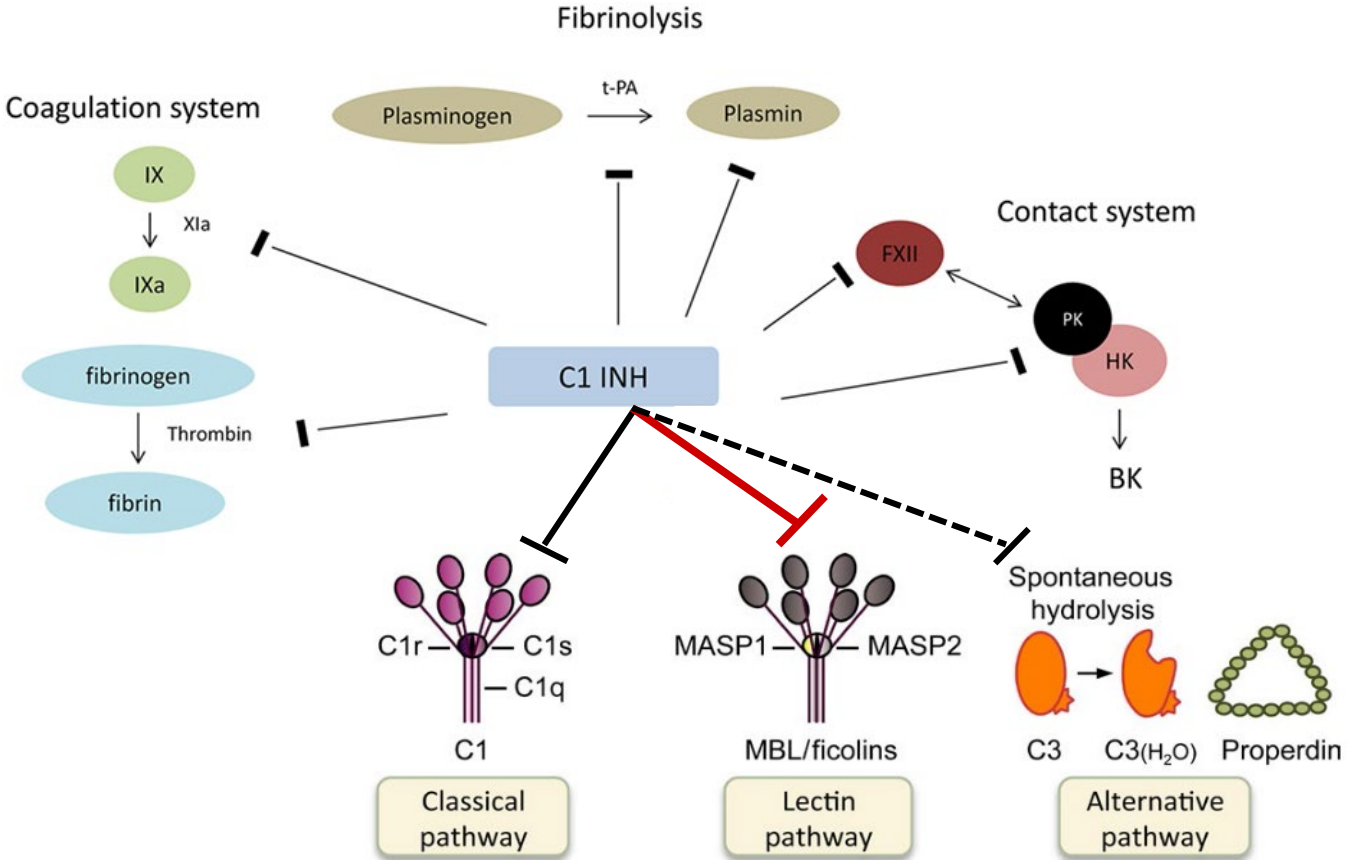
- Licensed for replacement therapy in patients with C1INH deficiency (hereditary angioedema)

Universitätsspital Basel

Morgan BP, Harris CL, Nat Rev Drug Discovery 2015

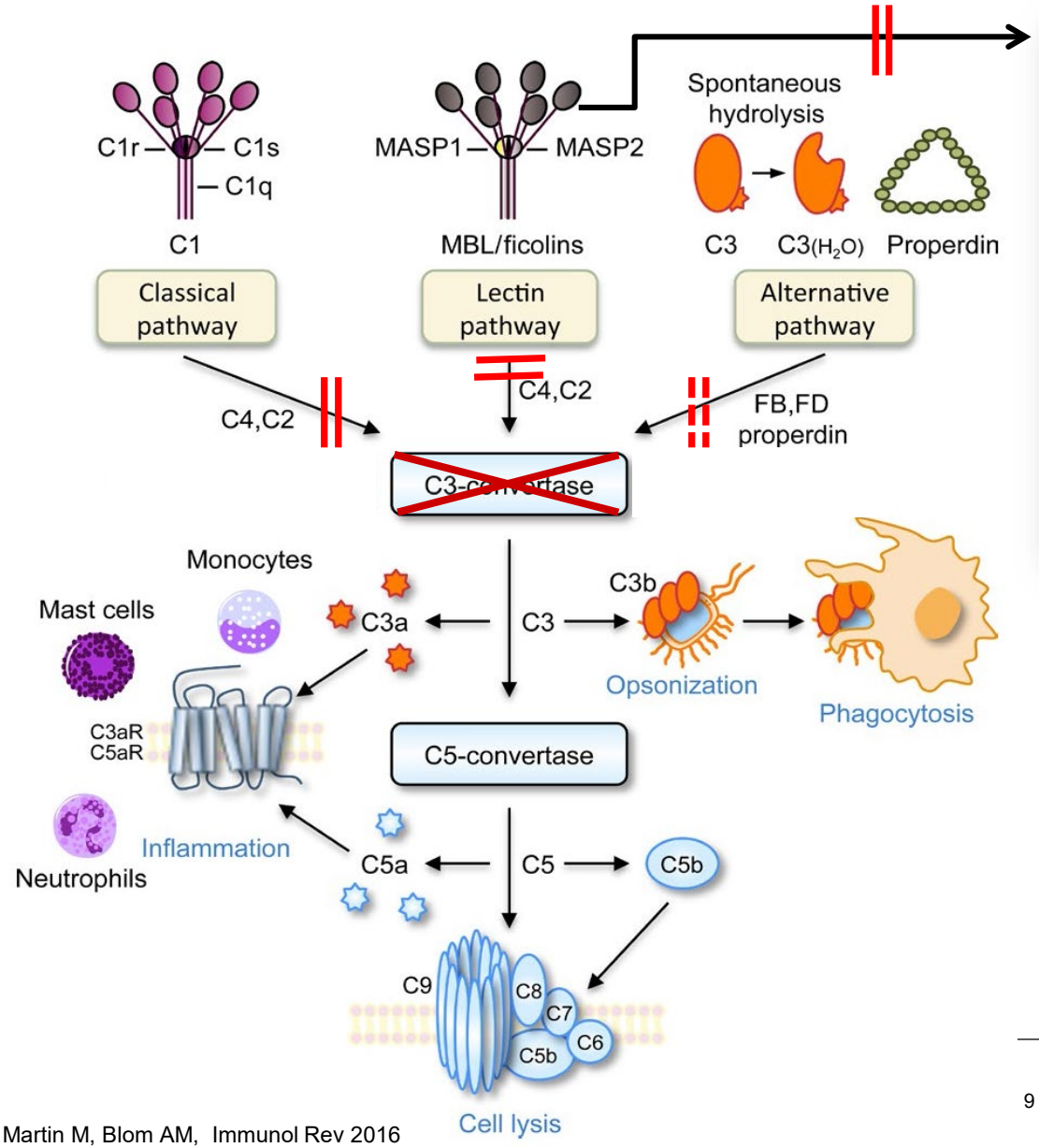
C1 esterase inhibitor (C1INH)

- Human plasma protein – ***multiple-action-multiple-target inhibitor***
  (complement, coagulation and contact (kinin) system, fibrinolysis)

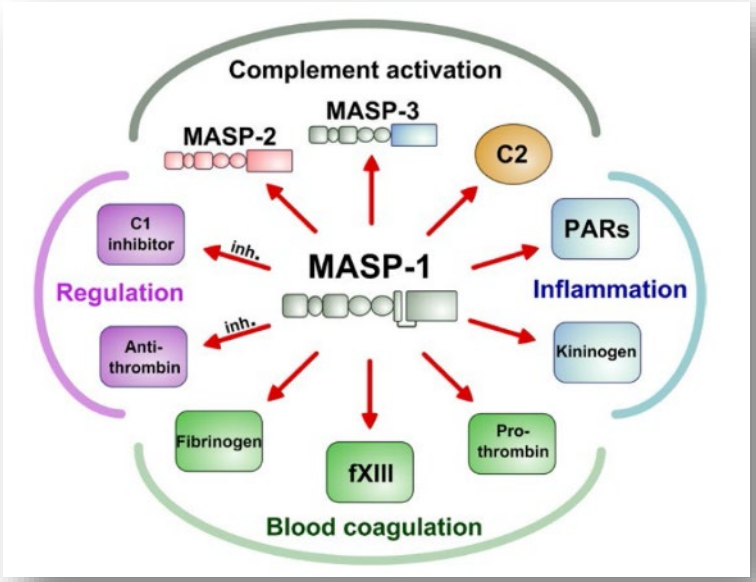


Panagiotou A, Frontiers Immunol 2018

C1INH is a potent MASP-1/-2 inhibitor



Martin M, Blom AM, Immunol Rev 2016

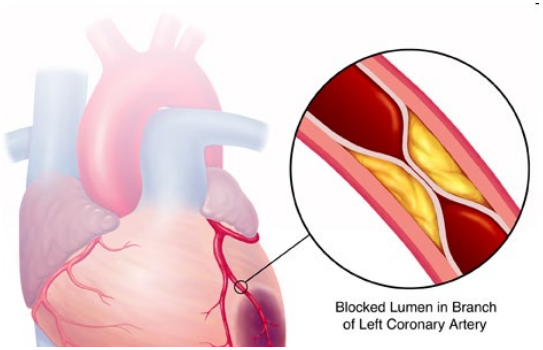


- ~~Platelet activation~~
- ~~Inflammation~~
- ~~Vascular permeability~~
- ~~Clot formation~~
- ~~Complement activation~~

Dobo J et al., Immunol Rev 2016

Universitätsspital Basel

Ischemia/reperfusion injury (IRI)

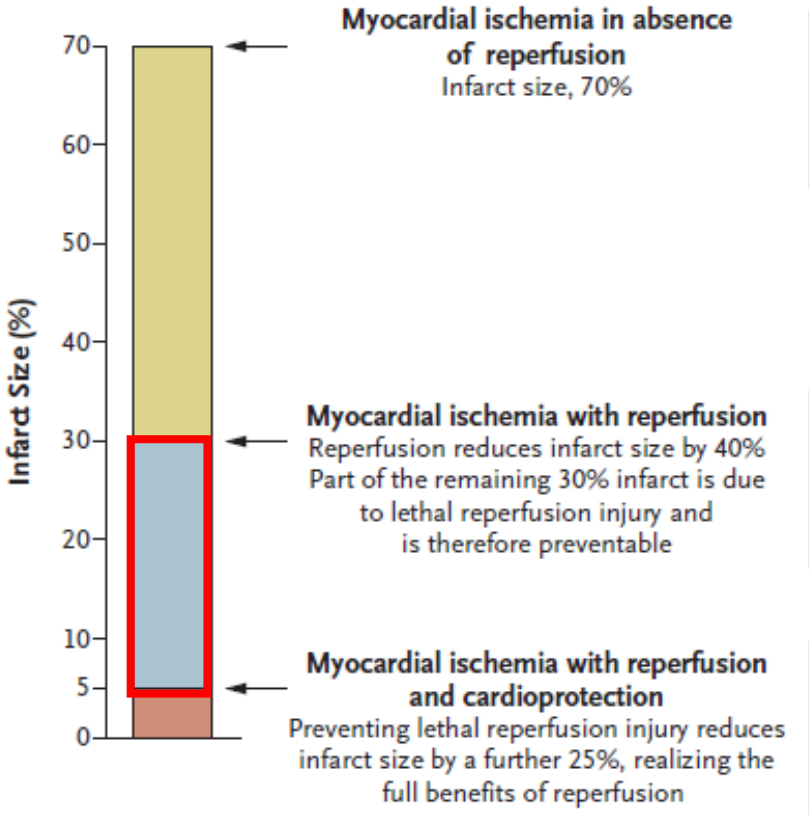


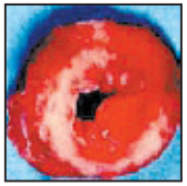
Ischemia

O_2 ↓

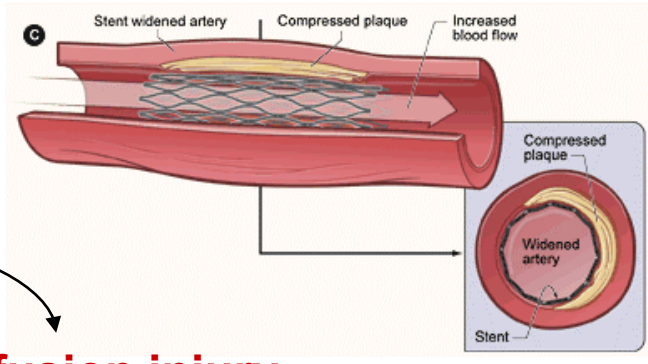
Hypoxic injury

www.msdmanuals.com





Reperfusion: spontaneous, angioplasty, thrombolysis



Reperfusion injury

Tissue damage

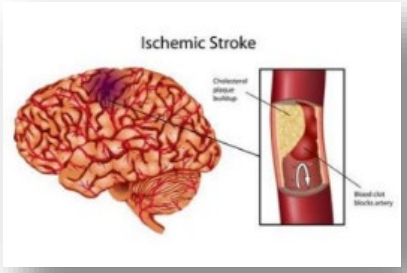
Yellon DM, NEJM. 2007

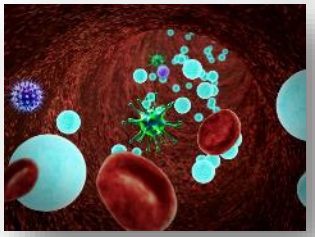
Universitätsspital Basel

Examples of IRI

IRI injury is a feature of many diseases

- Thromboembolic diseases (stroke, myocardial infarction)
- Major (cardiac) surgery
- Sepsis (DIC)
- Autoimmune diseases
- Transplantation
- Trauma / major bleeding
- …….





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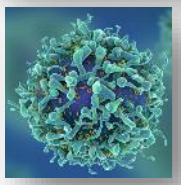
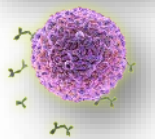
Mechanisms of IRI

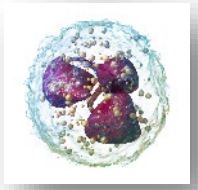
Macrophages



T cells



B-cells



Neutrophiles

Inflammation

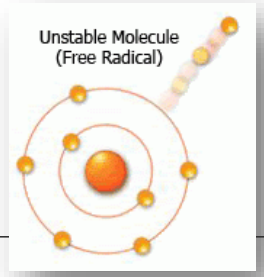
Coagulation system

Complement system

Cytokines

Endothelial cells

Free oxygen radicals

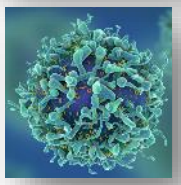


Kinin system

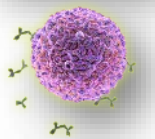
Tissue damage
Cell death

Mechanisms of IRI

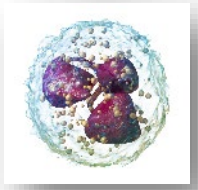
Macrophages



T cells



B-cells



Neutrophiles

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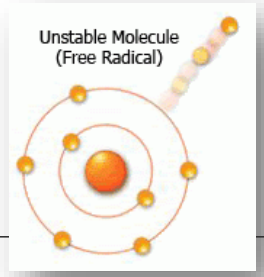
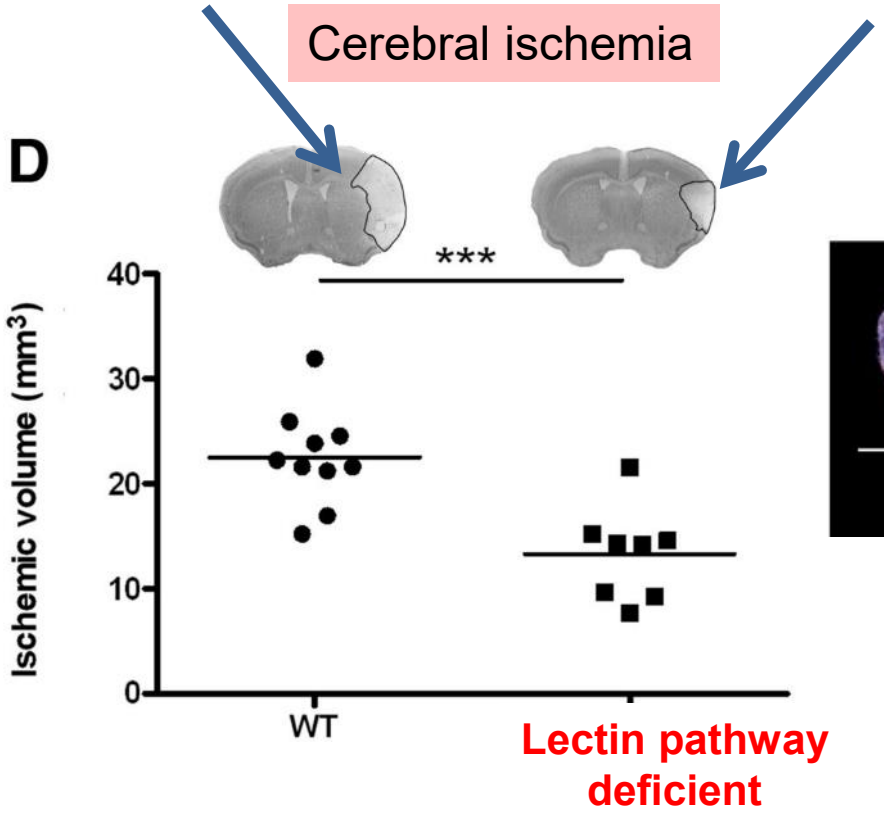
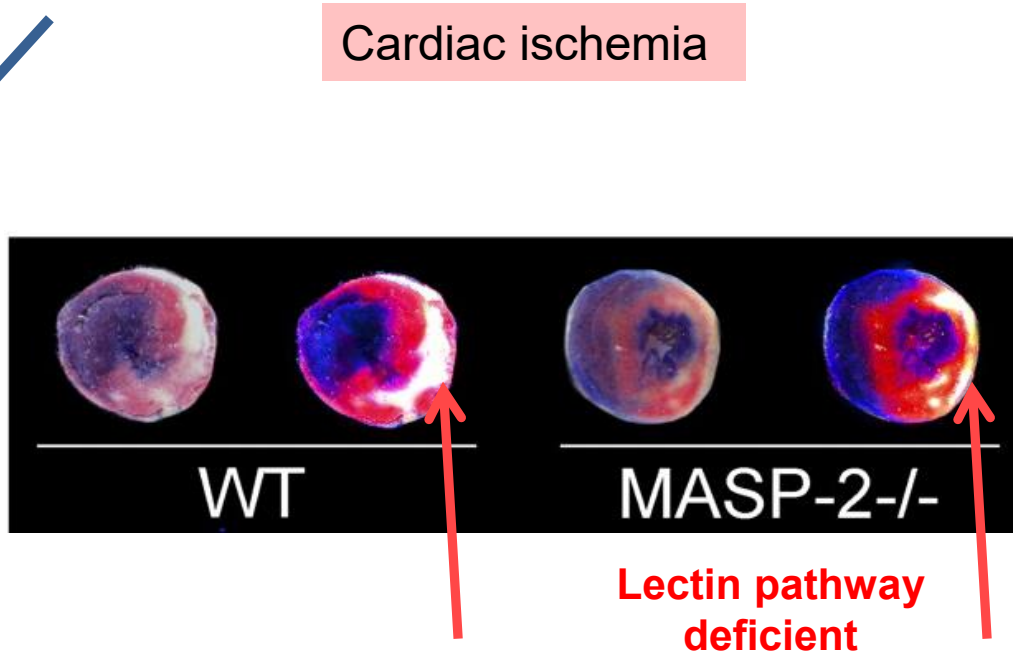


Kinin system

Tissue damage
Cell death

IRI and the lectin pathway of complement





Lectin pathway deficiency **attenuates** IRI in animal models (cardiac, cerebral, renal, muscle, gut ischemia)

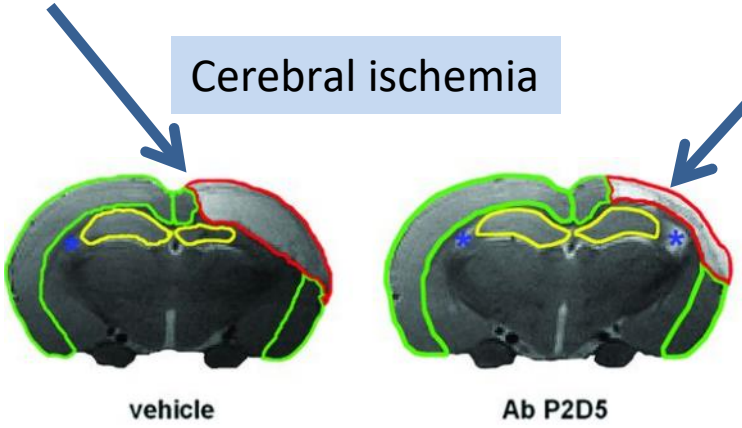
Gesuete R et al., Ann Neurol. 2009

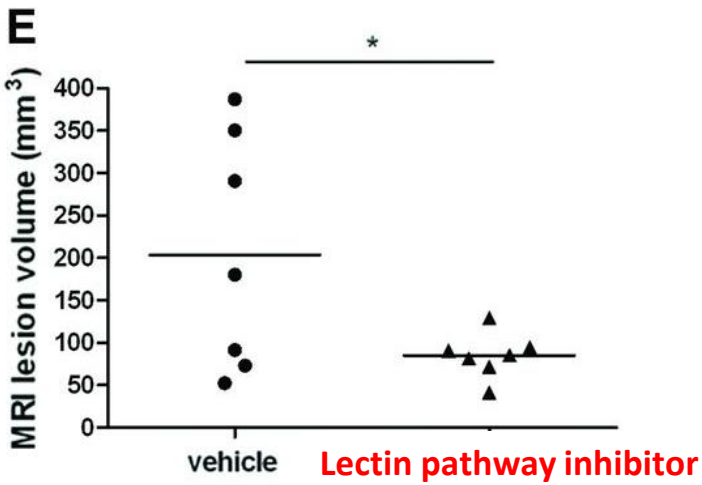
Schwaeble WJ et al., PNAS. 2011

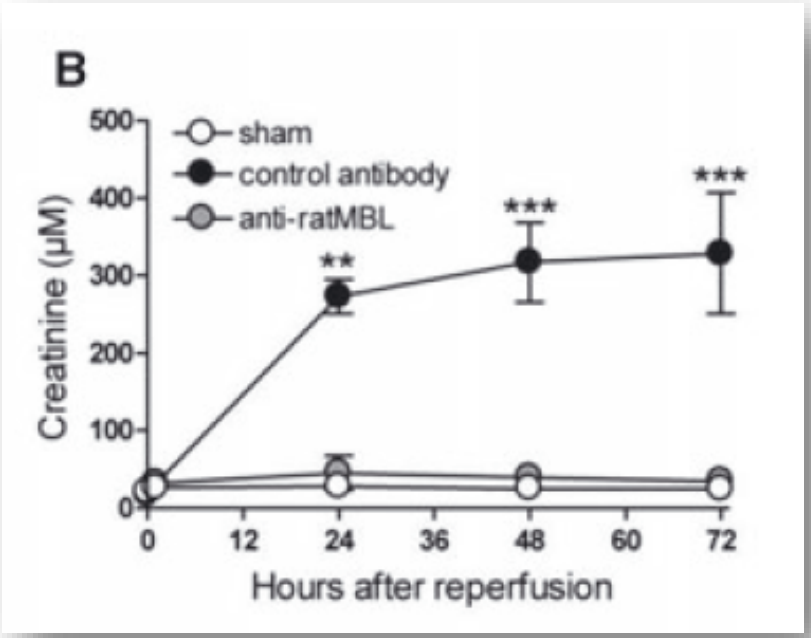
IRI and lectin pathway inhibition

Cerebral ischemia

Renal ischemia







Van der Pol et al., Am J Transplant 2012
Orsini F, Circulation 2012

Inhibition of the lectin pathway **limits** ischemic damage in animal models (cerebral, renal, intestinal ischemia)

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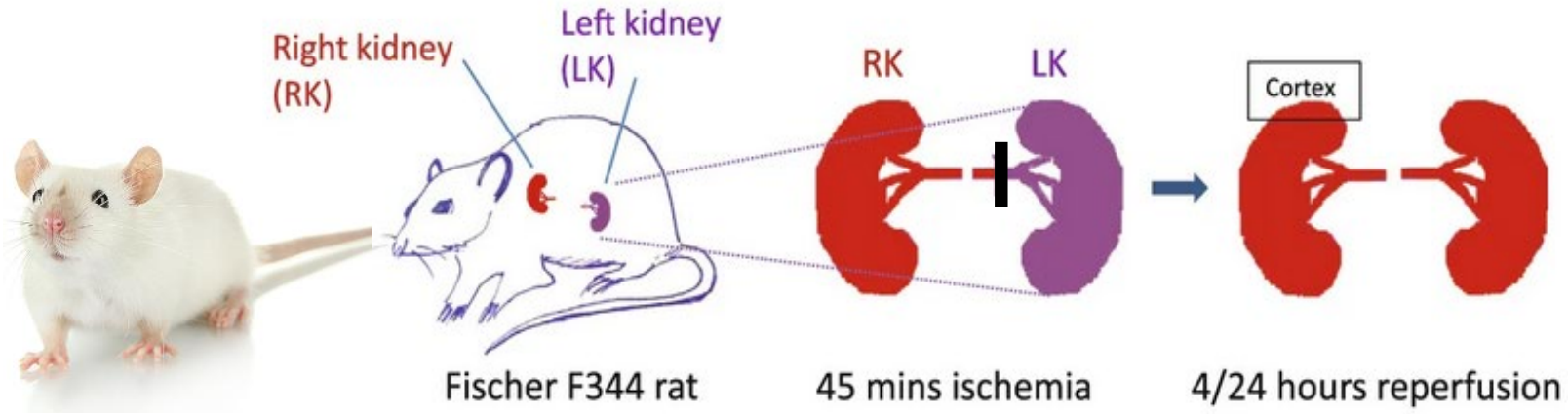
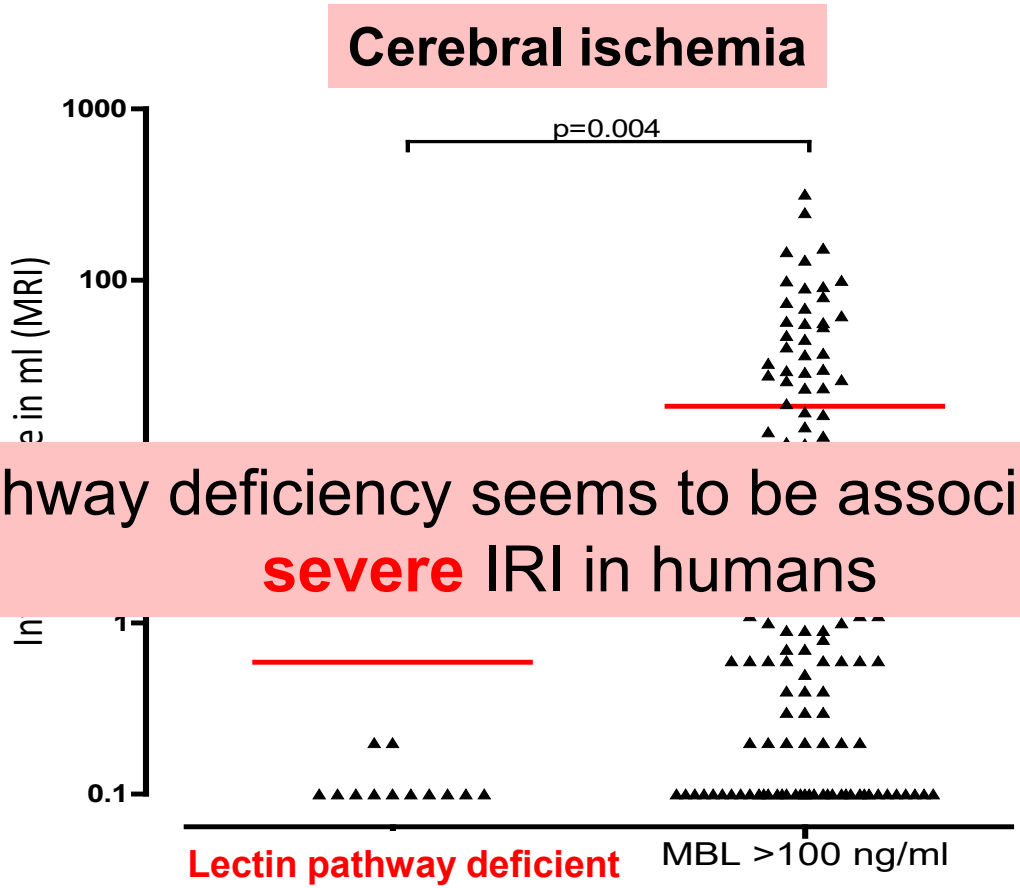
Of mice and humans….

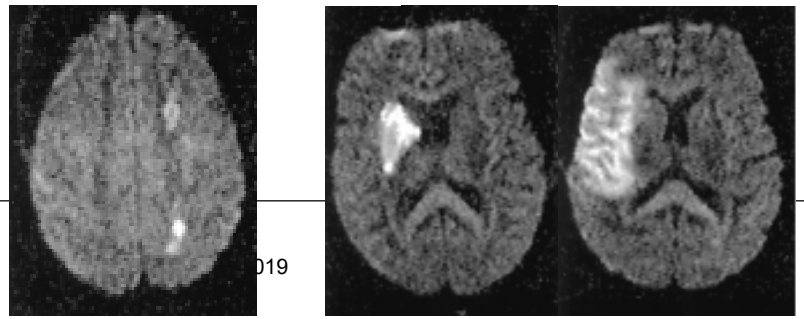


Huang H, Scientific Reports 2018

IRI and the lectin pathway in humans



Lectin pathway deficiency seems to be associated with **less severe** IRI in humans

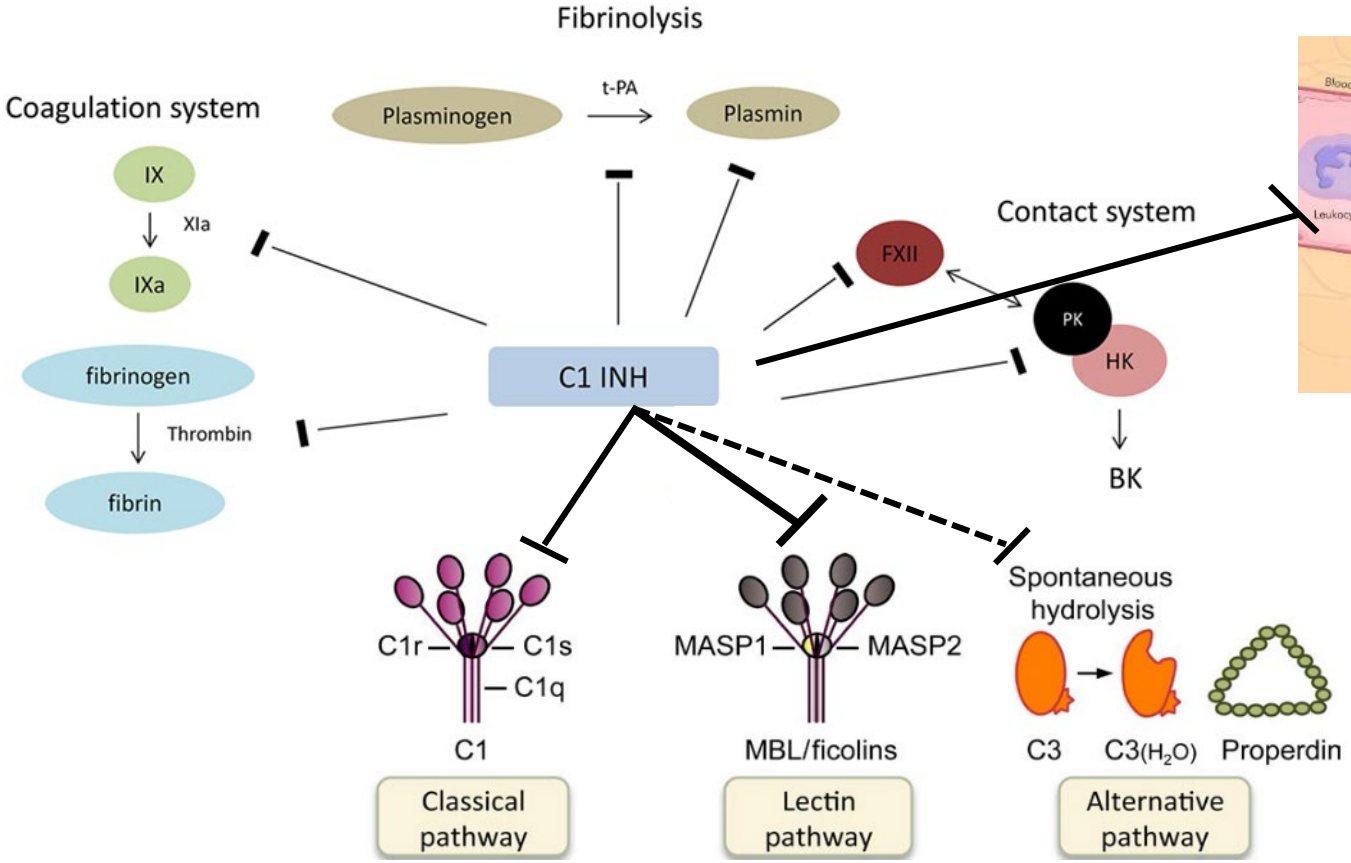


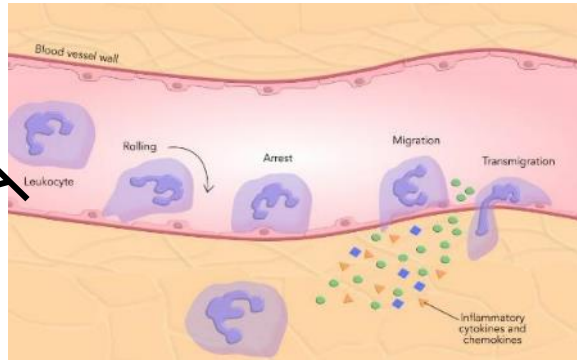
Osthoff M et al., PLoS One. 2011

IRI is a complex phenomenon

C1 esterase inhibitor (C1INH)

- Human plasma protein – ***multiple-action-multiple-target inhibitor***
  (complement, coagulation and contact (kinin) system, fibrinolysis)

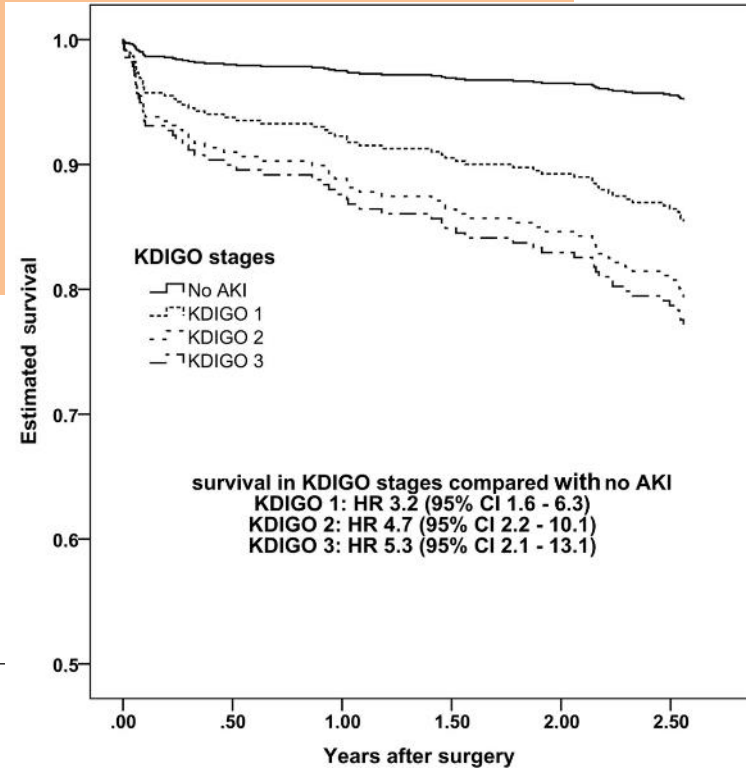




Panagiotou A, Frontiers Immunol 2018

Future applications of rhC1INH in IRI
Renal ischemia

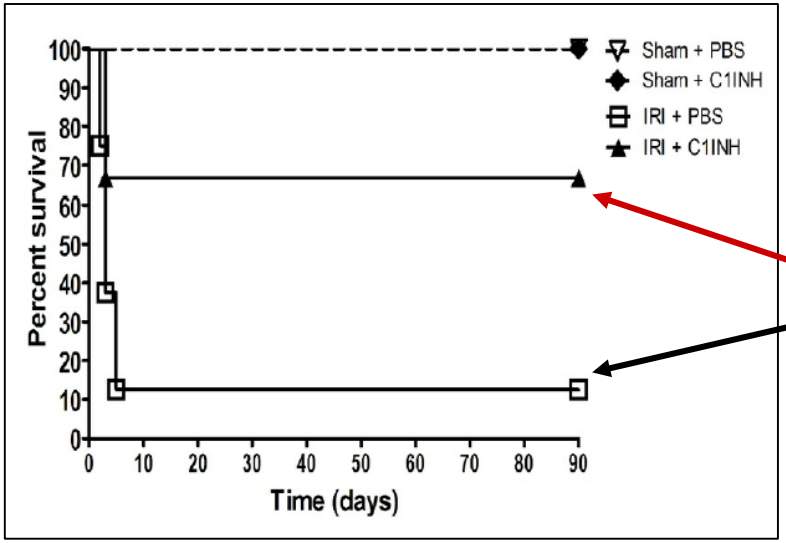
- **A reduction in renal perfusion is the consequence of many diseases**
  - Infections
  - Heart failure
  - Kidney transplantation
  - Trauma
  - Major surgeries
  - ….
- **Associated with a worse prognosis**
- **Very little interventions available**



Petäjä L, J Cardiothorac Vasc Anesth 2017

rhC1INH as potential treatment for renal IRI

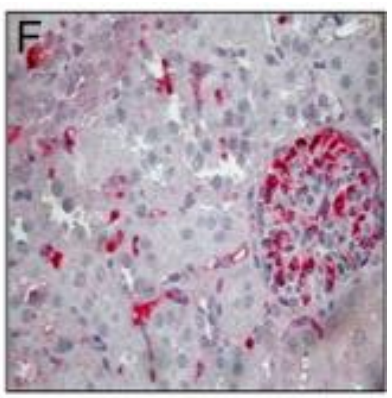
Survival



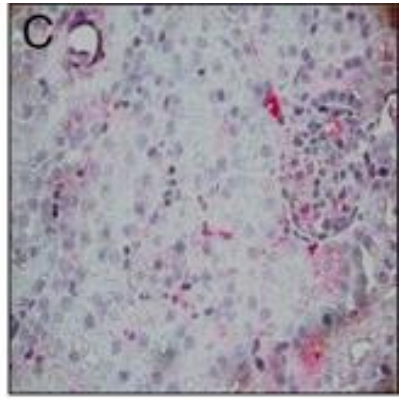
rhC1INH

placebo

Complement deposition in the kidneys



placebo

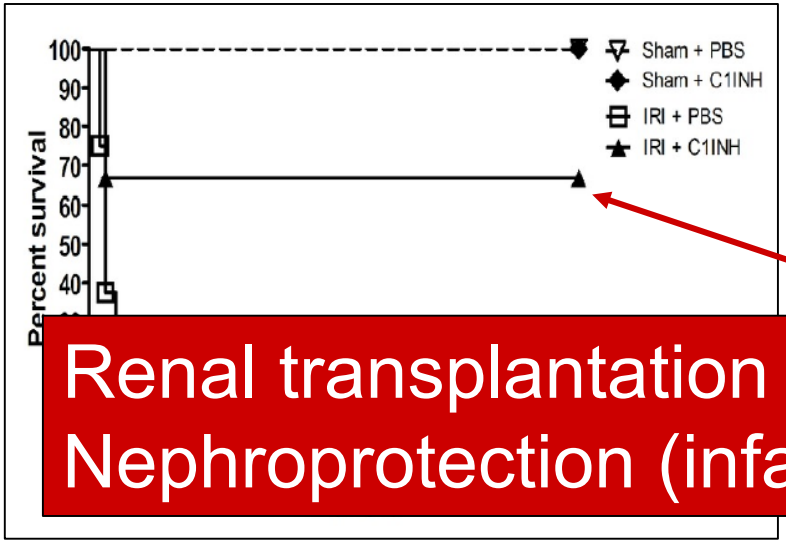


rhC1-INH

Castellano G, Am J Patholog 2010; Danobeitia JS et al., PLOS one 2017

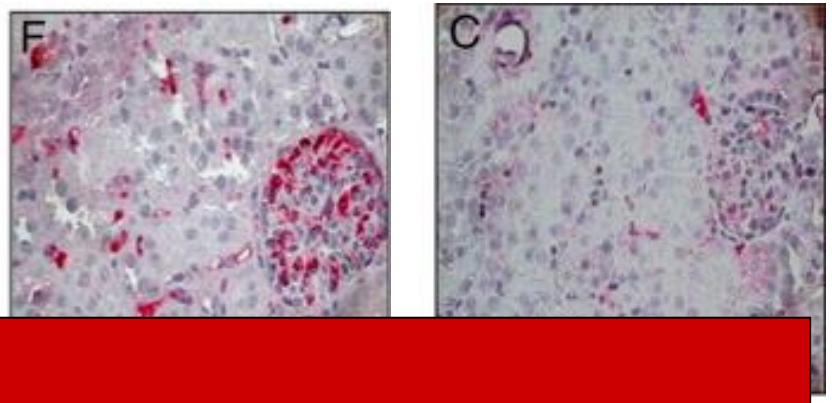
rhC1INH as potential treatment for renal IRI

Survival



rhC1INH

Glomerular complement deposition

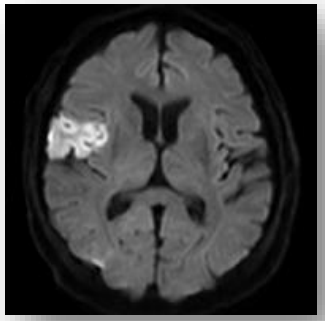


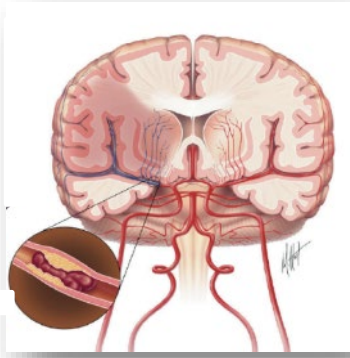
Renal transplantation
Nephroprotection (infarct, sepsis, surgery, trauma…)

Castellano G, Am J Patholog 2010; Danobeitia JS et al., PLOS one 2017

Future applications of rhC1INH in IRI

Ischemic stroke





- Third leading cause of death
- Leading cause of disability in adults

Treatment

- Intravenous fibrinolysis (clot lysis)
- Conservative management (70-80%!)

Good outcome up to 4.5 hours after onset of symptoms

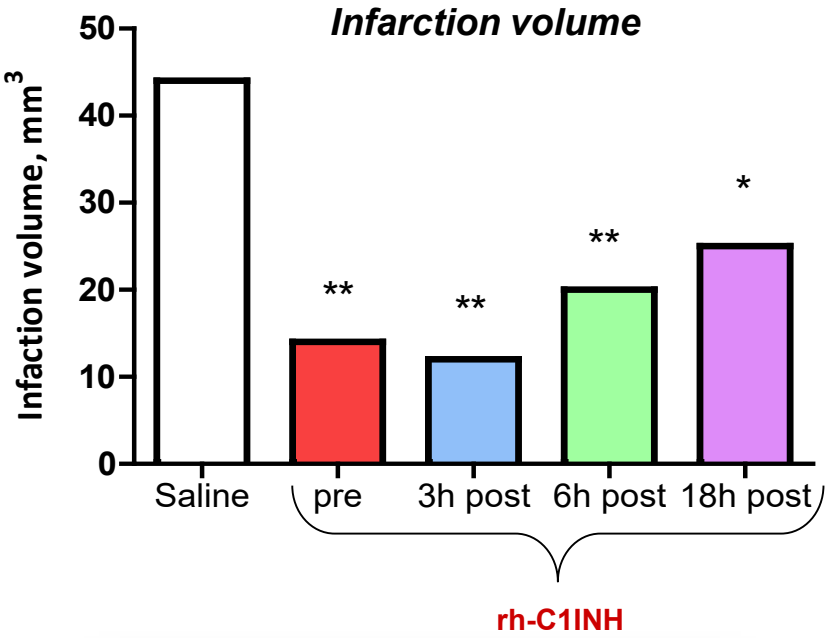
Future treatment

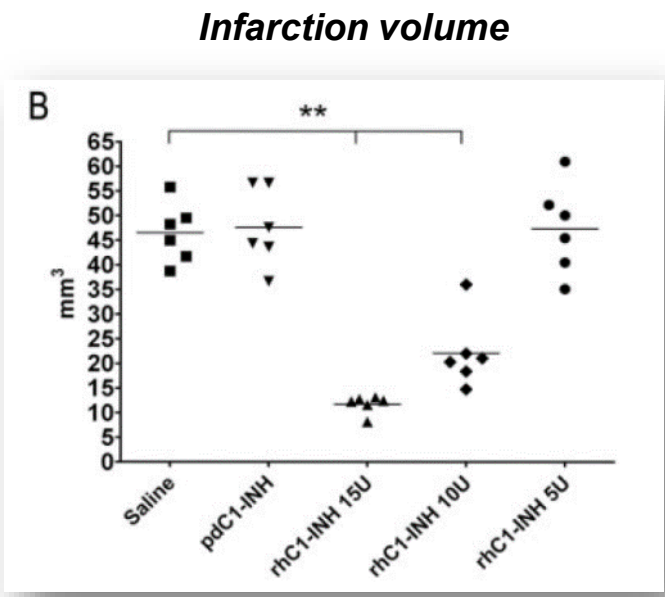
- Intravenous fibrinolysis +/- endovascular thrombectomy
- Only endovascular thrombectomy

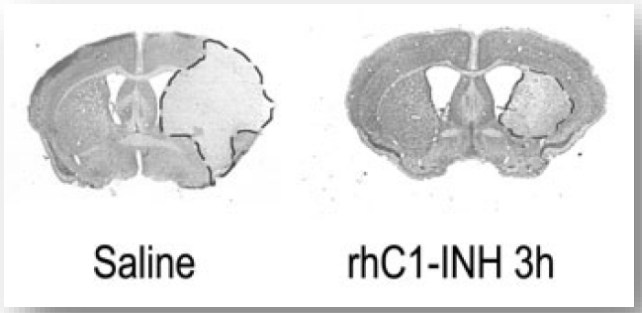
Good outcome up to 6 (-24h) hours after onset of symptoms

Emberson J et al., Lancet 2014

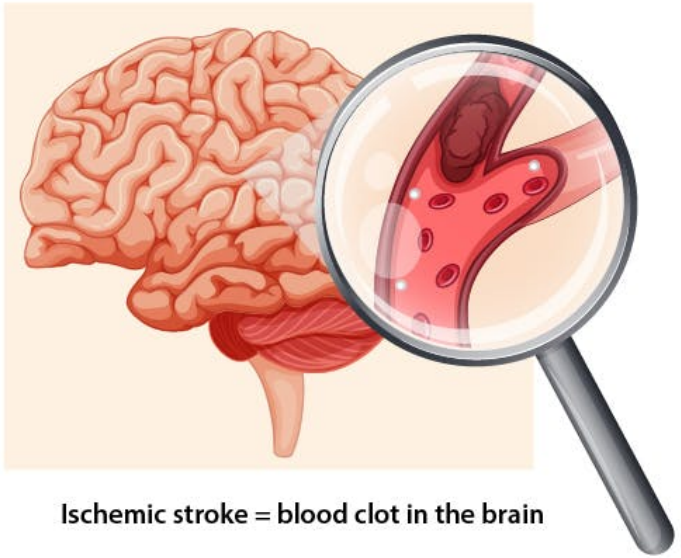
rhC1INH as potential treatment for cerebral IRI







Gesuete R et al., Ann Neurol. 2009



Is rhC1INH superior to plasma-derived products?

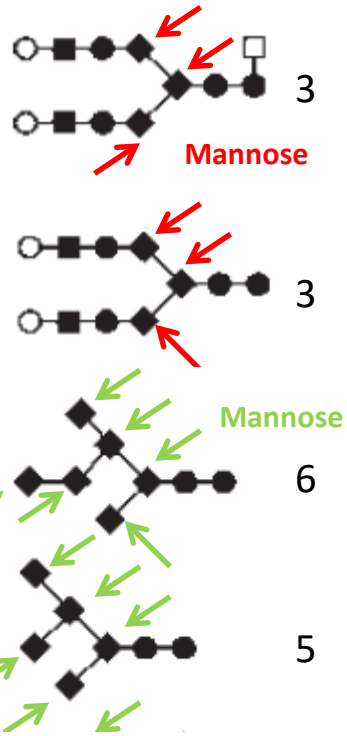
Same, same but different

Human plasma derived C1INH

Conestat alfa (rhC1INH)

N-glycans

99%



3%

5%

4%

9%

1%

oligomannose-type glycans
<1%

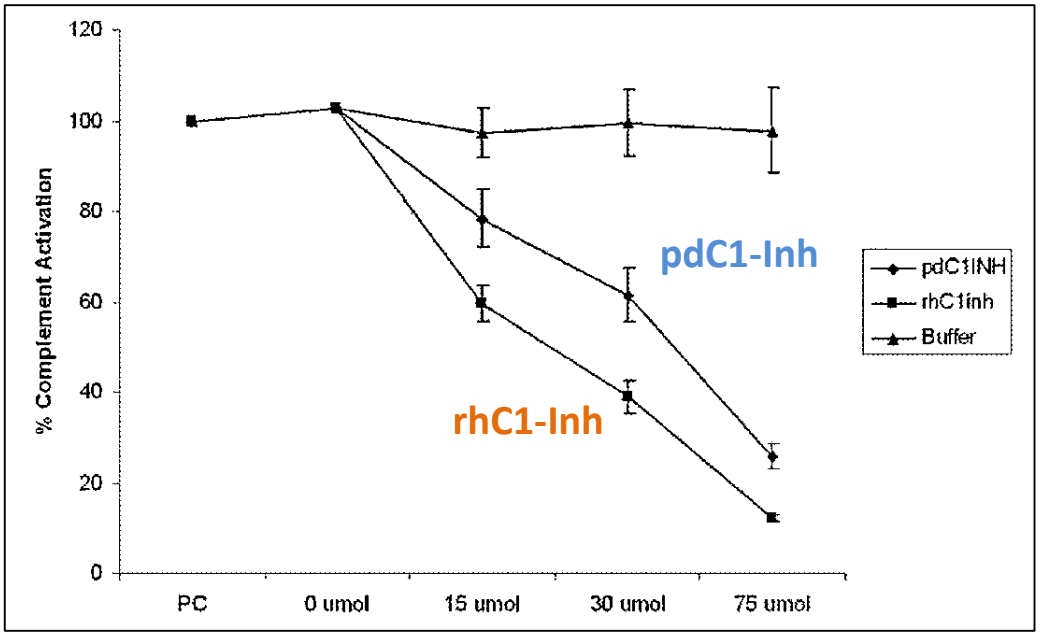
oligomannose-type glycans
15%

Half-life
30h

Half-life
3h

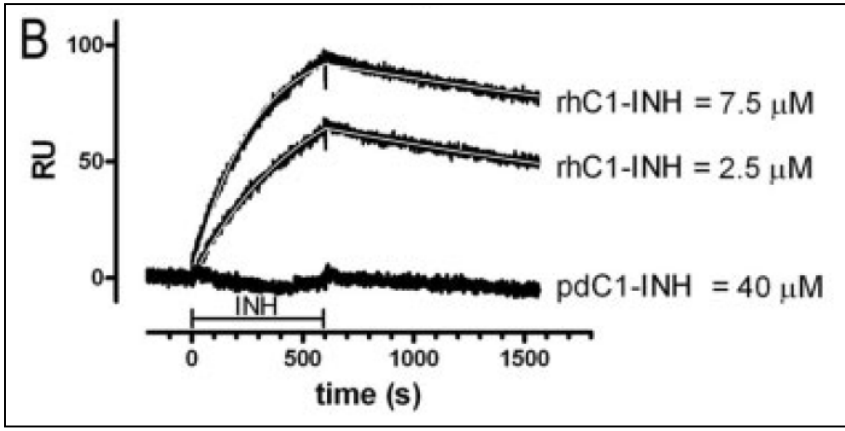
	k_{on} ($M^{-1}.s^{-1}$)			
	C1s	**Factor XIa**	**Factor XIIa**	**Kallikrein**
rhC1INH[a]	$6.1 \pm 0.3 \times 10^4$	$9.8 \pm 0.5 \times 10^2$	$6.9 \pm 0.5 \times 10^3$	$9.1 \pm 0.1 \times 10^3$
H-C1INH[a]	$5.1 \pm 0.3 \times 10^4$	$9.0 \pm 0.2 \times 10^2$	$5.7 \pm 0.4 \times 10^3$	$7.6 \pm 0.3 \times 10^3$

Lectin pathway inhibition



Lectin pathway inhibiton

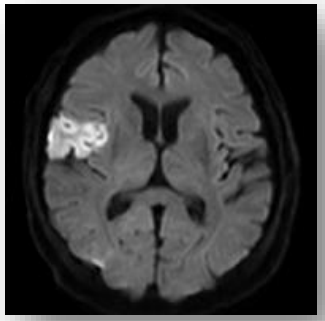
Binding to lectin pathway proteins



Gesuete R et al., Ann Neurol. 2009
US patent information 2006

Future applications of rhC1INH in IRI

Ischemic stroke



- Third leading cause of death
- Leading cause of disability in adults

Treatment

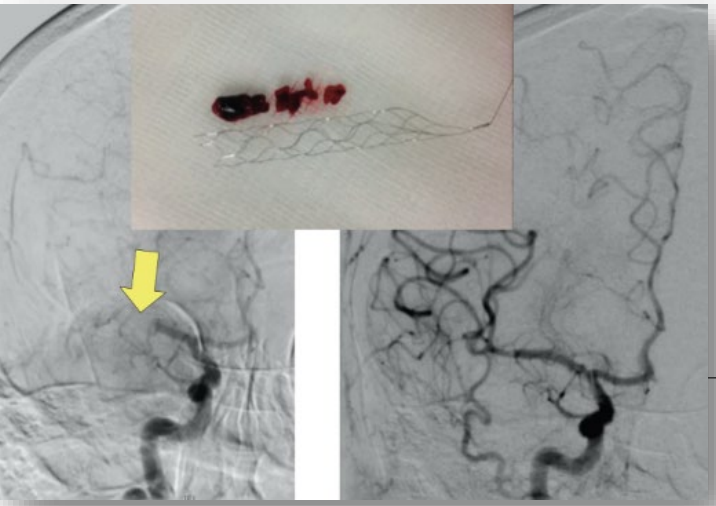
- Intravenous fibrinolysis
- Conservative management (70-80%!)

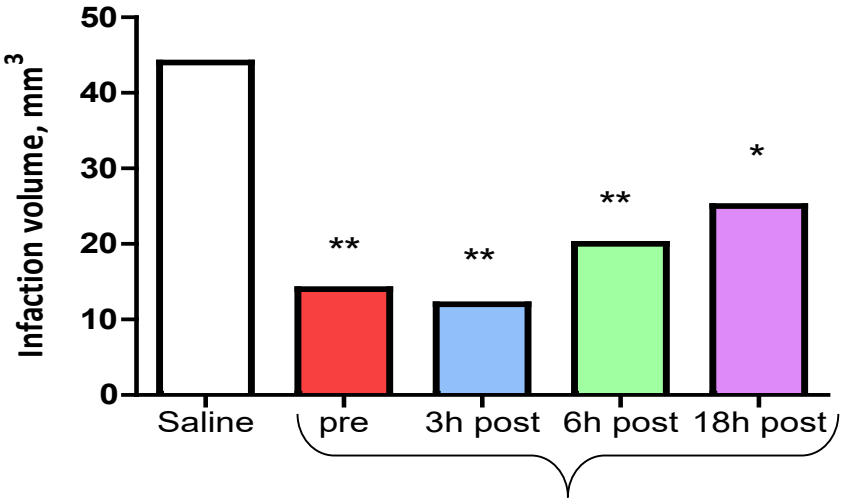
Good outcome up to 4.5 hours after onset of symptoms

Future treatment

- Intravenous fibrinolysis +/- endovascular thrombectomy
- Only endovascular thrombectomy

Good outcome up to 6 (-24h) hours after onset of symptoms





Emberson J et al., Lancet 2014

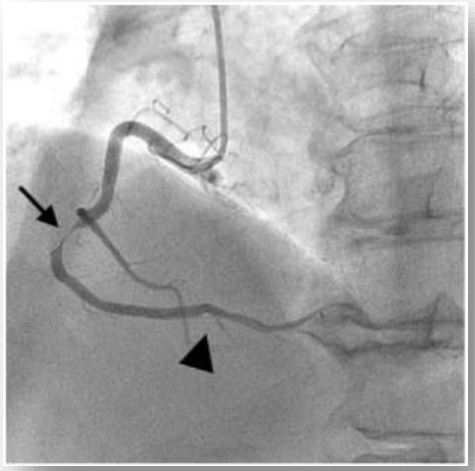
Gesuete R et al., Ann Neurol. 2009

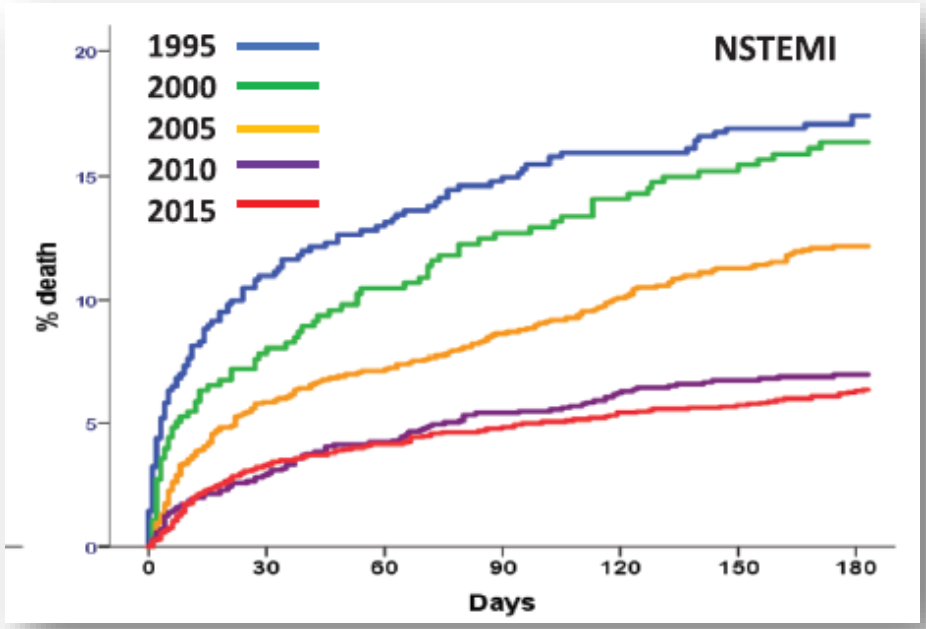
Future applications of rhC1INH in IRI
Myocardial infarction

- Major cause of death worldwide
- Effect of current treatment has reached a plateau.

Treatment

- Coronary angiography
- «Blood thinner»

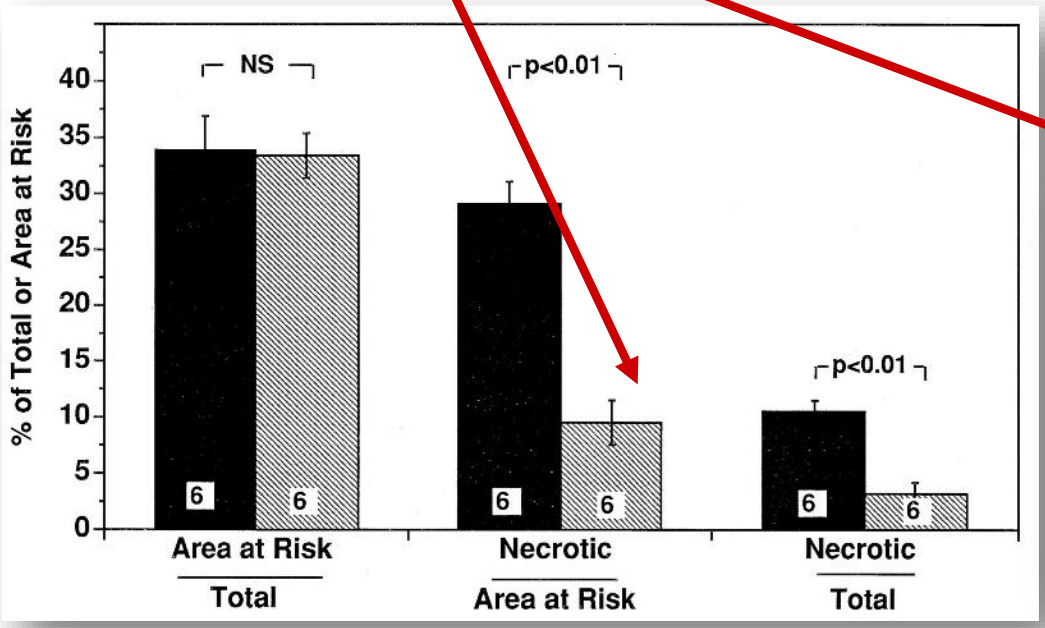


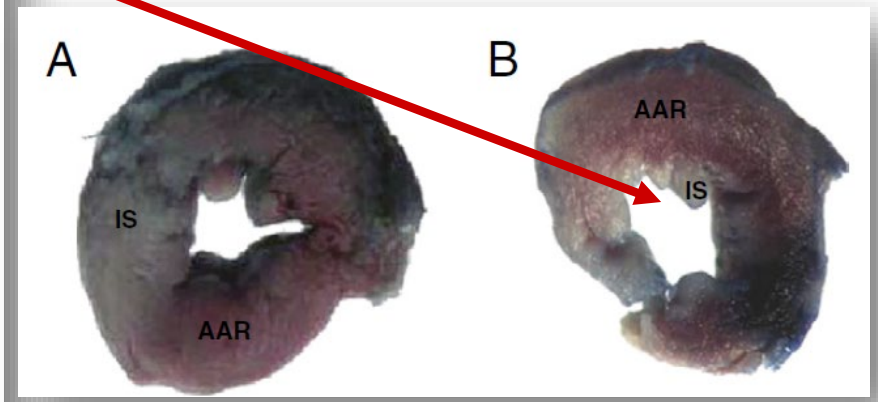


Puymirat E, Circulation 2017

Future applications of rhC1INH in cardiac IRI

C1INH

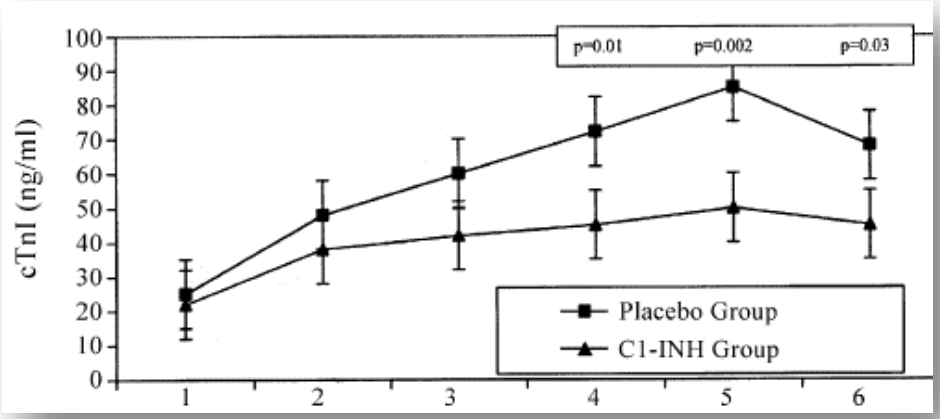


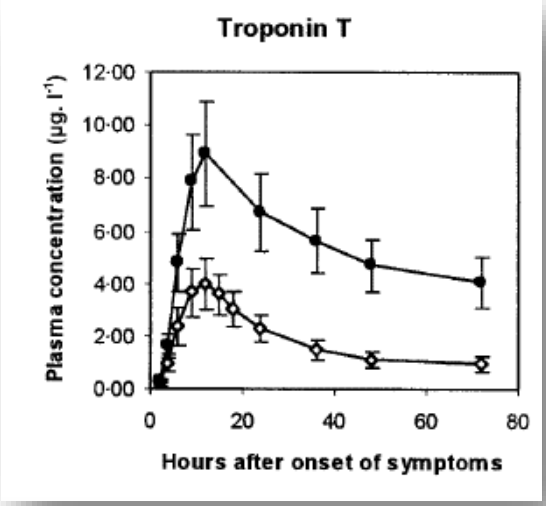


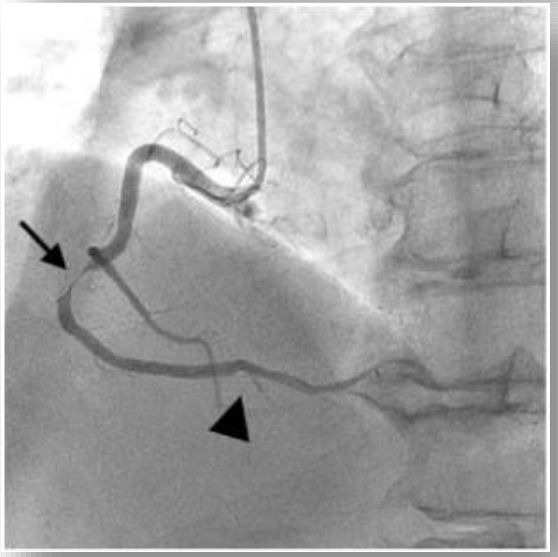
Buerke M, Circulation 1995

Future applications of rhC1INH in IRI

Myocardial infarction







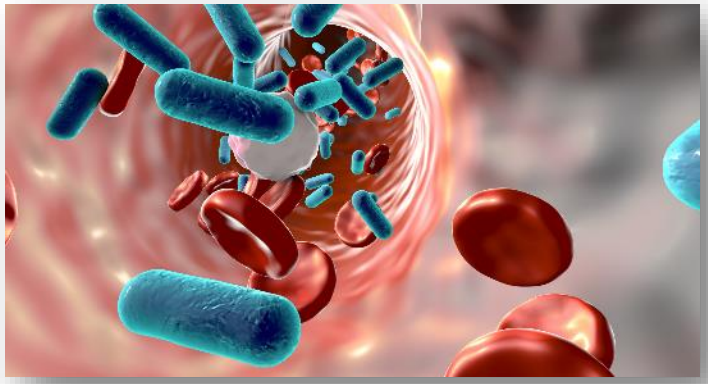
Fattouch K et al., Eur J Cardiothorac Surg 2007
Thielmann M et al., Eur J Cariothorac Surg 2006
De Zwaan C et al., Eur Heart J 2002

Various other potential future applications

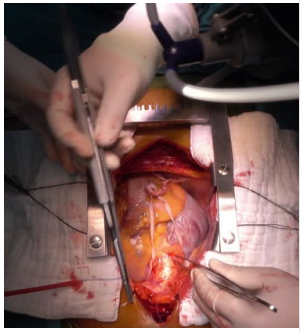
Traumatic brain injury

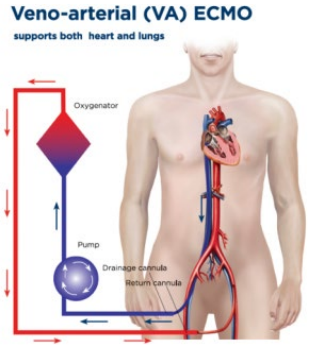
Transplantation

Sepsis Severe infections

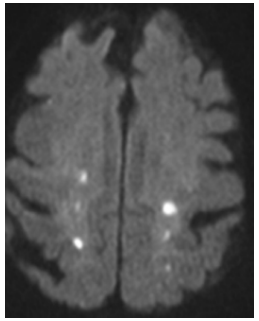


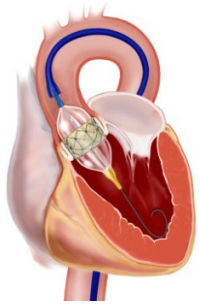
Cardiac surgery





Transcatheter aortic valve replacement





Conclusion

Ischemia/reperfusion injury is common!

Pharmacological interventions have not yet been successful

rhC1INH is a promising compound for the treatment of IRI

- Multiple-target, multiple-action inhibitor of important IRI pepetrators
- Successful intervention in animal models of IRI
- Safety is excellent
- ?superior to pdC1INH

Future trials in patients with myocardial infarction or stroke warranted

Thank you very much for your attention

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