APAAACI, HAE symposium

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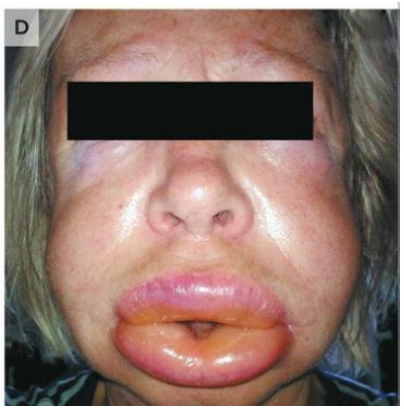
ADVANCES IN UNDERSTANDING OF THE PATHOPHYSIOLOGY OF HEREDITARY ANGIOEDEMA (HAE)

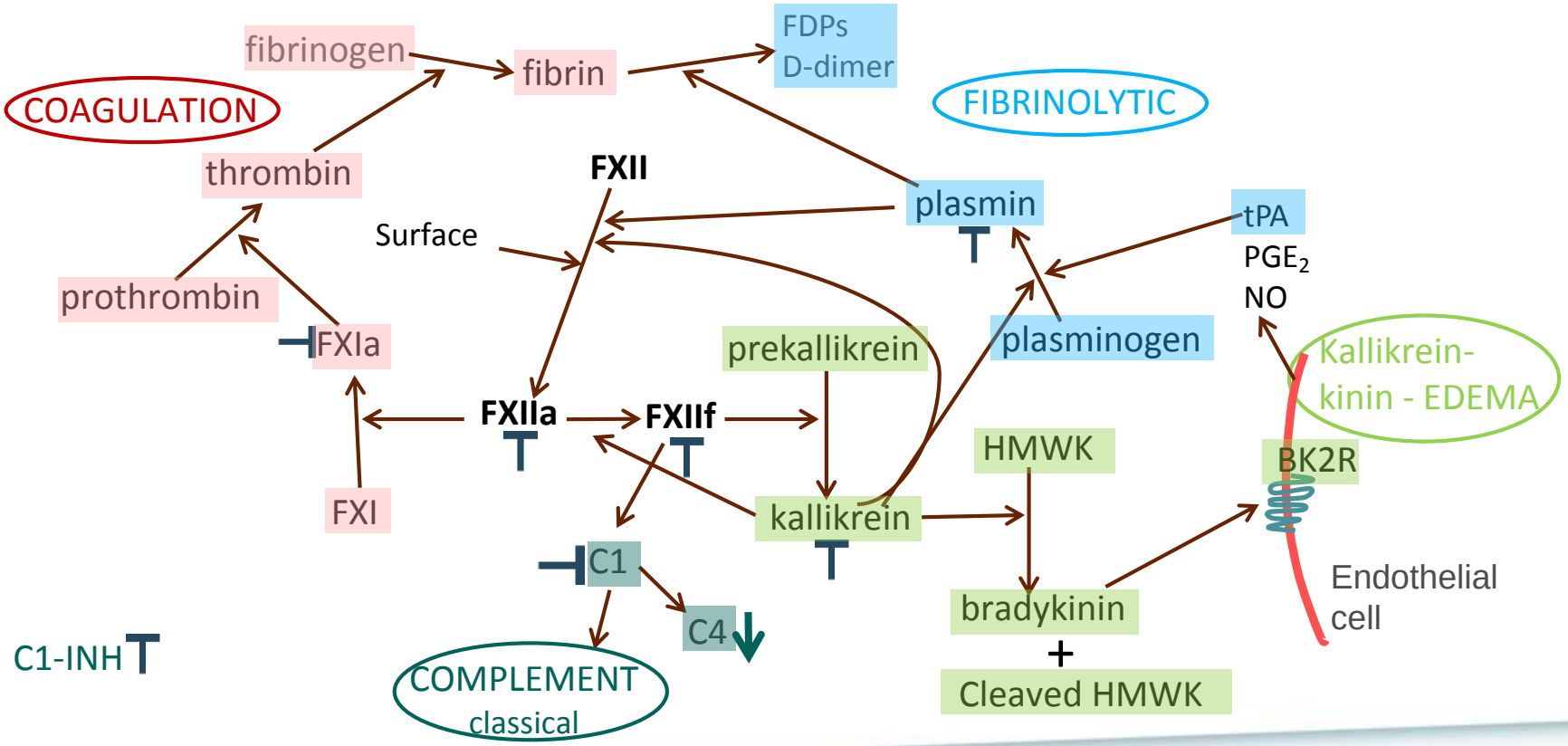
Hereditary Angioedema (HAE) – Background



- Patients suffer episodic swelling, without urticaria
  - face, oropharynx, GI system, genitalia, extremities
- Autosomal dom. ~ 1:50,000, no strong race bias
- Type I: *Serping1* gene mutations cause loss of expression of C1 esterase inhibitor (C1-INH)
- Type II: *Serping1* mutations lead to non-functional C1-INH
- Type III: HAE with normal C1-INH – over-active FXII?
- In all types, the potent vasodilator bradykinin (BK), is produced in excess, causing vascular leakage and edema

The contact system is pivotal in HAE pathophysiology

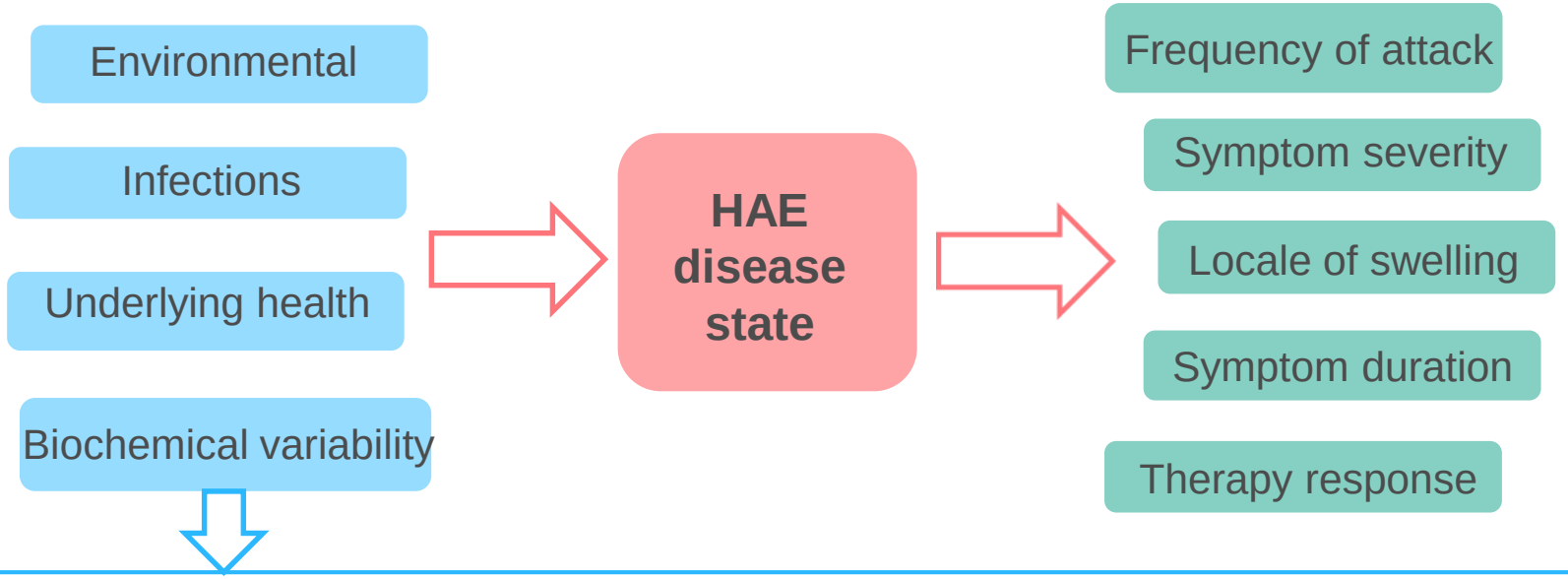
– Insufficient C1-INH or enhanced enzymatic activity leads to pathological bradykinin generation



HAE therapies

	Therapy	Mechanism
Acute therapies	C1-INH IV (Plasma & recomb.)	C1-INH replacement
	Ecallantide (small protein)	Kallikrein antagonist
	Icatabant (small molecule)	BK2R antagonist
Prophylactic therapies	C1-INH IV	C1-INH replacement
	Attenuated androgens e.g. Danazol	Enhances C1-INH secretion
	Lysine analogues e.g. Tranexamic acid	Anti-fibrinolytic, inhibits plasmin
Therapies in development	C1-INH SC (plasma, ↑conc.)	C1-INH replacement
	Monoclonal antibody – anti-kallikrein	Blocks enzymatic kallikrein activity
	Small molecule	Kallikrein antagonist (oral)
	Anti-sense nucleic acid	Prekallikrein knockdown
	Monoclonal antibody – anti-FXIIa	Blocks enzymatic FXIIa activity

Disease Variability in HAE



- While C1-INH levels are pivotal, other factors contribute to disease variation
  - C1-INH (>300 variants) - differences b/w complement & kallikrein regulation activity
  - BK catabolism - multiple enzymes e.g. ACE, APP, NEP
  - Contributions of fibrinolytic system
  - High variability in FXII concentration levels (60-140%)
  - Variability in endothelial susceptibility to leakage

Triggers for HAE attacks

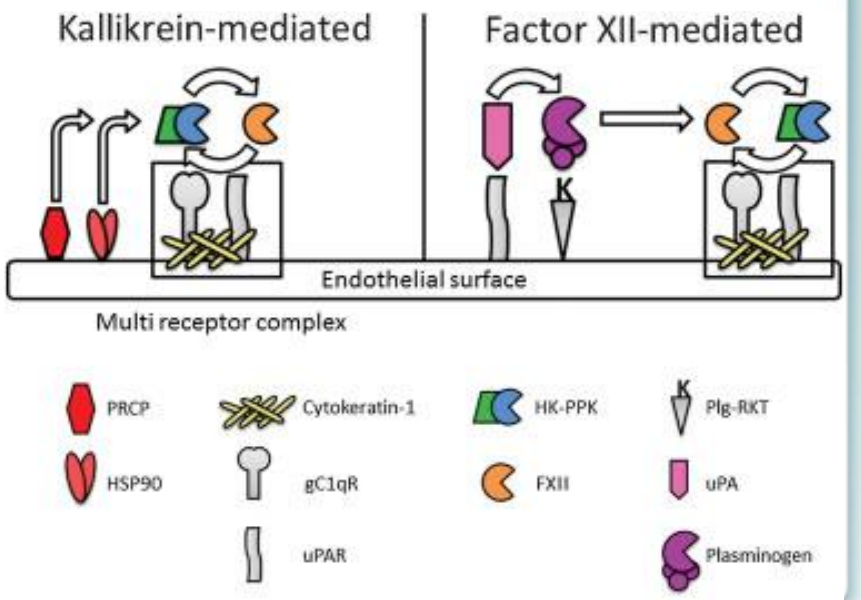
- Relationship b/w biochemical and HAE triggers poorly understood
  - HAE triggers: physical trauma, surgery, dental extraction, stress, infection, menstruation, underlying pathologies
- Multiple triggers of contact system activation proposed
  - FXII activation through contact at various physiological surfaces
    - eg. collagen, DNA, misfolded proteins, polyphosphates
  - Plasmin activation of FXII
  - Prolyl-carboxypeptidase (PRCP) activation of prekallikrein[a]
  - HSP90 activation of prekallikrein[b]
- In health, C1-INH prevents any trigger from leading to edema

a Shariat-Madar Z, Mahdi F, Schmaier AH 2002 J Biol Chem 277;
b Joseph, Tholanikunnel, Kaplan, 2002 PNAS 99

Plasminogen activation in HAE attacks

- Such activation may influence propagation of & precede HAE attacks
  - Tranexamic acid has prophylactic benefit in some patients
  - D-dimers elevated in patient attack samples, and often remission samples
  - tPA can be released from activated endothelial cells

- Activation models proposed, either kallikrein- or FXII-mediated[a]
- Both require FXII-driven amplification for pathological BK formation
- Plasminogen or FXII activation drives the FXII model
- PRCP, HSP90 or trace plasma kallikrein drives the kallikrein model



a de Maat, de Groot and Maas, 2014, Semin Thromb Hemost

HAE with normal C1-INH (HAE-nC1-INH; Type III)

- Patients suffer HAE attacks clinical similarities to type I and II
  - First described in 2000 by Bork et al[a]
- Prevalence – several hundred families, but maybe many more
- Mostly females, estrogen linkage - FXII gene estrogen response element
- Significant proportion of these patients have FXII mutation at aa309
  - mutation introduces new plasmin cleavage sites[b]
  - mutation leads to defective FXII glycosylation[c] – ↑FXII activity
- PAI-2 deficiency[d] in type III patients with and without FXII mutations
  - likely due to excess consumption
- FXII hyper-activity appears to overcome normal C1-INH regulation
  - fibrinolytic contribution; basis in patients without FXII mutation unclear

a Bork et al 2000, Lancet 356; b de Maat et al 2016 JACI; c Bjorkqvist et al 2015 JACI 125; d Joseph, Tholanikunnel, Wolf, Bork and Kaplan, 2016 J Allergy Clin Immunol, 137

Role for BK1R? – local or systemic activation

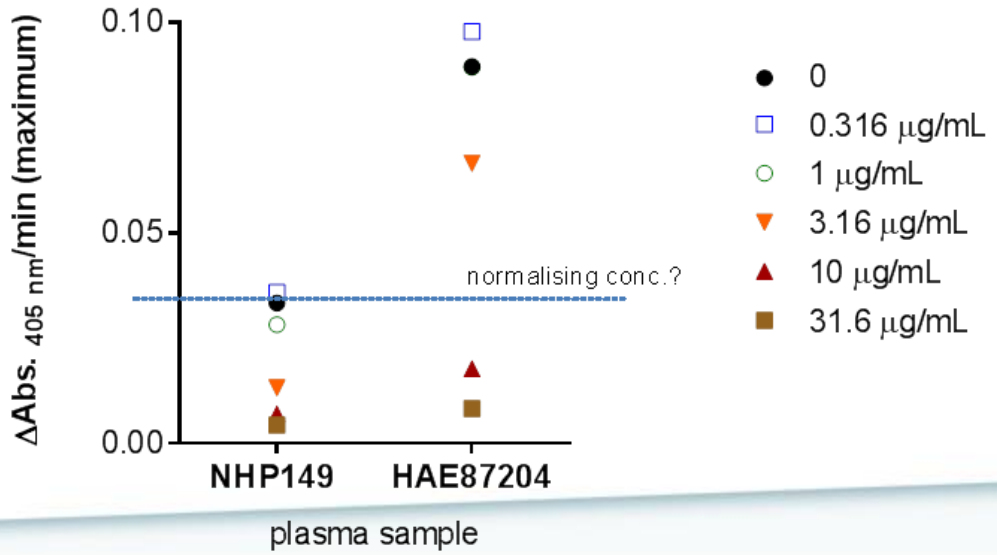
- BK engagement with constitutive BK2R believed to drive localised edema episodes
- BK1R up-regulated in inflammation – role for systemic activation?
- Supporting observations:
  - Episodes often involve swelling at multiple locales
  - Drops in blood pressure not observed
  - Modest level systemic C1-INH therapy alleviates symptoms
  - Prodromal symptoms suggest systemic activation
- Model proposed by Zonne et al[a] where:
  - Initial BK activation leads to BKR2 desensitisation
  - BK-mediated inflammation leads to BK1R up-regulation
  - Angioedema occurs at sites of endothelial BK1R expression

a Zonne, Hofman, Relan, Zeerleeder, Drouet, Zuraw and Hack, 2016. J Allergy Clin. Immunol.

FXII is pivotal in HAE: C1-INH is its main regulator

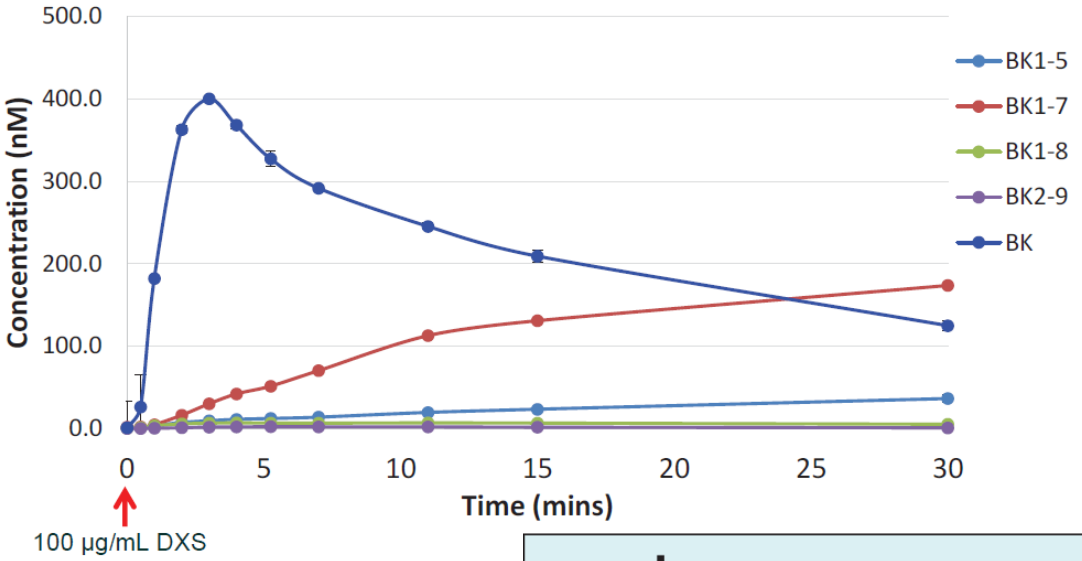
- FXII inhibition as a therapeutic strategy:
  - many contact system triggers but FXII key for pathological amplification
  - Hageman's patients have no enhanced thrombosis risk
  - FXII >90% regulated by C1-INH[a] ;kallikrein regulated ~ 50/50 C1-INH α_2-M[b]
  - Treatment with a FXII inhibitor could restore regulation of deficient C1-INH

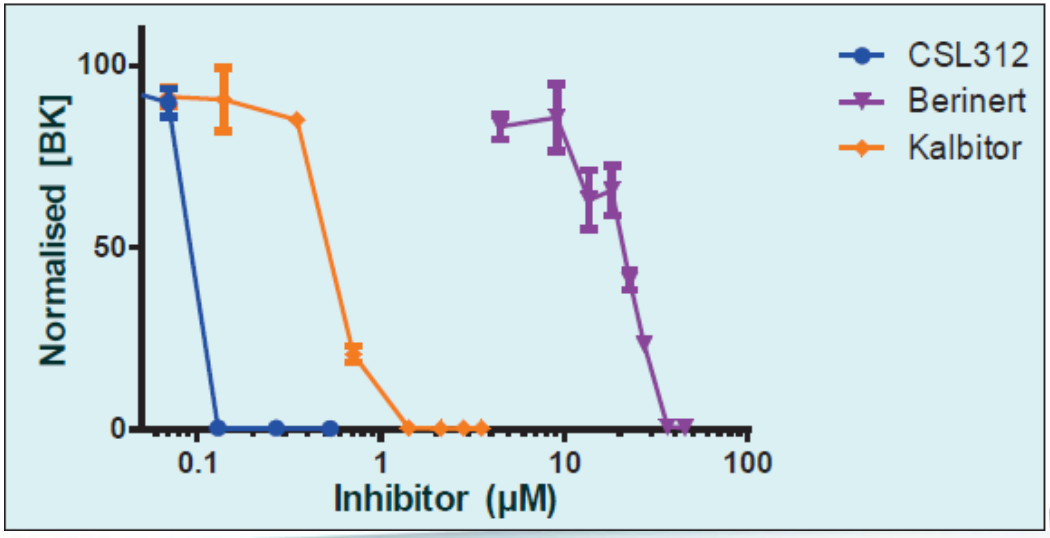
FXII antibody "normalises" kallikrein-kinin pathway of HAE plasma ex vivo



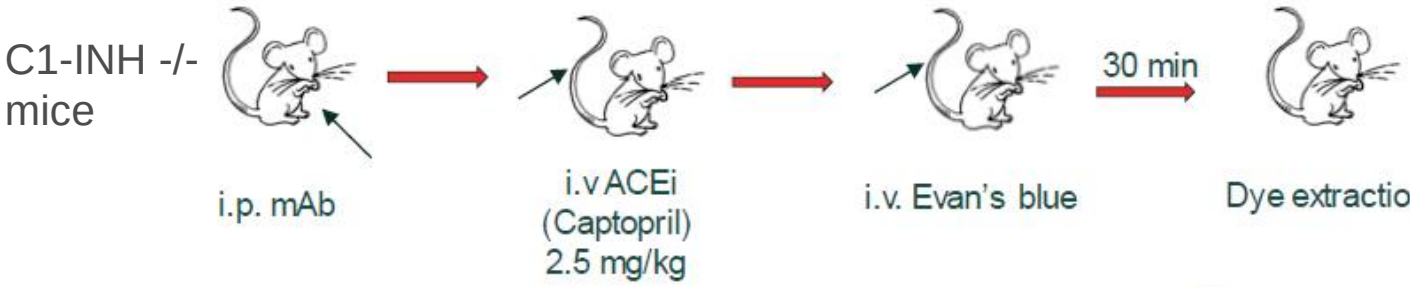
a Forbes et al. J Lab Clin Med. 1970, 76:809; b Schapira,et al 1982. J Clin Invest 69:462–468.

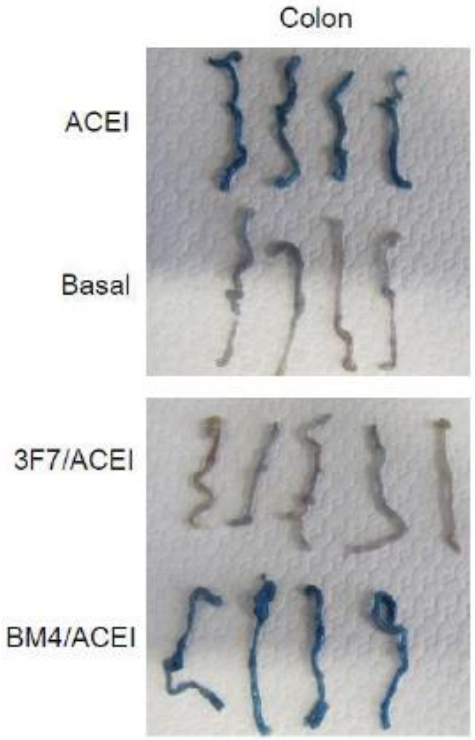
FXII inhibition prevents BK generation (LC-MS/MS assay)

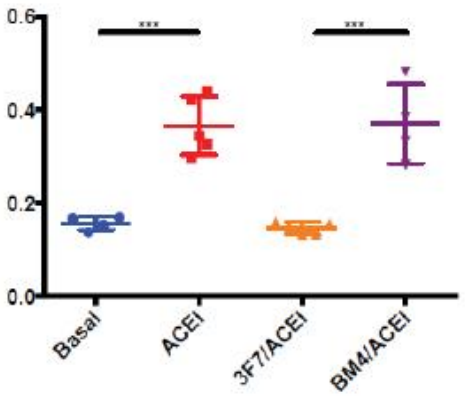


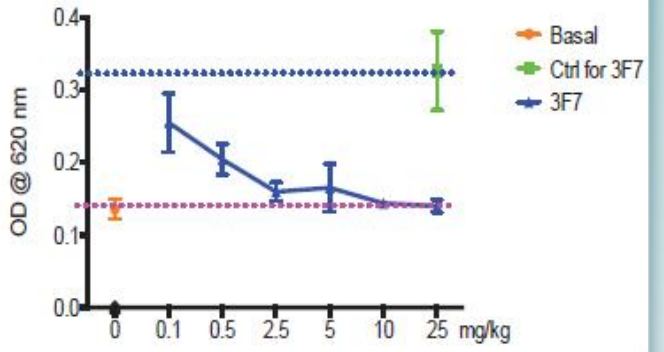


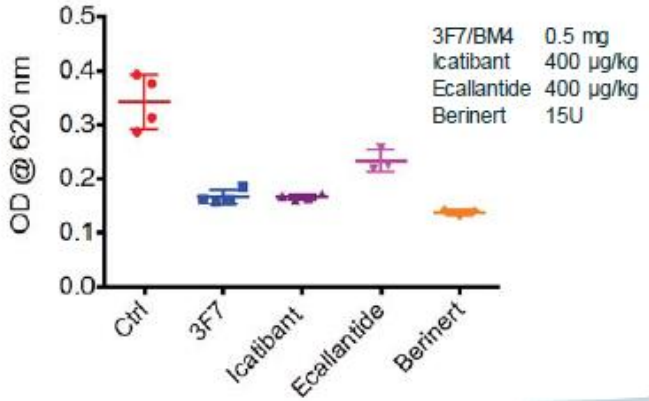
Anti-FXIIa mAb, inhibits ACEi-induced angioedema







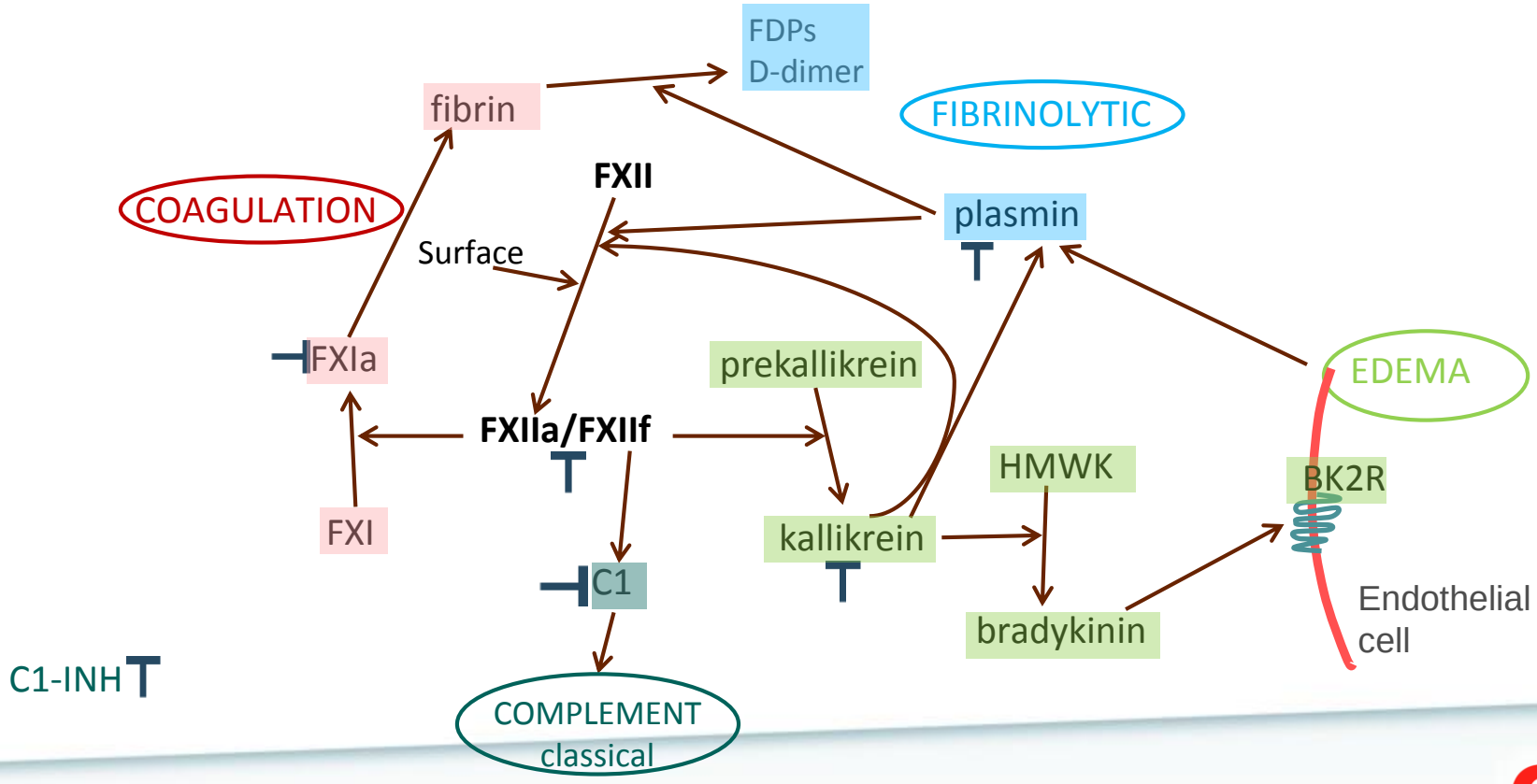




FXII antagonist mAb:
3F7 – CSL312 parent mAb

Pathways relevant to HAE pathophysiology

- The contact system, with FXII at it's apex is pivotal in HAE
  - Dysregulation of this system due to insufficient C1-INH or enhanced enzymatic activity leads to pathological bradykinin generation



SUMMARY

- HAE attacks are mediated by bradykinin
- Multiple pathways intersect the contact system
  - affecting disease variability and therapeutic response
- Mechanism underlying HAE triggers poorly understood
- Important pathophysiological role of fibrinolytic system
- HAE Type III may result from hyperactivity of FXII,
  - Disturbing the balance of contact activation and regulation
- FXIIa amplifies pathological bradykinin production – novel HAE target

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