Dedicated to Transglutaminase

- Company profile and background
- Transglutaminases
- Celiac disease
- Anticoagulation

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Unternehmen

- Gründung: 2007 als MBO aus N-Zyme BioTec in Darmstadt
- Gesellschafter: Management, High-Tech Gründerfonds, Dr. Jochen Klein, Prof. H.-L. Fuchsbauer, Prof. H.G. Gassen und R-Biopharm AG
- Fokus auf Transglutaminase und damit korrelierende Krankheiten
- Hybrid-Geschäftsmodell

Investitionen: Wirkstoff-Entwicklung /
niedermolekulare Transglutaminase-Blocker

Einnahmen: - Vertrieb von Spezialreagentien für F+E
- Antigene für die Diagnostik
- Meilensteinzahlungen von Dr. Falk Pharma (Zöliakie-Lizenz)

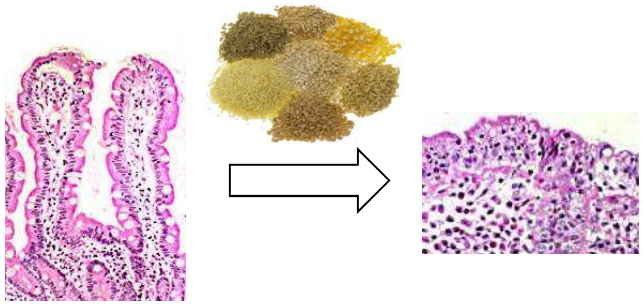
Transglutaminases

- Function: „*biological glue*“ – irreversible cross-linking of proteins

Name of Enzyme	Synonyms	Function	(validated?) Drug Target in:
Coagulation Factor XIII	Plasma Transglutaminase, Fibrin Stabilizing Factor	Blood coagulation and wound healing	**Thrombosis**
Transglutaminase 1 (TG1)	Keratinocyte Transglutaminase	Cornified envelope formation, skin differentiation	?
Transglutaminase 2 (TG2)	Tissue Transglutaminase	Apoptosis and cell differentiation; signal transduction; extracellular matrix formation; cell adhesion	**Celiac Disease** Neurodegenerative Diseases? Cancer? Scarring / Fibrosis?
Transglutaminase 3 (TG3)	Epidermal Transglutaminase	Cornified envelope formation, skin differentiation	?
Transglutaminase 4 (TG4)	Prostate Transglutaminase	Semen coagulation (in rodents)	?
Transglutaminase 5 (TG5)		Cornified envelope formation, skin differentiation	?
Transglutaminase 6 (TG6)	Neuronal Transglutaminase	Unknown	Neurodegenerative Diseases?
Transglutaminase 7 (TG7)		Unknown	?

Celiac Disease

- Prevalence about 1% in Europe and US
- Market volume: up to $ 8 bn in the seven major markets (Data Monitor 2009)
- Intolerance to cereal proteins (gluten)
  - Chronic inflammation of the small intestine
  - Autoimmune disease (auto TG2-antibodies)

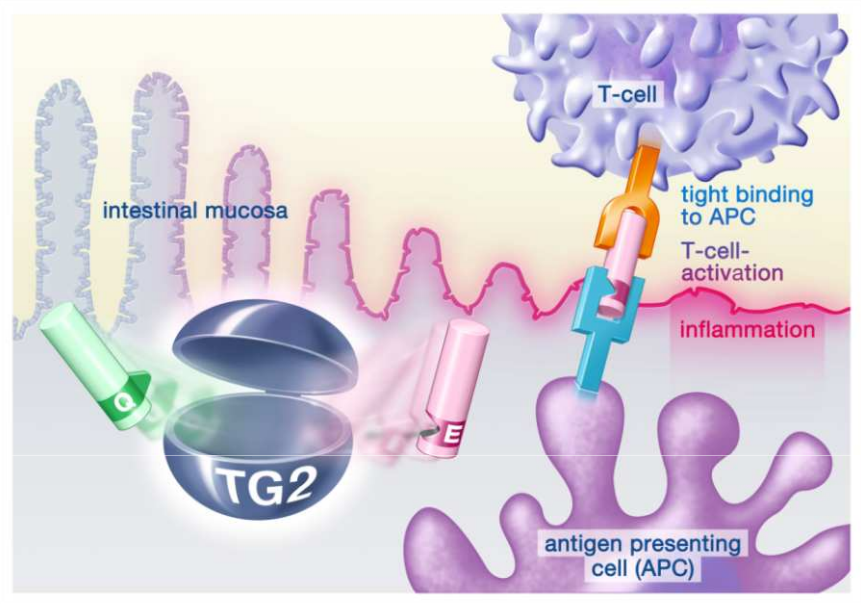


Symptoms

- Abdominal pain, diarrhoea, nutrient deficiency, fatigue, weight loss,
- Secondary diseases: osteoporosis, anaemia, ataxia, cancer …

- No therapy available: patients have to follow a strict gluten free diet!
- Challenging - especially the hidden gluten is almost impossible to avoid

Approach: TG2 blocker



- TG2 deamidates gliadin (gluten)
- Deamidated gliadin is recognized by APCs, leading to inflammation of the mucosa, degradation of the villi and (auto)-antibody release
- Vicious circle leading to expression and activation of TG2
- Therapeutic concept: blocking of dysregulated TG2
- Non-systemic, local & topical application

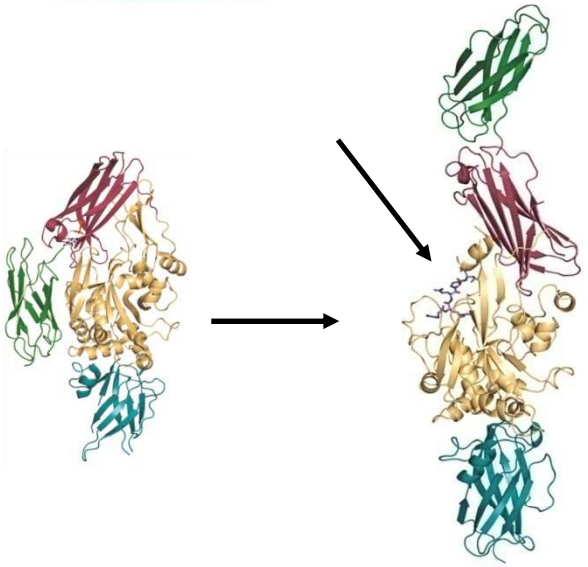
The quest: How to design the “perfect” molecule?

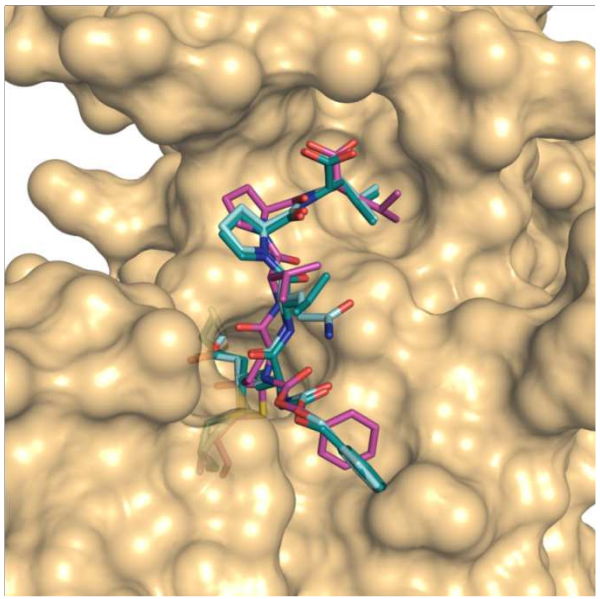
Drug discovery platform for Transglutaminase blockers

- Assay Development
- Transglutaminase profiling
- Lead identification via peptide screening
- Lead optimization
- Co-Crystallization / Structure based design
- Cellular Assays
- Initial toxicology

Structure based Design: TG2-Inhibitor Co-Crystallization

Structure based design



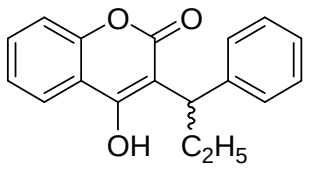


- TG2 undergoes a tremendous conformational shift
- Co-crystallization gives insight into main interaction sites
- Structure deciphers conformational requirements towards peptidomimetics

- Clinical drug candidate ZED1227
- Preclinical data package
- Licensed to Dr. Falk Pharma in November 2011 (rights for Europe)
- “CI3 Leuchtturmprojekt” with Falk & Universitätsklinikum Mainz

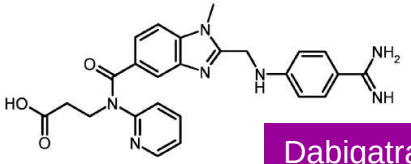
Orale Antikoagulation

- Verringerung thromboembolischer Vorfälle bei Risikopatienten z.B.:
  - Primärprävention von Schlaganfall bei Vorhofflimmern
  - Sekundärprävention nach Thromboembolien…
- Gestern (1939): Phenprocoumon (Marcumar®) / Vit.-K-Antagonist (FII, FVII, FIX, FX – erfordert engmaschiges Monitoring “INR”)
- Heute: NOAKs erobern den Markt (direkte FIIa / FXa Blocker)

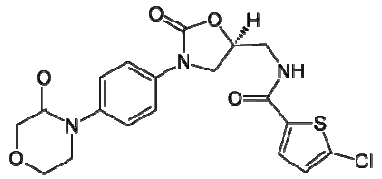


Phenprocoumon

Wirkstoff	Handelsname ®	Unternehmen	Target
Melagatran (Ximelagatran)	Exanta (2006 vom Markt)	AstraZeneca	FIIa (Thrombin)
Dabigatran (Dabigatranetexilat)	Pradaxa	Boehringer Ingelheim	FIIa (Thrombin)
Rivaroxaban	Xarelto	Bayer / (J&J)	FXa
Apixaban	Eliquis	Pfizer / BMS	FXa
Edoxaban	Lixiana	Daiichi Sankyo	FXa

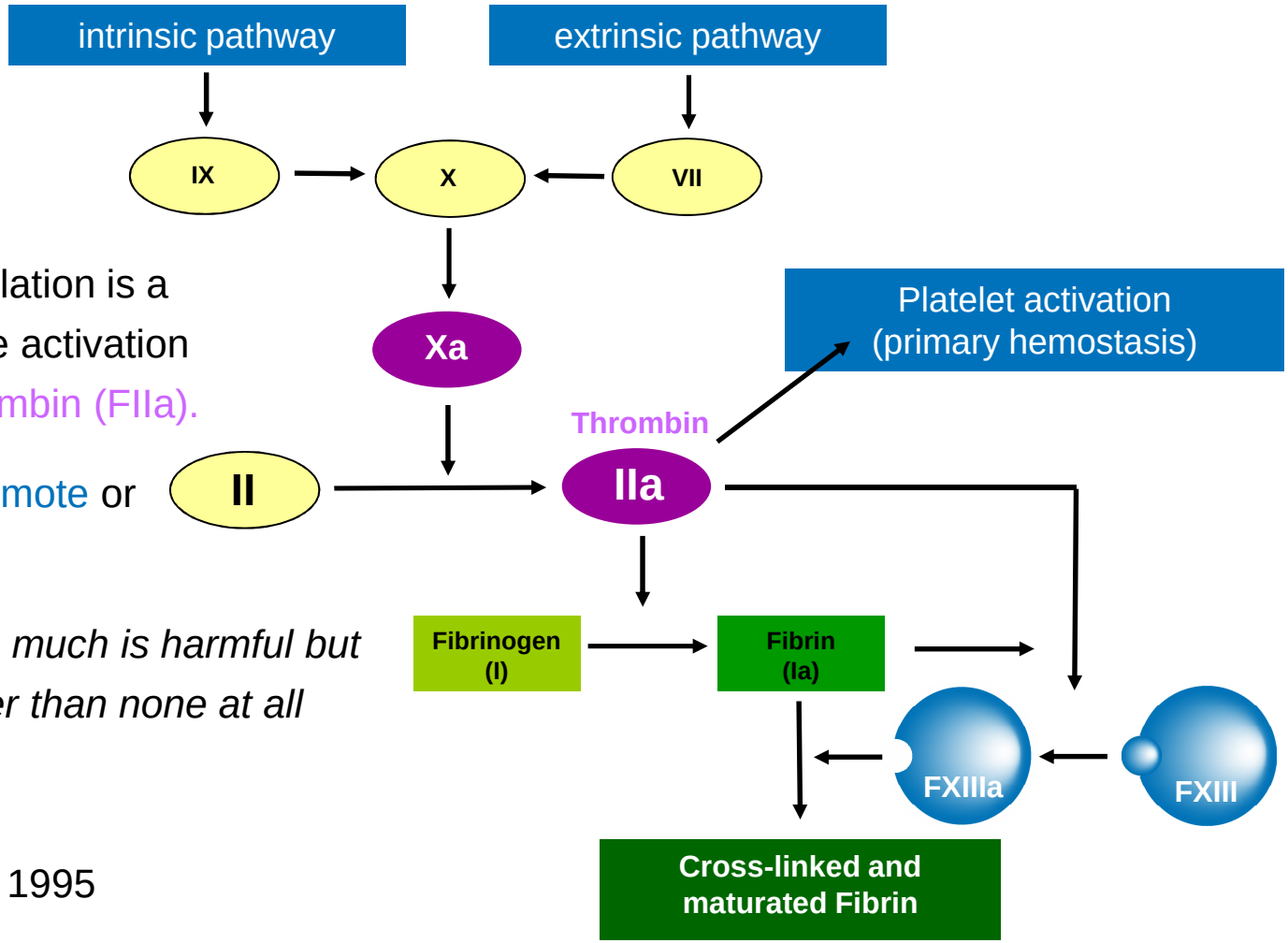


Dabigatran



Rivaroxaban

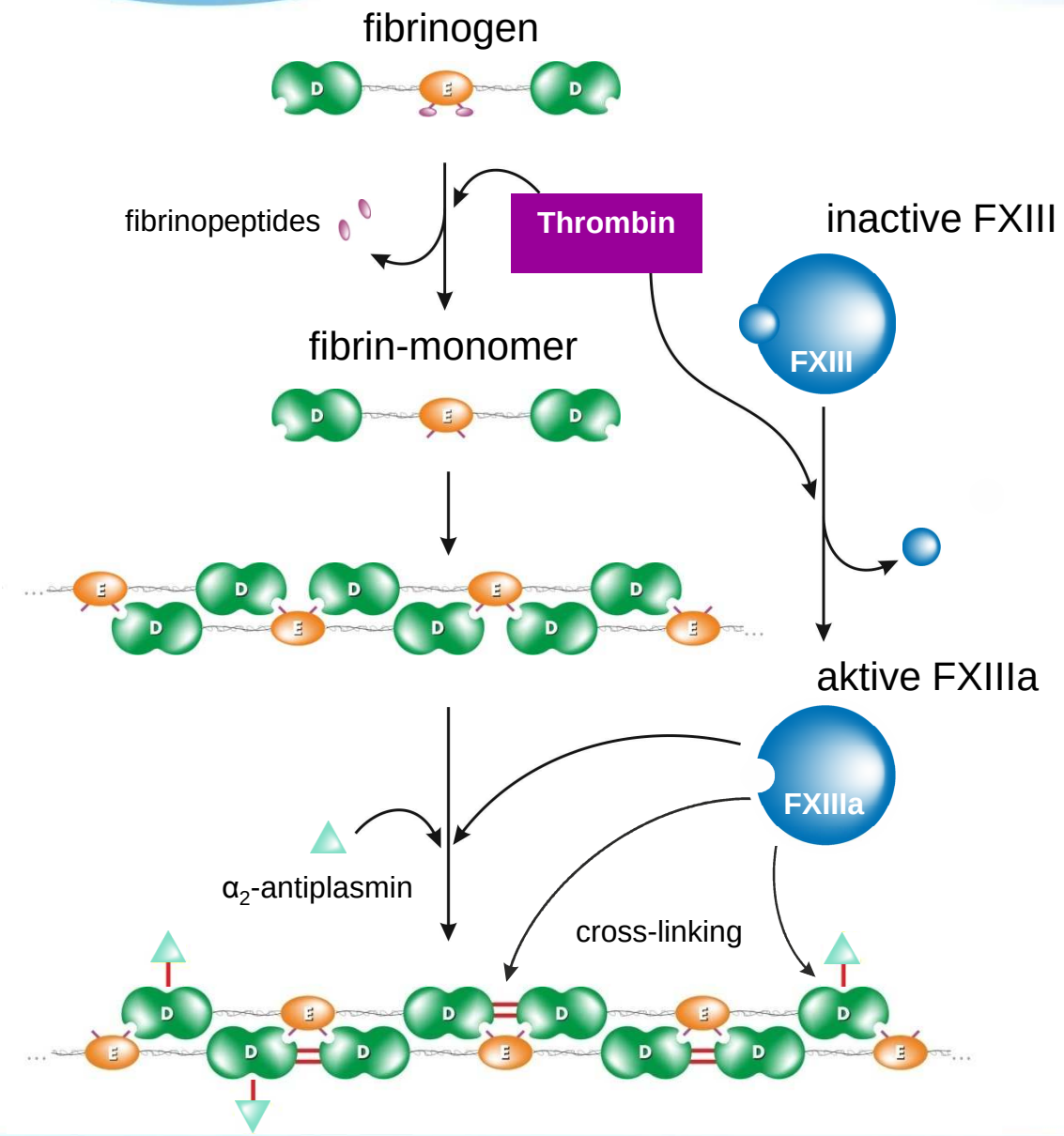
Plasmatic Blood Coagulation



- Plasmatic blood coagulation is a cascade, leading to the activation of the key player: Thrombin (FIIa).
- Thrombin can both promote or prevent blood clotting
- Thrombin paradox: *too much is harmful but a little bit is much better than none at all* (like red wine)

John H. Griffin, Nature 1995

Factor XIIIa



FXIIIa influences:

- Clot visco-elastic features
- Resistence to fibrinolysis by fibrin cross-linking and decoration with α_2-antiplasmin
- Stability and duration

FXIIIa does <u>not</u> influence:

- Thrombin level
- Platelet activation
- Primary plug formation

Medical Need

Anticoagulation with “NOAKs”: „efficacy means bleeding“!

- Substantial risk for major bleeding events (G.I., cerebral) due to thrombin inhibition, the major factor for platelet activation
- Benefit to risk ratio often excludes elderly patients from anticoagulation
- Accidents, unforeseen operations and overdosing: no antidots available

Potential of direct FXIIIa-Blocker

- Unique mode of action: no influence on thrombin generation and platelets: minor risk of bleeding events expected / different benefit to risk ratio

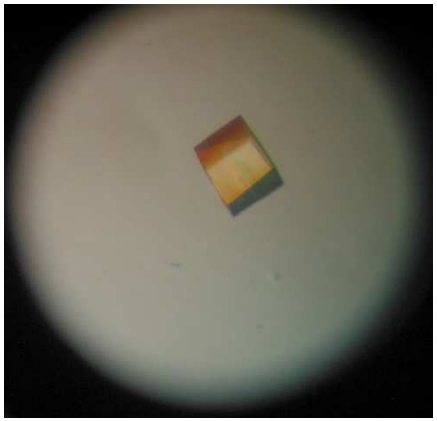
⇨ Clotstability ⇩

⇨ Fibrinolytic activity⇧

⇨ Antidots available (Fibrogammin, CSL and Novothirteen, NovoNordisk)

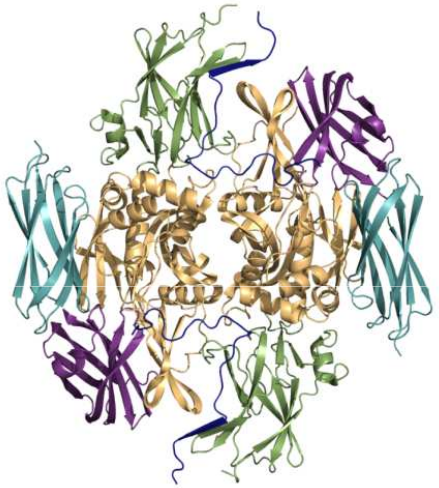
Structure based design targeting FXIIIa

Even tougher quest: how to design direct FXIIIa blockers?



Factor XIII forms a dimer
in the inactive conformation

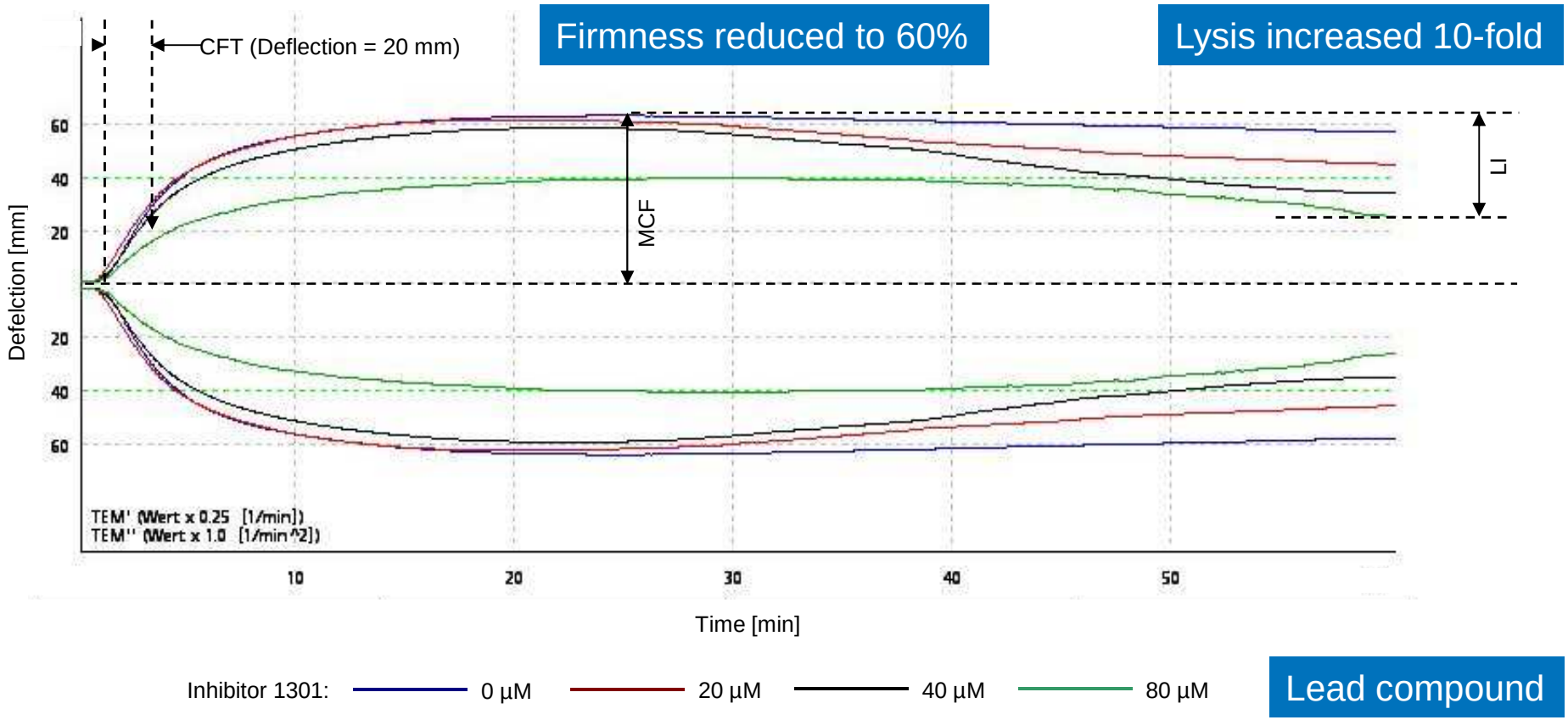
Yee V. *et al.*, 1994



Structure of FXIIIa - to be solved soon?

Novel direct FXIIIa blocker

- Significant influence on clot structure & lysis
- Thrombelastometrie (TEM) simulating *in vivo* situation



Lead compound

Thank you for your attention!

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