



Beth Israel Deaconess  
Medical Center



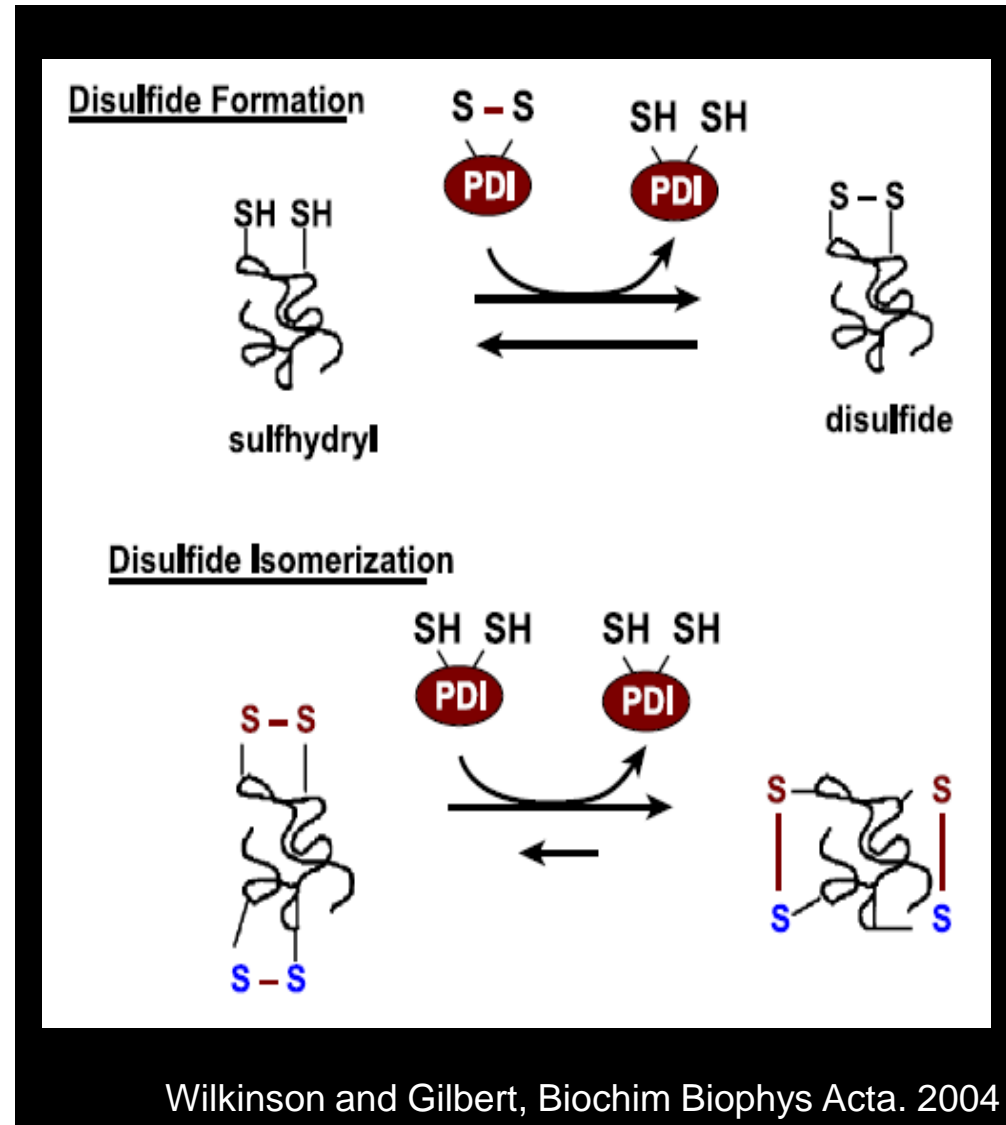
HARVARD MEDICAL SCHOOL  
TEACHING HOSPITAL

## PDI Inhibition and cancer associated thrombosis

Jeffrey Zwicker, M.D.

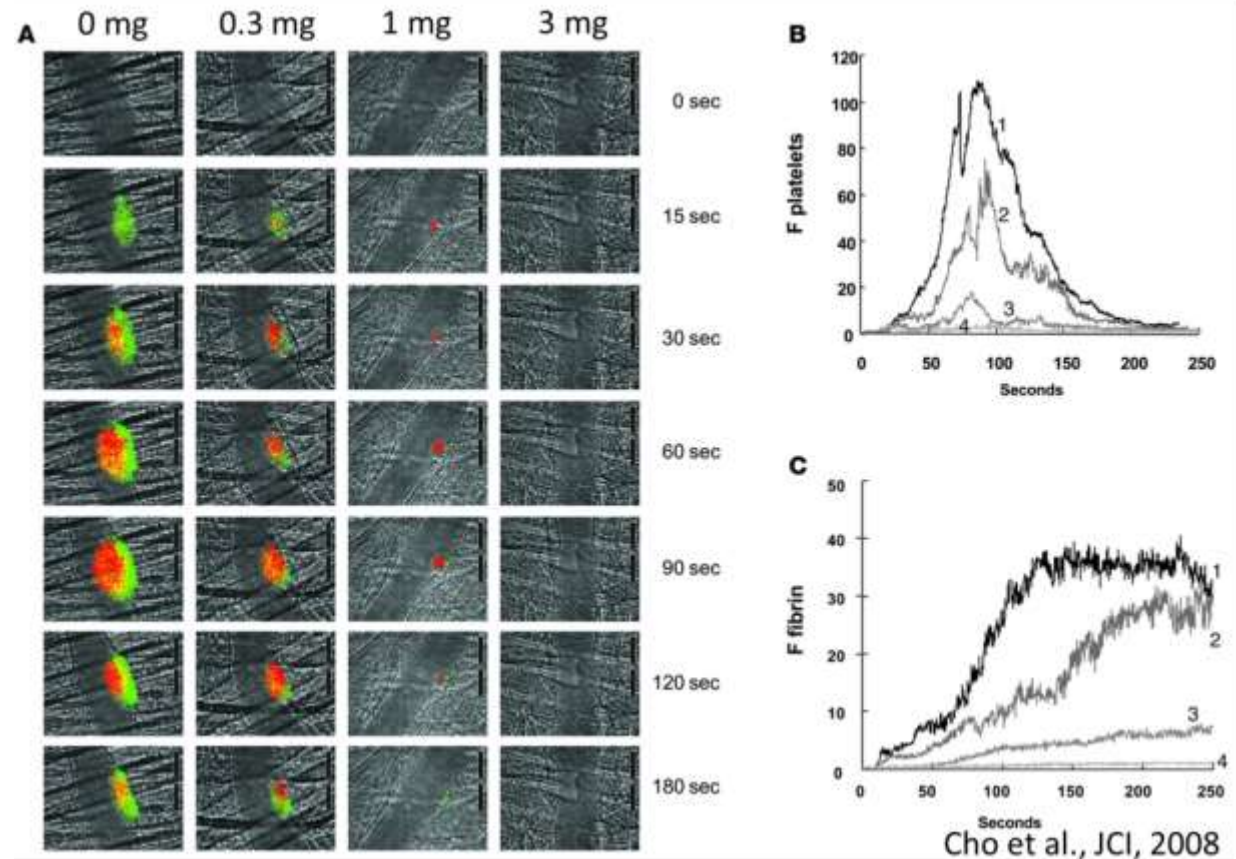
# Protein Disulfide Isomerase

- PDI catalyzes protein disulfide oxidation and reduction
- Regulates protein folding



# Protein disulfide isomerase as antithrombotic target

- Monoclonal antibody inhibition of PDI blocks both platelet accumulation and fibrin generation in vivo (Cho et al. JCI 2008)

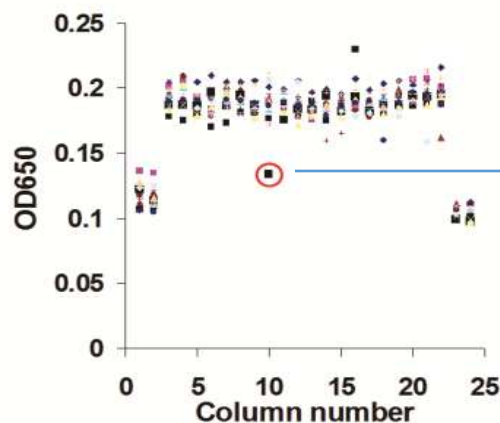


- Following platelet and endothelial activation PDI released and localized to external membrane surface (Chen et al BJH 1995; Jasuja et al. Blood 2010)

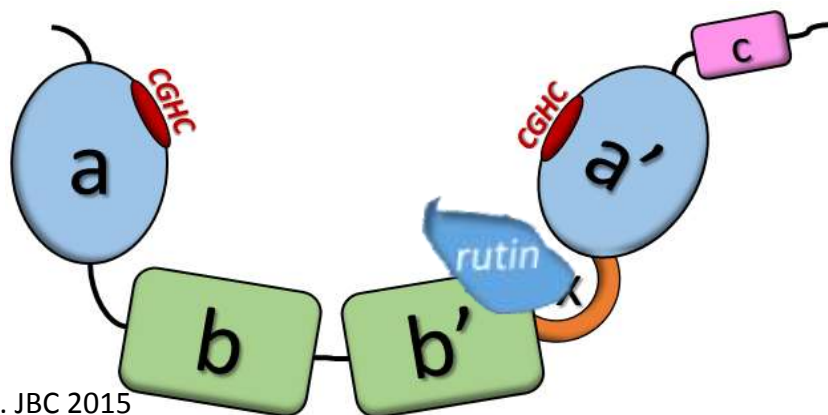
# Extracellular PDI as an antithrombotic drug target?

## PDI small molecule inhibitor screen

A.

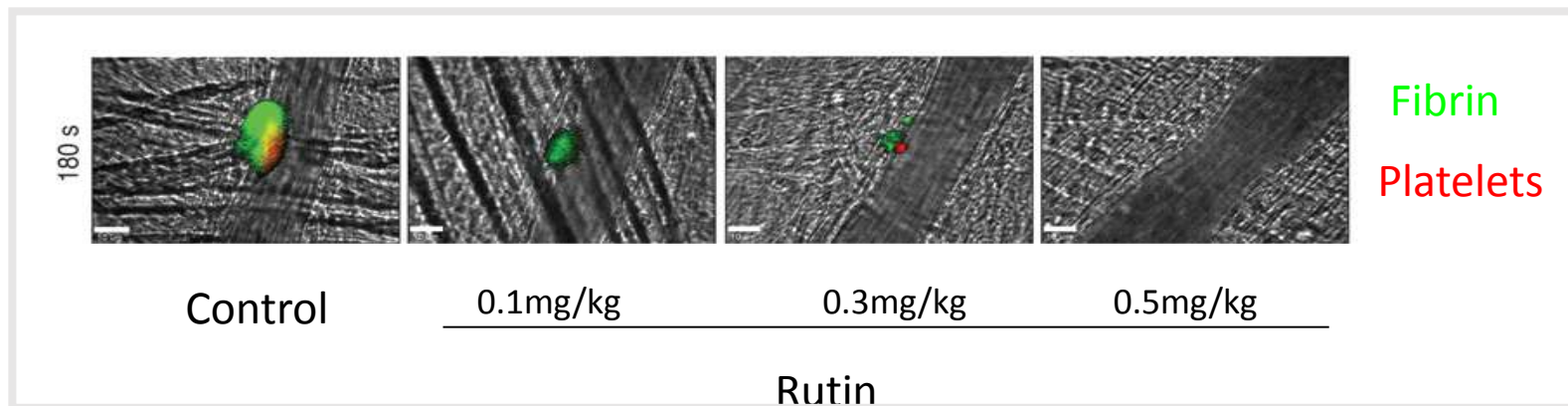


Rutin (Quercetin 3-rutinoside)

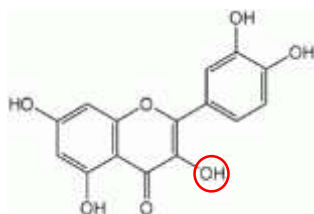


Jasuja et al. JCI 2012

- Quercetin-3-rutinoside, as a new inhibitor of PDI.



Decreased **platelet accumulation** and **fibrin deposition**



Name	2'	3'	4'	5'	3	IC <sub>50</sub> (μM) (95% confidence interval)
Quercetin	H	OH	OH	H	OH	>100
Tamarixetin	H	OH	OCH <sub>3</sub>	H	OH	>100
Isorhamnetin	H	OCH <sub>3</sub>	OH	H	OH	>100
Diosmetin	H	OH	OCH <sub>3</sub>	H	H	>100
Hyperoside	H	OH	OH	H	Galactose	5.9 (2.8–12.5)
Isoquercetin	H	OH	OH	H	Glucose	7.1 (4.3–12.0)
Quercetin-3-glucuronide	H	OH	OH	H	Glucuronic acid	5.9 (3.5–10.1)
Quercetin-3-rutinoside	H	OH	OH	H	Rutinoside	6.1 (1.1–10.7)
Datiscin	OH	H	H	H	Rutinoside	8.8 (3.2–24.3)

(Jasuja et al, JCI 2012)

# Quercetin

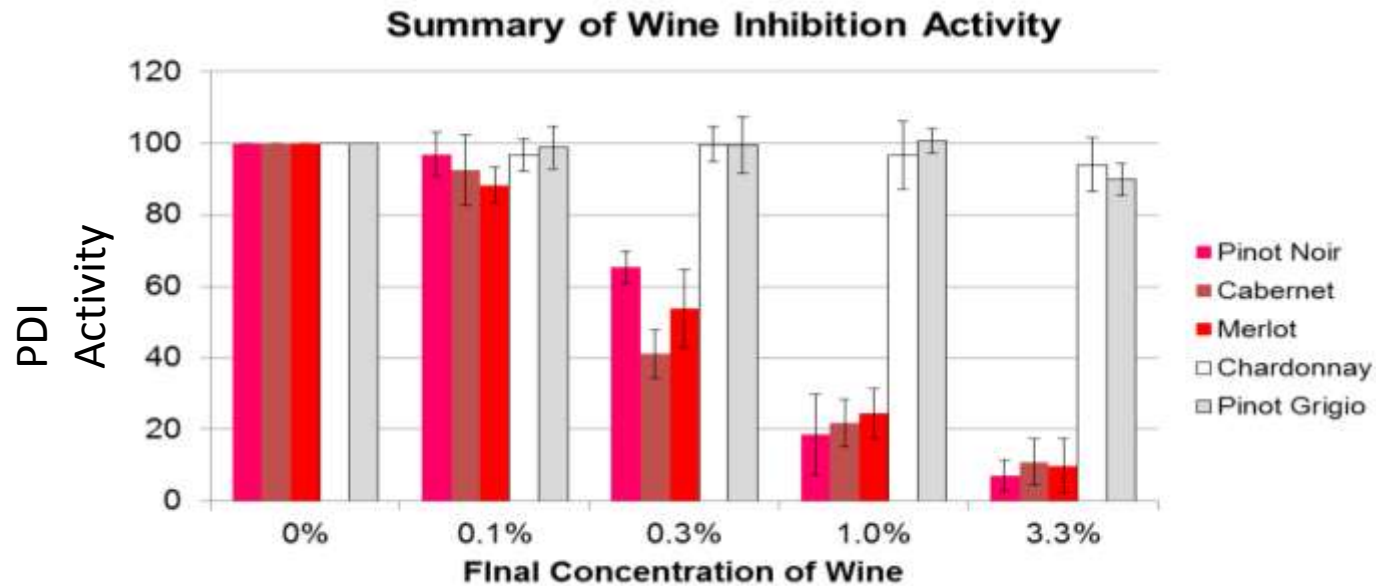
- Flavanol present in apples, onions, teas, berries, wine
- Rutin is poorly absorbed relative to other quercetin analogs
- Available as nutritional supplement



Uncaria crops in Brasil (courtesy of Quercegen Pharma)

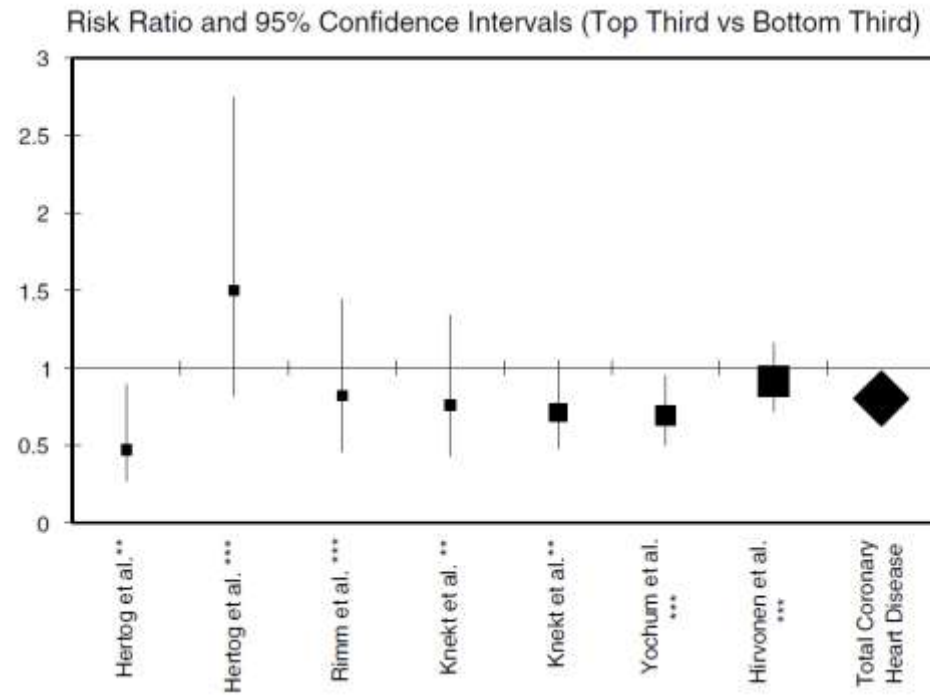


# Quercetins and French paradox?



# Quercetin and cardiovascular disease

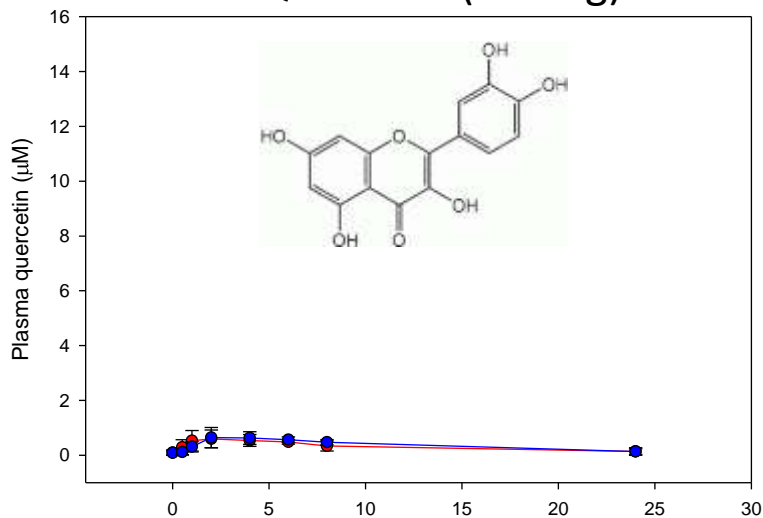
- Large epidemiologic studies suggests quercetin reduces stroke and myocardial infarction



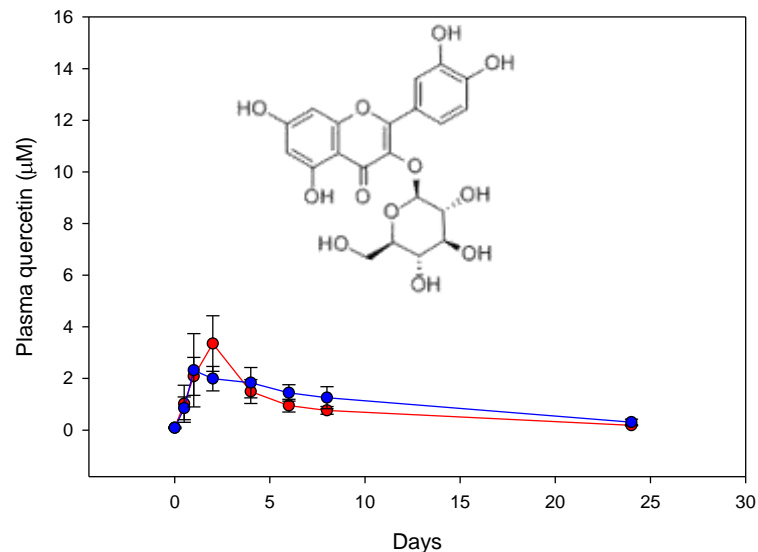


# Pharmacokinetics of isoquercetin in healthy adults

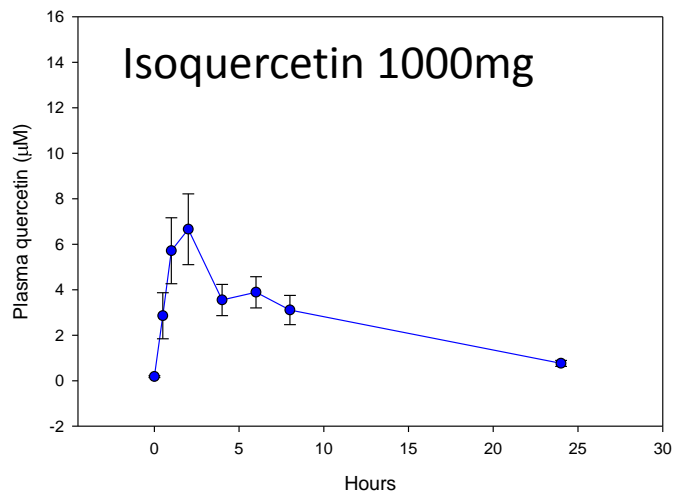
Oral Quercetin (500mg)



Oral Isoquercetin (500mg)

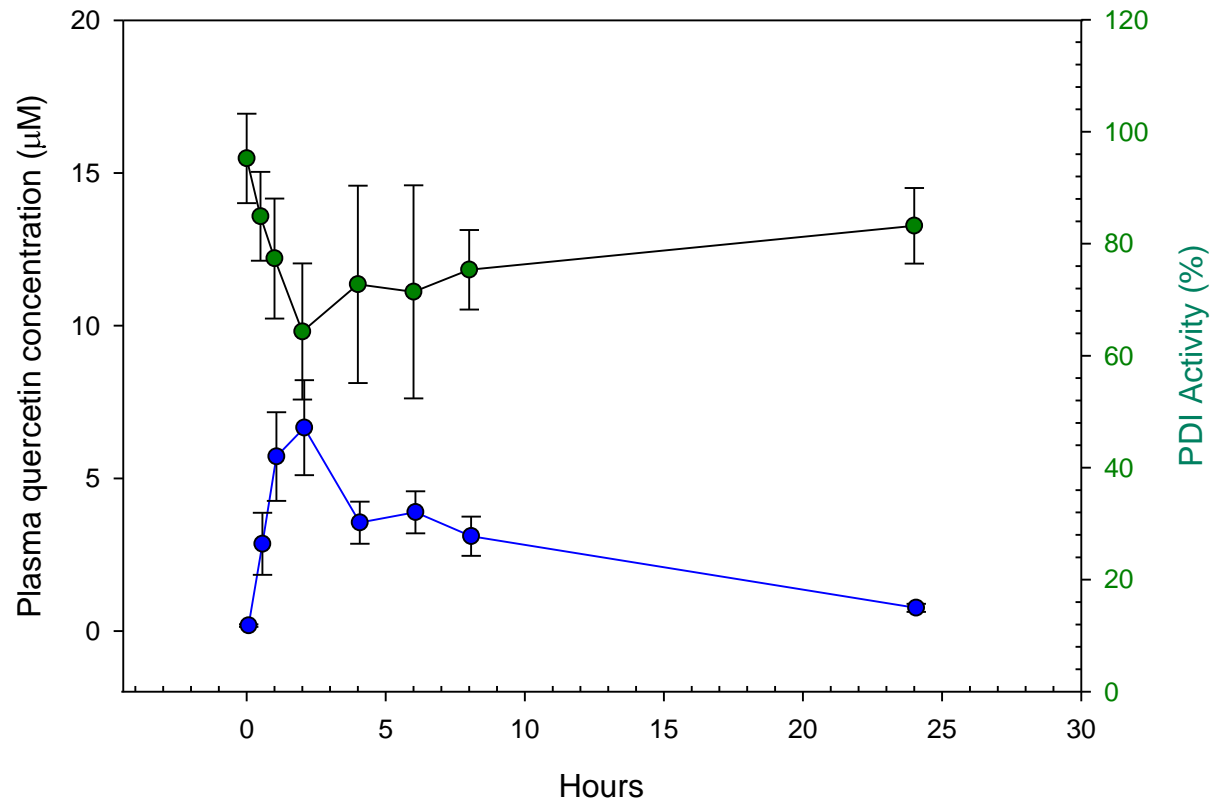


Isoquercetin 1000mg



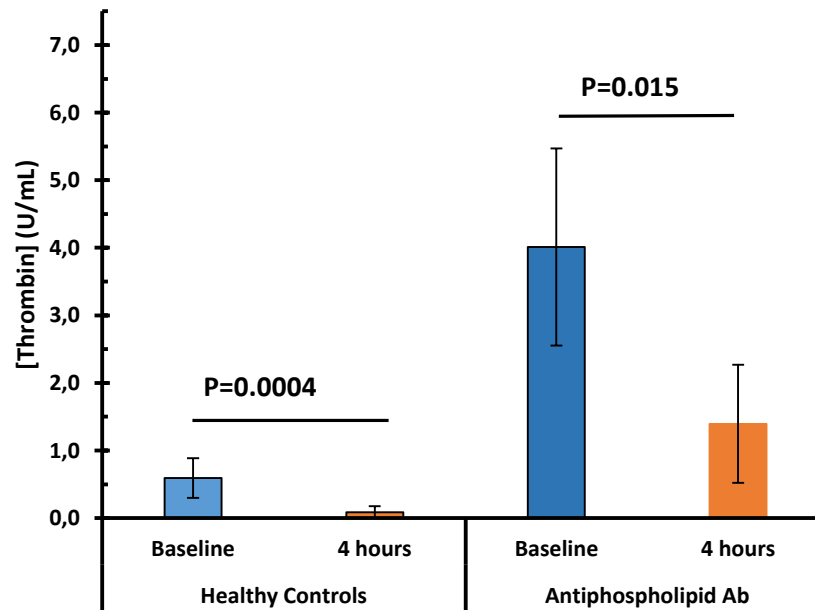
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Diosmetin	H	OH	OCH <sub>3</sub>	H	H	>100
Hyperoside	H	OH	OH	H	Galactose	5.9 (2.8–12.5)
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# Isoquercetin pharmacokinetics vs PDI inhibition in healthy adults

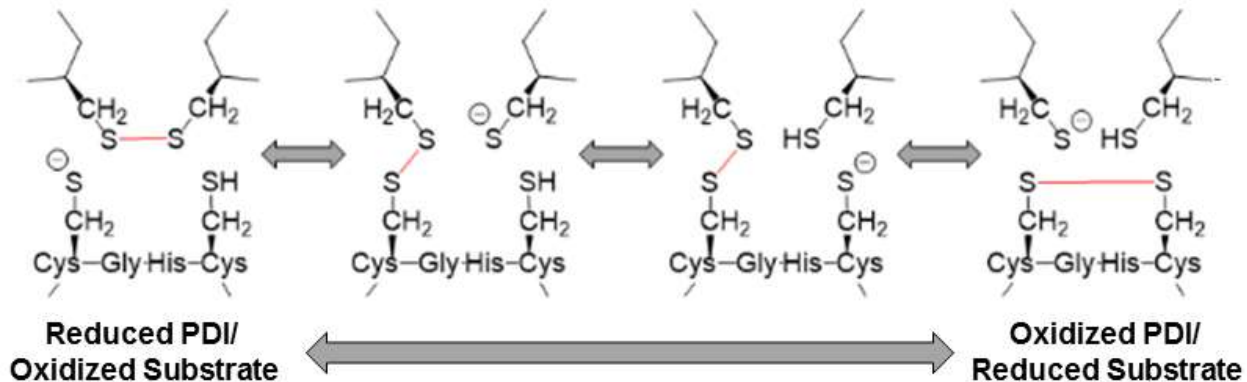
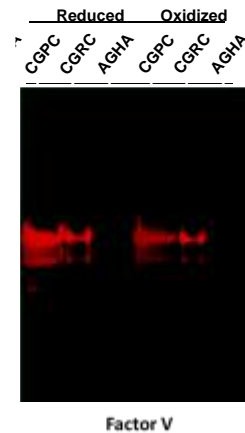
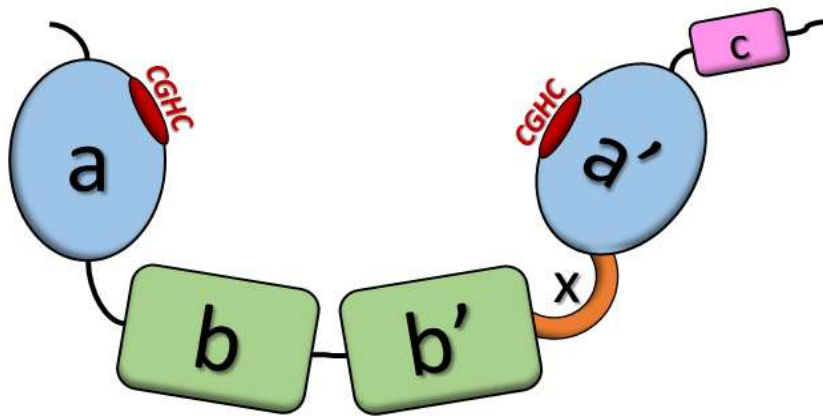


# Isoquercetin in patients with anti-phospholipid antibodies

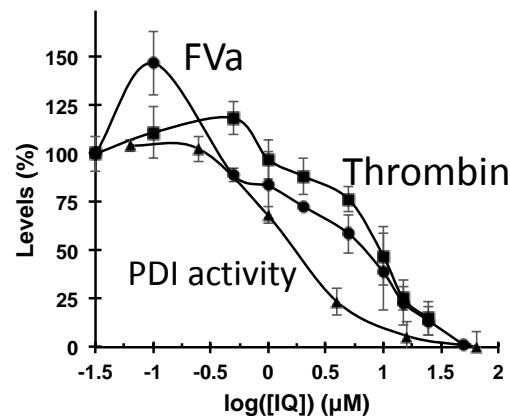
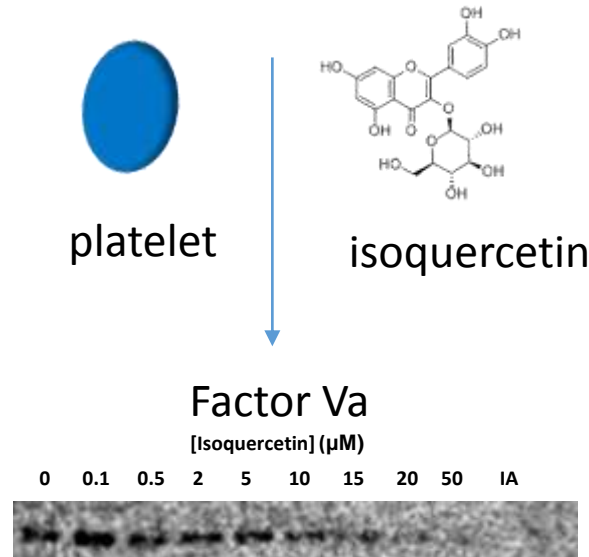
- Significant decrease in platelet-dependent thrombin generation at 4 hours



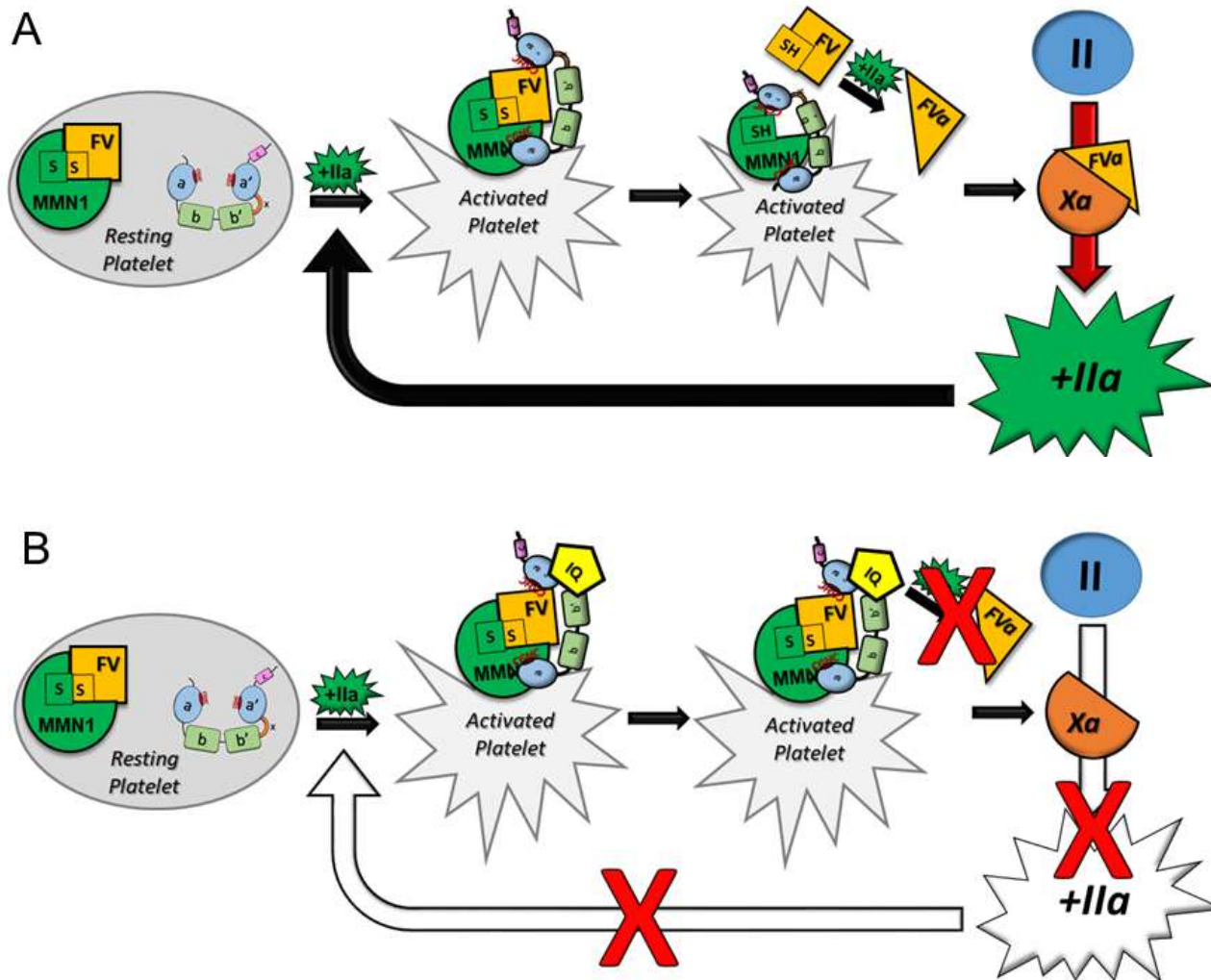
# Kinetic trapping mutants



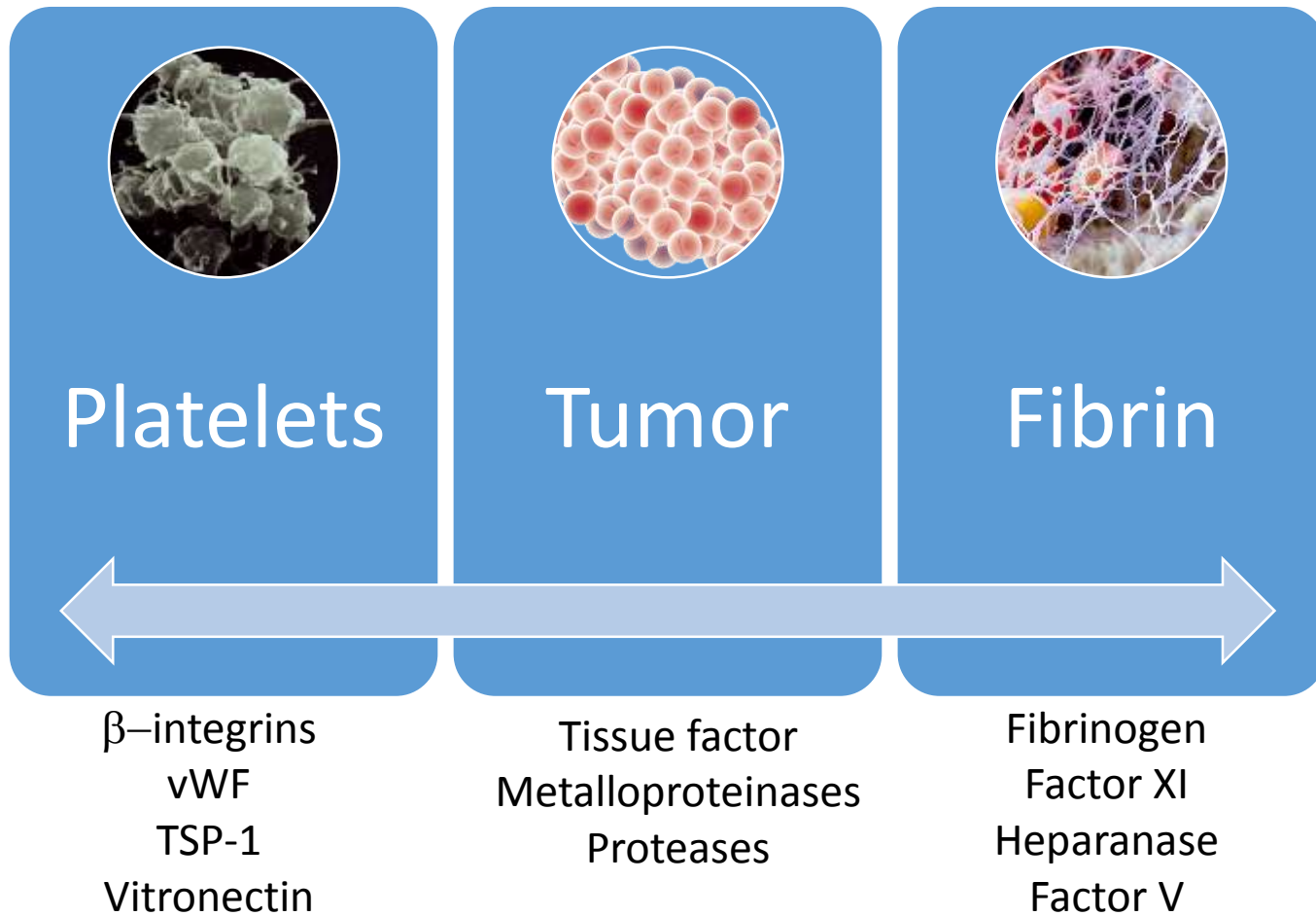
# Isoquercetin inhibits generation of platelet factor Va



# Platelet factor V hypothesis



# PDI-tumor intersection?





# Cancer Associated Thrombosis and Isoquercetin (CATIQ) Trial: Phase II

## Eligibility:

- Advanced pancreatic, NSCLC, colorectal cancer
- Within 4 weeks of 1<sup>st</sup> or 2<sup>nd</sup> line therapy

## Endpoints:

- Safety
- VTE
- D-dimer
- Thrombin generation

## PHASE II

### Cohort A (500 mg)

5 patients



25 patients



### Cohort B (1000 mg)



5 patients



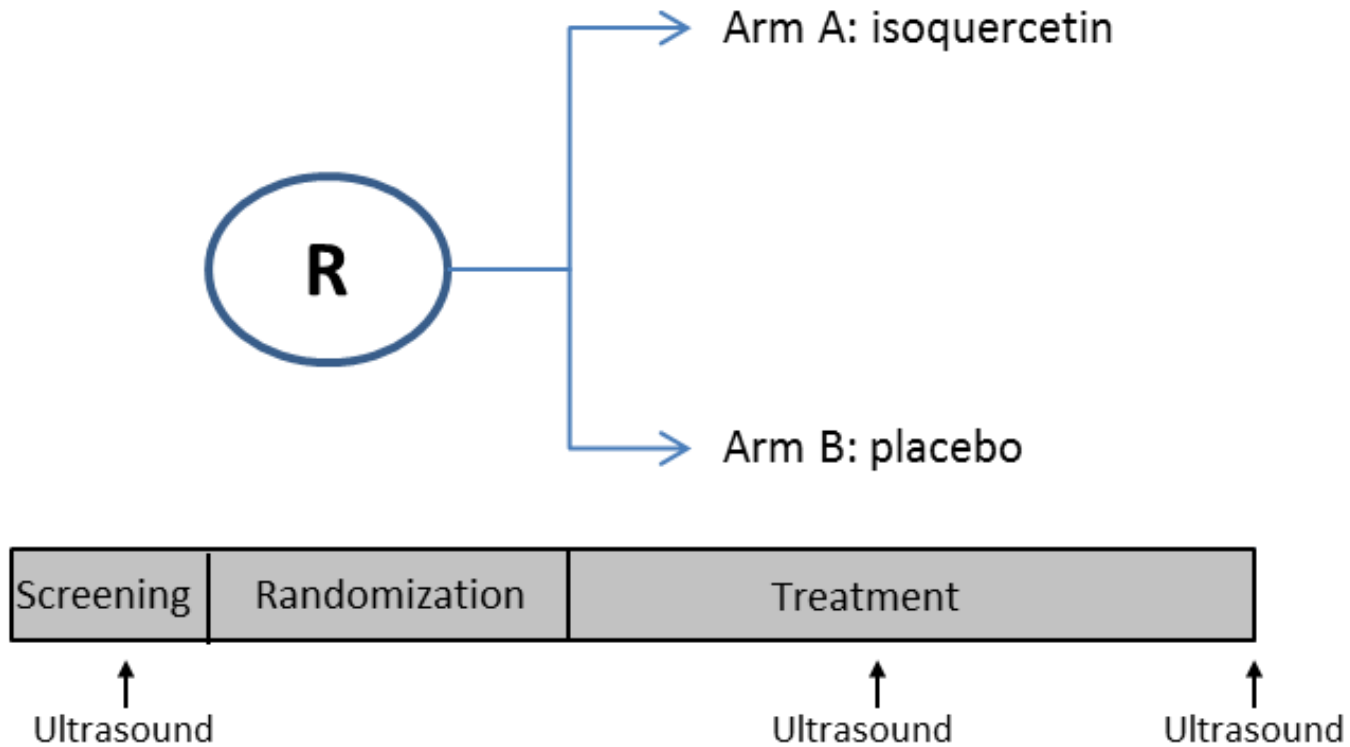
25 patients

# Investigator-initiated clinical trials: Life lessons

- There is no such thing as an easy trial
- The Zen of unanticipated delays
- Learn to swim like a salmon



# Phase III



# Acknowledgements

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Langwith

## Collaborators

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