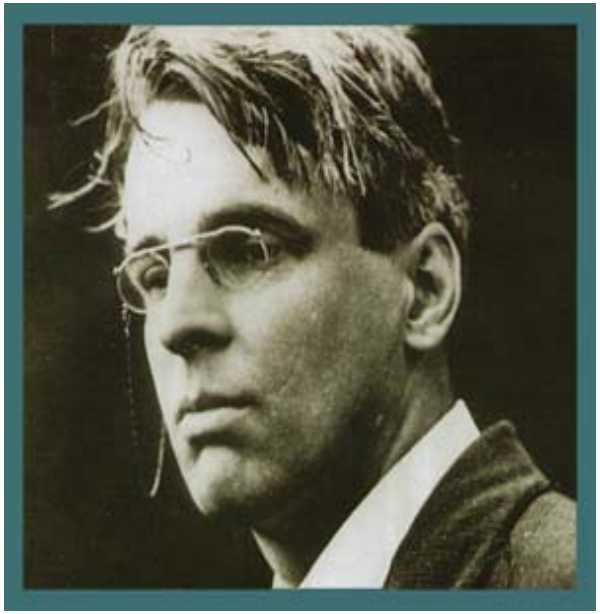
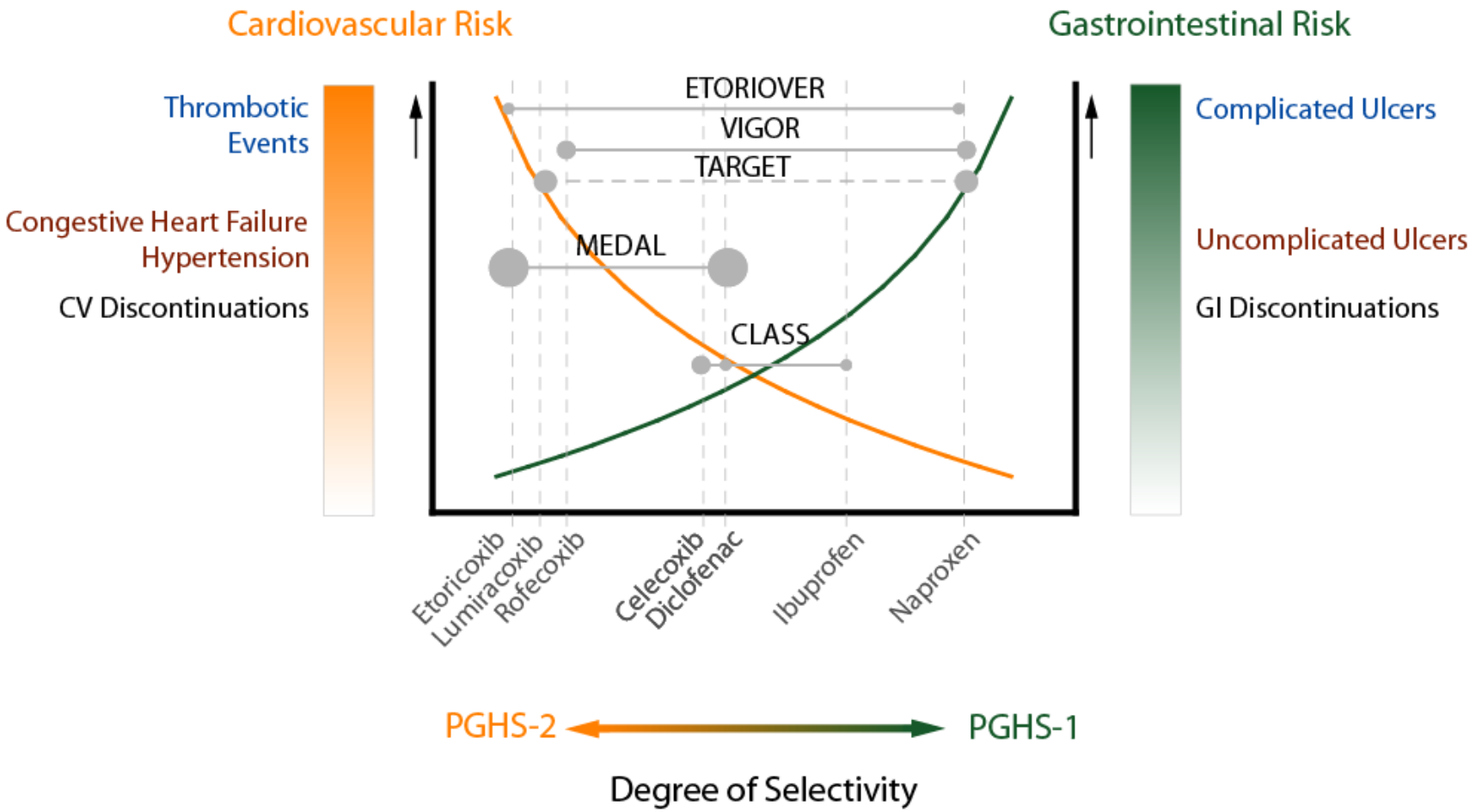
Slouching towards Jerusalem and the passionate intensity of personalization



Biomarker and surrogate skepticism along the way.

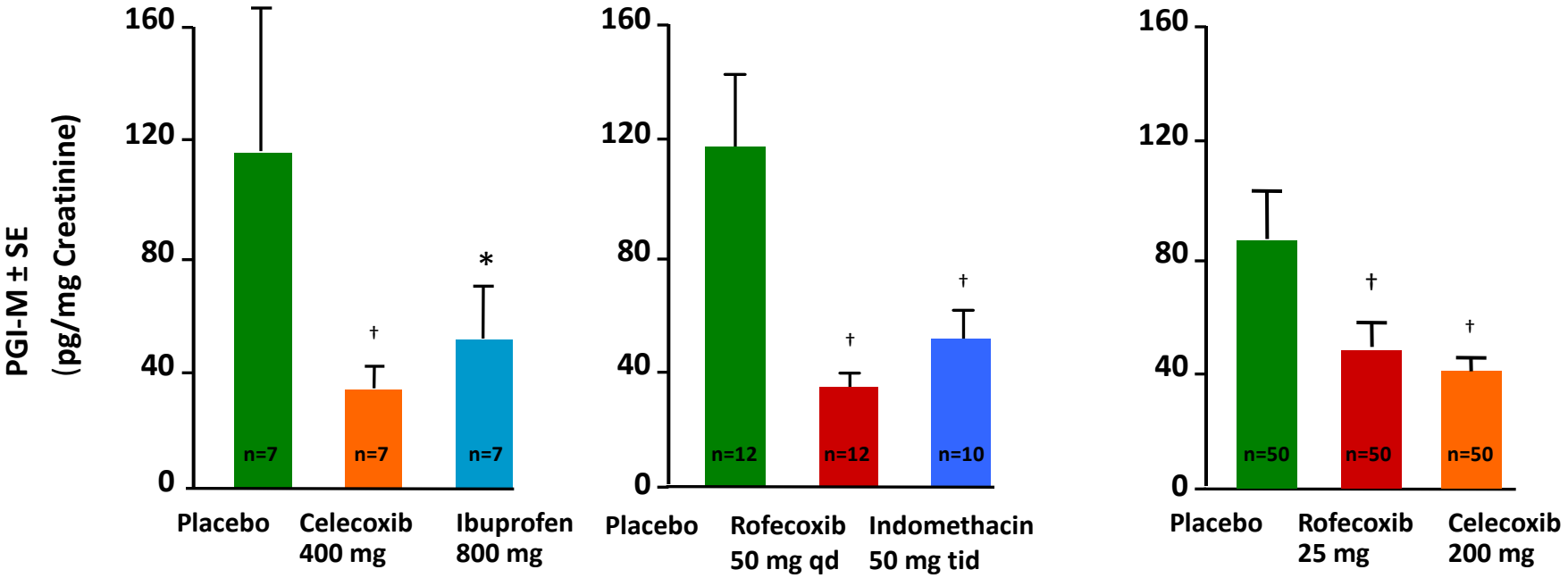
Elevation in BP as a biomarker of risk and reduction of BP as a surrogate of risk modification

- Ignored as a biomarker of risk as HDL was preferred as a biomarker of benefit – torcetrapib
- Ignored as a biomarker of risk as benefits predicted to outweigh risk – bevacizumab.
- Hailed as a “mechanism” of risk which with treatment would attenuate risk – celecoxib and rofecoxib.



FitzGerald GA TiPS 2007.

Inhibition of prostacyclin synthesis by celecoxib and rofecoxib



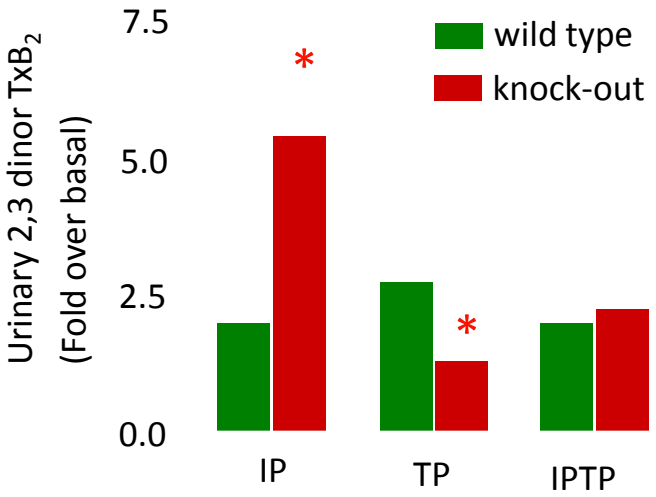
McAdam et al.
PNAS. 1999;96:272

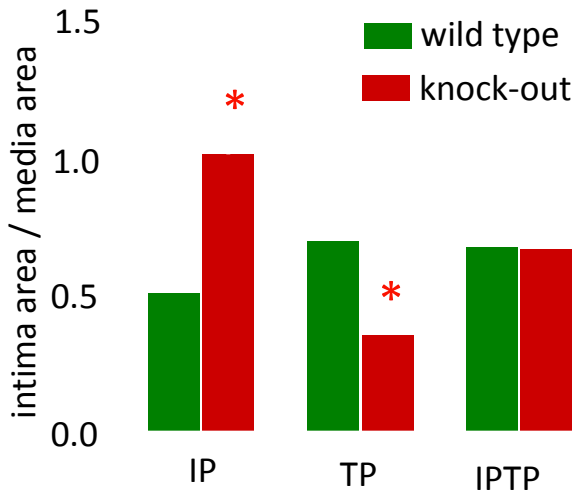
Catella-Lawson et al.
JPET. 1999;289:735.

Fries et al Gastroenterology
130:55-64, 2006

[1]PGI-M = 2,3-dinor-6-keto-$PGF_{1\alpha}$; † $P<0.01$ vs Placebo; * $P<0.05$ vs Placebo.

Prostacyclin modulates the Bioactivity of Thromboxane

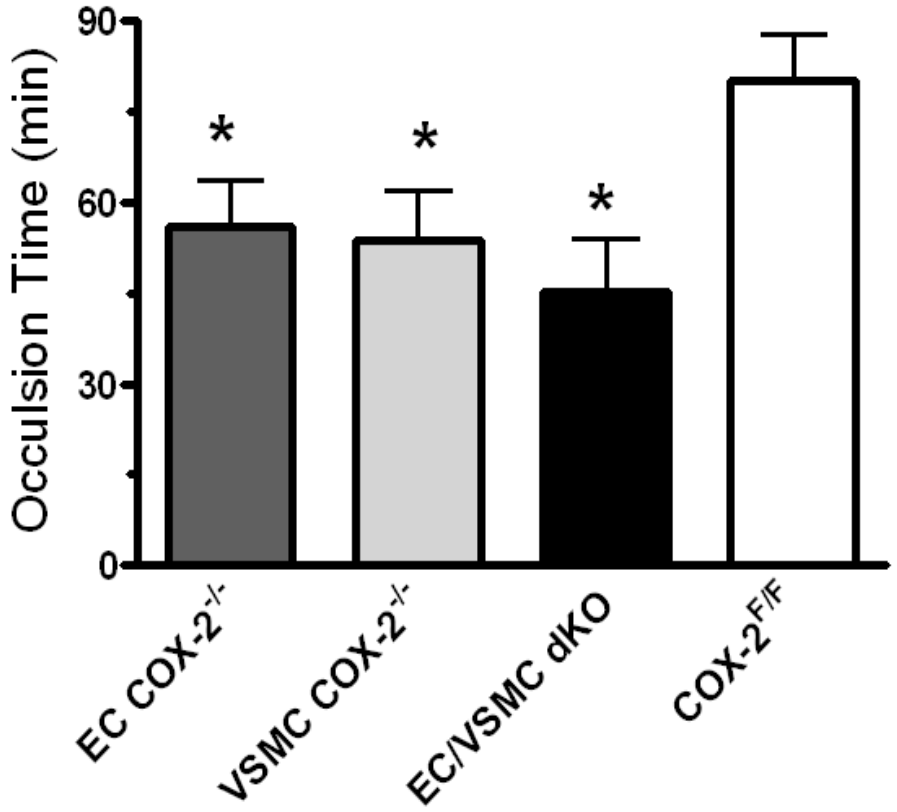




* p<0.05 vs. wild type

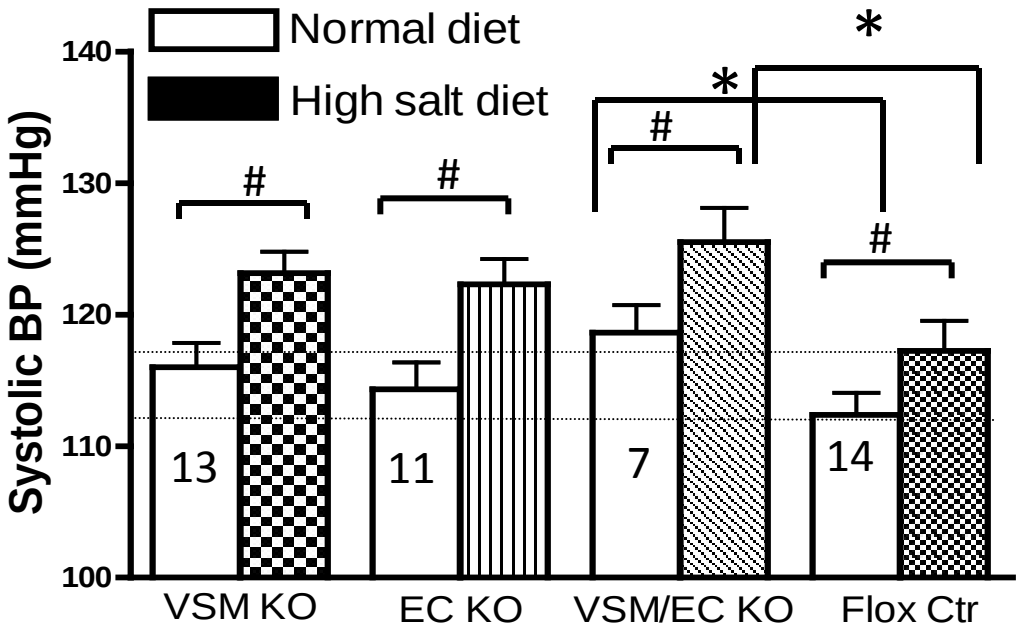
Cheng et al., Science 296:593, 2002

Vascular COX-2 restrains Thrombogenesis



Yu et al
unpublished

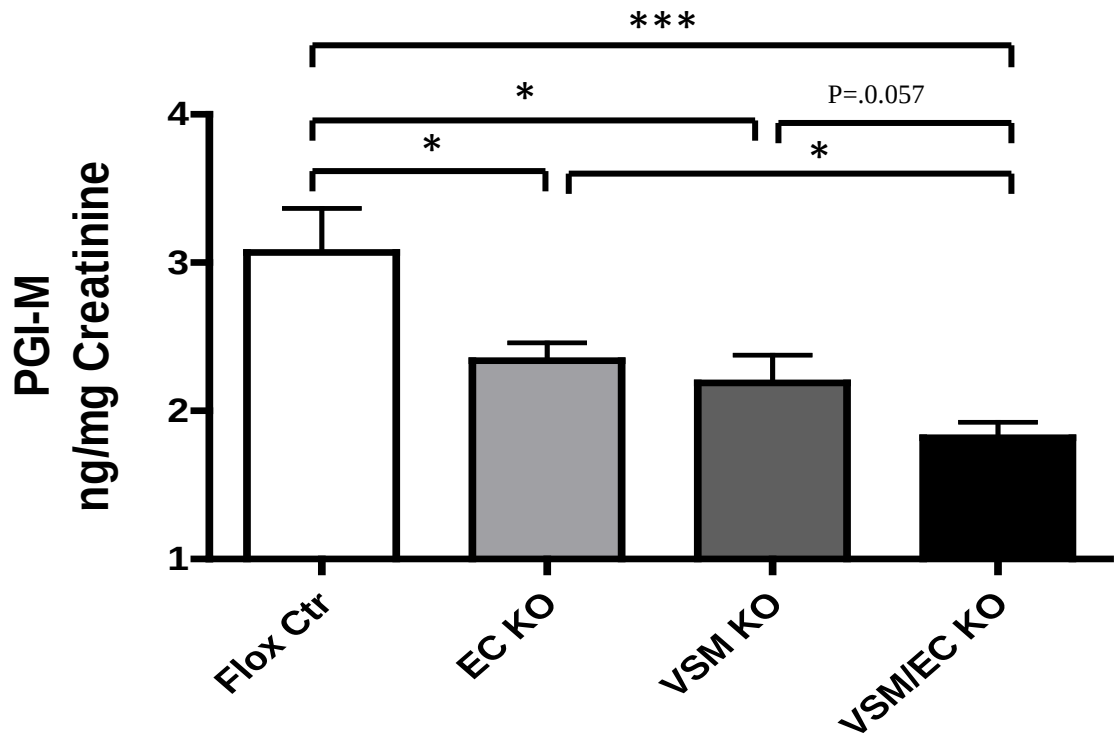
Deletion of Vascular COX-2 elevates Blood Pressure



Yu Y. et al unpublished

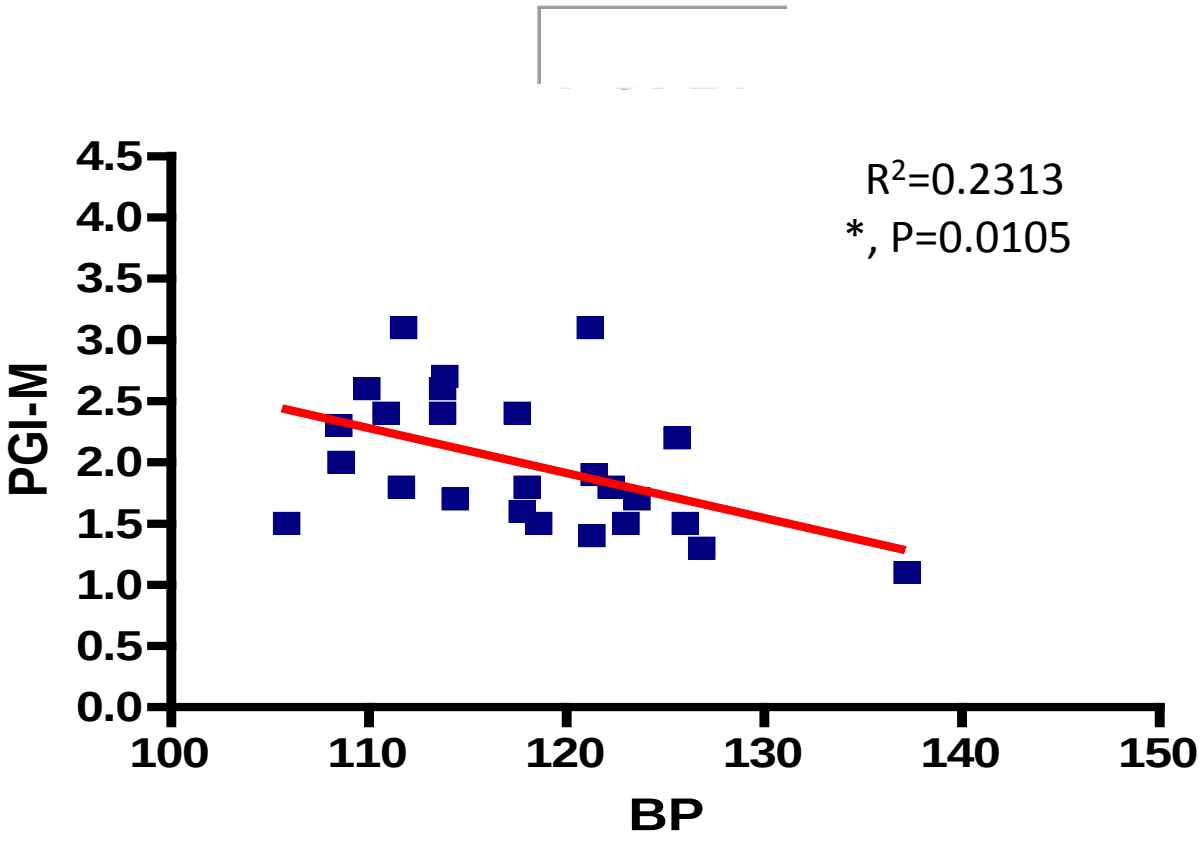
#, p<0.01, paired t test,
*, p<0.05, unpaired t test, n=7-14

Vascular COX-2 contributes to Urinary PGI-M



*, p<0.05; ***, p<0.001, n=16-22

Inverse correlation between BP and PGI_2 in EC and VSMC COX-2 KOs

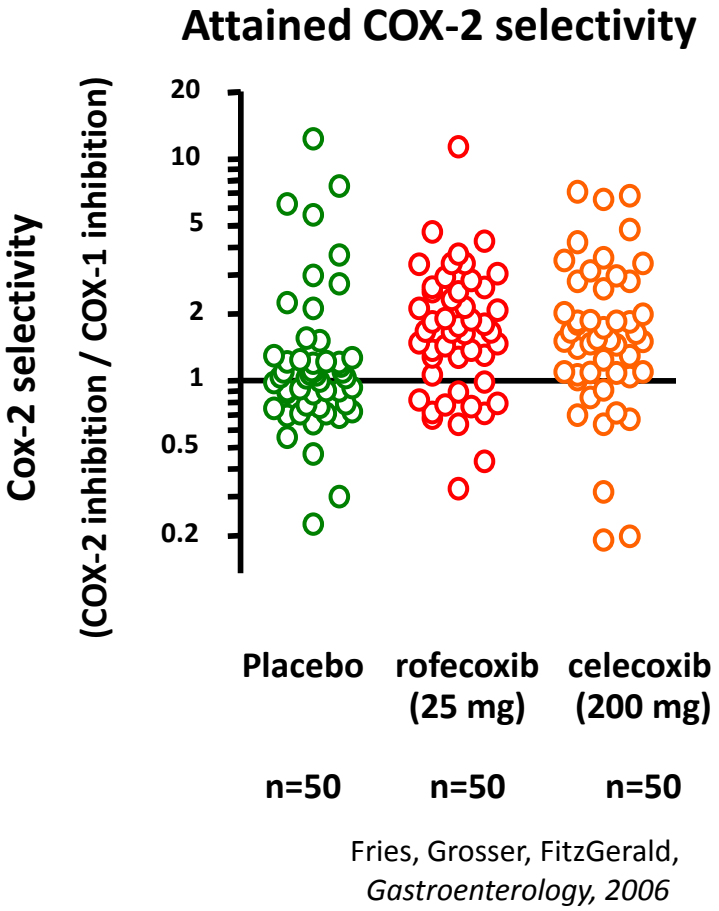


Yi et al 2008

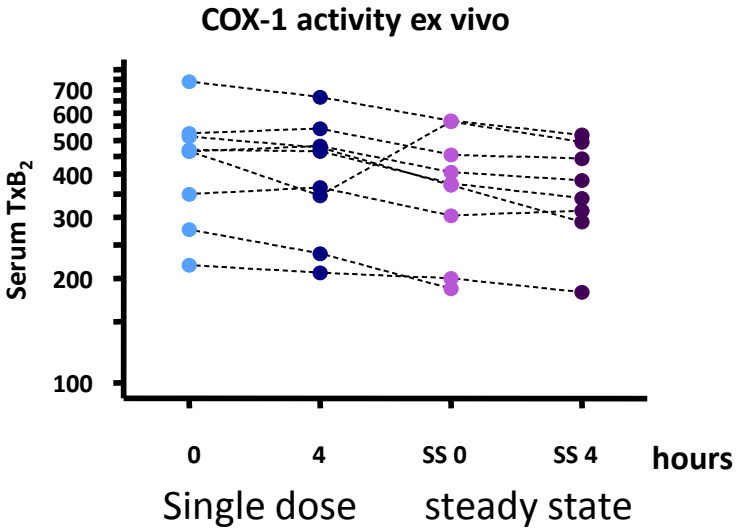
Magic Markers?

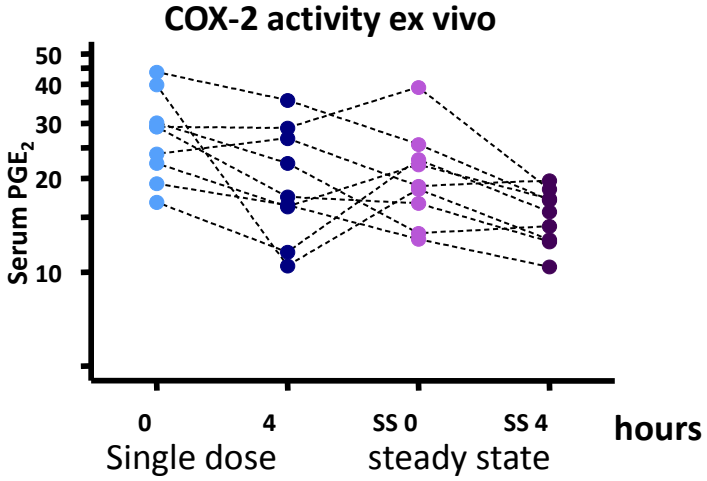
- Depressed PGIM predicted CV hazard and all elements of the human phenotype recapitulated in mice by disruption of the COX-2 dependent formation of PGI_2
- Manifestation of hazard relates to drug exposure, concomitant therapies and underlying CV risk
- Other biological systems promote and restrain hemostasis, hypertension, arrhythmogenesis etc
- How big is the variability problem?

Interindividual variability in the pharmacological response to COX-2 inhibition

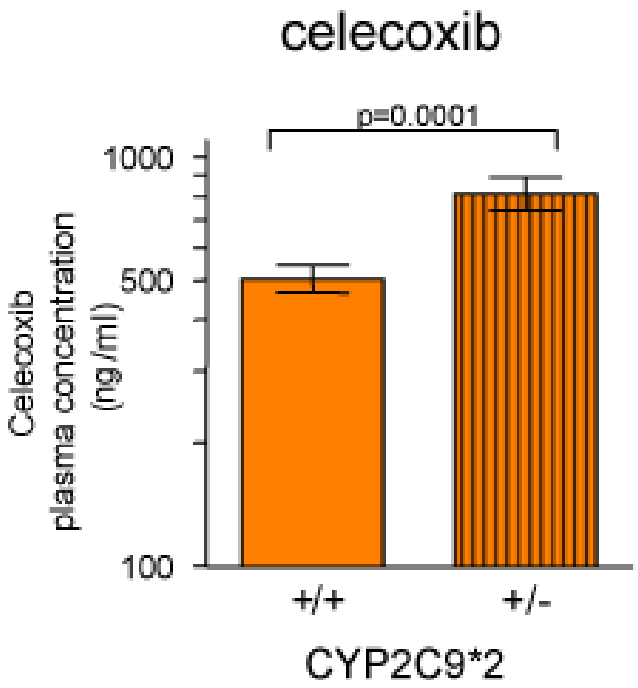


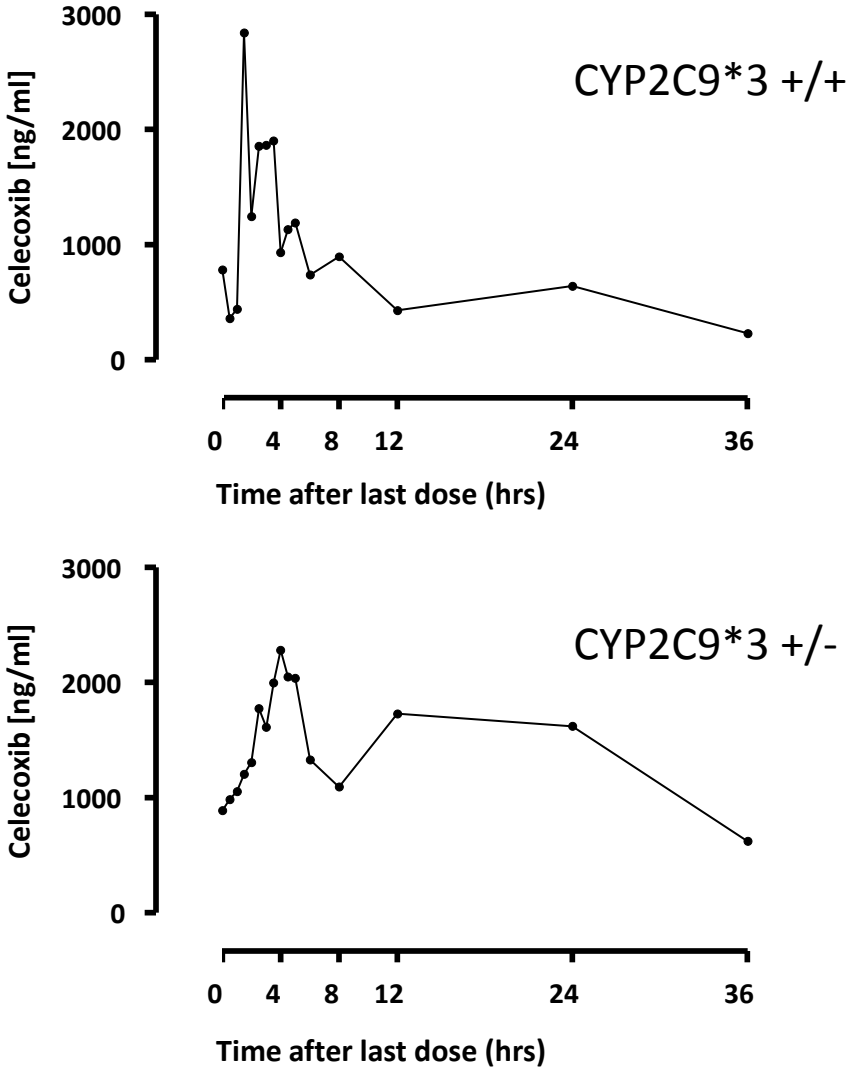
Fries, Grosser, FitzGerald,
Gastroenterology, 2006





Genetic contribution to interindividual variability





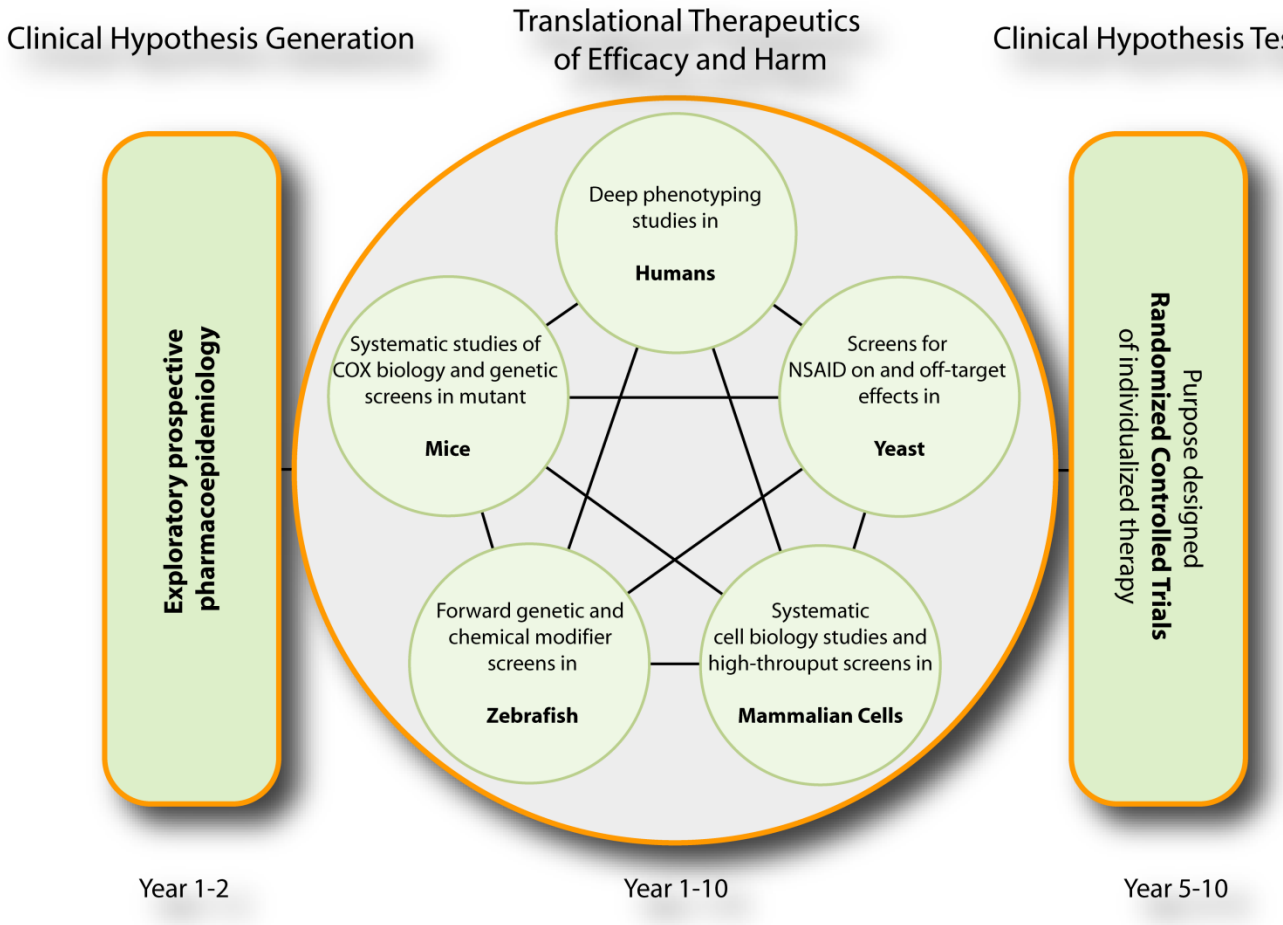
Fries, Grosser, FitzGerald, *Gastroenterology, 2006*

The Challenge of Personalization

- The contribution of genomics to variability in drug response was ~ 30% in healthy male volunteers under controlled conditions.
- How do we predict analgesic efficacy and cardiovascular risk?
- How do we detect emerging risk?
- How do we confer benefit that is incremental to clinical practice?

PENTACON

The Personalized NSAID Therapeutics Consortium

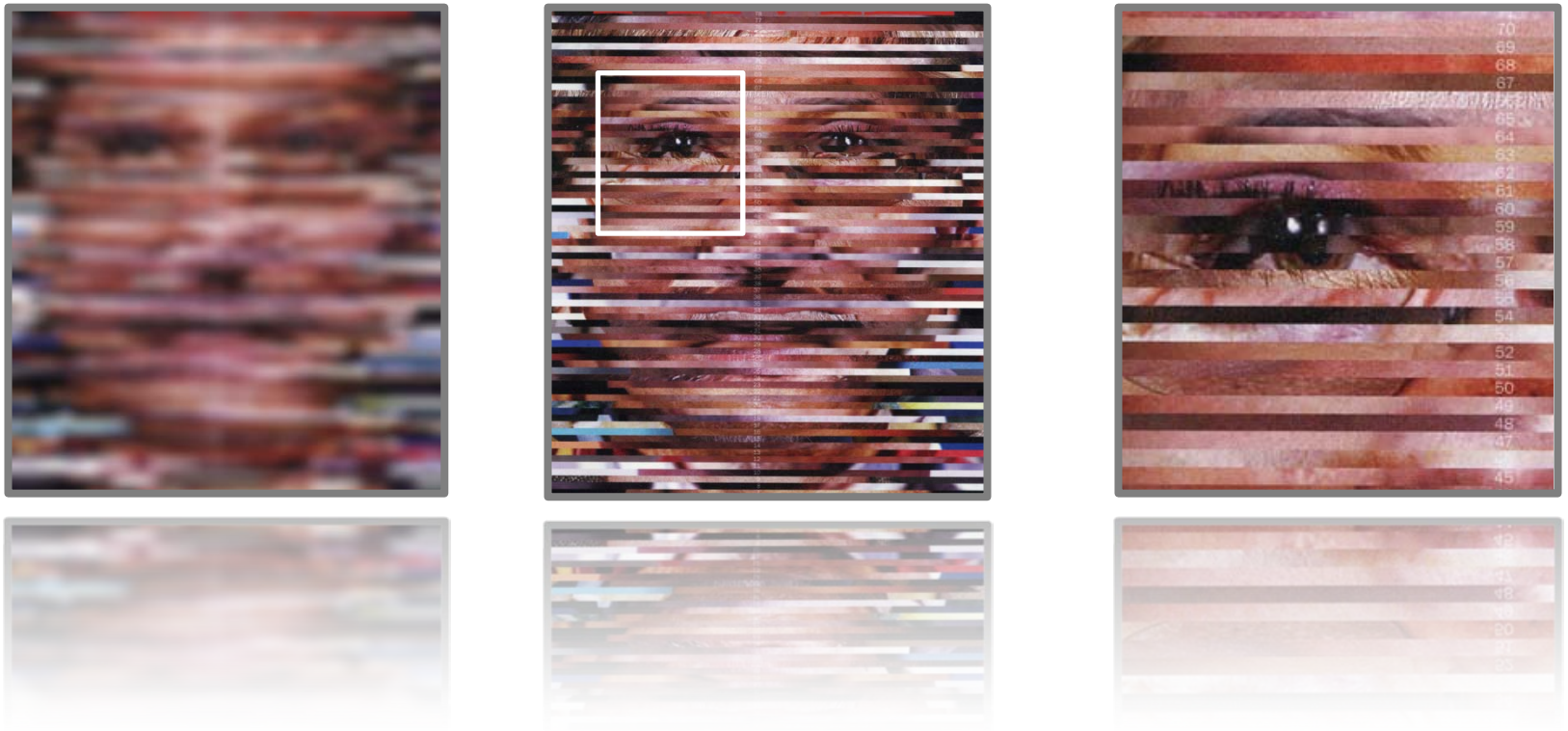


PENTACON

- Harness heterogeneous quantitative data from diverse model systems exposed to comparator NSAIDs at multiple doses
- Utilize systems approaches, progressively populated with human data to develop models that result in novel predictive hypotheses
- Test these hypotheses prospectively at scale.

Personalization of NSAID Therapy

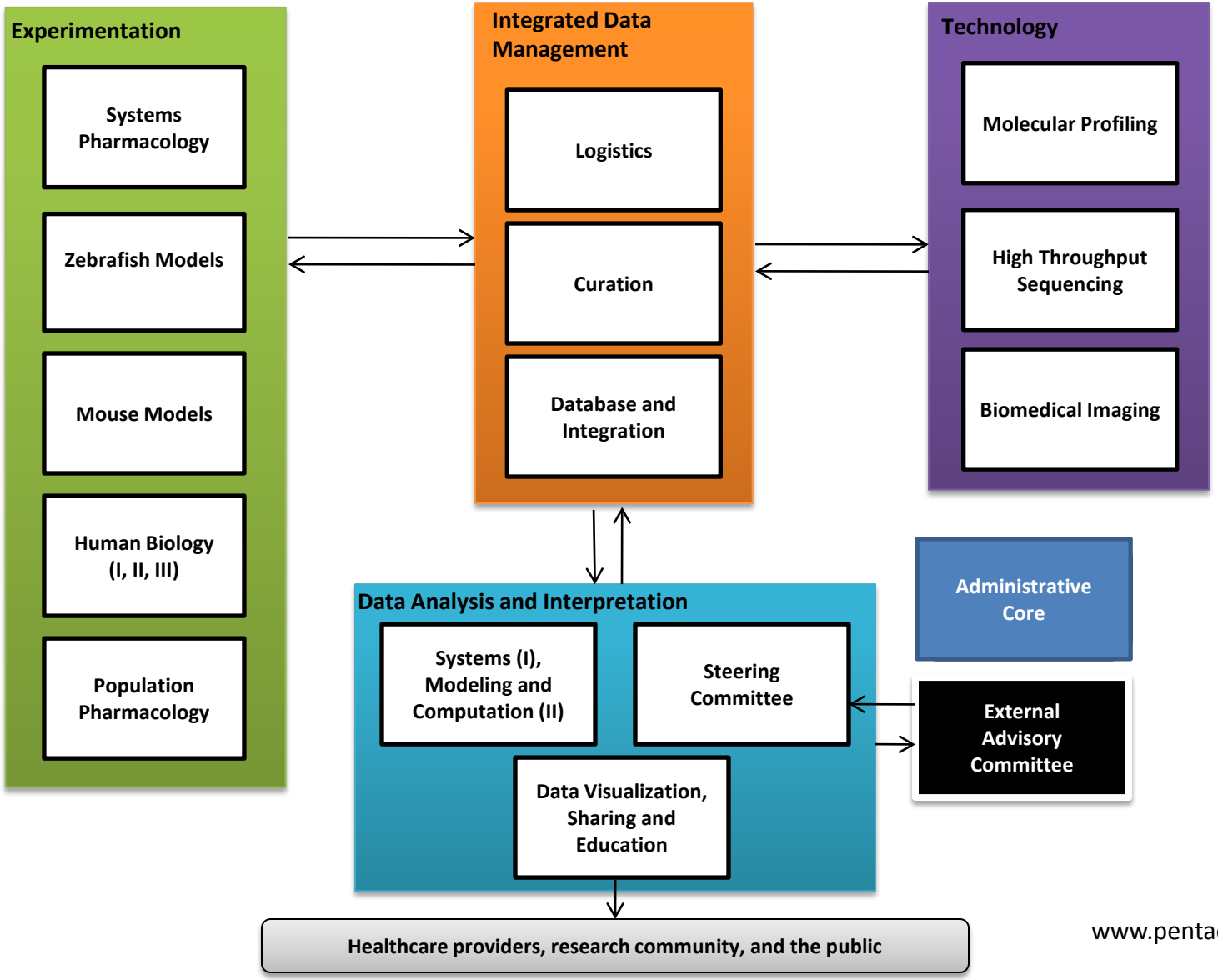
Can we develop algorithms which, when populated with an individual's pre- and post test drug exposure can predict (i) whether they should take and NSAID and (ii) if so which drug, at what dose and for how long?



The Time 100. http://www.time.com, 2008

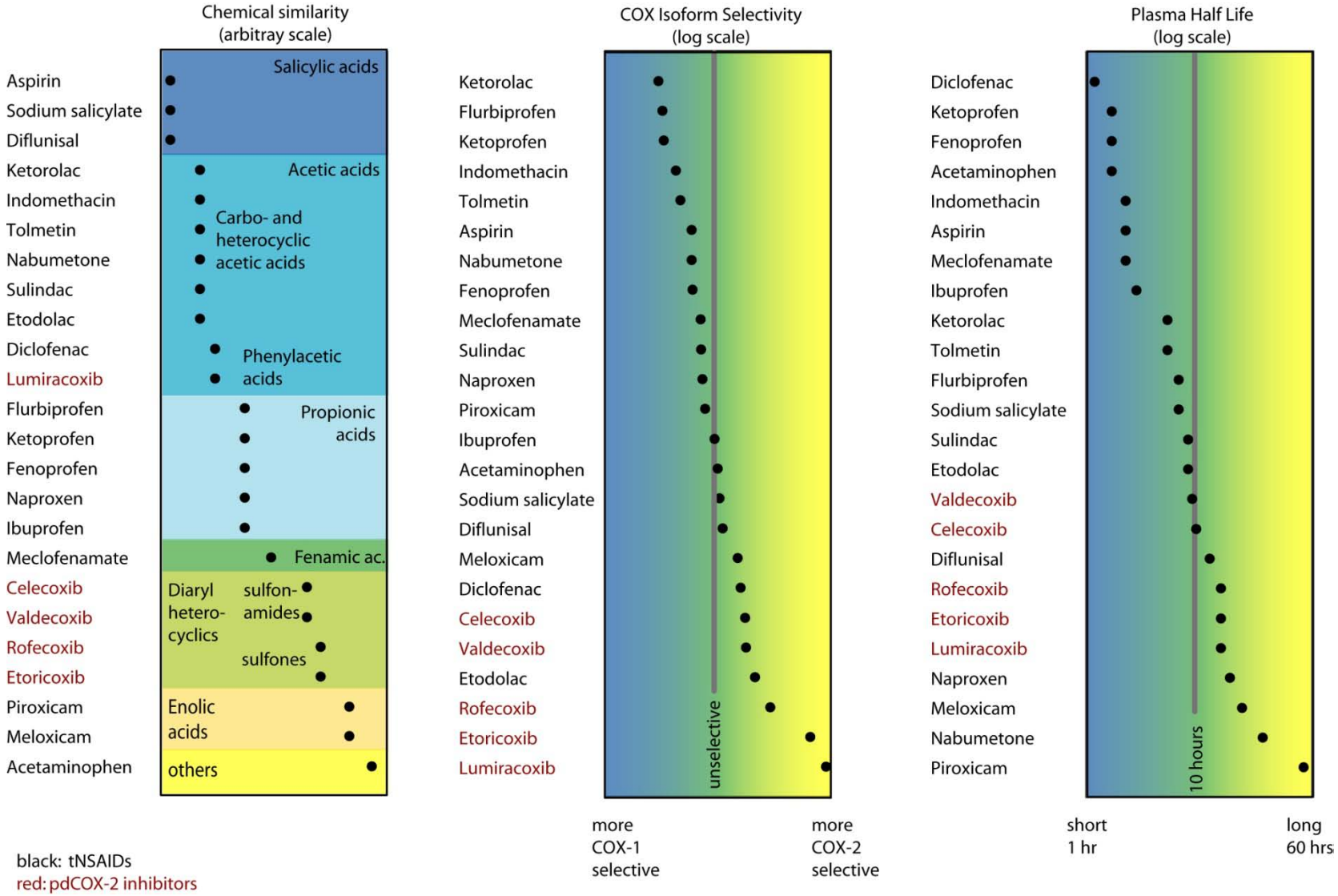
PENTACON

The Personalized NSAID Therapeutics Consortium

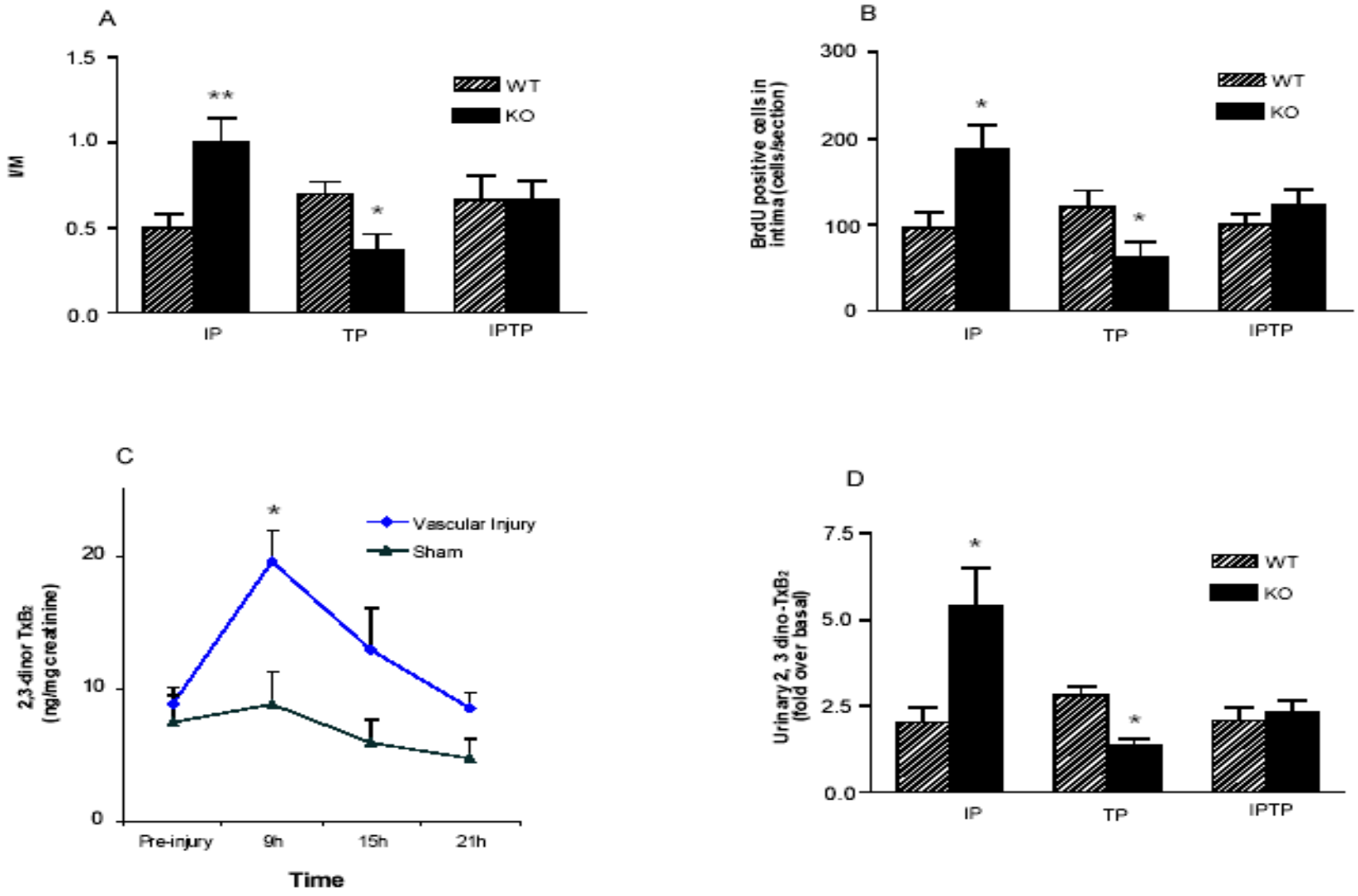


www.pentaconhq.org

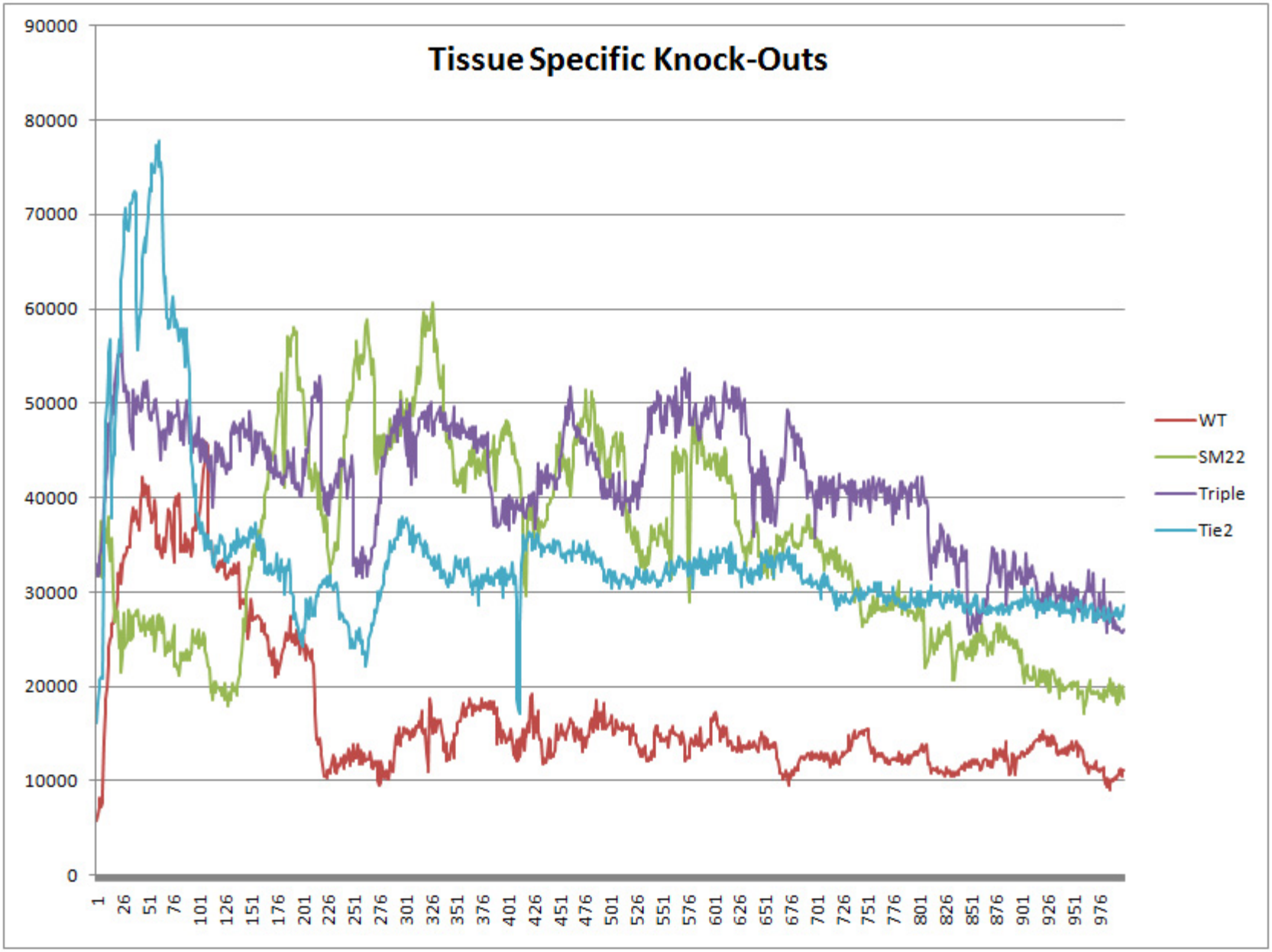
Heterogeneity of nonsteroidal antiinflammatory drugs



Prostacyclin modulates the cadiovascular response to thromboxane *in vivo*



Cheng et al Science 296: 539 – 541, 2002


Tissue Specific Knock-Outs
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
1
26
51
76
101
126
151
176
201
226
251
276
301
326
351
376
401
426
451
476
501
526
551
576
601
626
651
676
701
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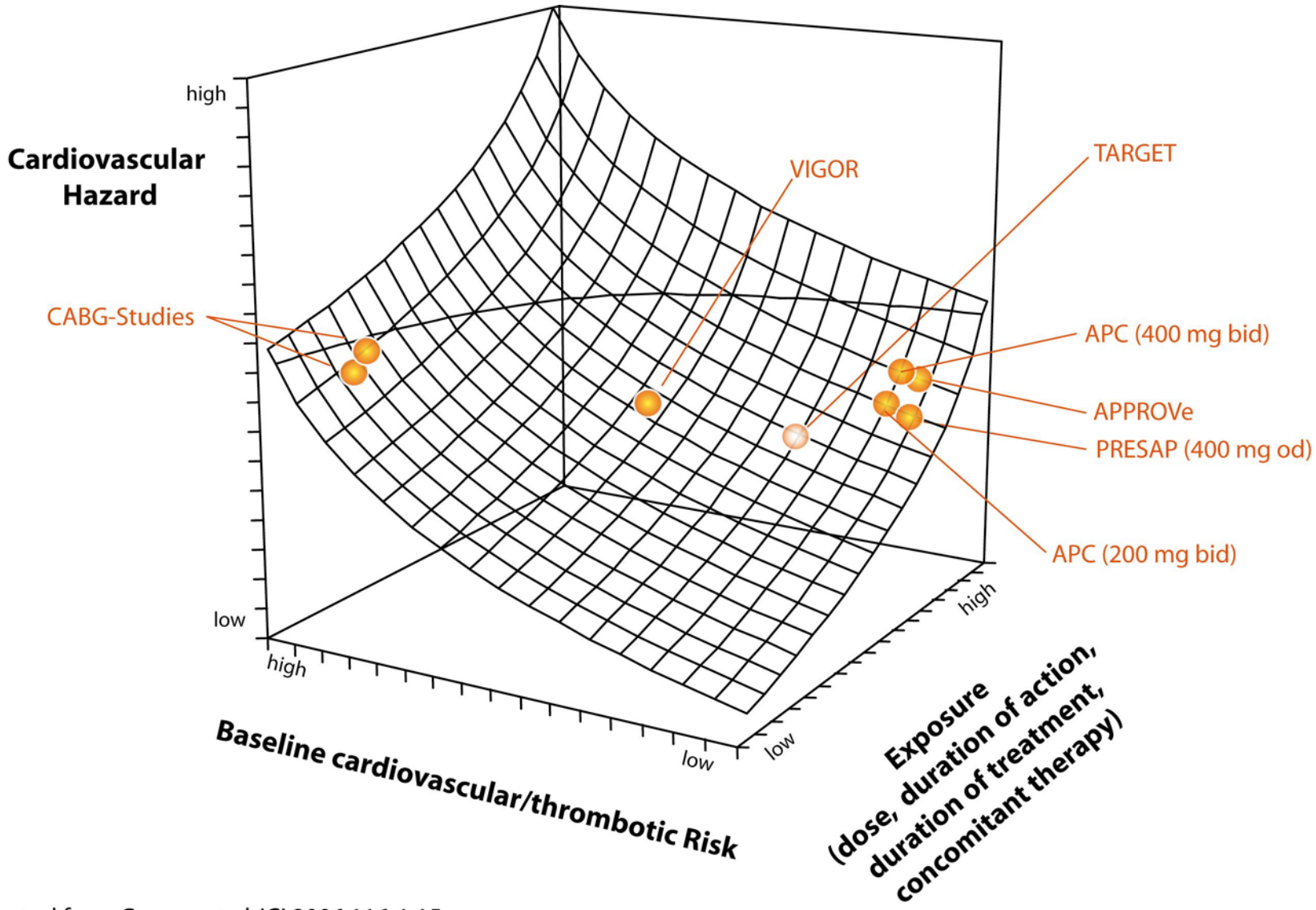
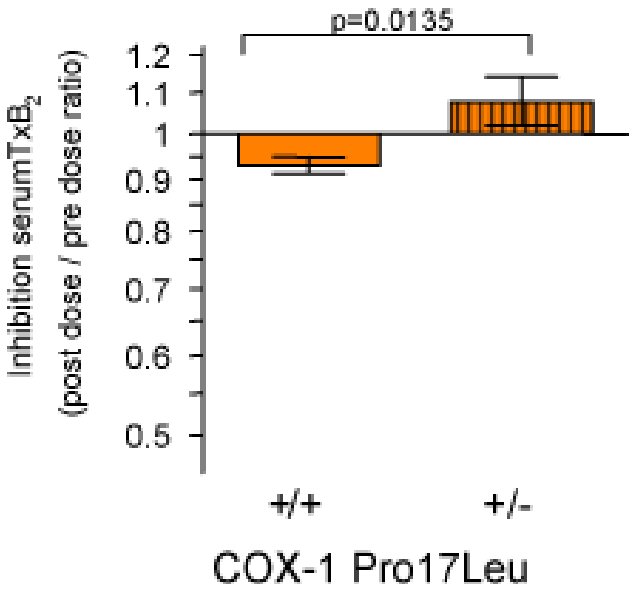
751
776
801
826
851
876
901
926
951
976
WT
SM22
Triple
Tie2



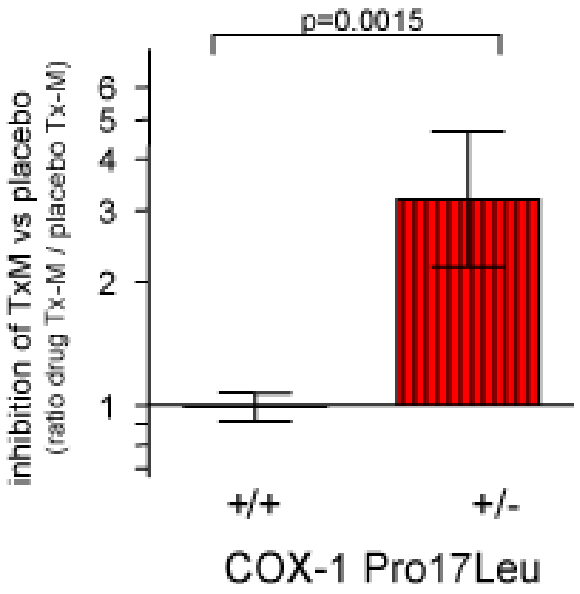
Adapted from Grosser et al JCI 2006;116:4-15

Genetic contribution to interindividual variability (ii)

Celecoxib

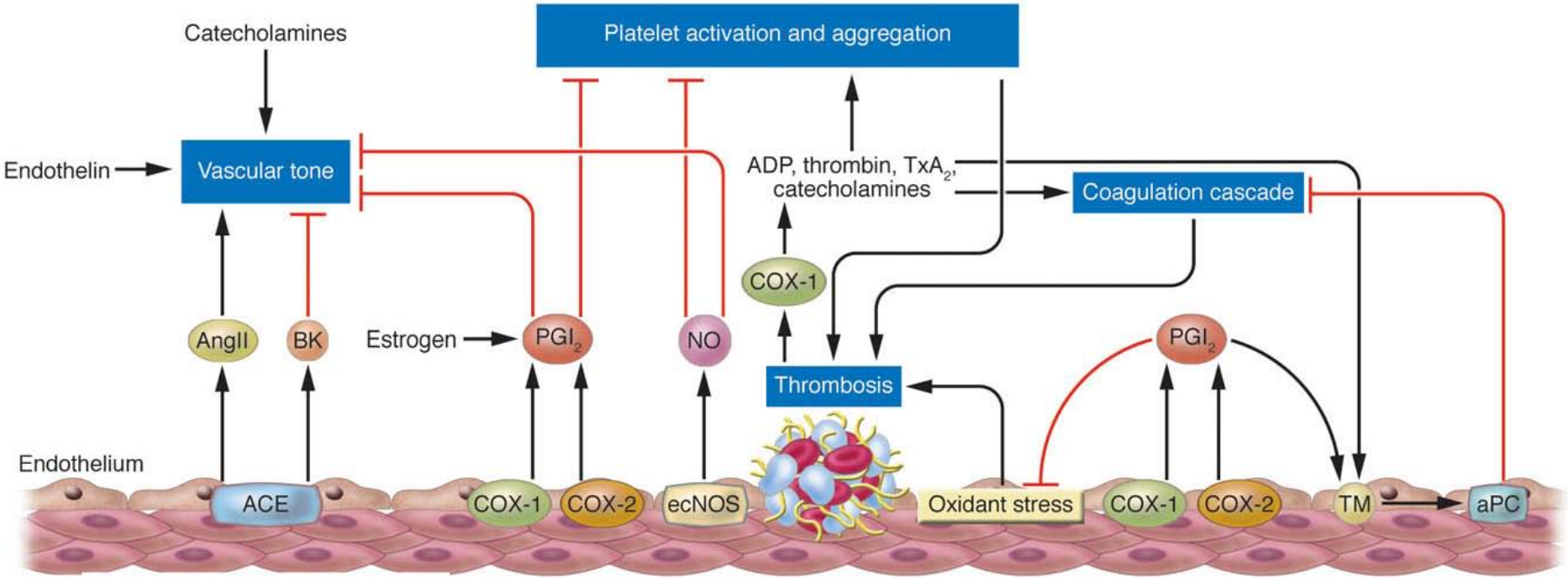


Rofecoxib



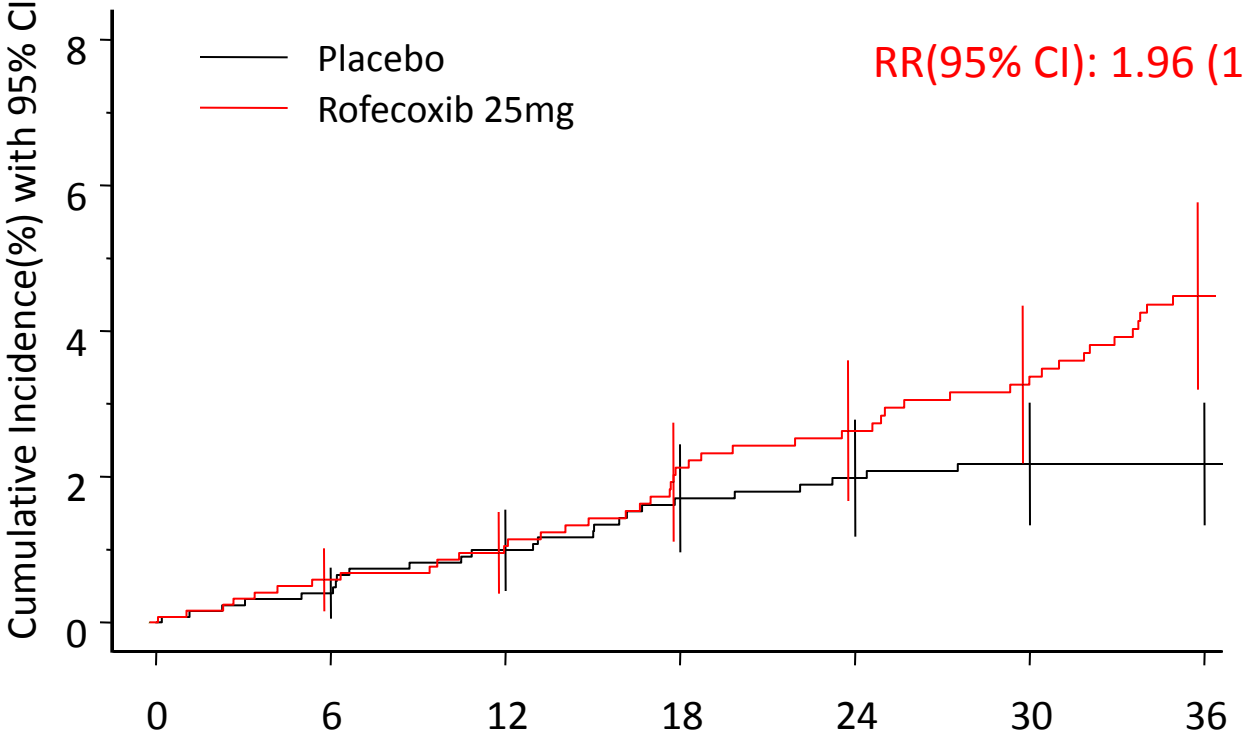
Fries, Grosser, FitzGerald, *Gastroenterology, 2006*

IT'S NOT A SIMPLE "BALANCE"



Confirmed Thrombotic Endpoint

Kaplan-Meier Estimates (95% CI)



Patients at Risk							
Placebo	1299	1192	1148	1079	1039	1002	470
Rofecoxib 25 mg	1287	1123	1050	986	935	898	411

* $p<0.05$

NSAIDs: Non-Steroidal Antiinflammatory Drugs

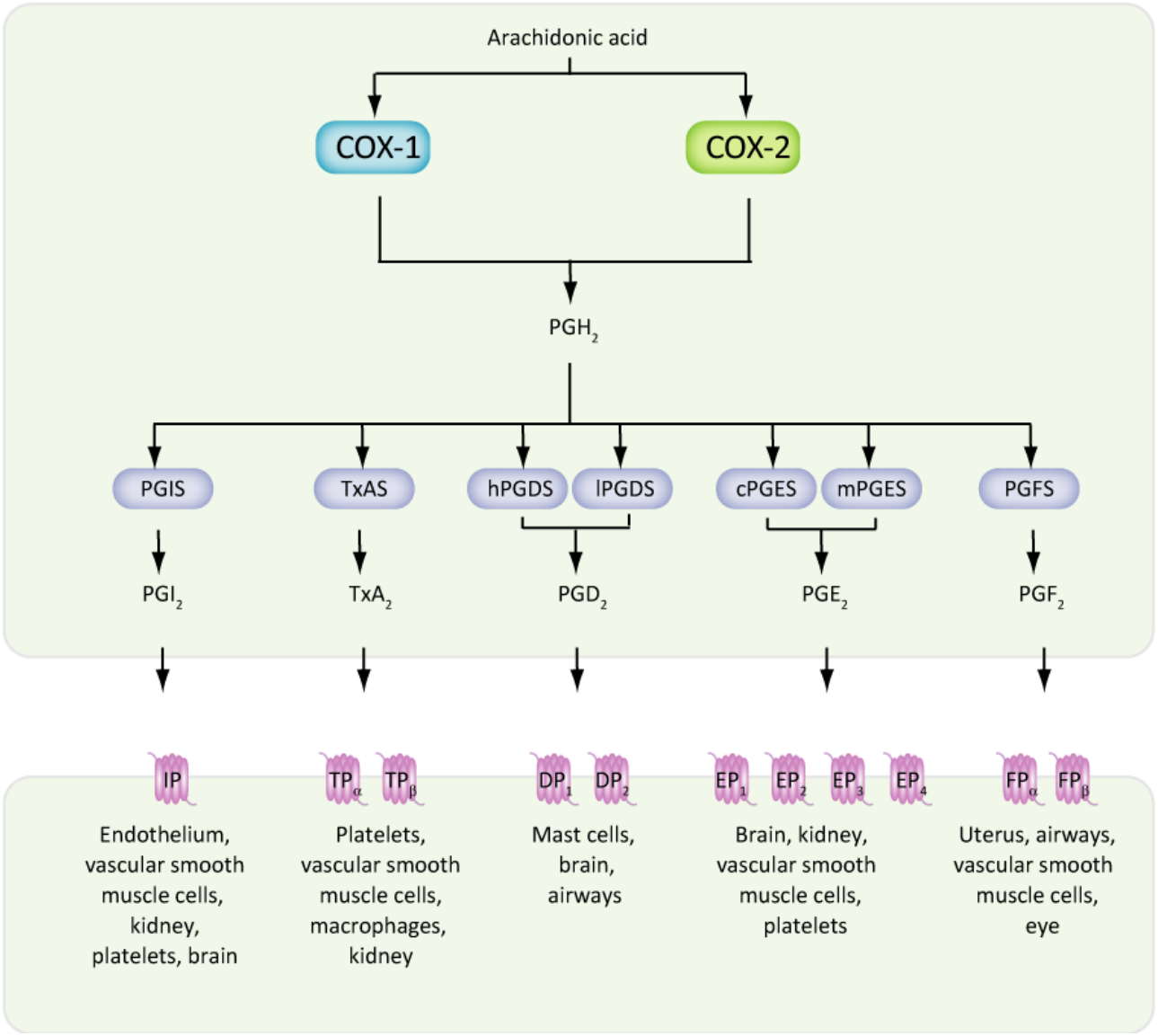
- Non-steroidal antiinflammatory drugs (NSAIDs) are the most commonly used pain killers in the world. Approximately 1000 NSAID containing drugs exist.

- 46 million U.S. adults with arthritis use an NSAID regularly or intermittently for pain control

- Some patients will have severe complications on NSAIDs:

all NSAIDs can cause: stomach ulcers, gastrointestinal bleeds, hypertension

some NSAIDs can cause: heart attack and stroke


Arachidonic acid
COX-1
COX-2
PGH2
PGIS
TxAS
hPGDS
lPGDS
cPGES
mPGES
PGFS
PGI2
TxA2
PGD2
PGE2
PGF2
IP
TPα
TPβ
DP1
DP2
EP1
EP2
EP3
EP4
FPα
FPβ
Endothelium, vascular smooth muscle cells, kidney, platelets, brain
Platelets, vascular smooth muscle cells, macrophages, kidney
Mast cells, brain, airways
Brain, kidney, vascular smooth muscle cells, platelets
Uterus, airways, vascular smooth muscle cells, eye