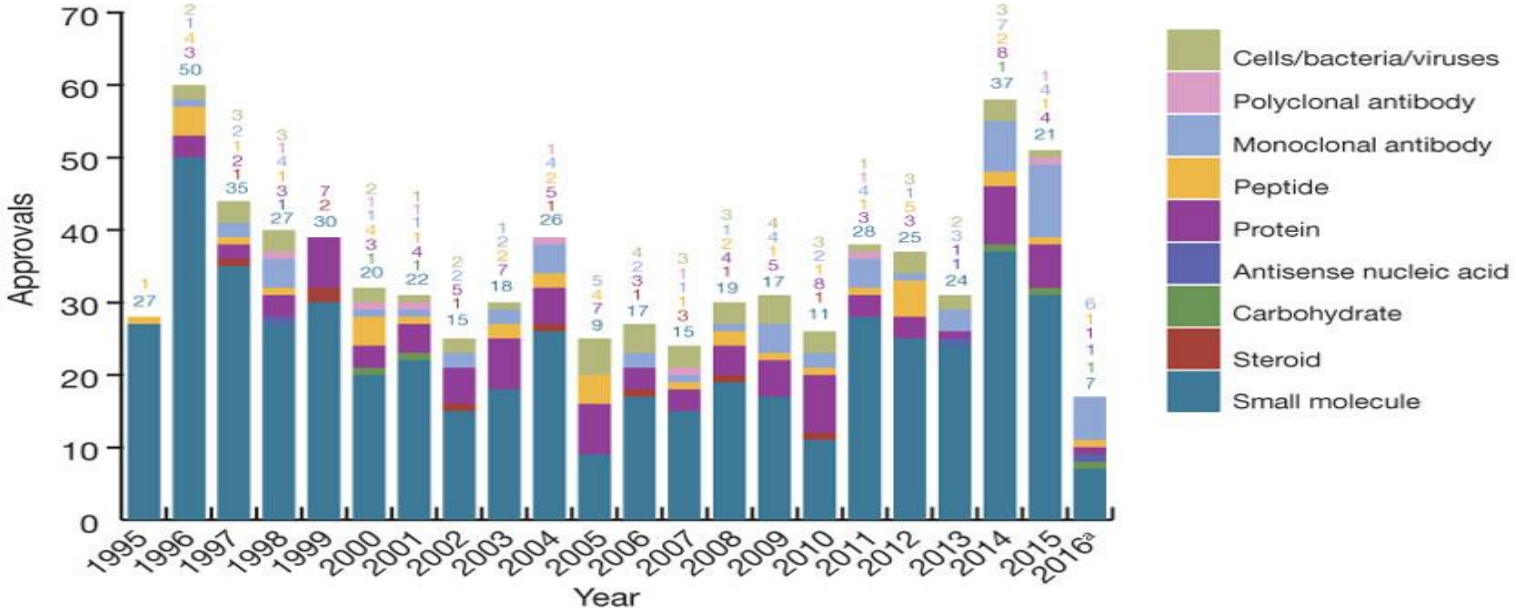
Translational Science in the Era of Precision Medicine

Translation of the promise of basic discoveries to realize novel therapeutics, diagnostics and approaches to management that benefit the public health

Revival of Drug Approvals?

The trend for fewer drug approvals continues in 2016.

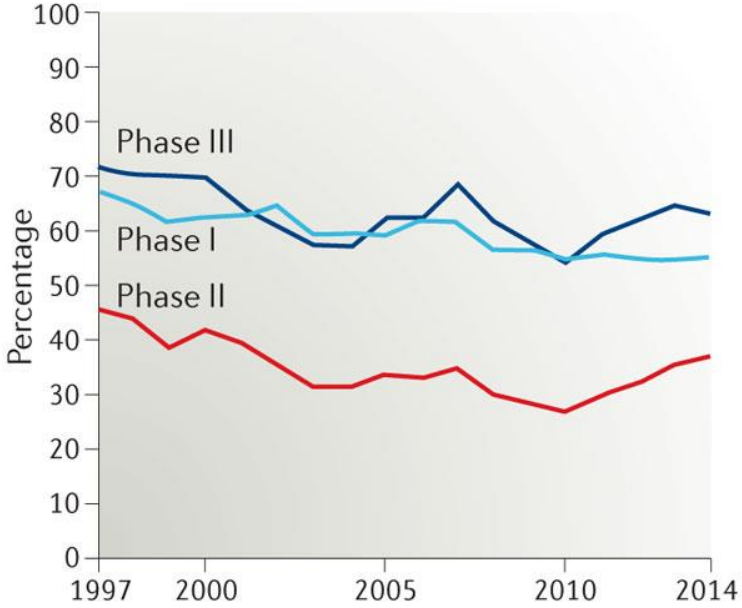


[a]2016 partial year ending Sept. 30.

Source: BioMedTracker, a service of Sagient Research (http://www.biomedtracker.com/)

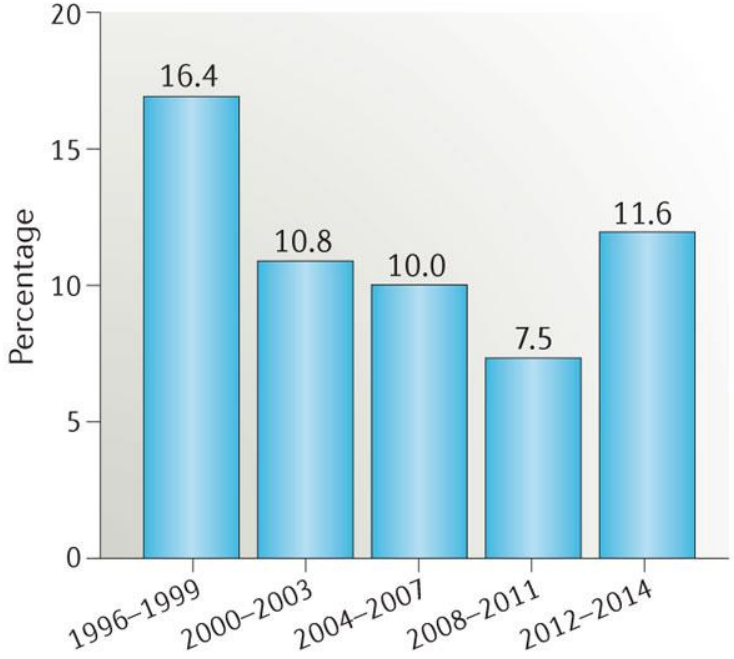
a Success rates by phase

Percentage likelihood of moving to next phase, 3-year rolling average*



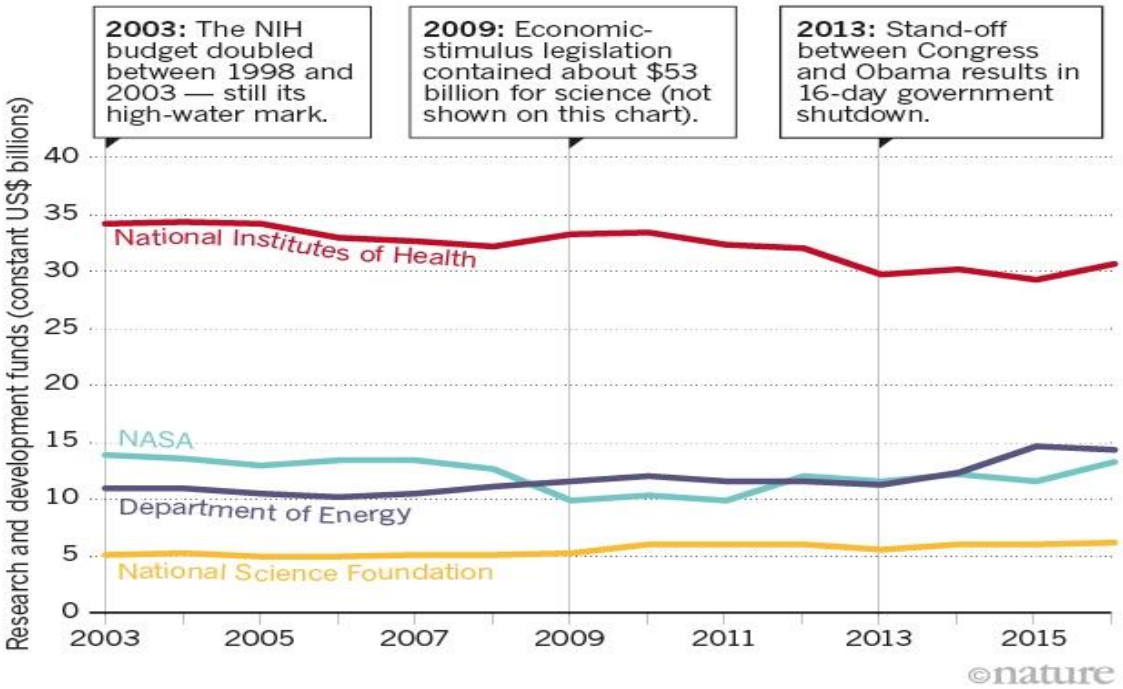
b Cumulative success rate Phase I to launch

Percentage likelihood of moving from Phase I to launch



BUDGET BATTLES

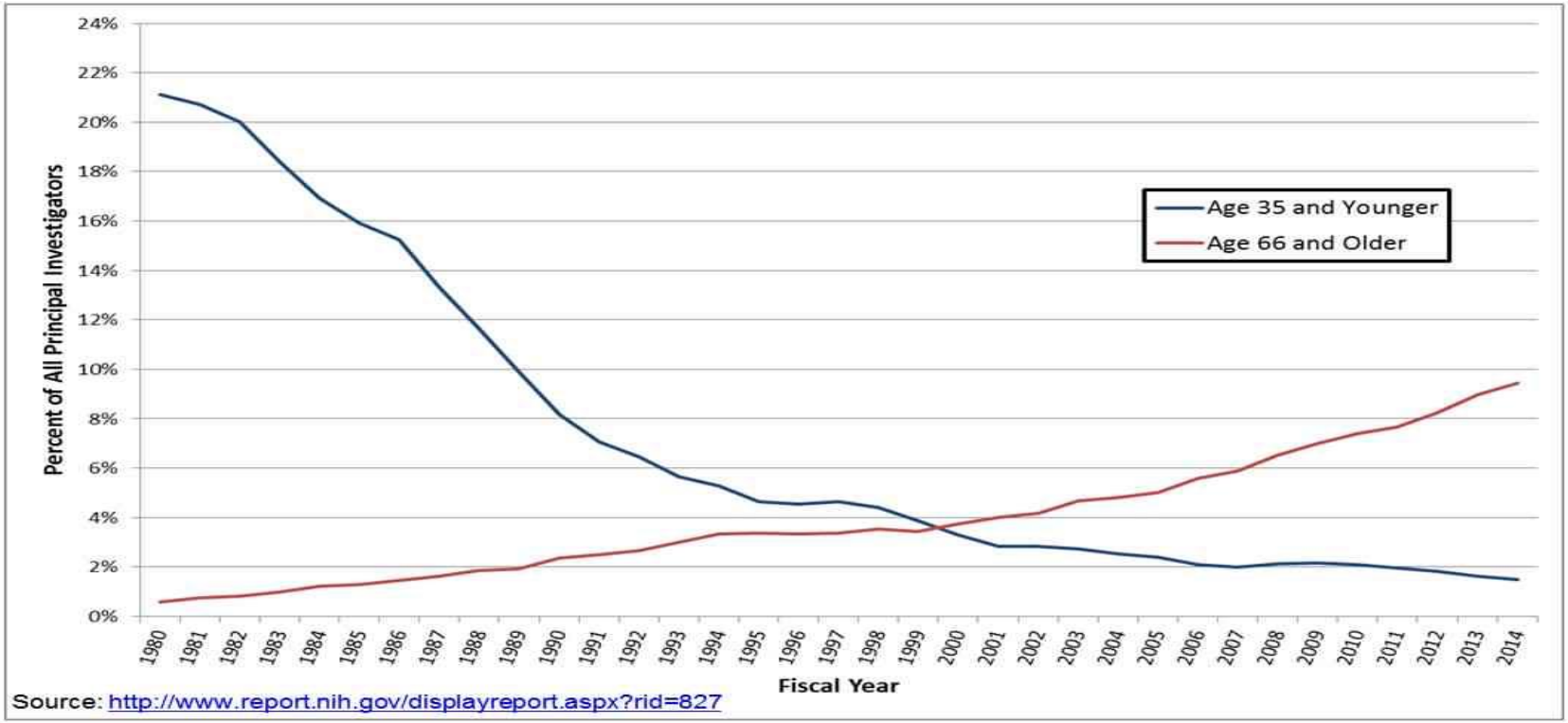
US President Barack Obama, who took office in January 2009, pushed to increase funding for science agencies. But Congress often rebuffed his proposals.



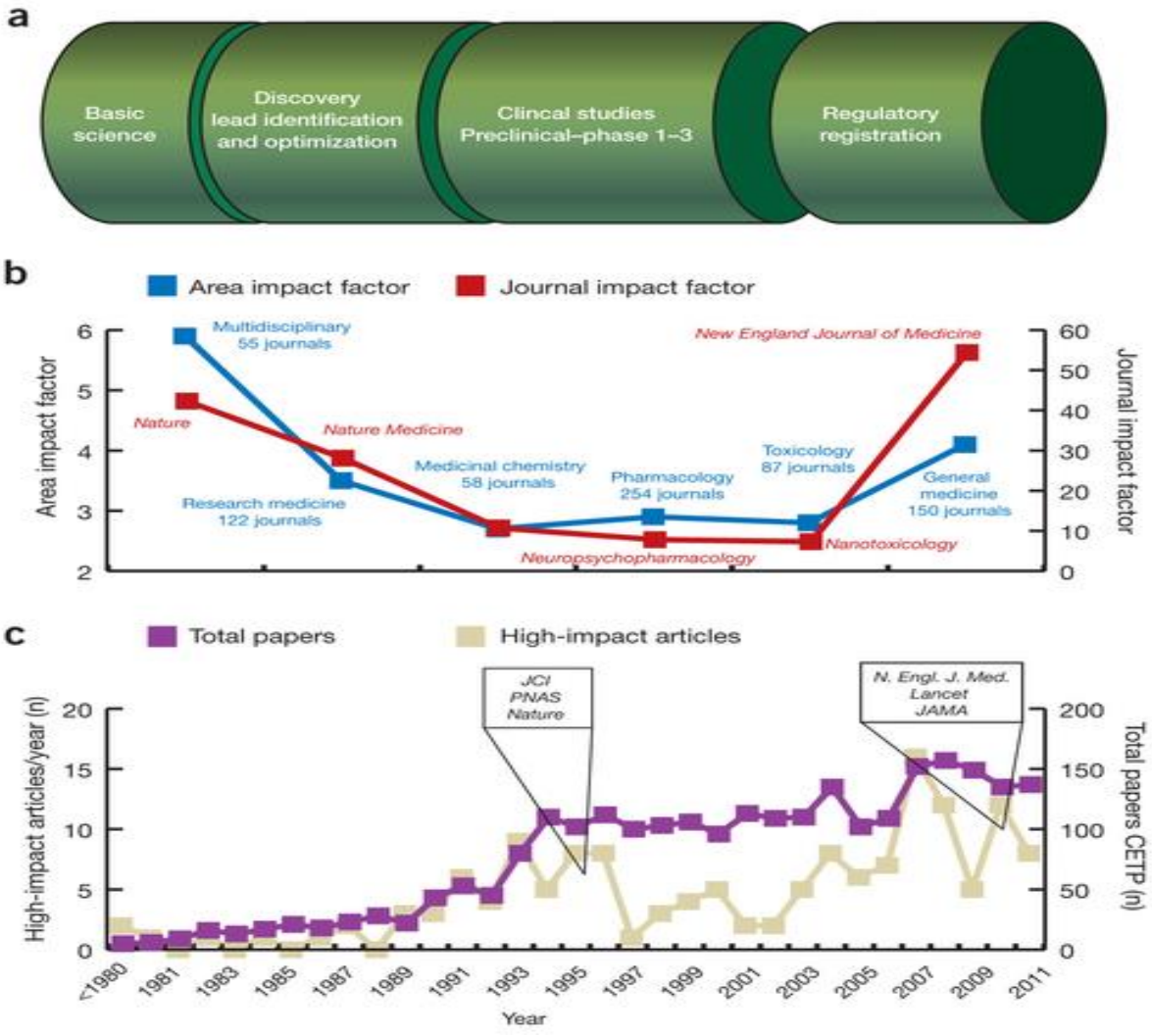
You ain’t seen nothing yet…

Percentage of NIH R01 Equivalent Principal Investigators of All Degrees: Age 35 and Younger vs. Age 66 and Older

Fiscal Year 1980 - 2014

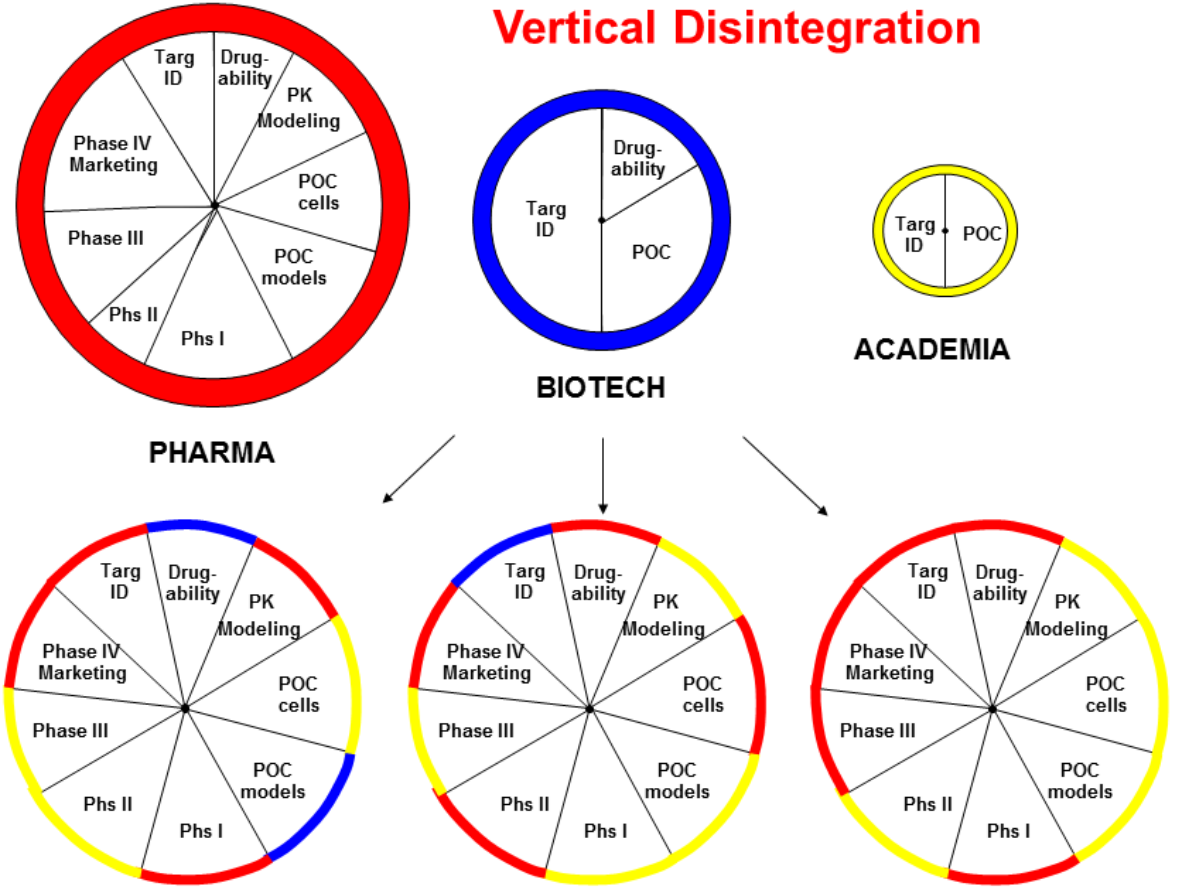


Source: http://www.report.nih.gov/displayreport.aspx?rid=827



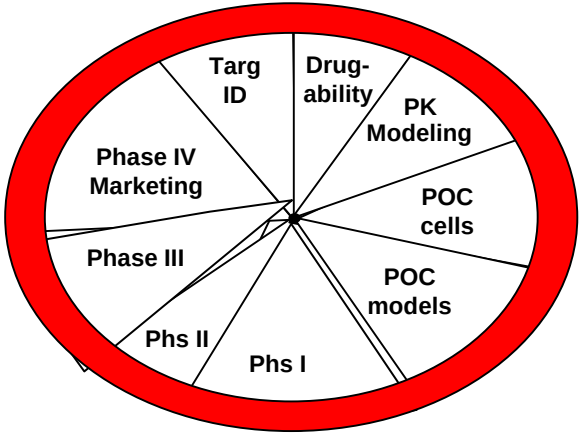
Pasterkamp et al
Nat. Biotech. 2016

Vertical Disintegration

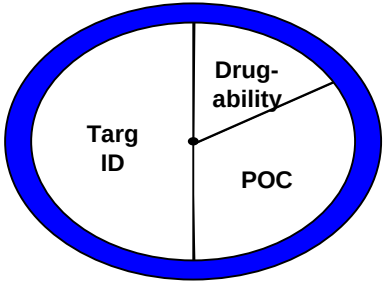


Skarke C and FitzGerald GA Sci Transl Med. 2010 Apr 7;2(26):26cm12.

Vertical Disintegration

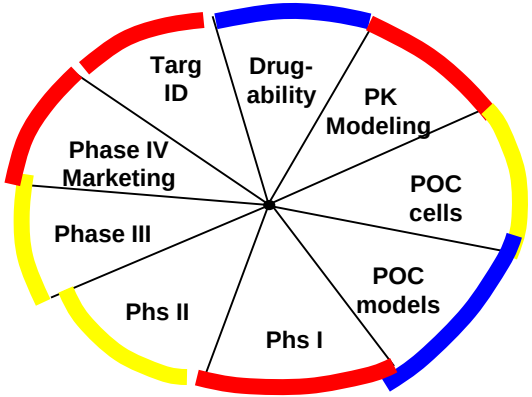


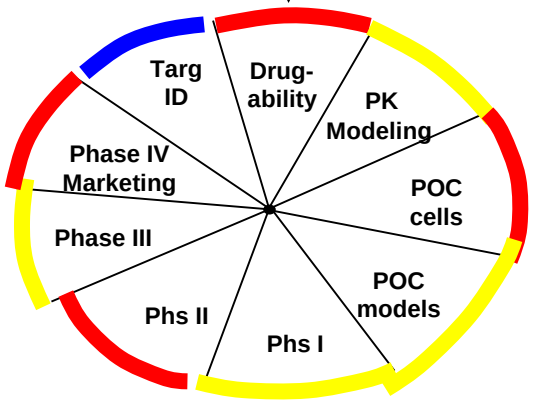
PHARMA

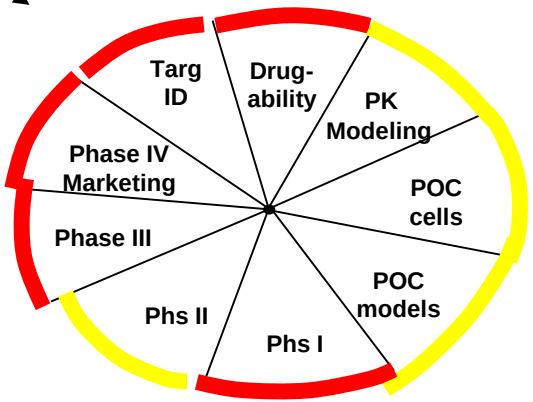


BIOTECH

ACADEMIA







Skarke C and FitzGerald GA Sci Transl Med. 2010 Apr 7;2(26):26cm12.

A New Era in Clinical Research

- A shift from detection of large average effects to information relevant to individual patient decisions
- Harvest EHR and linked biobank at scale to uncover unexpected disease associations (e.g. AD – IBD) and interrogate mechanism
- Use of iPS cells and deep phenotyping to establish POC: **Human Phenomic Science**
- Mendelian randomization – PCSK9
- More focused and creative trial design

FitzGerald GA Sci Transl Med. 2015 Apr 22;7(284):284fs15

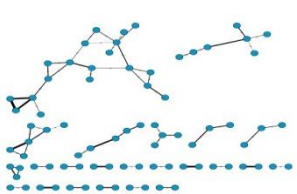
The Institute for Translational Medicine and Therapeutics

- Founded in 2004; first translational science institute
- Focus on T1 science and human capital
- Space and money: hires, cores
- Top down and bottom up funding calls
- Diversified educational programs
- Workshops and annual meeting

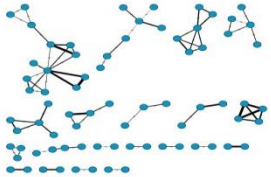
ITMAT MISSION

- To increase (through recruitment and education) the number of investigators who work between POC in model systems and elucidation of mechanisms in humans
- To identify and depress the barriers to their success

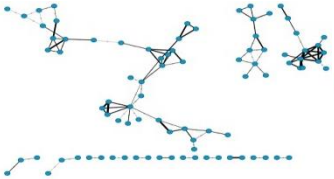
ITMAT Network Dynamics



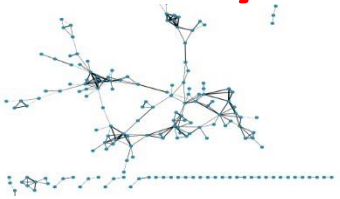
2005



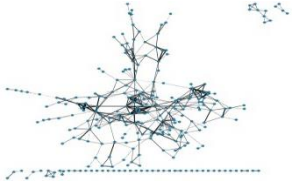
2006



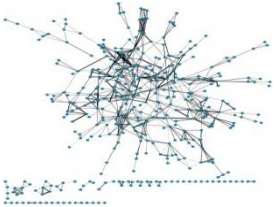
2007



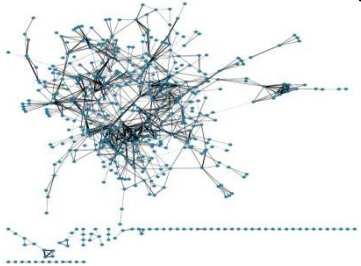
2008



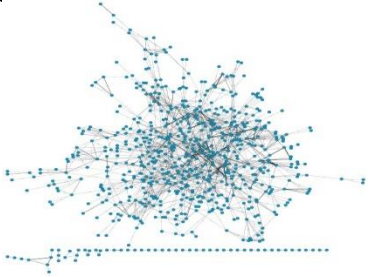
2009



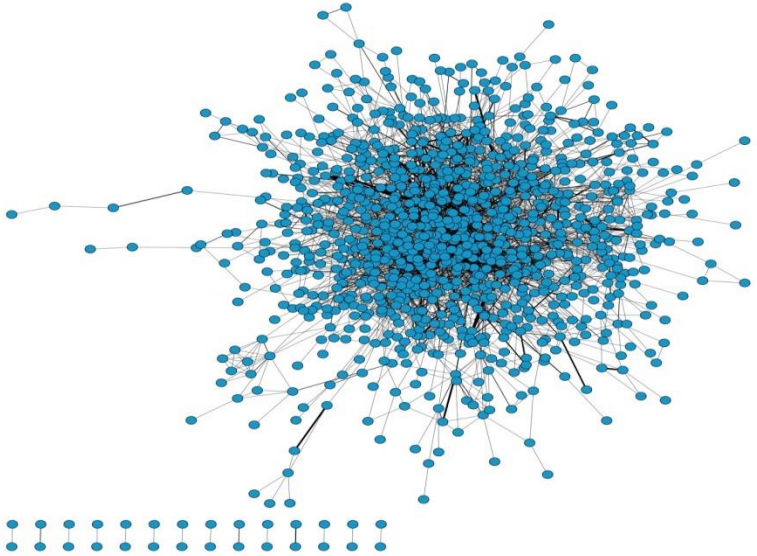
2010



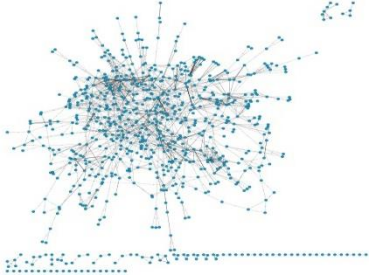
2011



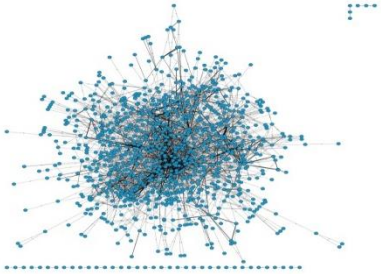
2012



2015



2013



2014

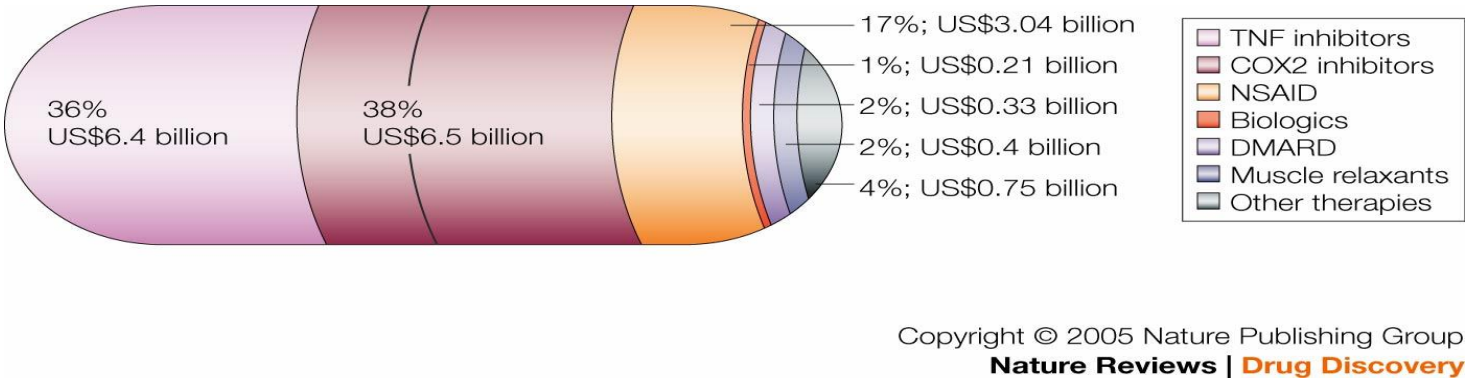
Exciting Times

- CAR-T cells for leukemia
- PD-1 blockade and B-Raf inhibitors in cancer
- CAR-T editing for PD-1 sensitivity
- PCSK9 inhibitors and refractory dyslipidemia
- Vaccines for herpes, malaria and MERS
- Topical chemo for lymphoma
- Gene therapy for blindness and rare diseases

Translational Science delivers… But how precisely?

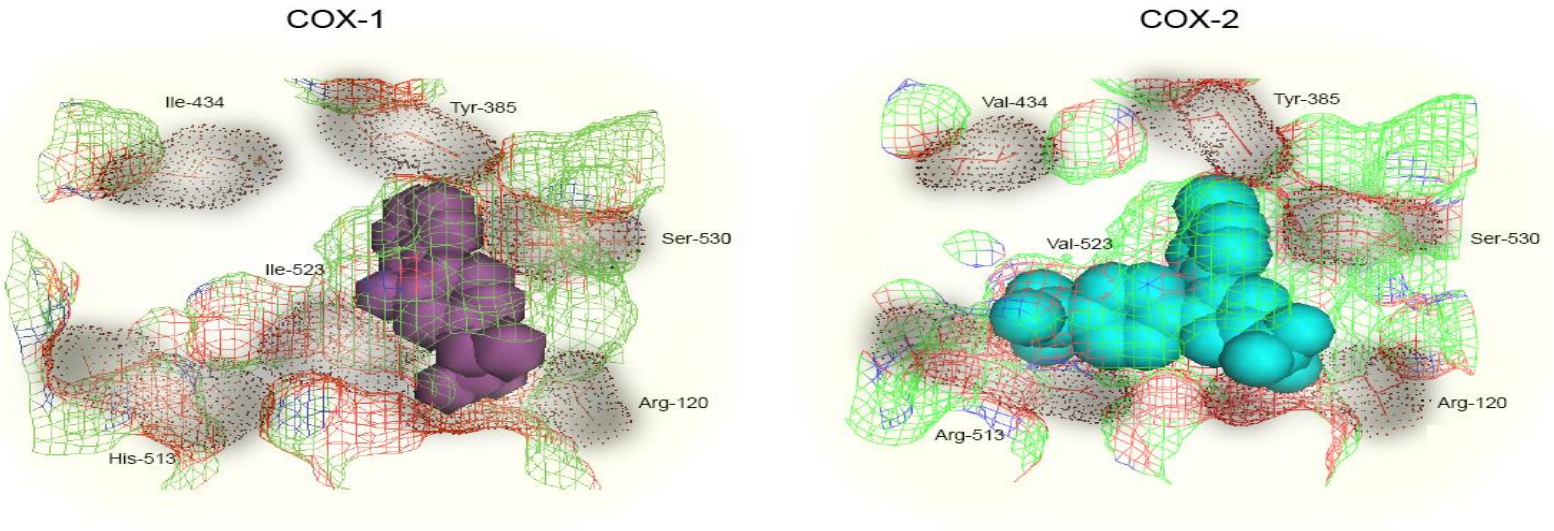
- PD-1 blockade works ~ 80% of the time in vitro but only ~ 30% of the time in vivo; how do you predict resistance; how do you avoid resistance; how do you detect emergence of resistance?
- How do you approach combinatorial strategies, often with drugs in development?
- How do you share equitably the benefits of Precision Medicine?

COX-2 Inhibitors: Translational Science and RCTs



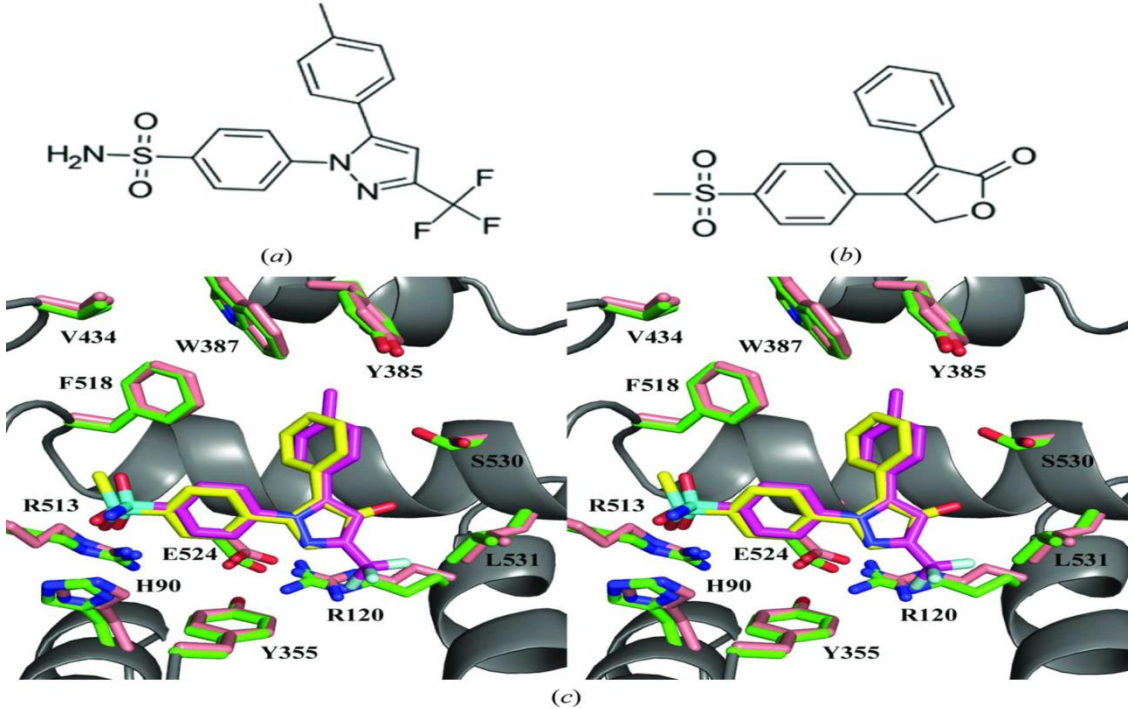
Nature Reviews | Drug Discovery

Translational Therapeutics of the AA Cascade



Differentially Regulated despite Structural Similarity

Comparison of celecoxib (a:) and rofecoxib (b) bound within the cyclooxygenase channel of COX-2.

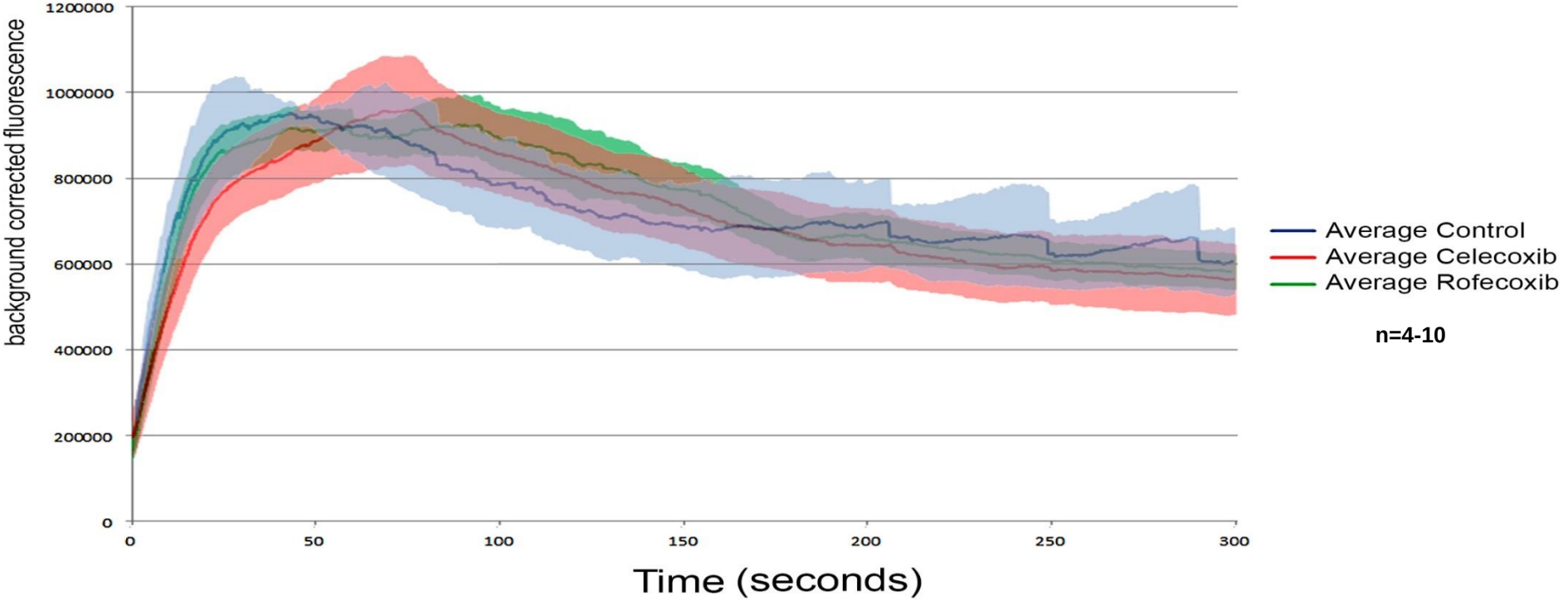


Acta Cryst F STRUCTURAL BIOLOGY COMMUNICATIONS

Orlando & Malkowski

Volume 72 | **Part 10** | October 2016 | Pages 772–776 | 10.1107/S2053230X16014230

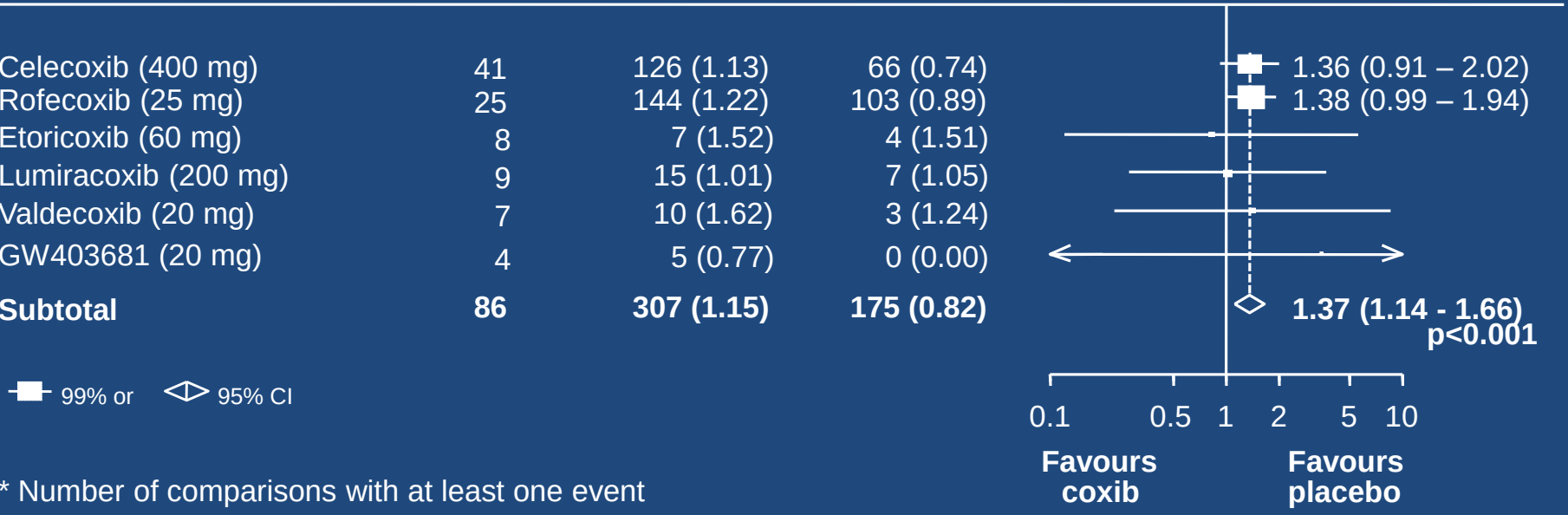
No additional effect of Celecoxib and Rofecoxib on throbogenesis in IP KO mice



COX-2 dependent prostacyclin mediates thrombogenesis induced by celecoxib and rofecoxib

Effect of COXIBS on major vascular events, by TYPE OF COXIB

Coxib (median dose)	No.*	Events (% pa) Allocated coxib	Events (% pa) Allocated placebo	Rate ratio (RR)
Celecoxib (400 mg)	41	126 (1.13)	66 (0.74)	1.36 (0.91 – 2.02)
Rofecoxib (25 mg)	25	144 (1.22)	103 (0.89)	1.38 (0.99 – 1.94)
Etoricoxib (60 mg)	8	7 (1.52)	4 (1.51)	
Lumiracoxib (200 mg)	9	15 (1.01)	7 (1.05)	
Valdecoxib (20 mg)	7	10 (1.62)	3 (1.24)	
GW403681 (20 mg)	4	5 (0.77)	0 (0.00)	
Subtotal	**86**	**307 (1.15)**	**175 (0.82)**	**1.37 (1.14 - 1.66) p<0.001**



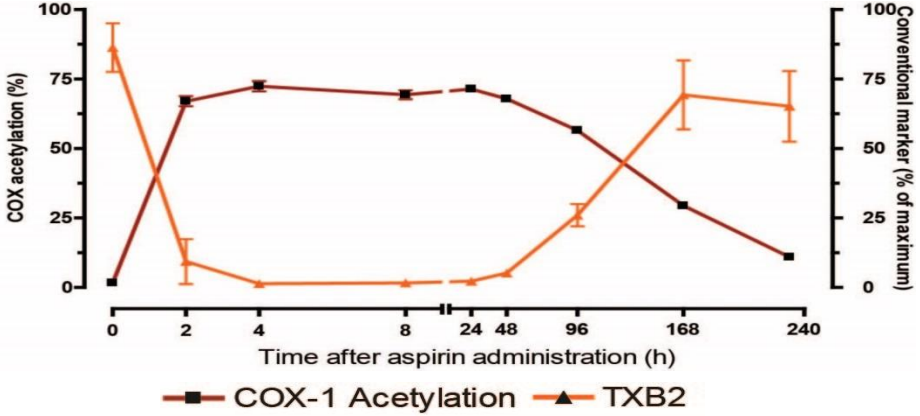
* Number of comparisons with at least one event

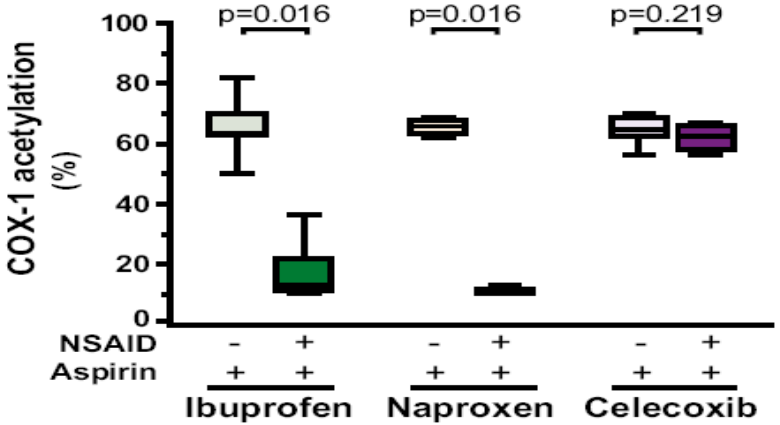
Heterogeneity between celecoxib and rofecoxib: $\chi^2_1 = 0.0$ (p=0.91)

PRECISION and SCOTT: Limitations of large RCTs

- Non-inferiority trials of celecoxib vs naproxen vs ibuprofen.
- Less efficacious doses bias relative safety profile for celecoxib
- High and asymmetric rates of drop out before completion favor celecoxib
- Relaxation of upr. bound obscures detection of asymmetric CV risk from celecoxib
- No randomization for aspirin usage or objective measurement of intake – bias favors celecoxib

COX-1 acetylation reflects aspirin exposure



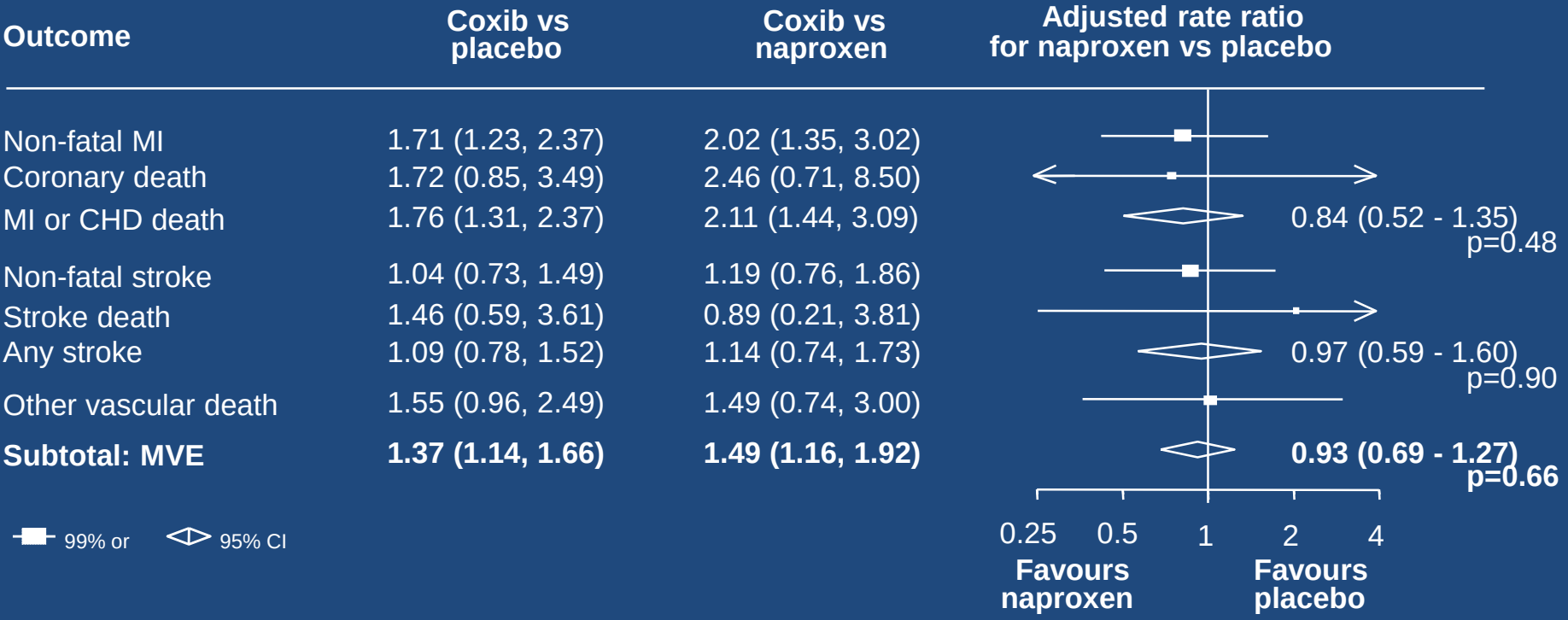


Interaction by mixed, but not COX-2 selective inhibitors to undermine antiplatelet effects of aspirin

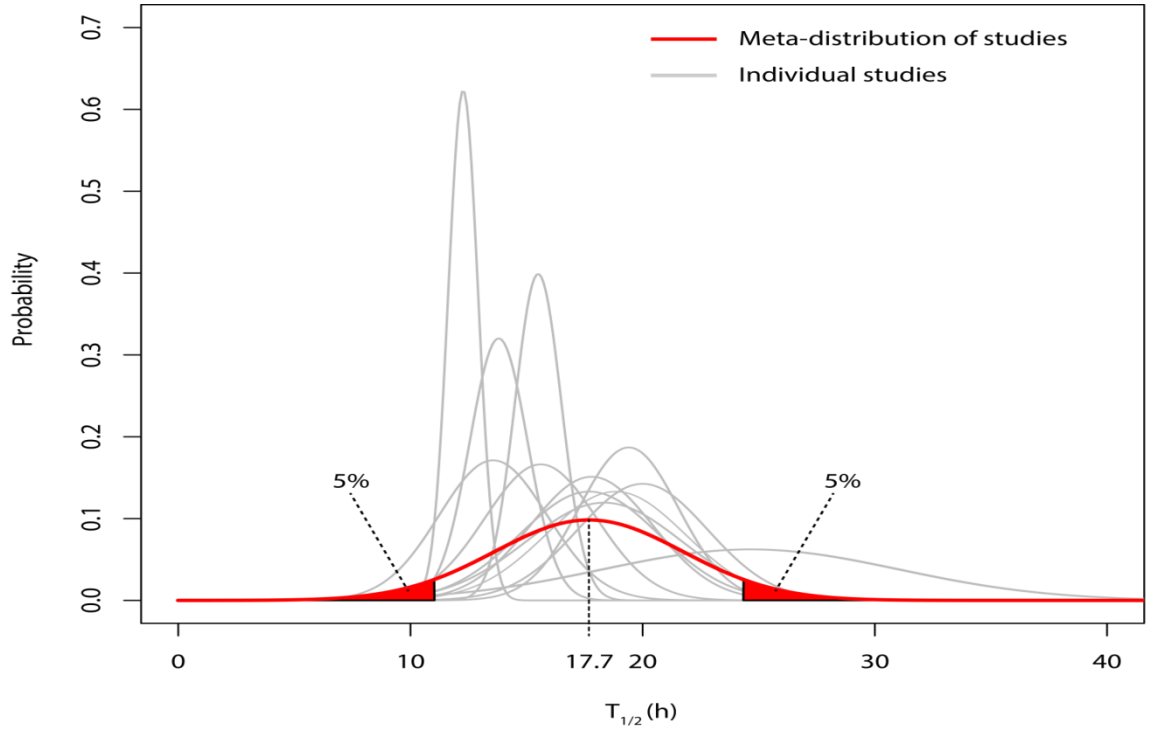
- ***Li X et al*. PNAS. 2014 ;111(47):16830**

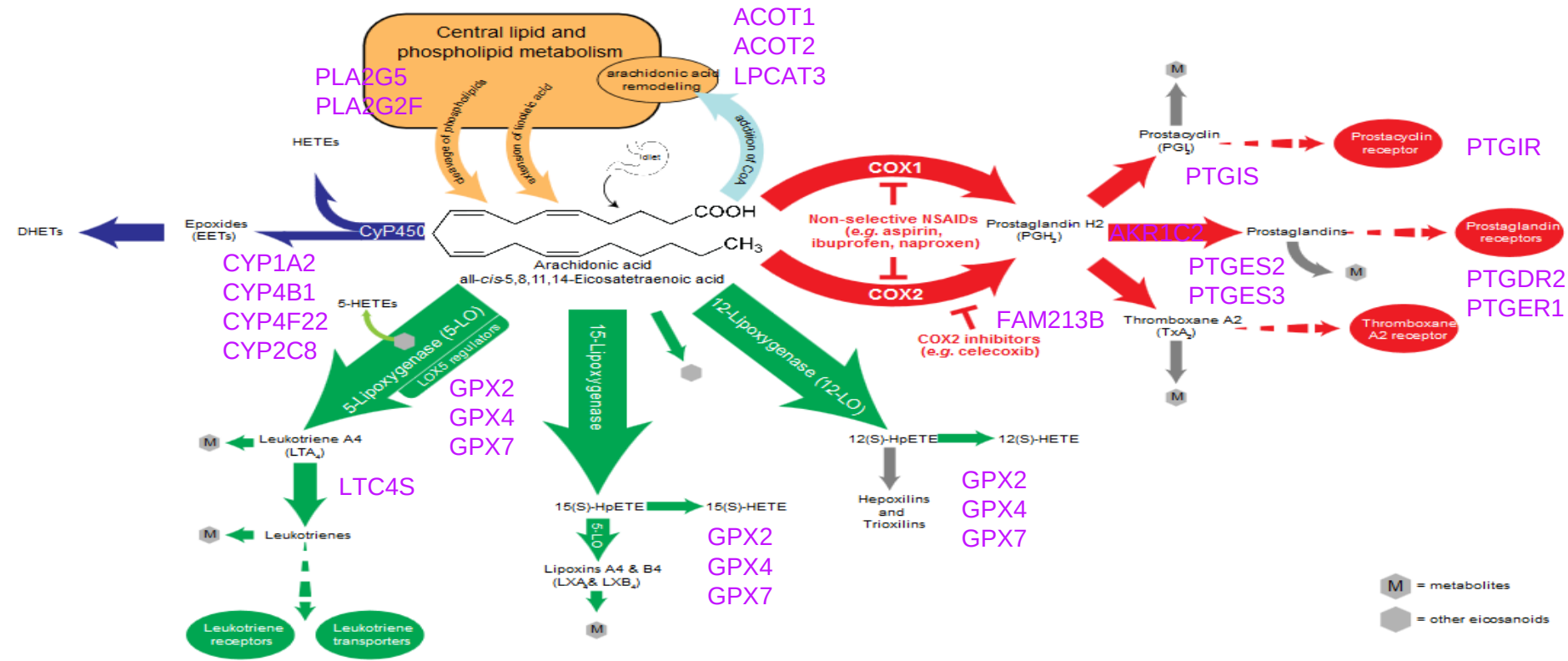
Effect of NAPROXEN on major vascular events

Outcome	Coxib vs placebo	Coxib vs naproxen
Non-fatal MI	1.71 (1.23, 2.37)	2.02 (1.35, 3.02)
Coronary death	1.72 (0.85, 3.49)	2.46 (0.71, 8.50)
MI or CHD death	1.76 (1.31, 2.37)	2.11 (1.44, 3.09)
Non-fatal stroke	1.04 (0.73, 1.49)	1.19 (0.76, 1.86)
Stroke death	1.46 (0.59, 3.61)	0.89 (0.21, 3.81)
Any stroke	1.09 (0.78, 1.52)	1.14 (0.74, 1.73)
Other vascular death	1.55 (0.96, 2.49)	1.49 (0.74, 3.00)
Subtotal: MVE	**1.37 (1.14, 1.66)**	**1.49 (1.16, 1.92)**

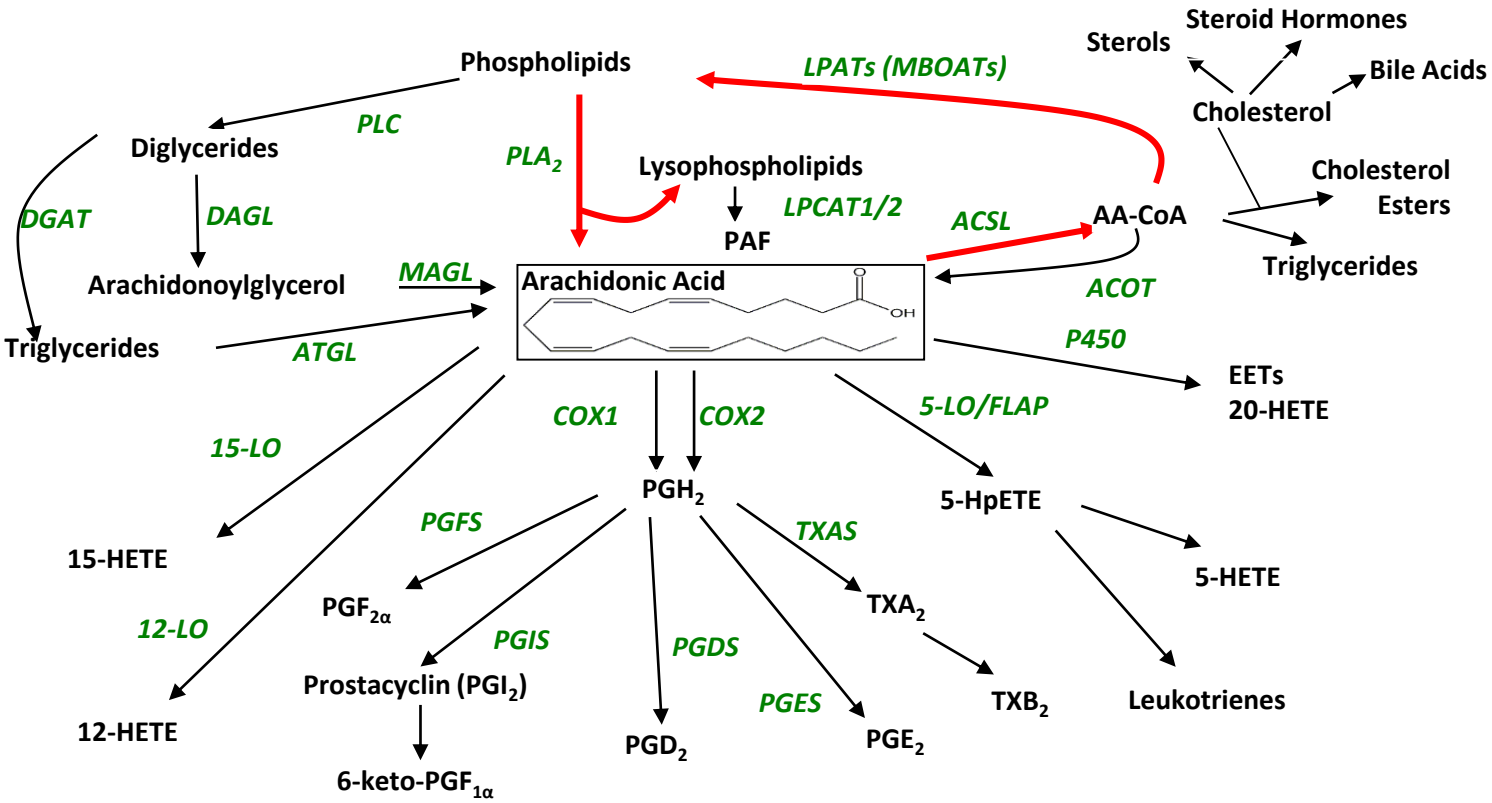


Inter-individual and inter-study heterogeneity of the half-life of Naproxen

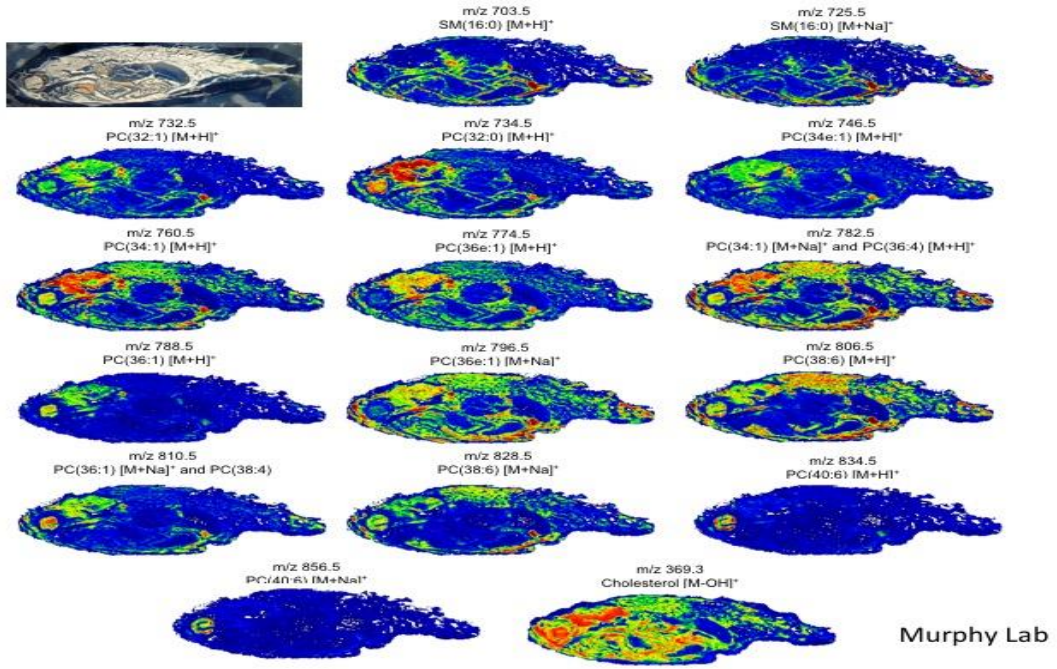



Central lipid and phospholipid metabolism
arachidonic acid remodeling
cleavage of phospholipids
release of linoleic acid
addition of CoA
Idiet
ACOT1
ACOT2
LPCAT3
PLA2G5
PLA2G2F
HETEs
DHETs
Epoxides (EETs)
CyP450
CYP1A2
CYP4B1
CYP4F22
CYP2C8
COOH
CH3
Arachidonic acid
all-cis-5,8,11,14-Eicosatetraenoic acid
COX1
Non-selective NSAIDs (e.g. aspirin, ibuprofen, naproxen)
COX2
COX2 inhibitors (e.g. celecoxib)
FAM213B
Prostaglandin H2 (PGH2)
Prostacyclin (PGI2)
PTGIS
Prostacyclin receptor
PTGIR
AKR1C2
Prostaglandins
PTGES2
PTGES3
Prostaglandin receptors
PTGDR2
PTGER1
Thromboxane A2 (TxA2)
Thromboxane A2 receptor
5-HETEs
5-Lipoxygenase (5-LO)
LOXS regulators
GPX2
GPX4
GPX7
Leukotriene A4 (LTA4)
LTC4S
Leukotrienes
Leukotriene receptors
Leukotriene transporters
15-Lipoxygenase
15(S)-HpETE
15(S)-HETE
5-LO
Lipoxins A4 & B4 (LXA4 & LXB4)
12-Lipoxygenase (12-LO)
12(S)-HpETE
12(S)-HETE
Hepoxilins and Trioxilins
M = metabolites
= other eicosanoids

Lipidomics in Pentacon



Spatiotemporal Lipidomic Perturbations

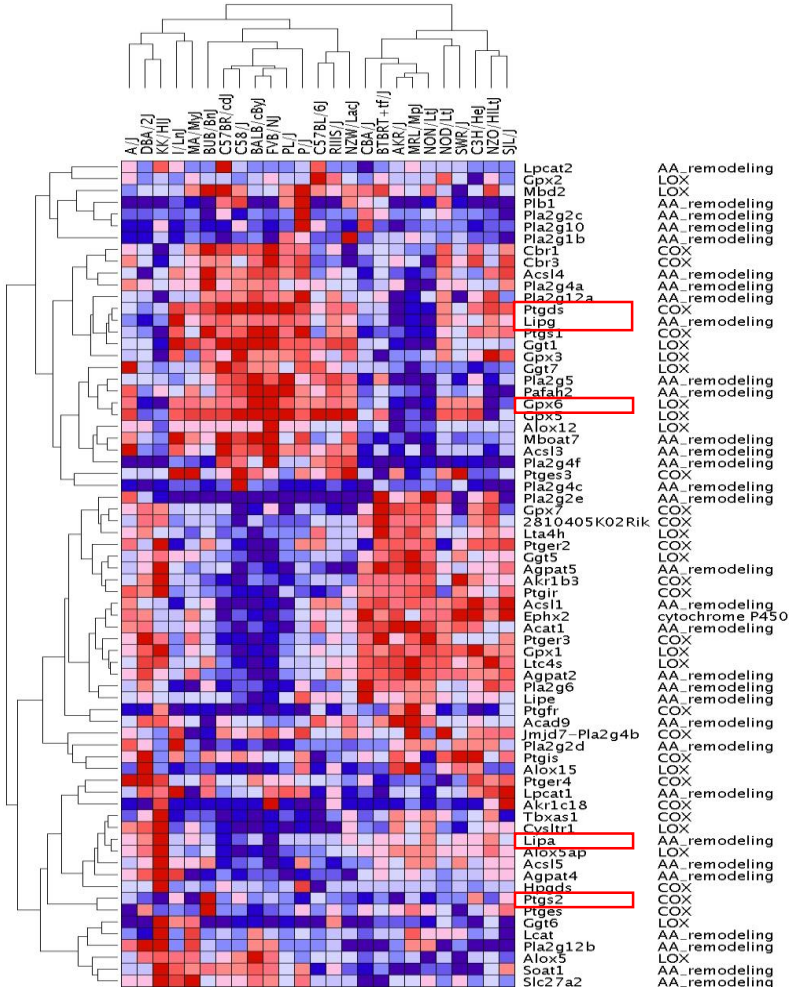


Spatial mapping of discrete lipid entities under positive ion imaging mass spectrometry. Using MALDI-MS it is possible to define detailed anatomical maps for specific lipids in entire organisms at a resolution of 20-50 mM.

Differential expression: largest fold differences between strains

Tissue	Gene	Fold difference
Adipose	*Lipg*	1934
Adrenal gland	*Ggt1*	1469
Adipose	*Ptgs2*	1034
Spleen	*Pla2g1b*	968
Adrenal gland	*Slc27a2*	761
Kidney	*Akr1c18*	553
Adipose	*Ptgds*	508
Kidney	*Alox15*	417
Skeletal muscle	*Slc27a2*	309
Adipose	*Lipa*	274
Adipose	*Gpx6*	258
Adrenal gland	*Pla2g2d*	213
Adipose	*Alox12*	206
Adipose	*Ggt1*	188
Skeletal muscle	*Agpat2*	161
Skeletal muscle	*Ptger3*	140
Lung	*Slc27a2*	112
Macrophage	*Ptgs2*	99
Adipose	*Pla2g5*	93
Liver	*Akr1c18*	90
Adrenal gland	*Pla2g2f*	76
Adrenal gland	*Acsl4*	74
Macrophage	*Gpx3*	66
Adrenal gland	*Pla2g12b*	66
Lung	*Alox15*	63

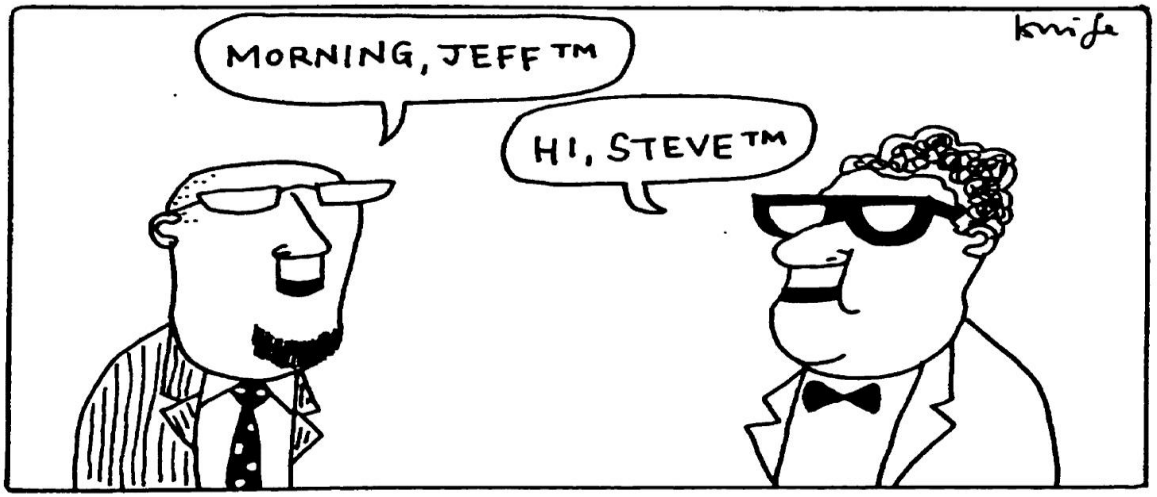
High expression
Low expression



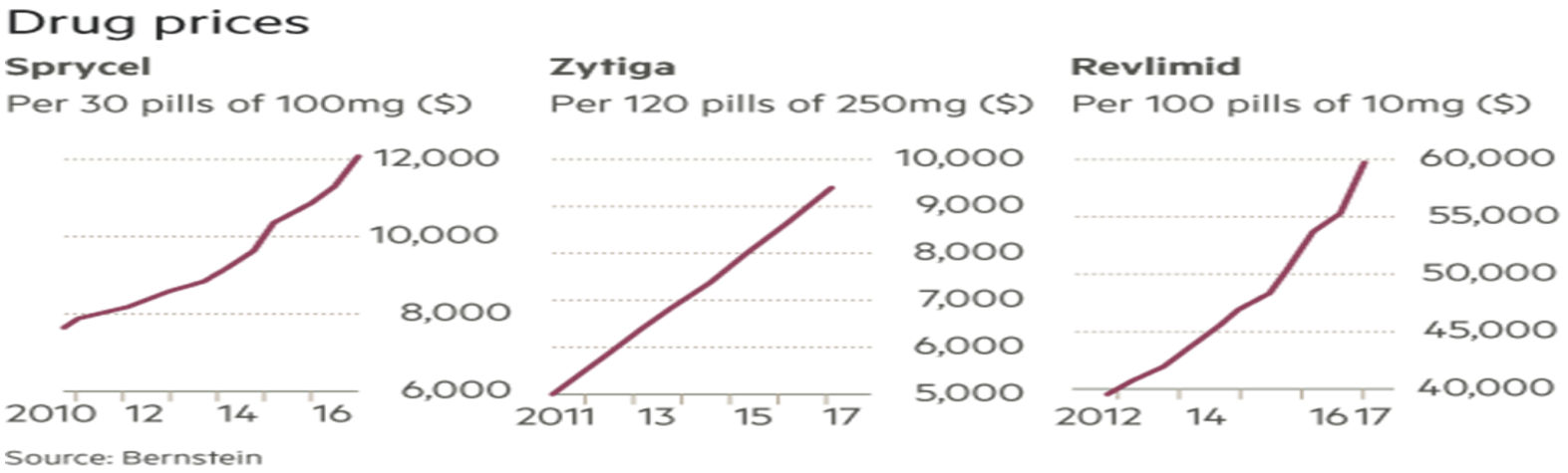
Precision Medicine for NSAIDs

- Pharmacological probes (celecoxib vs naproxen)
- Multiple dose response curves at different times of day in cells, fish, mice and humans
- Deep phenotyping in humans at extremes of COX-2 expression in B lymphocytes ex vivo
- Multi-omic and broad lipidomic interrogation
- Genetic modifiers from inbred fish and mice
- Network, structure based and dynamical modelling to develop predictive algorhithms
- BP and thrombogenesis as CV risk surrogates

Fostering Entrepreneurship at a Price



THE DAY BEGINS AT A
COPYRIGHT LAW OFFICE



Aspen Pharmaceuticals, Busulfan, the Italians and 1500%

Drug Pricing: A Hot Political Issue

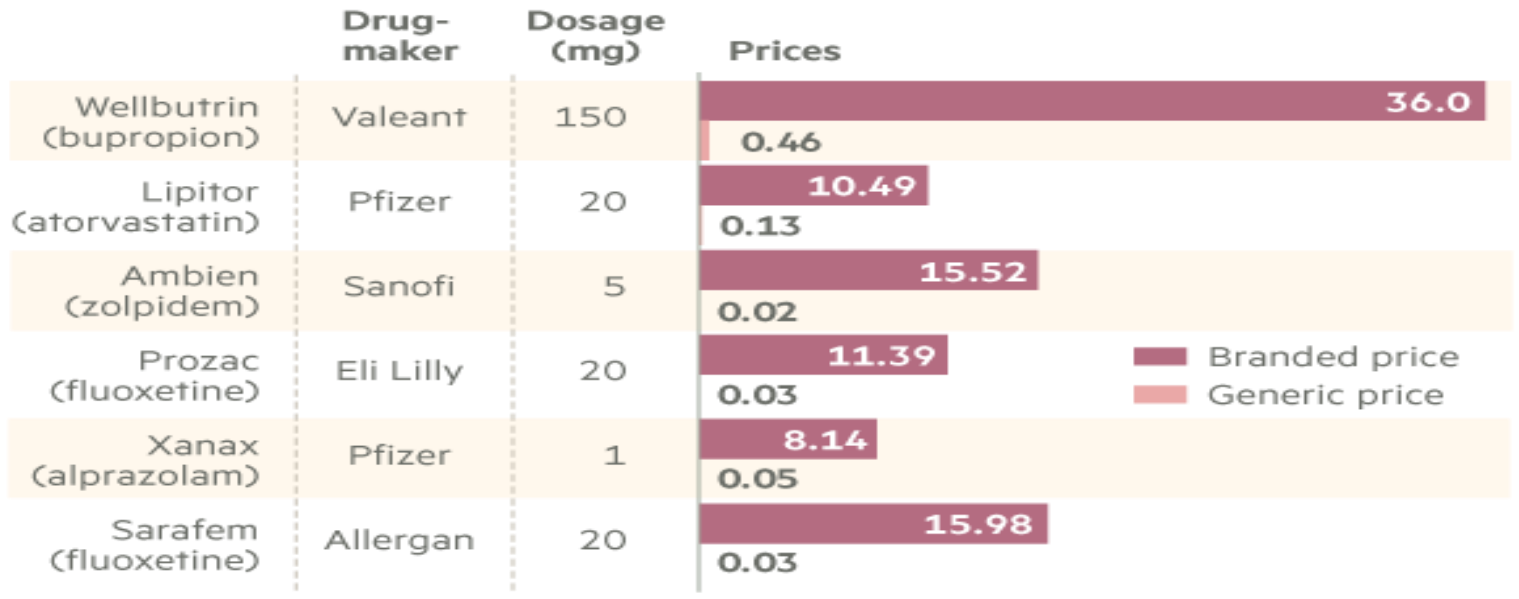
- 50-70% of pharmaceutical profitability from 5% of the global population in the US
- Branded cancer drugs least affordable in India and China, most affordable in Oz and UK with US in between (monthly cost at PPP)
- Generic medicines now 90% of US market: cost more ($650/mo) than in the UK ($450) or Oz ($210) FT June 6th 2015

The Shkreli Effect

"No substitutes, please. I want Crestor as prescribed."

Generic v brand price

$



Sources: FT research; National Average Drug Acquisition Cost database

FT

DTC advertising, Co-Pays, Evergreening and Pay for Delay

Will Precision Medicine approaches prove cost effective? Will its benefits be equitably shared?

Costs per patient of managing selected disorders

These approximate estimates are drawn from references (*10*–*13*). CFTR, cystic fibrosis transmembrane conductance regulator.

DISEASE ENTITY	MANAGEMENT PLAN	~COST/YEAR ($)	~COST/LIFETIME ($)
Cystic fibrosis	General support	25,000	750,000
	Drug to enhance CFTR function (Kalydeco)	300,000	5,000,000
Gaucher disease	Regular enzyme replacement	200,000	5,000,000
Hemophilia A	Prophylactic or periodic factor administration	300,000	5,000,000–10,000,000
Sickle cell disease	General medical support and hydroxyurea as standard of care	25,000	1,000,000

Stuart H. Orkin, and Philip Reilly Science 2016;352:1059-1061

The Gene Therapy Example

- ~$10Bn invested over the past 20 years
- Promise in immunodeficiency disorders, hemophilia B, congenital blindness , beta-thalassemia and metachromatic leukodystrophy.
- Despite generating no revenue 5 companies valued at > $4Bn
- *One time therapy*; autologous $CD34^+$ cells expressing adenosine deaminase; $700k
- Orphan disease act and ultrarare disorders

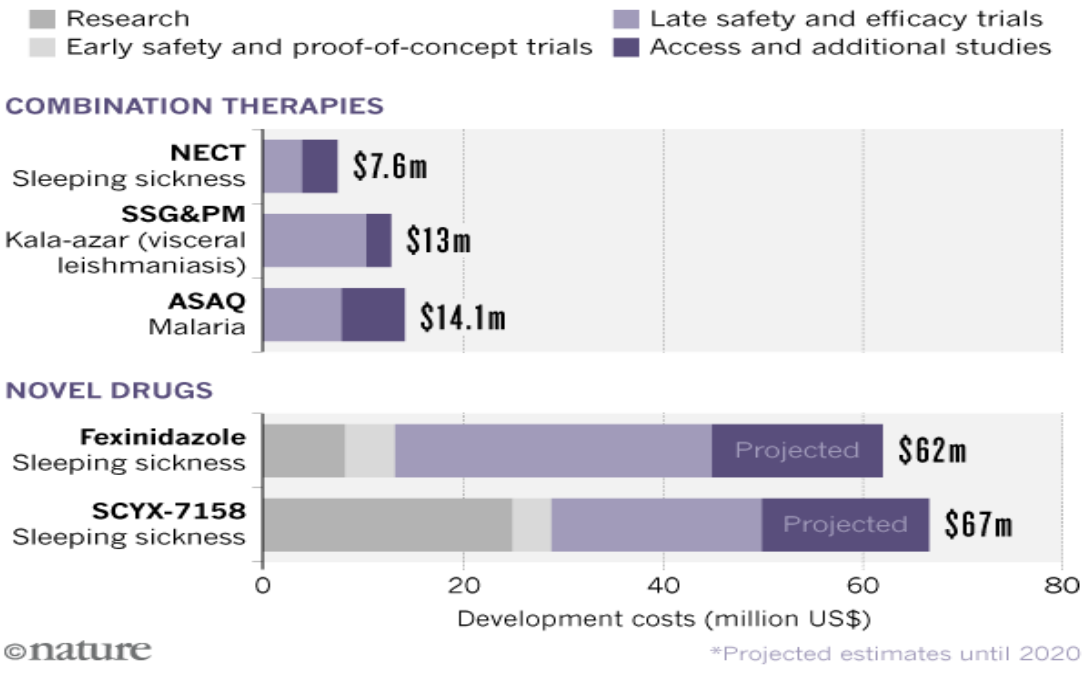
Orkin and Reilly Science 2016

How do we foster innovation while containing cost and spreading benefit?

- The true cost to the patient in the US is opaque: transparency on negotiated discounts
- Trumpenomics: share the pain - Switzerland.
- EU initiatives on reimbursement based on results. Transparent evaluations of drug benefit.
- Regulatory initiatives to accelerate competition. Abolish pay for delay.
- Lessons from the altruistic sector : IP reform

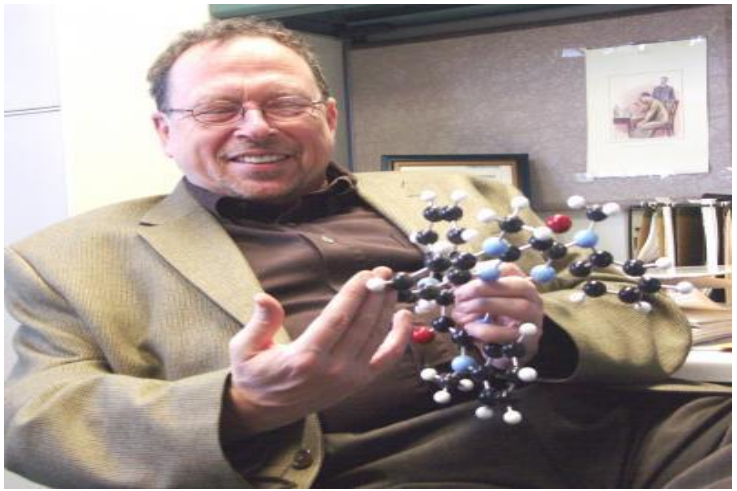
DISCOUNT DRUGS

The Drugs for Neglected Diseases initiative (DNDi) has produced several drugs in the past decade for a fraction of what pharmaceutical companies are said to spend. Factoring in the cost of failed candidates (not included below), the DNDi estimates that it can develop combination therapies for between US$10 million and $45 million, and make a completely new drug from scratch for $110 million to $170 million.



*Projected estimates until 2020

IP is focused on the Composition of Matter



Perhaps a 1:40,000 chance of becoming an approved drug

IP for free

Create a Pot of Gold

•Charities – Wellcome, Gates etc

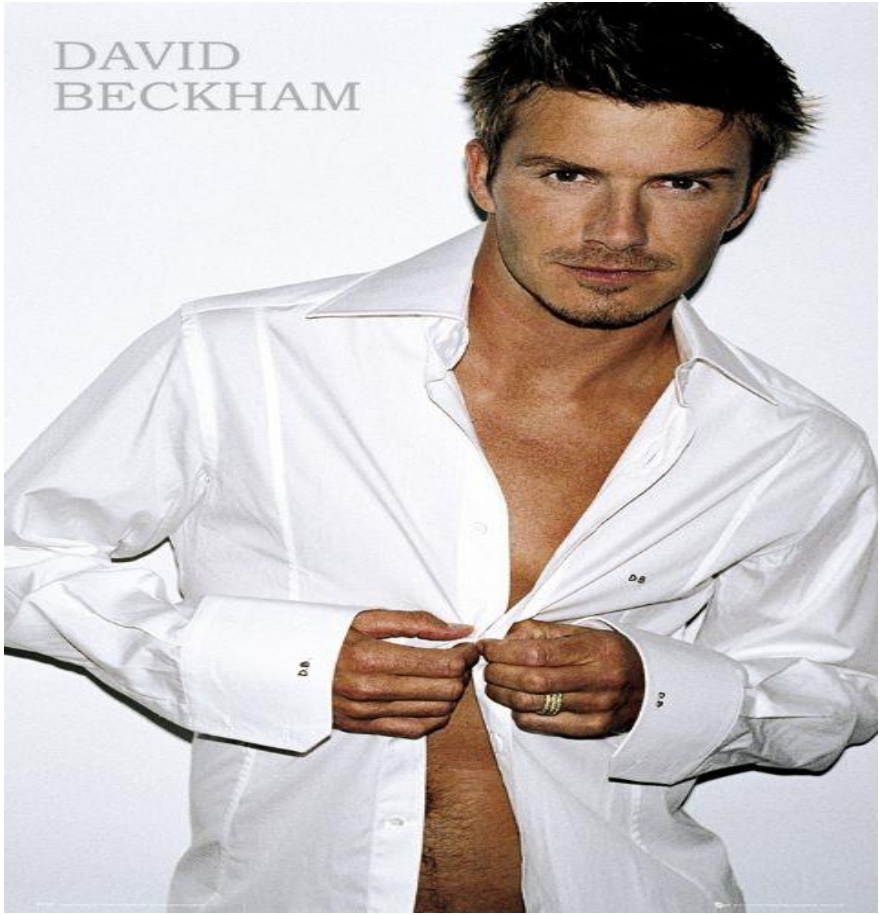
•Companies – Pharma, Oil etc

•Governments – Global treaties for underserved populations

• Credit Default Swaps

•Tradable shares in intellectual Property

Modeling Success



IP Reform

- Modeling drug targets; biological networks; PK/PD; market share and pricing
- Model the barriers to success and prospectively allocate relative reward
- Use the courts to resolve discrepancies
- Postpone reward until value actually realized

FitzGerald GA Science. 2012 Oct 26;338(6106):483-4.

The Dominant (if disputed) IP

Conclusion

- Drug is risky and expensive but life altering breakthroughs continue to be made
- Create the infrastructure to allow academia to play in modular space; this will accelerate the process, decrease cost and increase efficiency
- The challenge is to parse variability of drug response and to shift towards a more personalized approach to understand and treat safely common syndromes, such as pain
- Its time for IP reform in drug development

The older I get, the surer I am that I’m not running the show