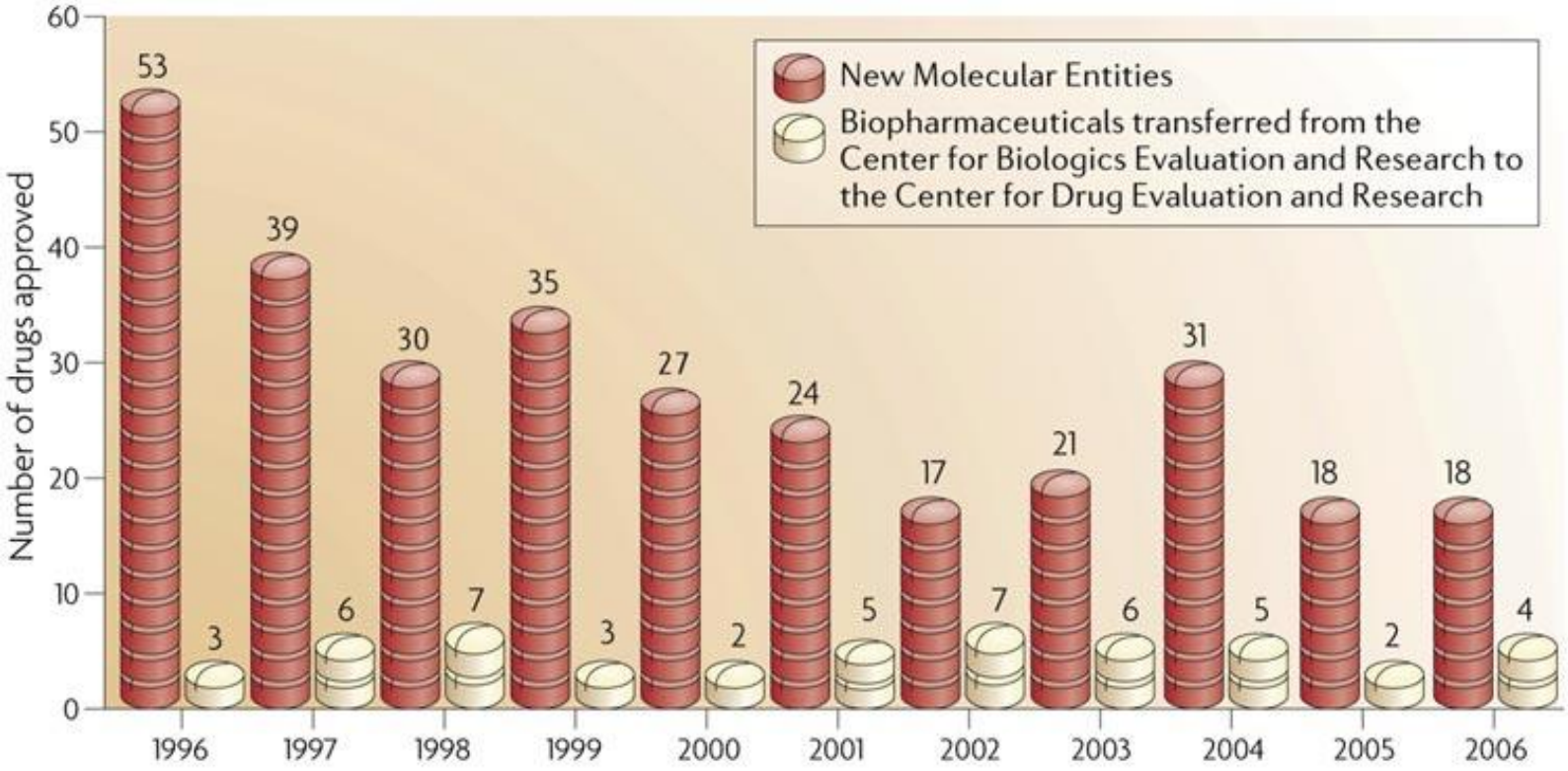
Building Capacity for the Science Base

A JET PROPULSION LAB FOR THE FDA?



Nature Reviews | Drug Discovery

Owens *Nature Reviews Drug Discovery* **6**, 99–101 (February 2007) | doi:10.1038/nrd2247

nature REVIEWS DRUG DISCOVERY

A BROKEN MODEL OF DRUG DEVELOPMENT

- High cost of goods in the US has insulated drug development from reform
- A strategy of merger has further undermined a highly inefficient and costly process
- Downward pressures on the cost of goods
- Pervasive concern about drug safety.

THE BALANCE OF BENFIT AND RISK

Table 1. Risks and Benefits of Rofecoxib Therapy in the VIGOR Trial.*

Variable	Rofecoxib Group	Naproxen Group	Difference†
		number of events	
All gastrointestinal events	56	121	−65
Complicated events‡	16	37	−21
Serious thromboembolic events	47	20	+27

* Data on gastrointestinal events are from Bombardier et al.[1] Data on serious thromboembolic events are from Shapiro.[2]

† A minus sign indicates fewer events in the rofecoxib group, and a plus sign more events in the rofecoxib group.

‡ Complicated events were defined as perforation, obstruction, or severe upper gastrointestinal bleeding.[1]

Curfman GD et al NEJM 2006

J.K. Galbraith said:

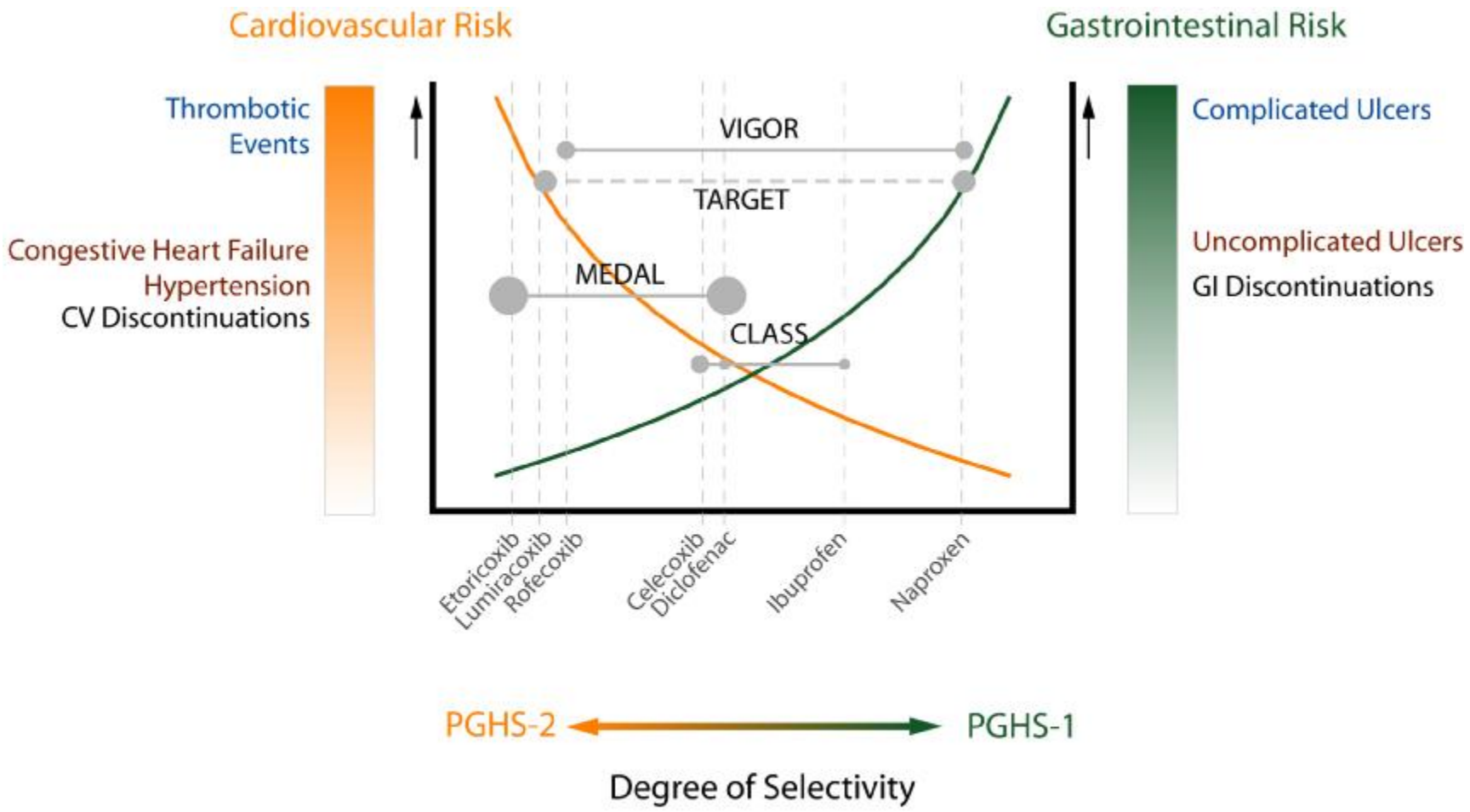
"Faced with the choice between changing one's mind and proving there is no need to do so, almost everyone gets busy on the proof."

OBSERVATIONAL STUDIES PRIOR TO VIOXX WITHDRAWL

- Some but not all, detected hazard from 50mg/day Vioxx
- Virtually all saw no signal at 25mg: use lower doses
- Virtually all missed signal from any dose of Celebrex
- All missed any signal from Bextra

SERIAL EXPERTISE (AND SOME DENIAL): A NINE YEAR SAGA (AND COUNTING)

- Clinical pharmacology: biomarkers of drug action
- Generation of relevant mouse models
- Observational studies
- Randomized placebo controlled clinical trials
- Interpretation of comparator RCTs



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

LESSONS

- Industry not incented to invest in mechanistic research post IND, even when a hazard emerges – Avastin, Torcetrapib
- FDA not equipped to do so
- Science poorly informed the epidemiology
- The limitations of each approach were poorly appreciated
- Placebo controlled trials designed to identify a new indication

TRANSLATIONAL MEDICINE AND THERAPEUTICS

- Develop and project mechanism based quantitative biomarkers from model systems into humans.
- Evoking phenotypic responses in humans to guide individualization of rational dose selection
- Harness the unbiased technologies to select amongst molecules directed against a single target

A JPL FOR THE FDA?

- An educational incubator for Translational Therapeutics in partnership with the FDA
- Site(s) for mechanistic studies in cells, model systems and people to pursue , refine or propose hypotheses related to drug action
- Site(s) for design of studies to be performed de novo to address such hypotheses independently of, or in partnership with sponsors
- Site(s) to focus on an integrated approach to the personalization of medicine

A JPL FOR THE FDA

- Major deficit in human capital: ? Build on the educational initiatives in CTSAs
- Major investment in Translational Medicine and Therapeutics in focused areas
- Access to compounds in development for independent investigation
- Investment incremental to FDA budget.
- A step qualitatively and quantitatively distinct from (but complementary to) CERTs.

COST

- EDUCATION: Harness investment in CTSAs – incremental ~$2M/yr initially in one or two sites. Complement with tuition vehicles ~$5M/year.
- INTEGRATIVE RESEARCH: 3-4 Extramural Centers in major disease areas ~ $10M each per year in 5 yr cycles.
- INFORMATICS INVESTMENT: Harness CTSA and FDA investments :~$5M per Center per year.

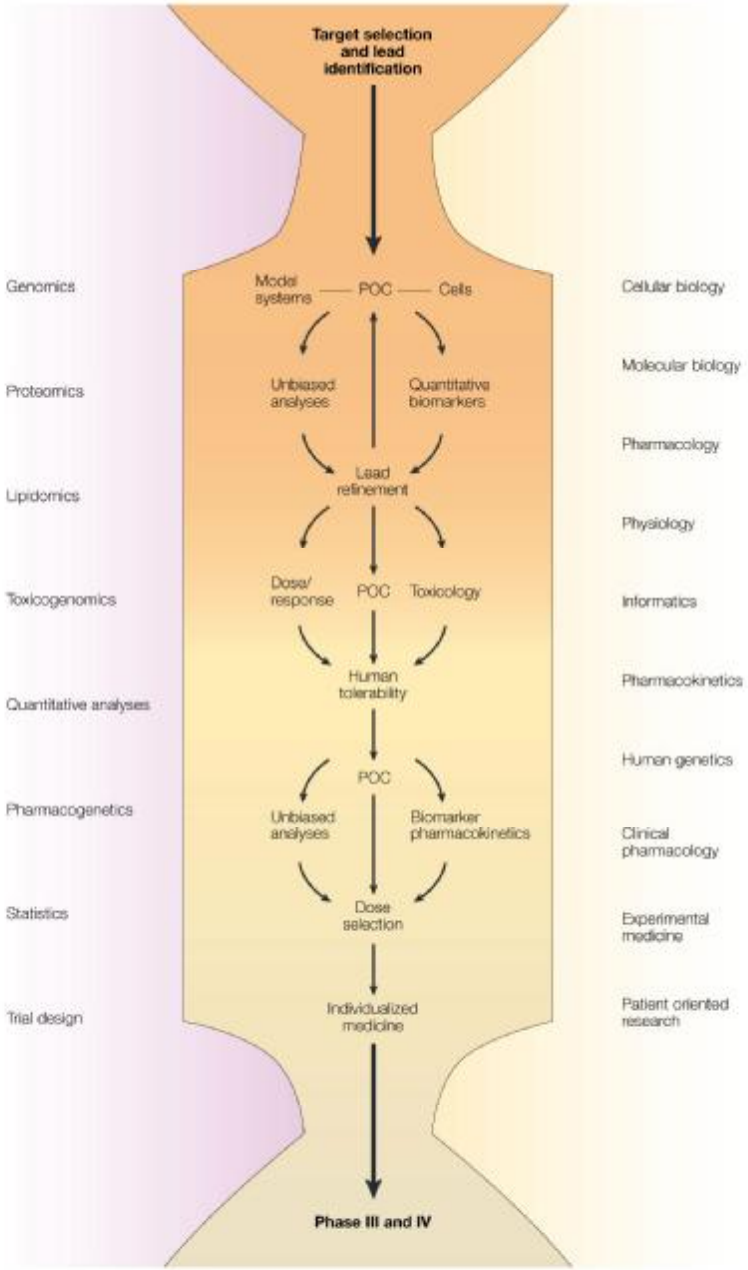
A VIRTUOUS CIRCLE

- Speeds the development of safe and effective medicines for the public health
- Accelerates understanding of factors that personalize the likelihood of risk and benefit
- Moves the economic model up the value chain in a strategically vital industry

Predictive Pharmacology in Humans

"…..trials much larger than those necessary to detect efficacy and safety in arthritis will be necessary to determine whether cardiovascular consequences of inhibiting PGI_2 biosynthesis will modulate the anti-inflammatory benefit to be derived from chronic administration of COX-2 inhibitors in humans".

McAdam et al PNAS 1999 Jan 5;96(1):272-7



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