Assessing investment risk: Peeling the drug candidate onion

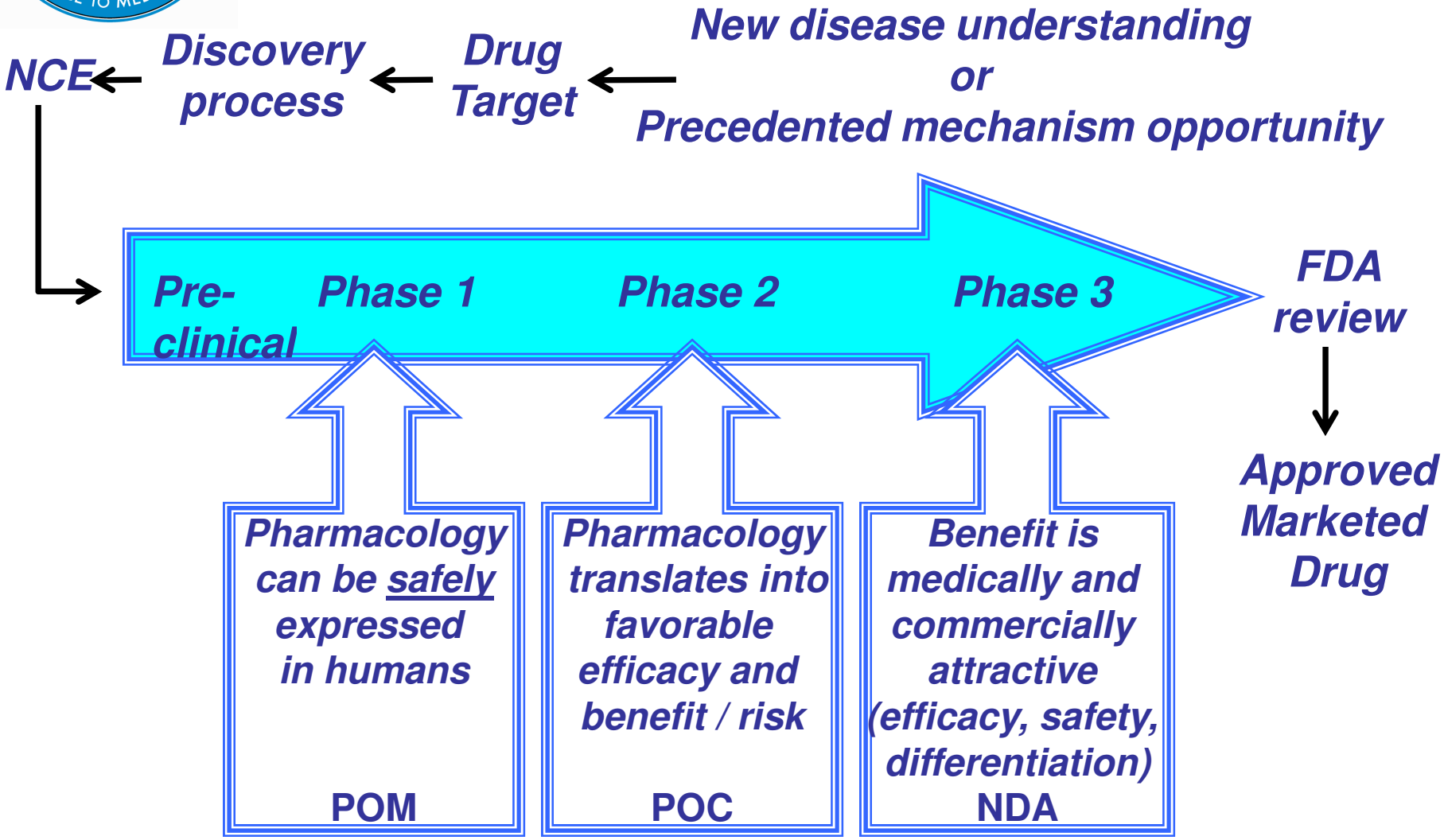
Bruce H. Littman, M.D.
President
Translational Medicine Associates, LLC
http://transmedassociates.com

Today's presentation…

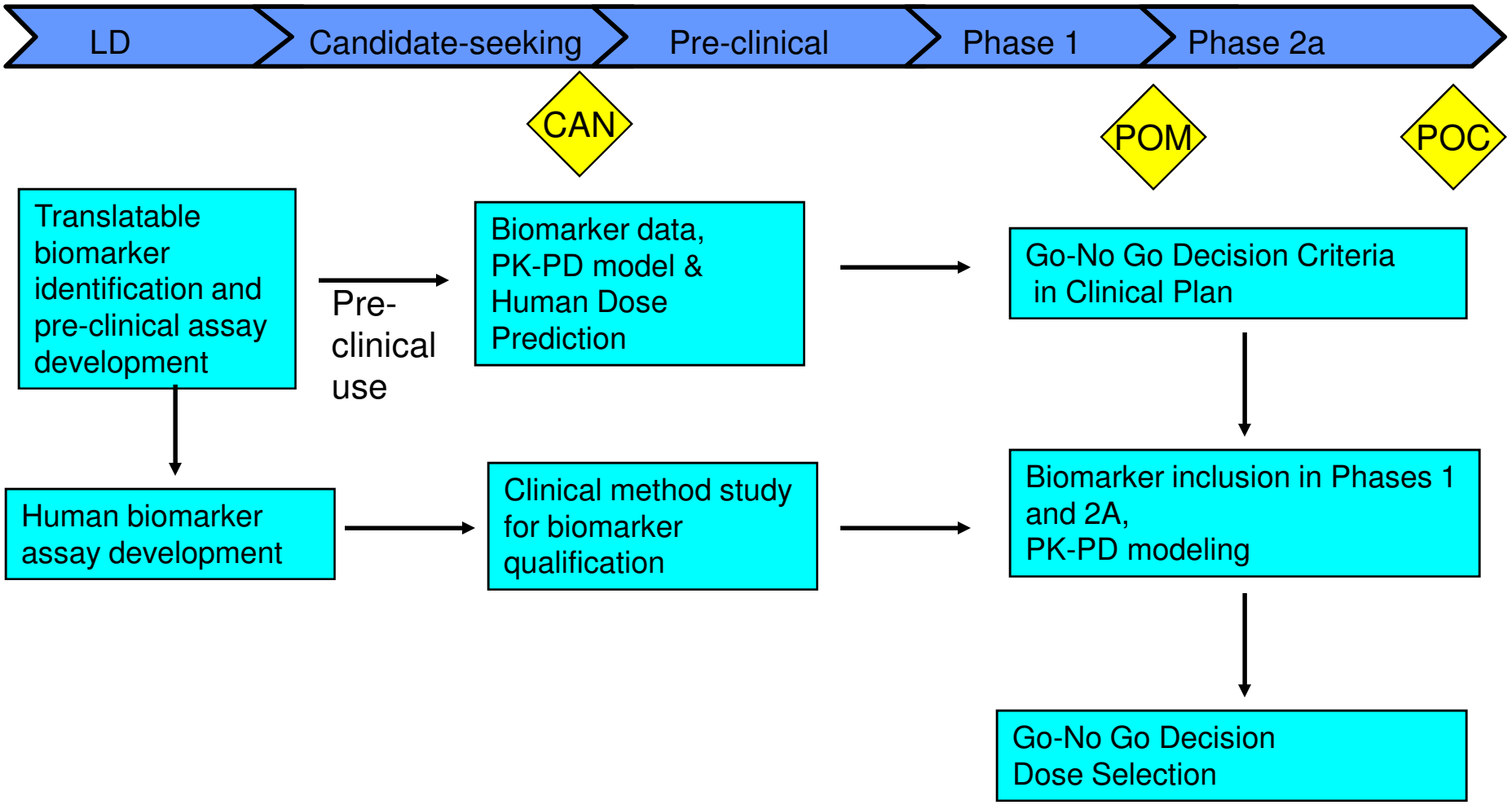
- Overview of clinical drug development and how portfolio decisions should be made

- Signs of increased risk for drug development candidates

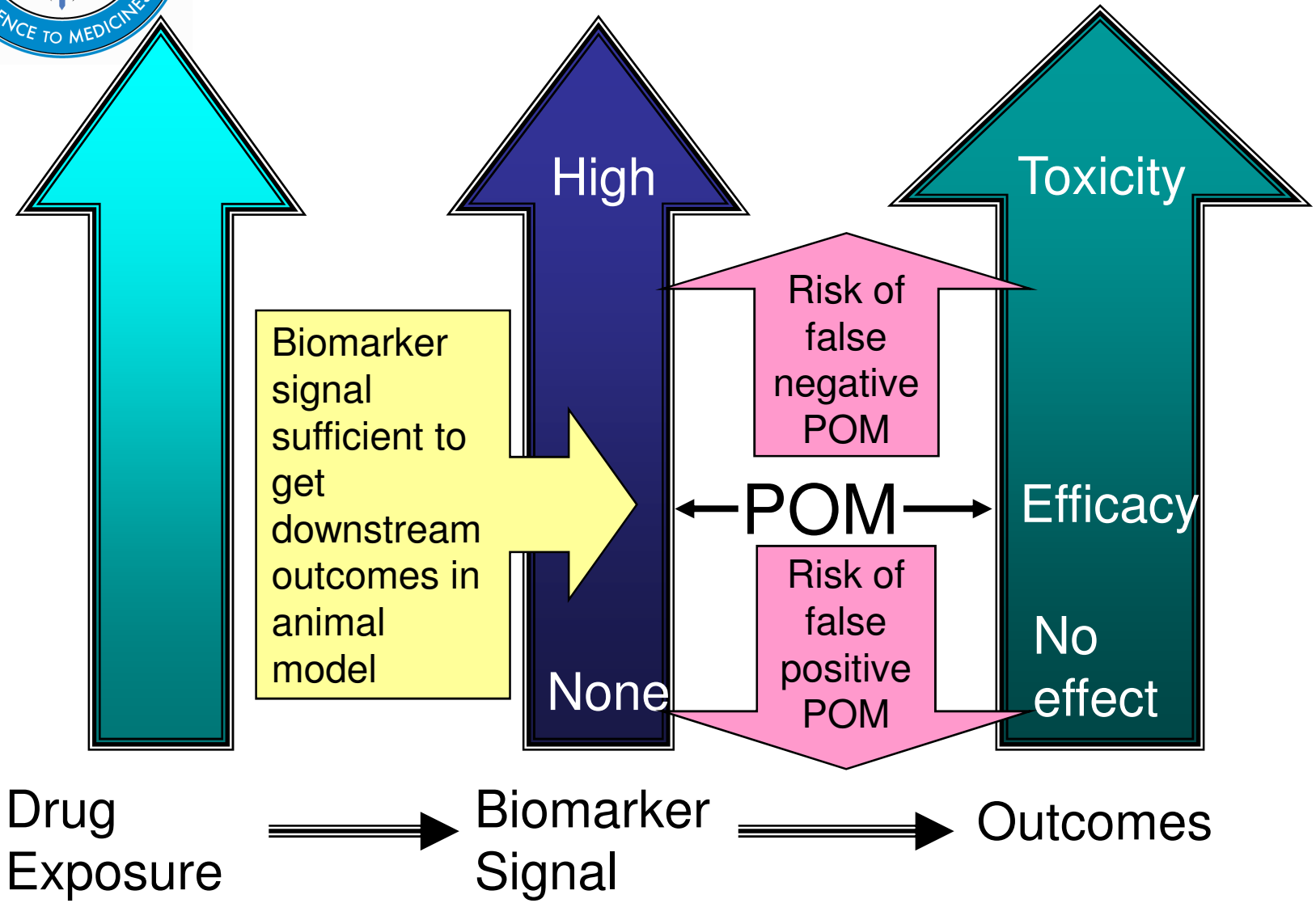
Phases of clinical drug development test three key hypotheses…



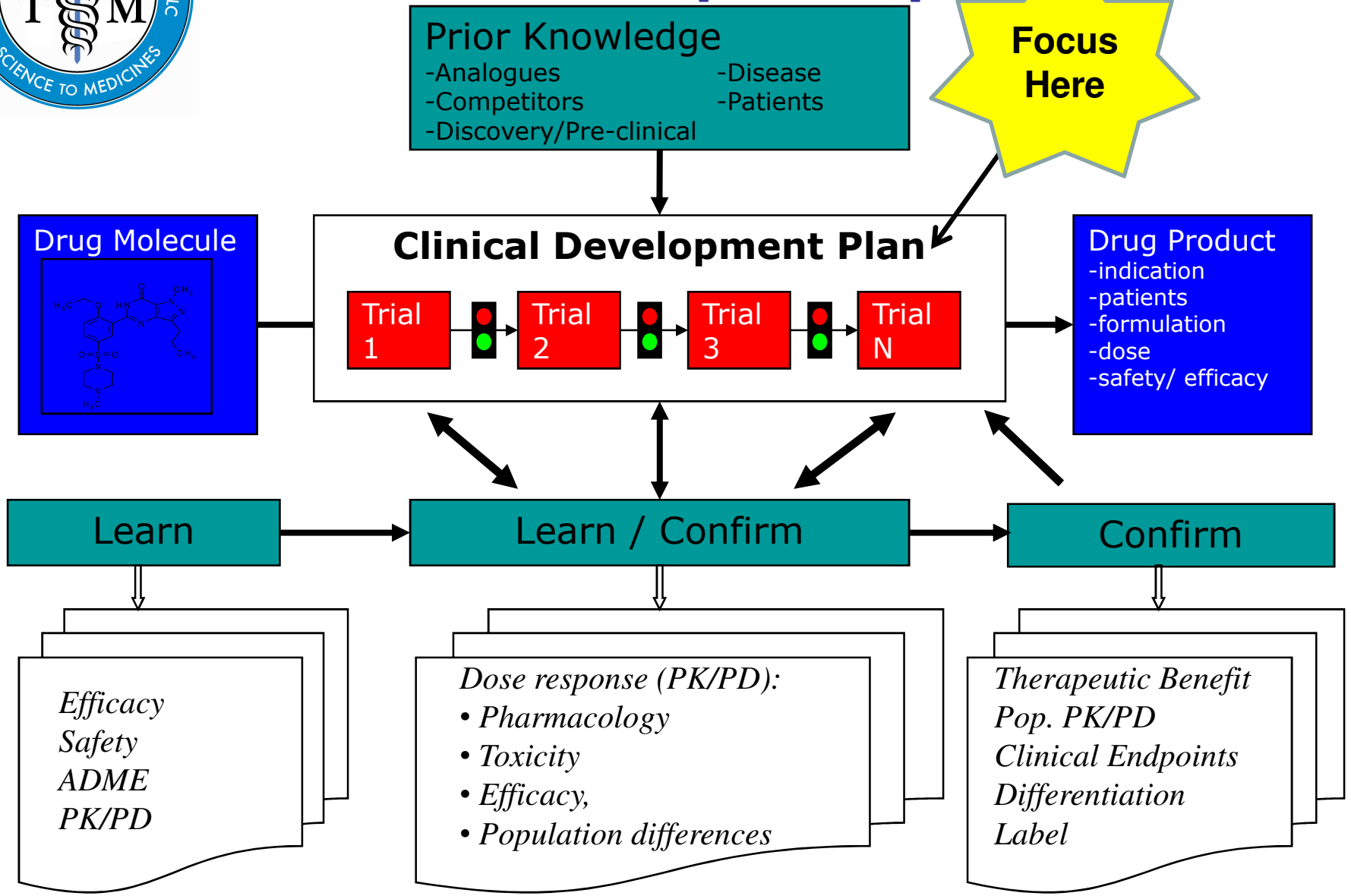
Translational phase: pre-clinical to POM and POC…



POM criteria: how much pharmacology?



Clinical development plan



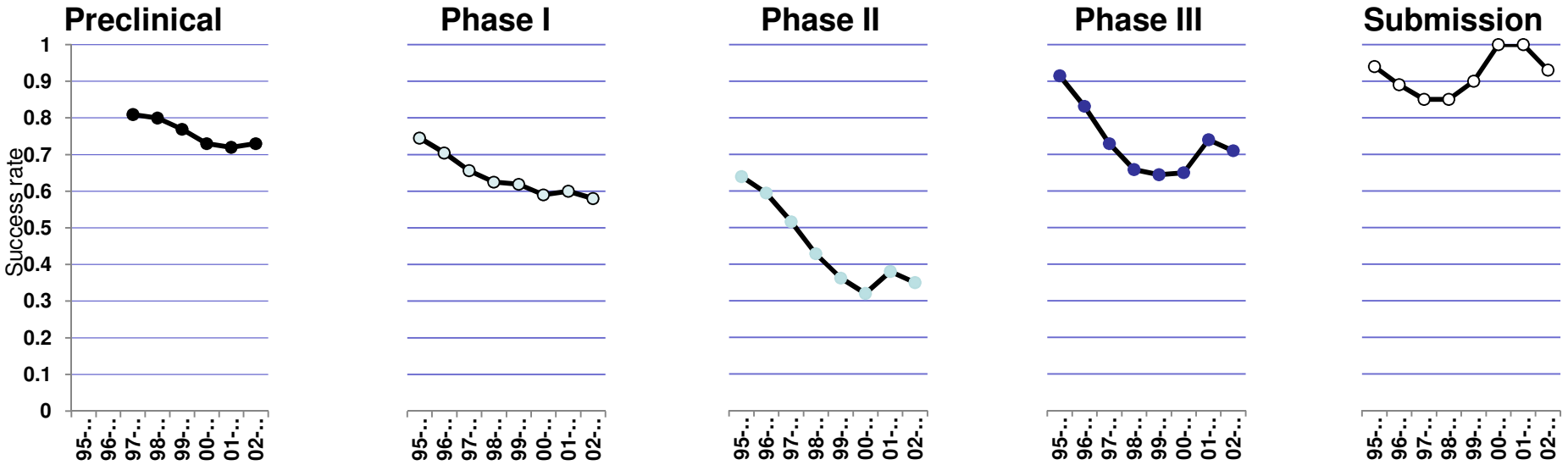
How much risk is in the plan?

- Logical progression of data acquisition to make the next development investment decision
  - Pharmacology evaluated quickly in phase I
  - PK/PD and dose selection in phase I and IIA
  - Efficacy and safety issues addressed in first studies especially for unprecedented mechanisms
  - Key differentiation and commercial requirements addressed prior to phase III

How much risk is in the candidate?

- Physicochemical properties
  - Solubility
  - Log octanol/water partition coefficient (clogP)
  - ADME characteristics
- Synthesis/COG
- Formulation needs
  - Oral bioavailability
  - Controlled release

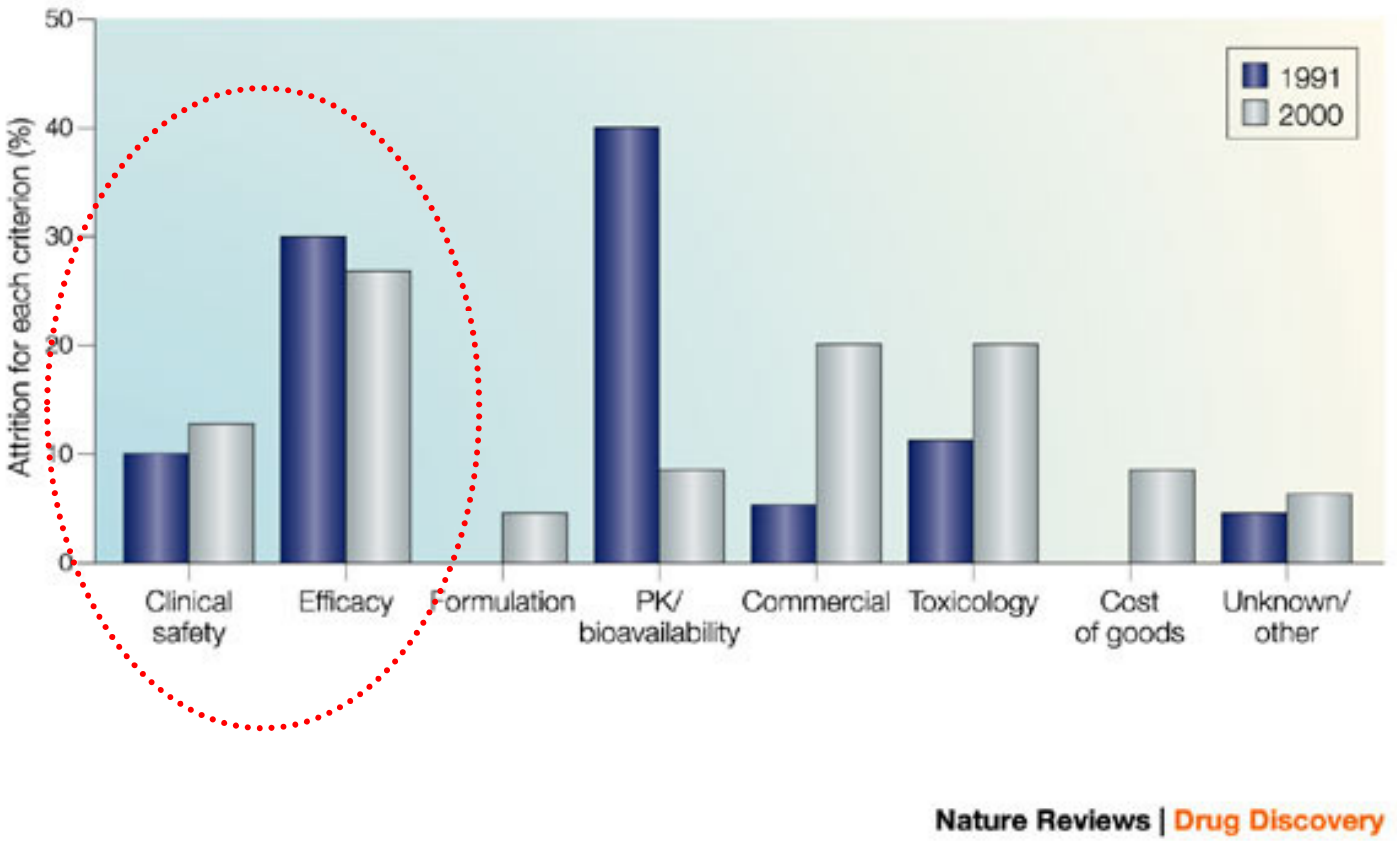
Trends in success rates by phase (CMR methodology)…



Year of entry into phase

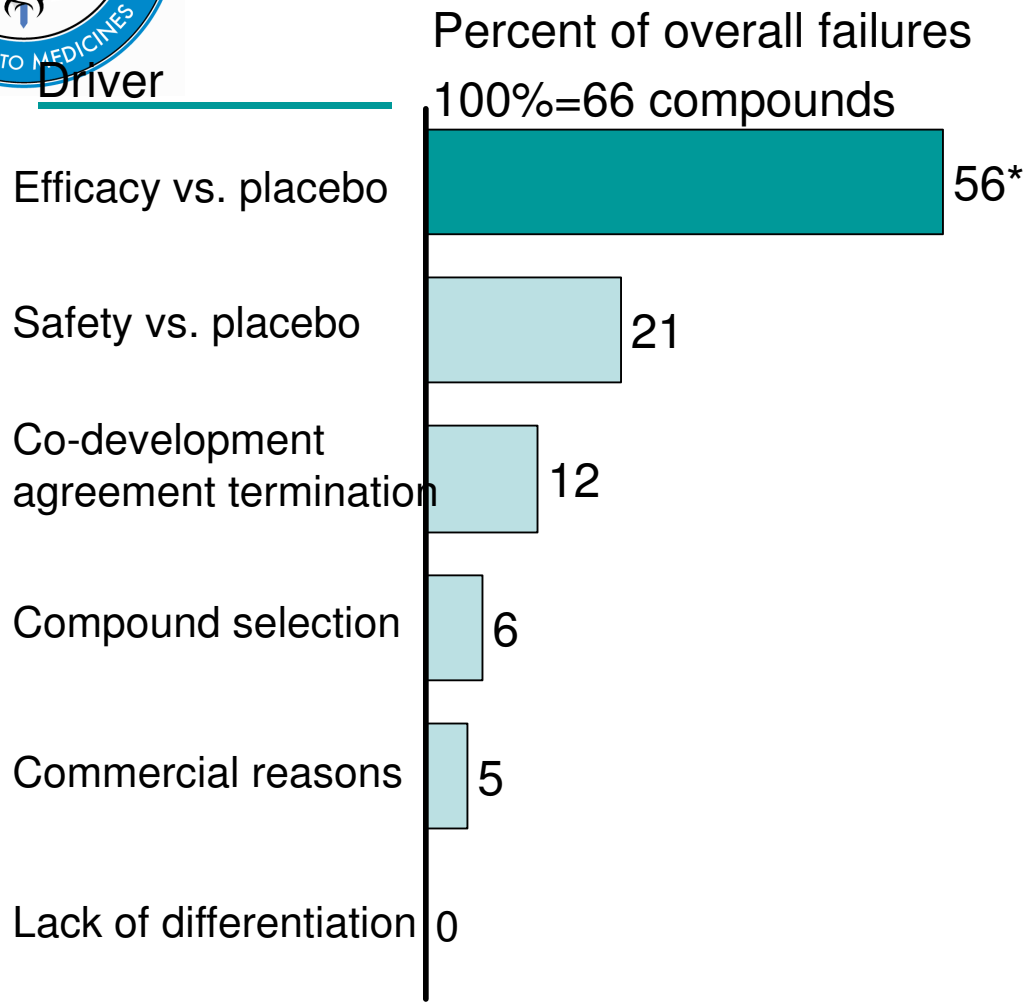
Between phase success rates have been calculated based on ASs that entered the phase in question during the time period specified. For example, for the 1994-1996 time window, ASs were monitored until the end of 1999; for the 1995-1997 time window ASs were monitored until the end of 2000.

Unacceptable safety and efficacy in humans remain high…



Adapted from: Kola and Landis, Nature Review Drug Discovery, 2004 (3):711-715

Case studies: causes of phase 2 failures…



Description

- Failure to demonstrate significant difference from placebo in treatment effects
- Confirmation of safety issues in earlier trials or in similar marketed compounds
- Withdrawal of R&D license or termination of collaborative alliance
- Existence of a better compound within same company
- High COGS or low forecasted sales
- Existence of a safer, more efficacious or more convenient product

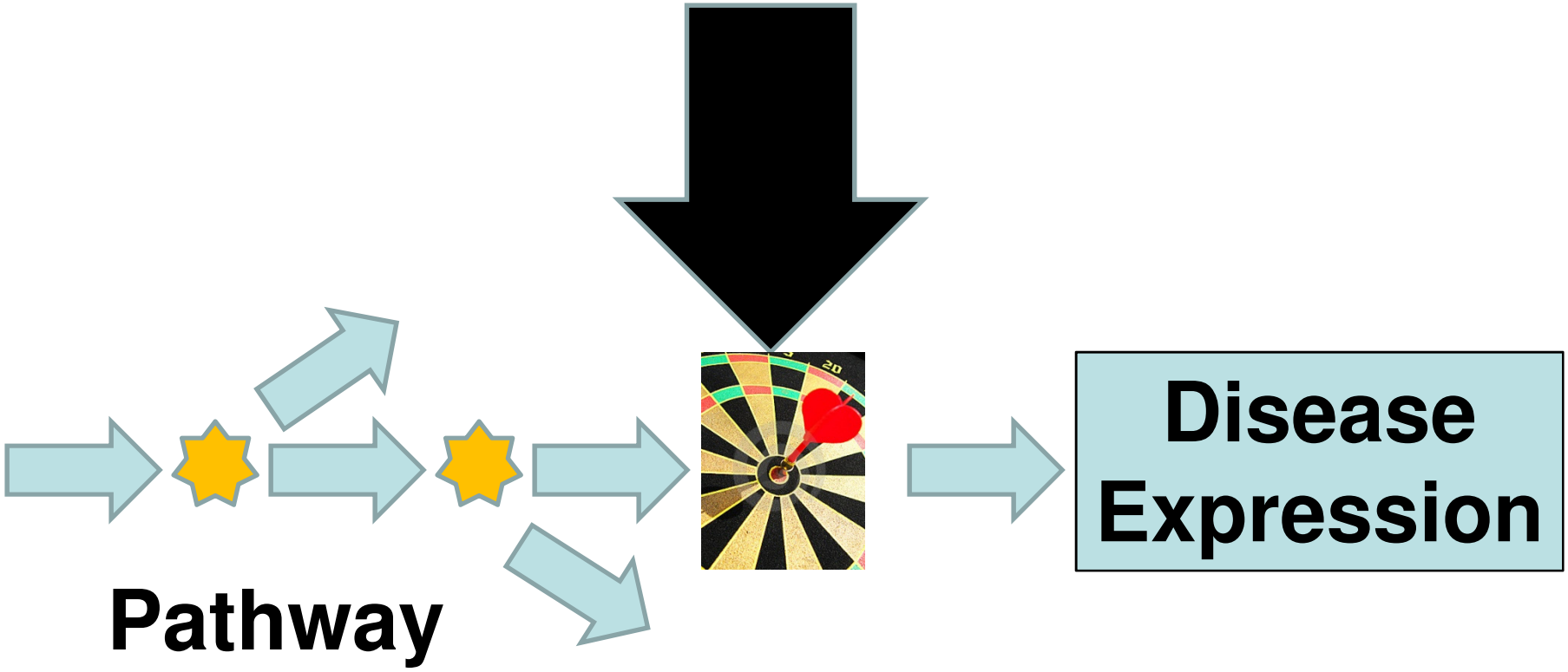
* Only 1 indication RIP out of 37 indication RIPs by efficacy vs. placebo had an established MOA

Source: EvaluatePharma, Pharmaprojects; Factiva, Literature Search; team analysis

Higher risk of failure…

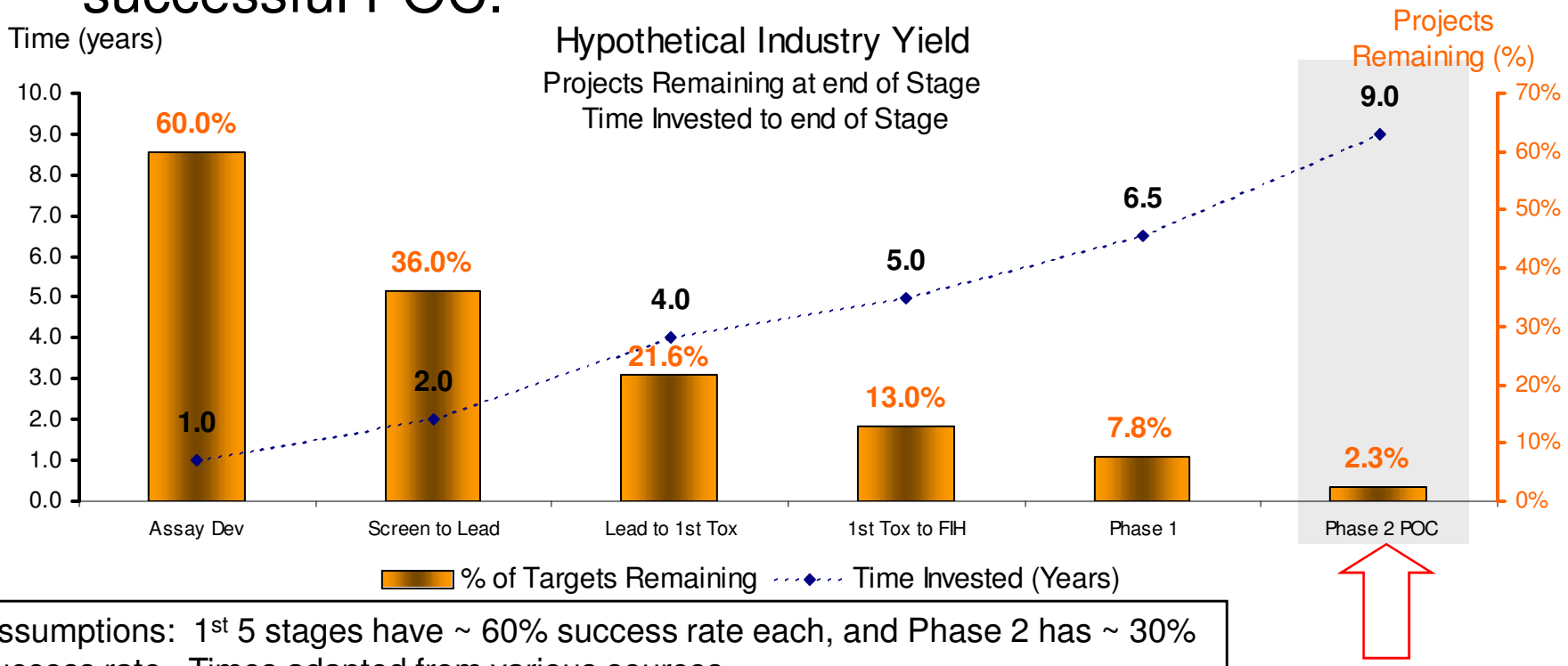
- **Unprecedented target**
- **Black box mechanism**
- **Unusual dose response (e.g. “U” shaped)**
- **Negative POM, narrow TI (vs. MTD) or unable to measure pharmacology in phase I**
- **Drug interactions and QTc prolongation**
- **Small molecule vs. biologic**
- **Complicated synthesis for small molecules (COG)**
- **Dose selection in phase III**
- **High efficacy hurdle (differentiation needed)**

The drug target…



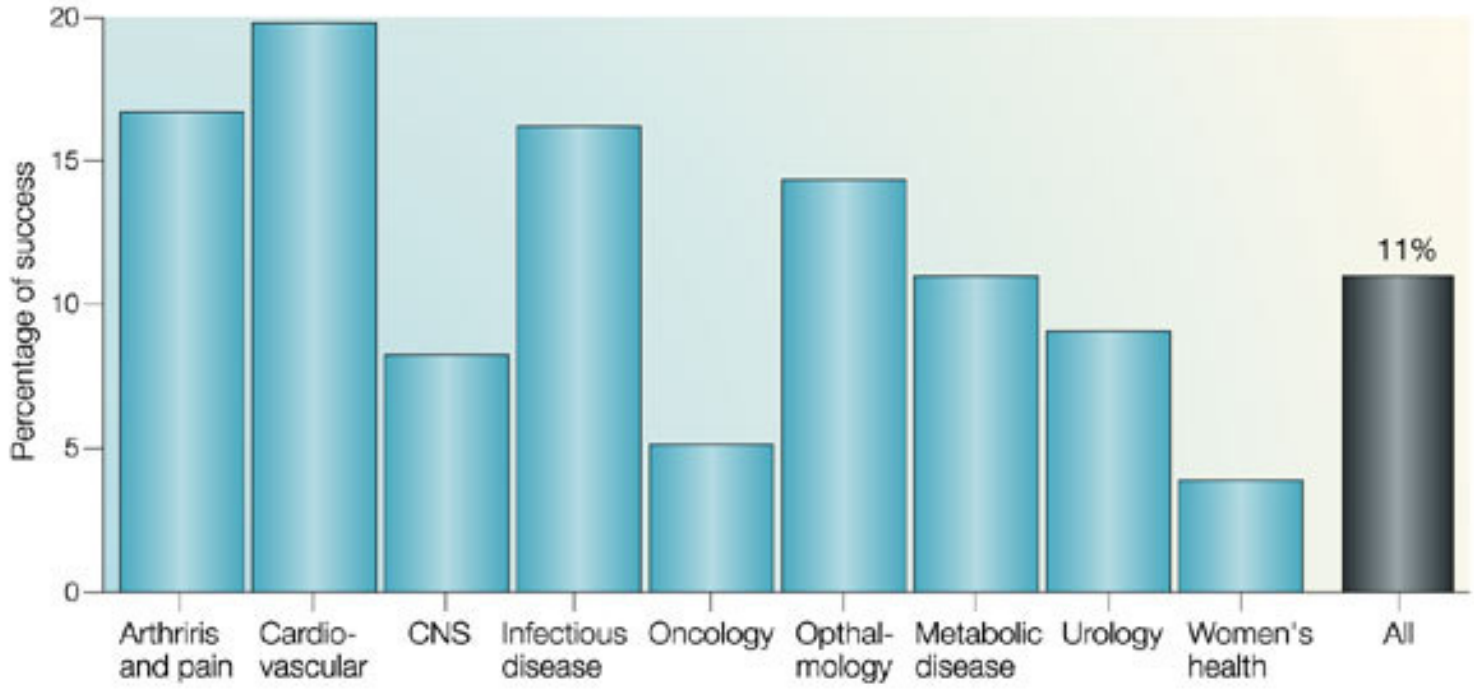
Idea Survival to Clinical POC…

- 2% of Discovery projects will be successful to Commercial POC, and it will take 9 years to achieve successful POC.



Assumptions: 1st 5 stages have ~ 60% success rate each, and Phase 2 has ~ 30% success rate. Times adapted from various sources.

Probability of success for drugs with new mechanisms is low…



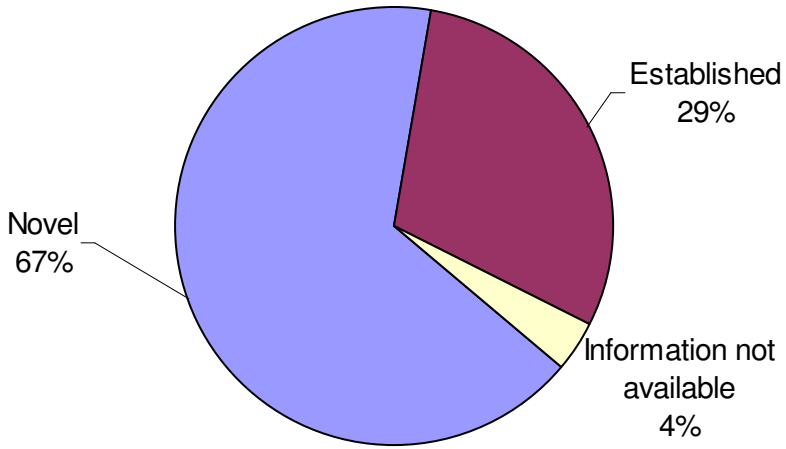
Nature Reviews | Drug Discovery

Adapted from: Kola and Landis, Nature Review Drug Discovery, 2004 (3):711-715

Target novelty…

- 2/3 of drug candidates entering 1st human trials are associated with novel targets/mechanisms.
- Novel candidates are much more likely to terminate development before the start of Phase 3 (2x – 4x risk factor)

NCE by Target Novelty (2000-2004)



For active substances reaching 1st human dose between 2000 and 2004.

How much risk is in the target for the indication in mind…

- Is there precedence for the drug target?
  - Literature on efficacy of the mechanism even for a failed drug
  - Successful biological drug validates target for small molecule drug
    - Herceptin for EGFR TK inhibitors
  - Human genetic variation validates target
    - CCR5 antagonist for resistance to HIV
    - JAK3 inhibitor for immunosuppression
- Target in a pathway known to be important for disease expression (pathway precedence)
  - Prostaglandin receptor antagonists and COX inhibitors
- Is the target expression limited to disease tissues?
  - Safety issues (TI) more likely for target that is widely expressed
- Pick the lowest risk vs. highest commercial indication first

Novartis strategy…

- CEO “Vasella's goal is to institutionalize the lessons from one of the company's most successful creations, the cancer drug Gleevec”
  - Focus research on smaller, narrowly defined groups of patients first and expand indications later
    - Pushback from the senior executives in sales and marketing
    - Business model focused on small groups of patients would ever make money
  - Anti-Interleukin-1 monoclonal antibody tested first in Muckle-Wells syndrome caused by a single genetic mutation
    - Small population and causes rashes, joint pain and fatal kidney damage in children
    - Results positive and rapidly established dose and safety profile convincing to FDA, approved for this indication rapidly and could go directly to phase III in other indications
    - Next focus on larger indications: RA, etc.

Business Week, June 11, 2009

Mechanisms are promiscuous…

coronary ischemia → male erectile dysfunction → pulmonary hypertension

neuronal regeneration

altitude sickness

diabetes

hypertension

Case study: Failure of LTB4 receptor antagonists…

- High levels of LTB4 in tissues from patients with inflammatory disease
  - Chemotactic for inflammatory cells
  - Antagonists active in rodent models of arthritis, heart transplant, multiple sclerosis, asthma, psoriasis, etc.
- Pfizer and other companies developed very potent LTB4 receptor antagonists (e.g. CP 195543, SC 53228, CGS 25019C, ONO 4057, LY 293111 Na, and BIIL 284 BS)
  - Reduced inflammatory cell infiltration in LTB4 skin challenge in psoriasis patients and neutrophils in BAL fluid in asthma patients
- No efficacy in phase II studies conducted by multiple companies in rheumatoid arthritis, ulcerative colitis, asthma, COPD, and psoriasis

Warning signs: higher risk of failure…

- Unprecedented target
- Black box mechanism
- Unusual dose response (e.g. “U” shaped)
- Negative POM, narrow TI (vs. MTD) or unable to measure pharmacology in phase I
- Drug interactions and QTc prolongation
- Small molecule vs. biologic
- Complicated synthesis for small molecules (COG)
- Dose selection in phase III
- High efficacy hurdle (differentiation needed)

Black box mechanism…

- Unknown drug target for compound with favorable *in vitro* and *in vivo* efficacy in preclinical models
  - Scientific basis for efficacy and safety missing
  - Discovery of the mechanism of action later is expensive and often not successful
  - Justification for human experimentation is anecdotal rather than based on knowledge of disease

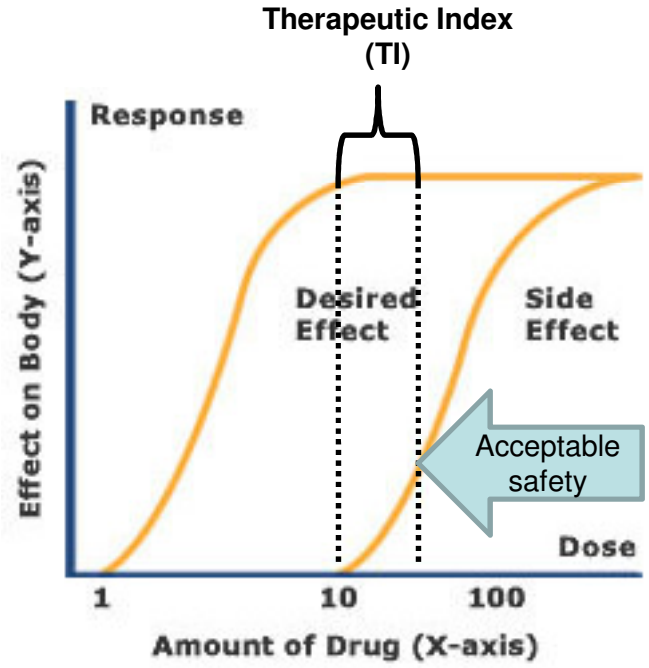
Case study: Tenidap's novel unknown mechanism…

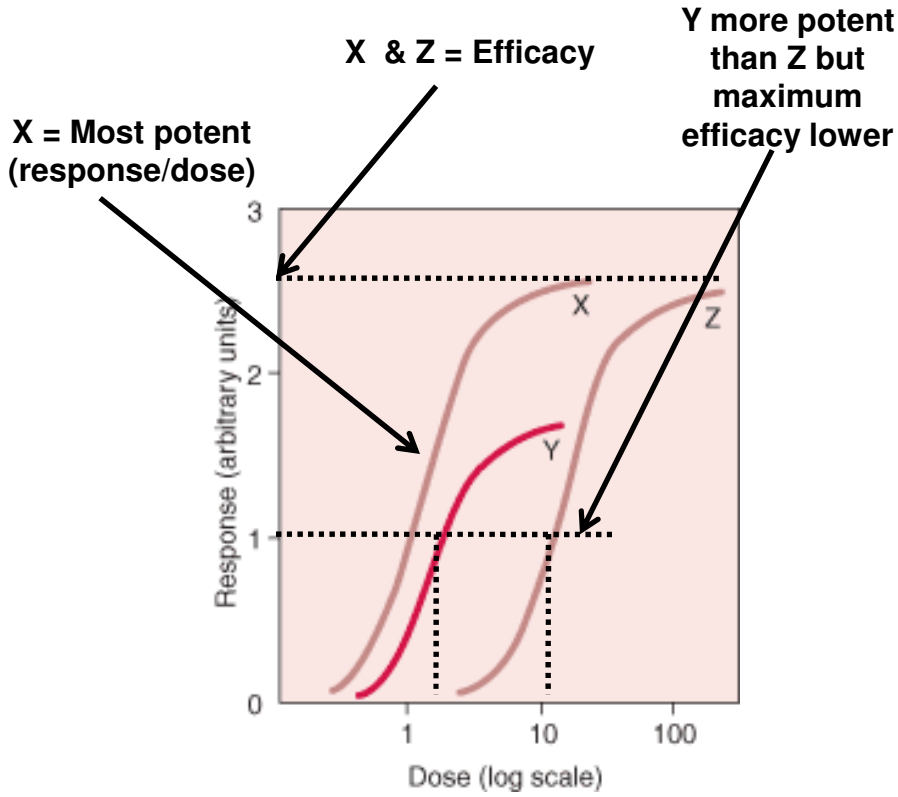
- Late 1980's Pfizer compound to replace Feldene (piroxicam) for RA and OA
  - Inhibited cellular production of prostaglandins and leukotrienes in vitro
    - Duel COX and 5-LO inhibition postulated
  - *In vivo* inhibited production of prostaglandins and found to be a very potent non-selective inhibitor of COX but no 5-LO inhibition
  - In RA studies unexpected results suggested a mechanism that also modulated cytokine production at higher doses
    - Unlike NSAIDs, reduced plasma IL-6 and CRP and reduced x-ray progression in RA patients
    - Reduced IL-1β and TNFα in vitro
    - Mechanism unknown despite 2 years of looking
  - Reversible proximal renal tubule safety issues not seen with NSAIDs
  - Not approved by FDA

Warning signs: higher risk of failure…

- Unprecedented target
- Black box mechanism
- Unusual dose response (e.g. “U” shaped)
- Negative POM, narrow TI (vs. MTD) or unable to measure pharmacology in phase I
- Drug interactions and QTc prolongation
- Small molecule vs. biologic
- Complicated synthesis for small molecules (COG)
- Dose selection in phase III
- High efficacy hurdle (differentiation needed)

Typical dose response curves for efficacy or safety…





Adapted from Merck manual, November 2007

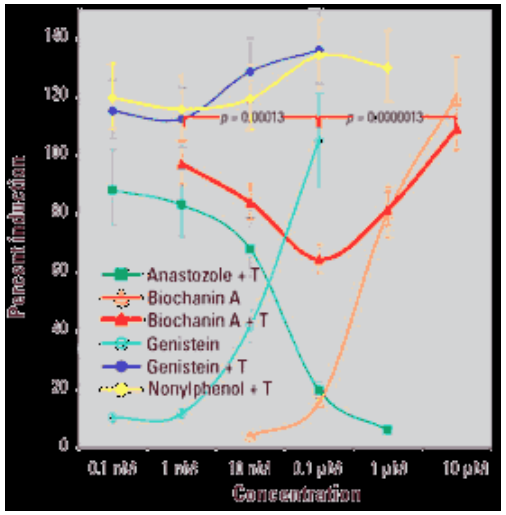
Unusual dose response curves for efficacy or safety increase risk…

"All substances are poisons: there is none which is not a poison. The right dose differentiates a poison and a remedy."
Paracelsus (1493-1541)

Hormesis has been defined as a dose-response relationship in which there is a stimulatory response at low doses, but an inhibitory response at high doses, resulting in a U- or inverted U-shaped dose response.

Estrogen antagonists (e.g. tamoxifen) exhibit species differences with respect to their estrogenic and anti-estrogenic properties making translation difficult.

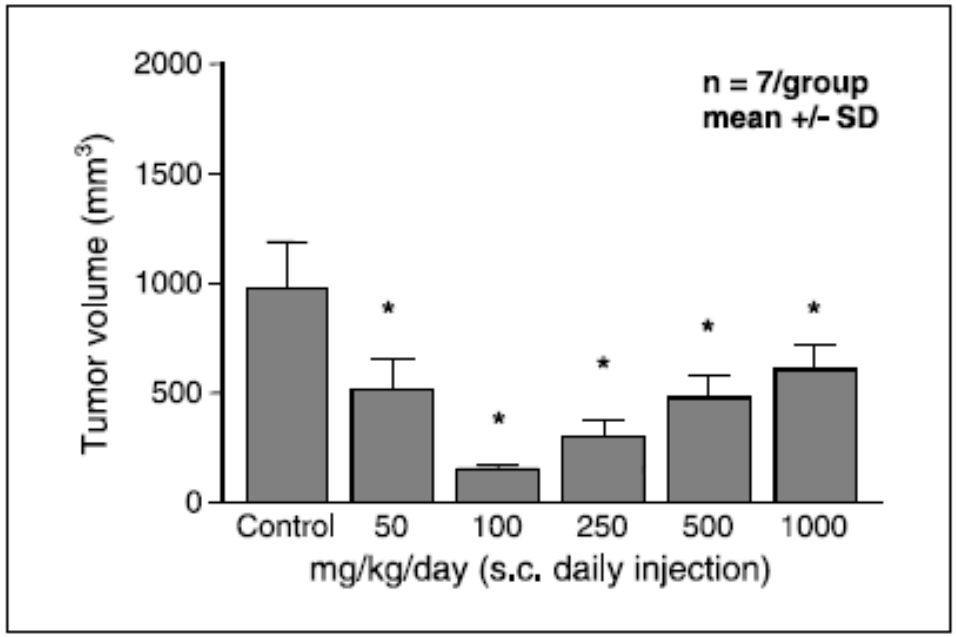
Estrogenic effects of various compounds vs. testosterone



- Relationships of pharmacology may not translate across species
- Difficult to translate NOAEL doses and exposures
- Higher risks in humans

Unusual dose response curves for efficacy or safety increase risk…

Inhibition of angiogenesis and tumor growth by human endostatin in xenograft model:



Therapeutic Efficacy of Endostatin Exhibits a Biphasic Dose-Response Curve
Celik,O.Su¨ru¨cu¨,C. Dietz,et al.
Cancer Res 2005; 65: (23). December 1, 2005

Figure 1. Treatment of human pancreatic carcinoma (BxPC-3) with human endostatin. Mean (± SD) tumor volume after a 20-day treatment with different dosages of rhEndostatin (50, 100, 250, 500, and 1,000 mg/kg/d) in BxPC-3 tumor–bearing mice (group sizes, $n = 7$). Endostatin was given s.c. once daily. Tumors were measured every 3 to 5 days. *, $P < 0.001$, tumor volume in all treatment groups were significantly different compared with the control group.

Warning signs: higher risk of failure…

- Unprecedented target
- Black box mechanism
- Unusual dose response (e.g. “U” shaped)
- Negative POM, narrow TI (vs. MTD) or unable to measure pharmacology in phase I
- Drug interactions and QTc prolongation
- Small molecule vs. biologic
- Complicated synthesis for small molecules (COG)
- Dose selection in phase III
- High efficacy hurdle (differentiation needed)

Risk of ignoring a negative POM with a narrow TI…

Thorax 1991;46:184–189

Effect of a 5-lipoxygenase inhibitor on leukotriene generation and airway responses after allergen challenge in asthmatic patients

Kok P Hui, Ian K Taylor, Graham W Taylor, Paul Rubin, James Kesterson, Neil C Barnes, Peter J Barnes

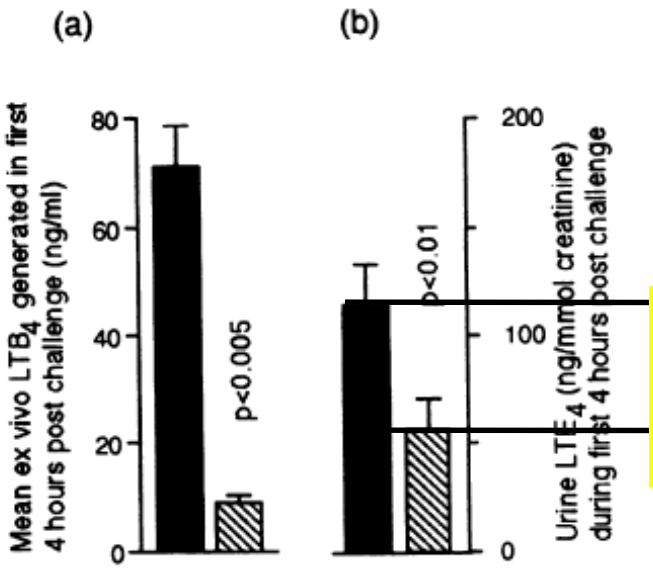


Figure 4 Effect of zileuton (▩) and placebo (■) on (a) mean ex vivo leukotriene (LT) B_4 production and (b) urine LTE_4. Mean ex vivo LTB_4 production refers to mean whole blood calcium ionophore stimulated LTB_4 production for four hours after allergen challenge. Urine LTE_4 is the total urinary excretion of LTE_4 over four hours. Values are means with 1 SEM.

Zileuton 800 mg dose:
~50% inhibition of urinary LTE4

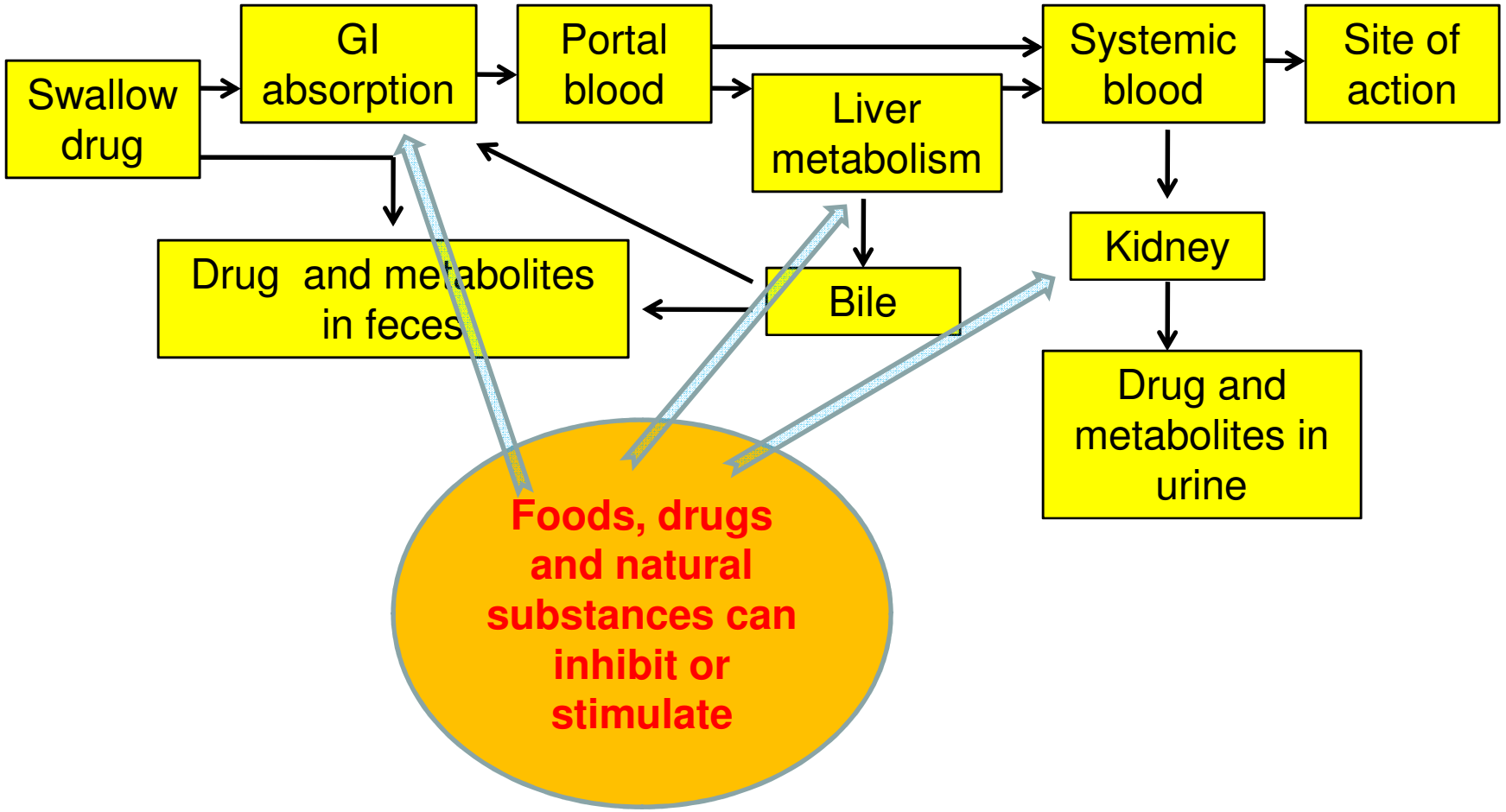
Candidate 5-LO inhibitor

- MTD: Nausea and vomiting
- Used published method and compared candidate at MTD to zileuton in same study
- Less than 50% inhibition of urinary LTE4 at MTD
- Large phase IIB asthma and COPD studies conducted with no significant efficacy

Warning signs: higher risk of failure…

- Unprecedented target
- Black box mechanism
- Unusual dose response (e.g. “U” shaped)
- Negative POM, narrow TI (vs. MTD) or unable to measure pharmacology in phase I
- Drug interactions and QTc prolongation
- Small molecule vs. biologic
- Complicated synthesis for small molecules (COG)
- Dose selection in phase III
- High efficacy hurdle (differentiation needed)

Drug ADME and interaction concepts…



FDA website has useful information on drug interactions……

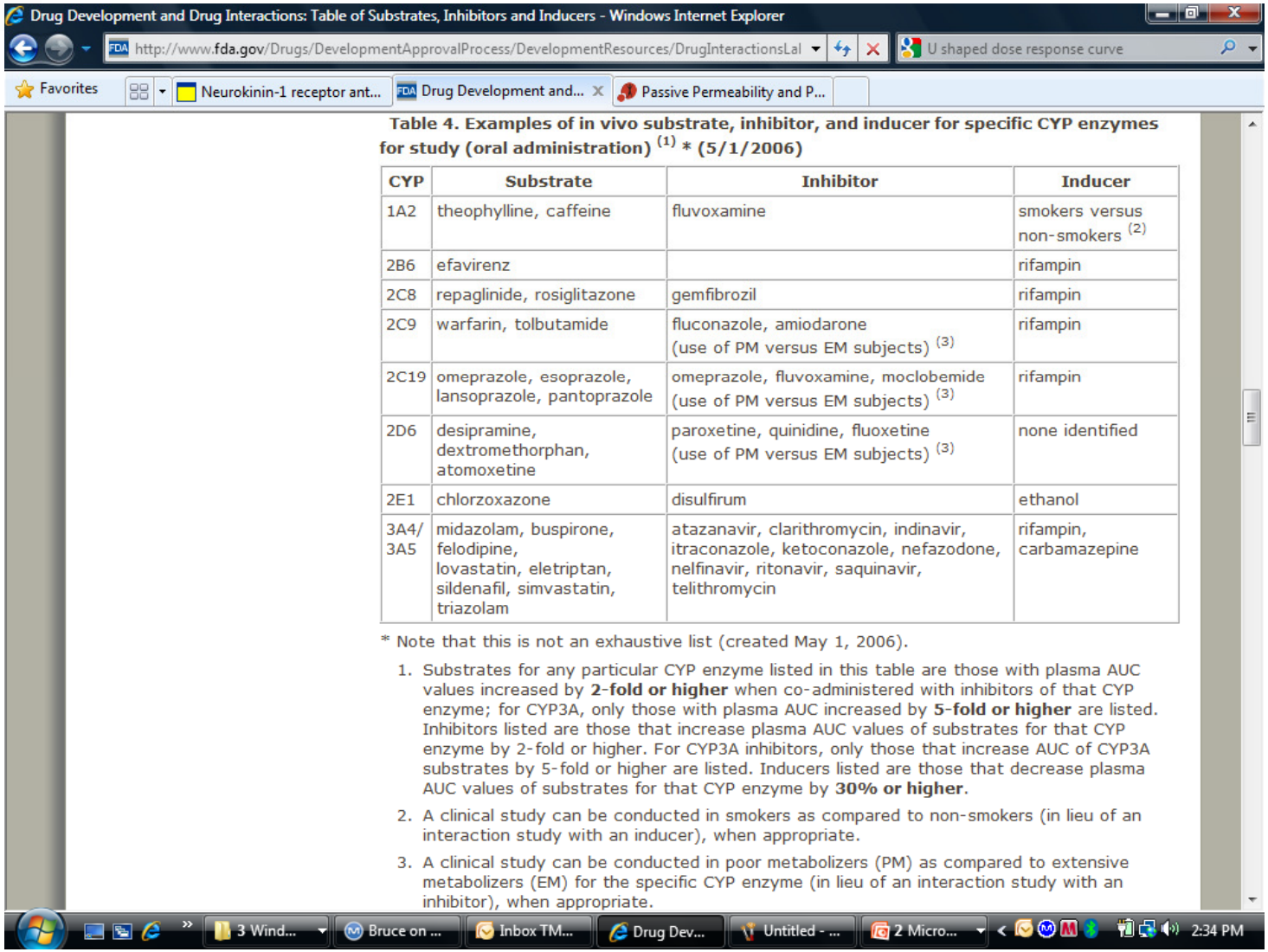


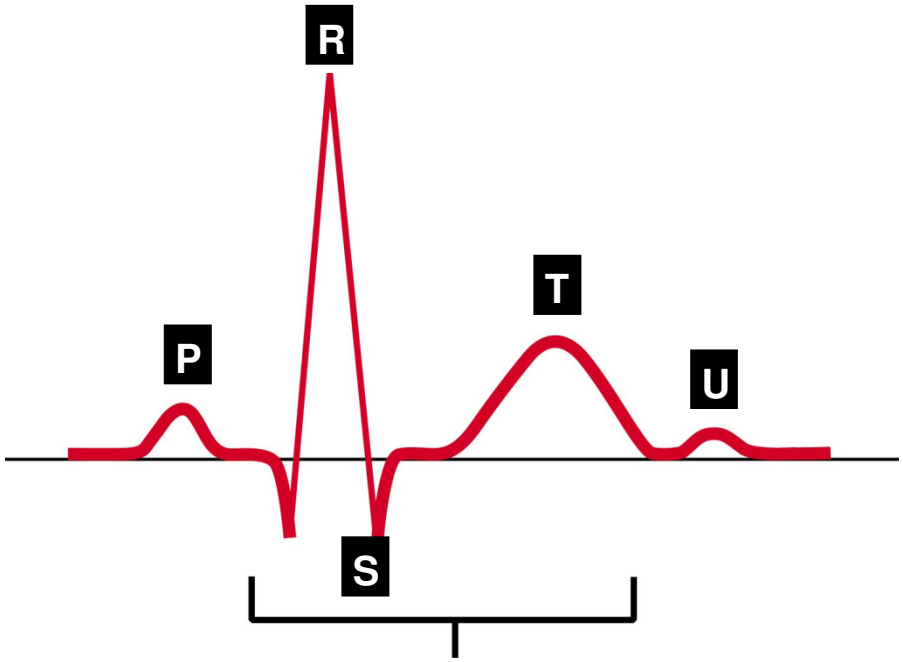
Table 4. Examples of in vivo substrate, inhibitor, and inducer for specific CYP enzymes for study (oral administration) [1] * (5/1/2006)

CYP	Substrate	Inhibitor	Inducer
1A2	theophylline, caffeine	fluvoxamine	smokers versus non-smokers [2]
2B6	efavirenz		rifampin
2C8	repaglinide, rosiglitazone	gemfibrozil	rifampin
2C9	warfarin, tolbutamide	fluconazole, amiodarone (use of PM versus EM subjects) [3]	rifampin
2C19	omeprazole, esoprazole, lansoprazole, pantoprazole	omeprazole, fluvoxamine, moclobemide (use of PM versus EM subjects) [3]	rifampin
2D6	desipramine, dextromethorphan, atomoxetine	paroxetine, quinidine, fluoxetine (use of PM versus EM subjects) [3]	none identified
2E1	chlorzoxazone	disulfirum	ethanol
3A4/ 3A5	midazolam, buspirone, felodipine, lovastatin, eletriptan, sildenafil, simvastatin, triazolam	atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin	rifampin, carbamazepine

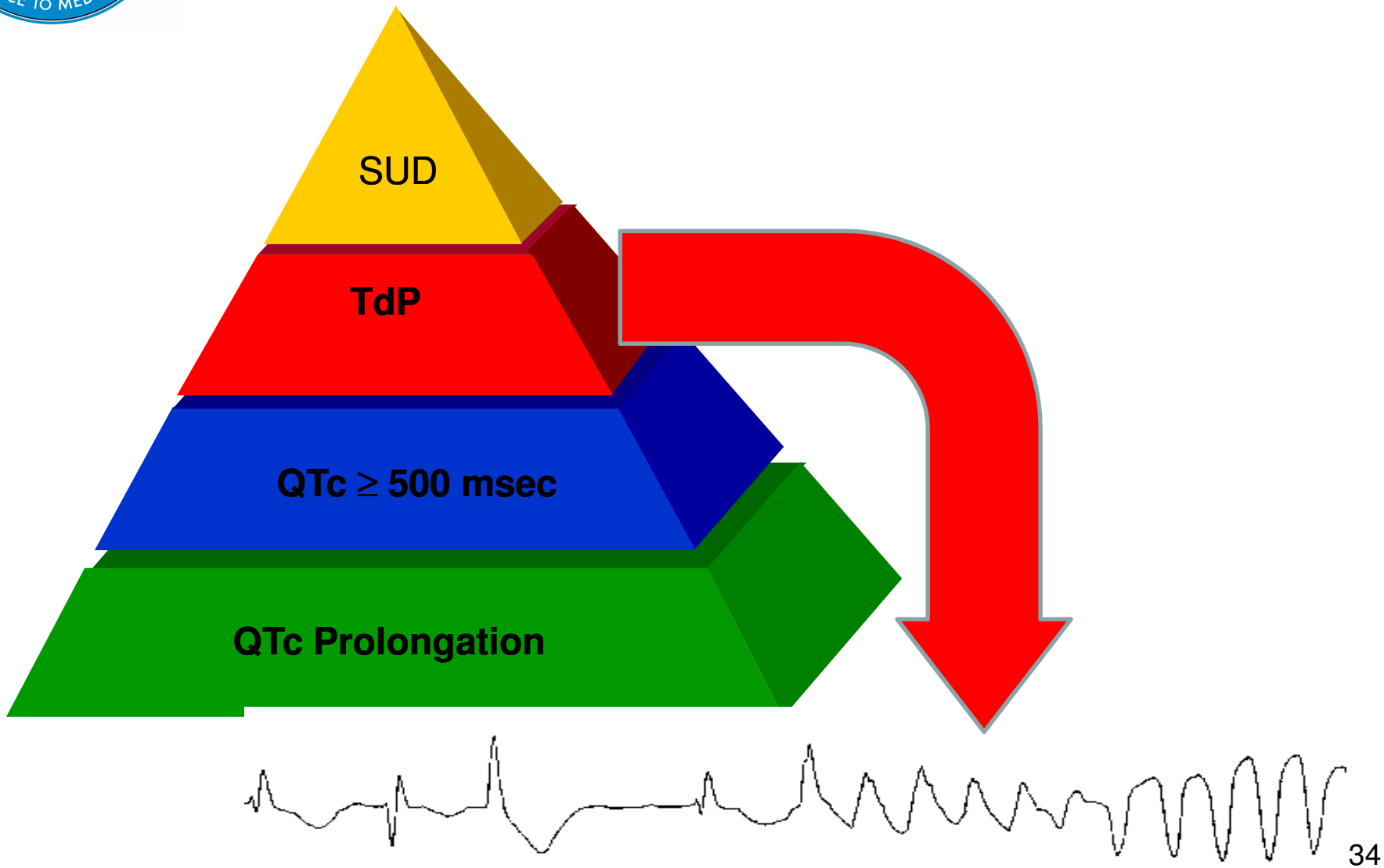
* Note that this is not an exhaustive list (created May 1, 2006).

1. Substrates for any particular CYP enzyme listed in this table are those with plasma AUC values increased by **2-fold or higher** when co-administered with inhibitors of that CYP enzyme; for CYP3A, only those with plasma AUC increased by **5-fold or higher** are listed. Inhibitors listed are those that increase plasma AUC values of substrates for that CYP enzyme by 2-fold or higher. For CYP3A inhibitors, only those that increase AUC of CYP3A substrates by 5-fold or higher are listed. Inducers listed are those that decrease plasma AUC values of substrates for that CYP enzyme by **30% or higher**.
2. A clinical study can be conducted in smokers as compared to non-smokers (in lieu of an interaction study with an inducer), when appropriate.
3. A clinical study can be conducted in poor metabolizers (PM) as compared to extensive metabolizers (EM) for the specific CYP enzyme (in lieu of an interaction study with an inhibitor), when appropriate.

QT interval overview…



QTc: Surrogate marker for sudden death unexplained death…



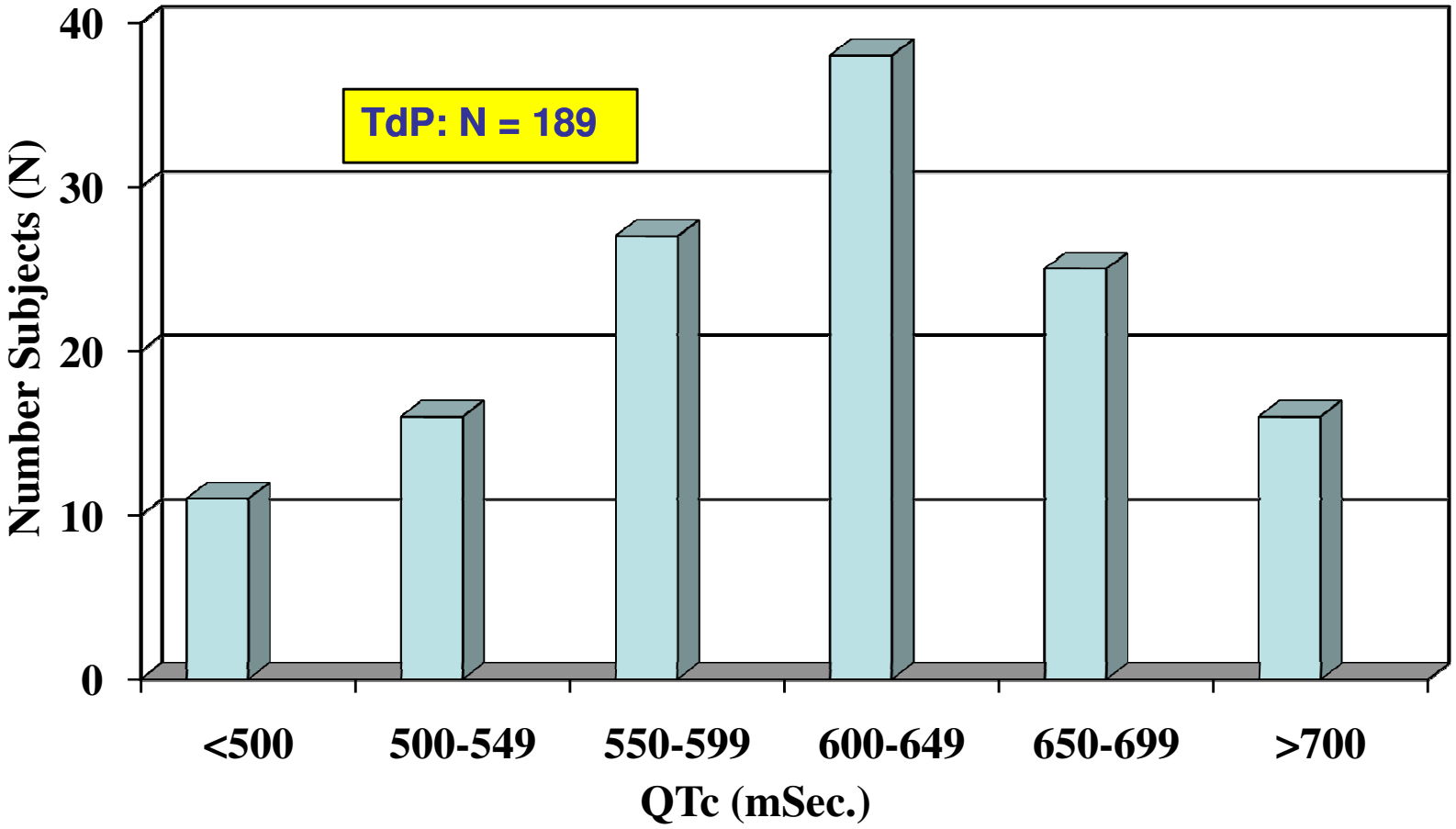
QTc prolongation: Surrogate marker for TdP risk…

Table 3 Likely prognostic significance of 1x clinical dose mean maximum or peak placebo-corrected effects on QTc interval.

Mean maximum or peak placebo-corrected increase in QTc interval	*Likely potential torsadogenic risk*
≤5 ms	None
6–10 ms	Unlikely
11–15 ms	Possible
16–20 ms	Probable
21–25 ms	Almost definite
≥26 ms	Definite

Br J Clin Pharmacol, **54**, 188–202

Torsades de Pointes: QTc and non-antiarrhythmic drugs…



Many approved drugs do cause QTc prolongation…

Table 1 Non-class III drugs reported to cause QT interval prolongation and/or torsade de pointes.

Non-class III cardiovascular drugs		*Non-cardiovascular drugs*		
Sodium channel blockers	Neuroleptics	Antidepressants	Antimicrobials	Anticancer drugs
Quinidine	Chlorpromazine	Amitriptyline	Erythromycin	Anthracycline
Disopyramide	Triflupromazine	Protriptyline	Co-trimoxazole	Aclarubicin
N-acetyl-procainamide	Promazine	Nortriptyline	Sulfamethoxazole	5-fluorouracil
Lorcainide	Perphenazine	Butriptyline	Pentamidine	Acodazole
3-Methoxy-O-desmethyl-encainide (MODE)	Fluphenazine	Desipramine	Amantidine	Adriamycin
Ajmaline	Prochlorperazine	Imipramine	Grepafloxacin	Tamoxifen
	Trifluoperazine	Lofepramine	Levofloxacin	S9788
Antianginals	Triethylperazine	Clomipramine	Moxifloxacin	502U83
Prenylamine	Haloperidol	Doxepin	Sparfloxacin	Arsenic trioxide
Fendiline	Trifluoperidol	Maprotiline	Gatifloxacin	Efavirenz
Lidoflazine	Droperidol	Dothiepin	Clarithromycin	
Bepridil	Penfluridol	Citalopram	Spiramycin	Miscellaneous
Aprindine	Fluspirilene	Zimeldine	Fluconazole	Vincamine
Terodiline	Risperidone	Fluoxetine	D0870	Probucol
Perhexiline	Ziprasidone		Antimoniates	Glibenclamide
Amiodarone	Amisulpride	H_1-Antihistamines		Epoprostenol
Tedisamil	Chlorprothixene	Terfenadine	Serotonin (5-HT_2)-antagonists	Chloral hydrate
Mibefradil	Thiothixene	Astemizole	Ketanserin	Amiloride
	Thioridazine	Diphenhydramine	Amperozide	Bromocriptine
α_1/β blockers	Sertindole	Promethazine	Retanserin	Sevoflurane
Sotalol	Pimozide	Hydroxyzine	Pipamperone	Cisapride
Oxprenolol	Zotepine			Tacrolimus
Nifenalol	Quetiapine	Antimalarials	Serotonin (5-HT_3)-antagonists	Levacetylmethadol
Indoramin	Olanzapine	Halofantrine	Dolasetron	Lubelozole
Melperone		Chloroquine	Zatosetron	Tiapride
Amosulalol		Arteether		Tizanidine
				Rivastigmine
Inotropic agents				Cocaine
Dobutamine				Domperidone
				Bupivacaine

Br J Clin Pharmacol, **54**, 188

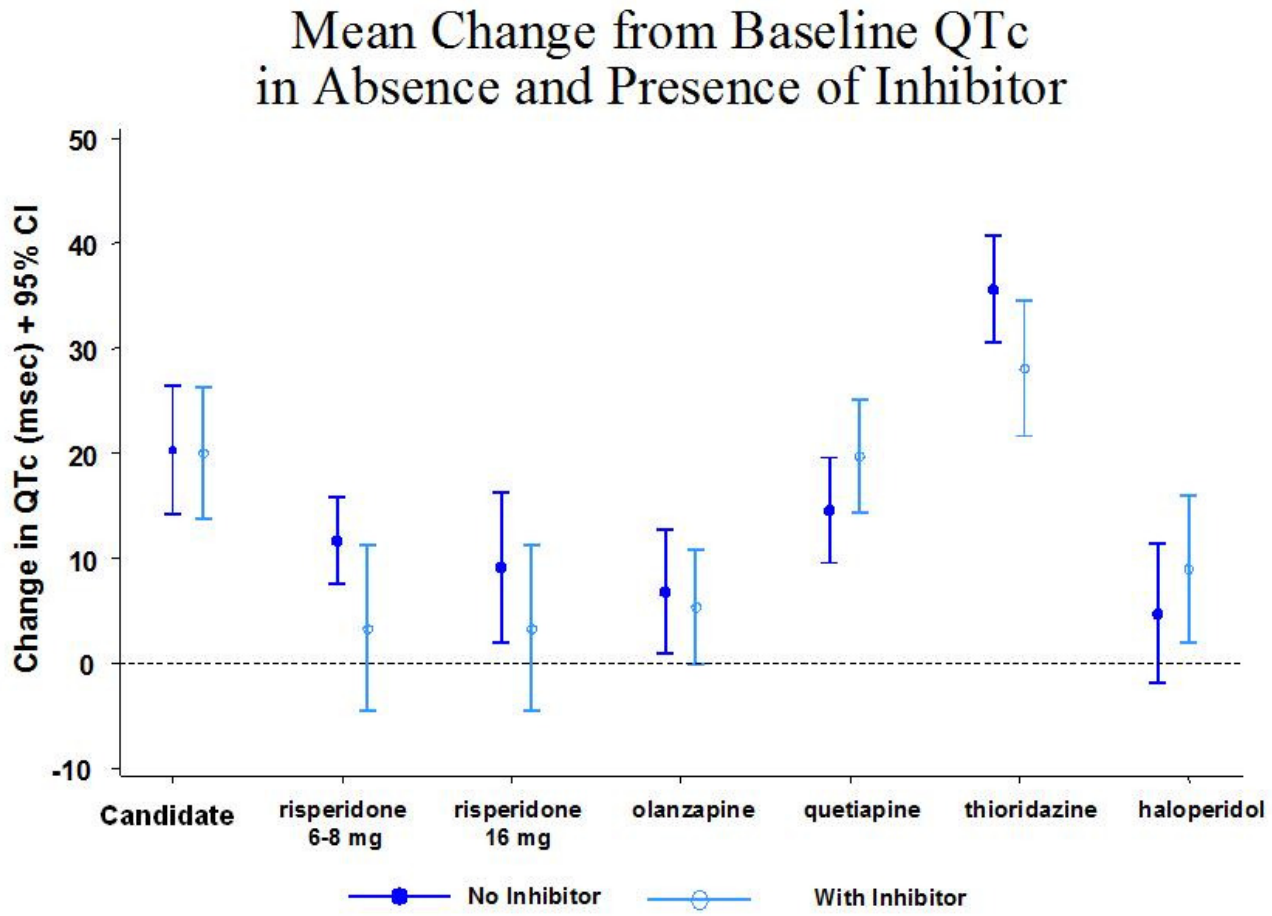
Case study: CNS candidate drug…

Incidence of Categorical QTc Increases; Phase II/III Studies

Drug Candidate and Comparators

	Candidate N=2492		Haloperidol N=535		Risperidone N=259		Placebo N=374	
	n	%	n	%	n	%	n	%
Incidence								
QTc ≥450 msec*	131	5.3	13	2.4	11	4.2	10	2.7
QTc ≥480 msec*	6	0.2	1	0.2	0	0	1	0.3
QTc ≥500 msec*	2	0.1	0	0	0	0	1	0.3
Increase from Baseline:								
≥30 msec	480	20.3	61	11.7	40	16.6	45	12.2
≥60 msec	48	2.0	5	1.0	2	0.8	4	1.1
≥75 msec	7	0.3	3	0.6	1	0.4	2	0.5
≥15%	64	2.7	9	1.7	4	1.7	4	1.1
≥25%	4	0.2	0	0	0	0	2	0.5
Baseline QTc (msec)								
Median	401.1		401.9		400.5		400.0	
Range	314-494		320-461		321-517		321-507	

QTc prolongation requires additional studies…



QTc Population (Mean) Values: FDA View…

- < 5 msec: no significant concern
- 8-10 msec: FDA has approved drugs with this degree of QTc prolongation
- 10-20 msec: FDA has approved drugs with this degree of QTc prolongation
- > 20 msec: Considered to be an anti-arrhythmic

CPMP (European) guidelines for corrected QTc individual values…

QTc change from baseline

- < 30 msec: Unlikely to raise significant concerns
- 30-60 msec: More likely to represent a drug effect and raise concern
- > 60 msec: Raises clear concerns, re: TdP

QTc

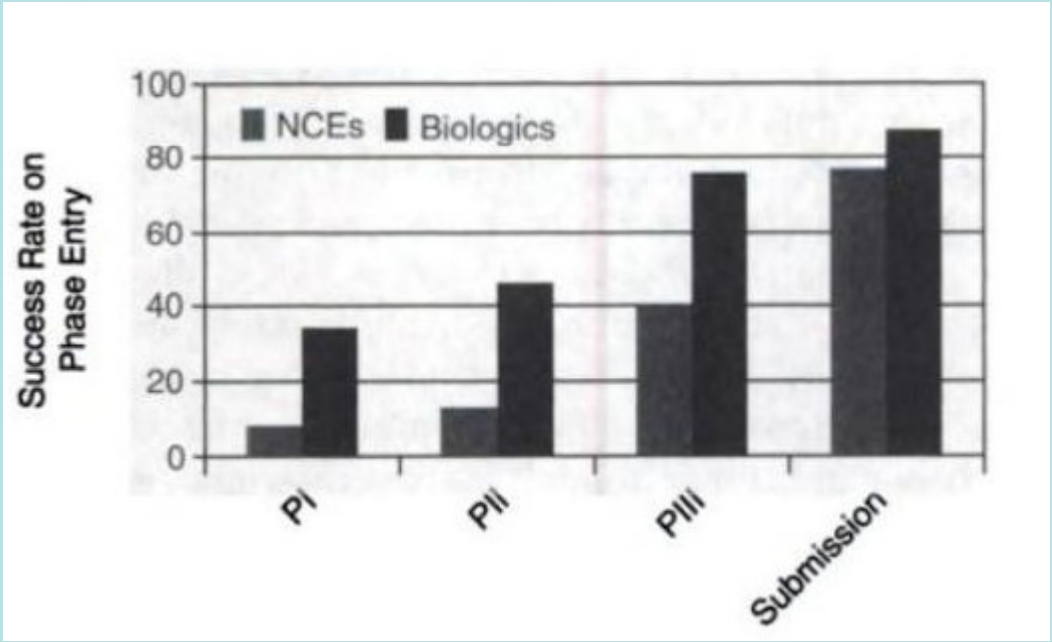
- > 500 msec: Raises clear concerns, re: TdP

Warning signs: higher risk of failure…

- Unprecedented target
- Black box mechanism
- Unusual dose response (e.g. “U” shaped)
- Negative POM, narrow TI (vs. MTD) or unable to measure pharmacology in phase I
- Drug interactions and QTc prolongation
- Small molecule vs. biologic
- Complicated synthesis for small molecules (COG)
- Dose selection in phase III
- High efficacy hurdle (differentiation needed)

Biologics fail less often than small molecules…

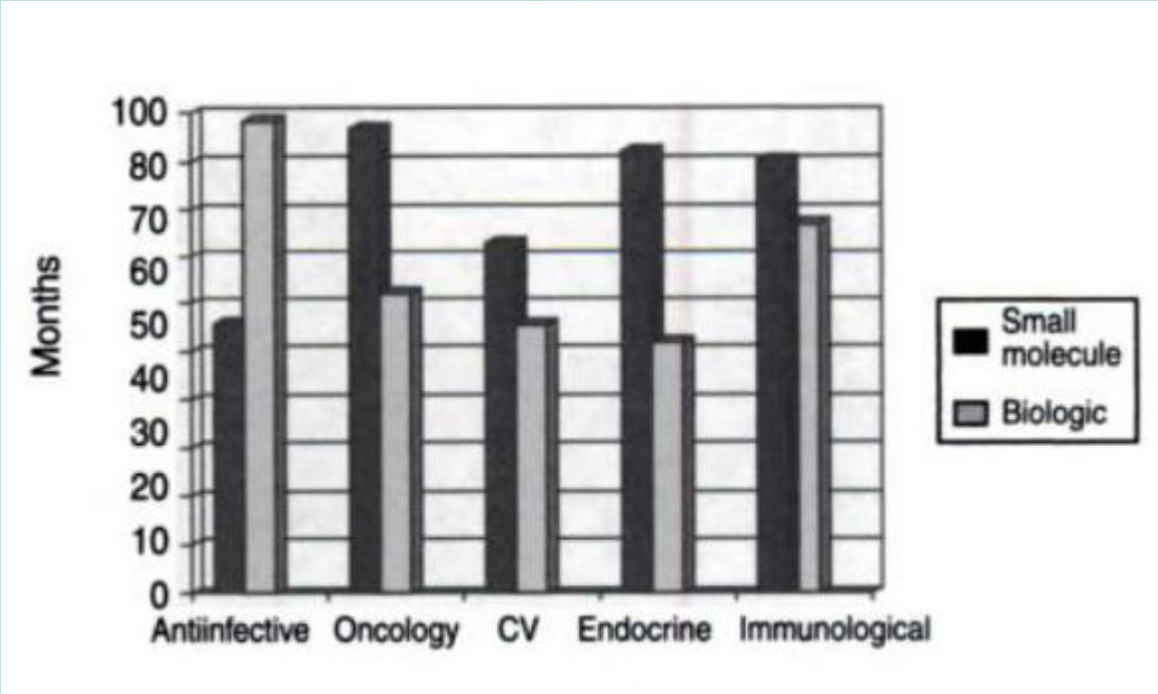
Higher potency and selectivity with better safety: lower risk development.



From Industry Success Rates 2002, CMR International, Surrey, U.K. (2002)

Biologic drug development is cheaper and faster…

Mean time for clinical development of approved therapeutics: 1983-2001.



From: J.M. Reichert , A guide to drug discovery: Trends in development and approval times for new therapeutics in the United States. *Nature Reviews Drug Discovery* 2, 695-702 (September 2003).

Case study: biologic vs. small molecule for TNFα inhibition…

- Precedented mechanism with biologics in RA, IBD, psoriasis, etc. (Remicade, Humira, Enbrel)
- Great competitive advantage for small molecule oral TNFα inhibitor
  - PDE_4 inhibitors reduce TNFα production *in vitro* and in animal models and active in disease models
  - Multiple companies developed selective oral PDE_4 inhibitors (Pfizer, Merck, GSK, others)
    - Some caused vasculitis and cardiac abnormities in toxicology studies
    - All found to be poorly tolerated in humans with nausea and vomiting that limited dose

Warning signs: higher risk of failure…

- Unprecedented target
- Black box mechanism
- Unusual dose response (e.g. “U” shaped)
- Negative POM, narrow TI (vs. MTD) or unable to measure pharmacology in phase I
- Drug interactions and QTc prolongation
- Small molecule vs. biologic
- Complicated synthesis for small molecules (COG)
- Dose selection in phase III
- High efficacy hurdle (differentiation needed)

Complicated synthesis creates hurdles…

- Delays manufacture of API for key steps in drug development
  - Regulatory toxicology studies with same API planned for FIH to ensure all impurities qualified
  - Supplies for phase II and III
- Creates issues that consume resources
  - Lot to lot impurity inconsistencies that must be qualified in safety studies or eliminated
  - Chemistry FTEs improving synthesis
- Increases cost of goods due to lower yields
  - Bigger issue for low potency compounds
  - If highest commercially acceptable dose does not achieve desired clinical profile the project dies

Warning signs: higher risk of failure…

- Unprecedented target
- Black box mechanism
- Unusual dose response (e.g. “U” shaped)
- Negative POM, narrow TI (vs. MTD) or unable to measure pharmacology in phase I
- Drug interactions and QTc prolongation
- Small molecule vs. biologic
- Complicated synthesis for small molecules (COG)
- **Dose selection in phase III**
- High efficacy hurdle (differentiation needed)

A program with dose selection in phase III has more risk…

- What prevented earlier identification of phase III dose?
  - Poor understanding of the relationship between pharmacology and registerable endpoints
  - Variable or hard to interpret data in phase I and II
  - Progressing a program without allowing time to interpret earlier results
  - Endpoints that require large numbers and long time without surrogates or biomarkers

Warning signs: higher risk of failure…

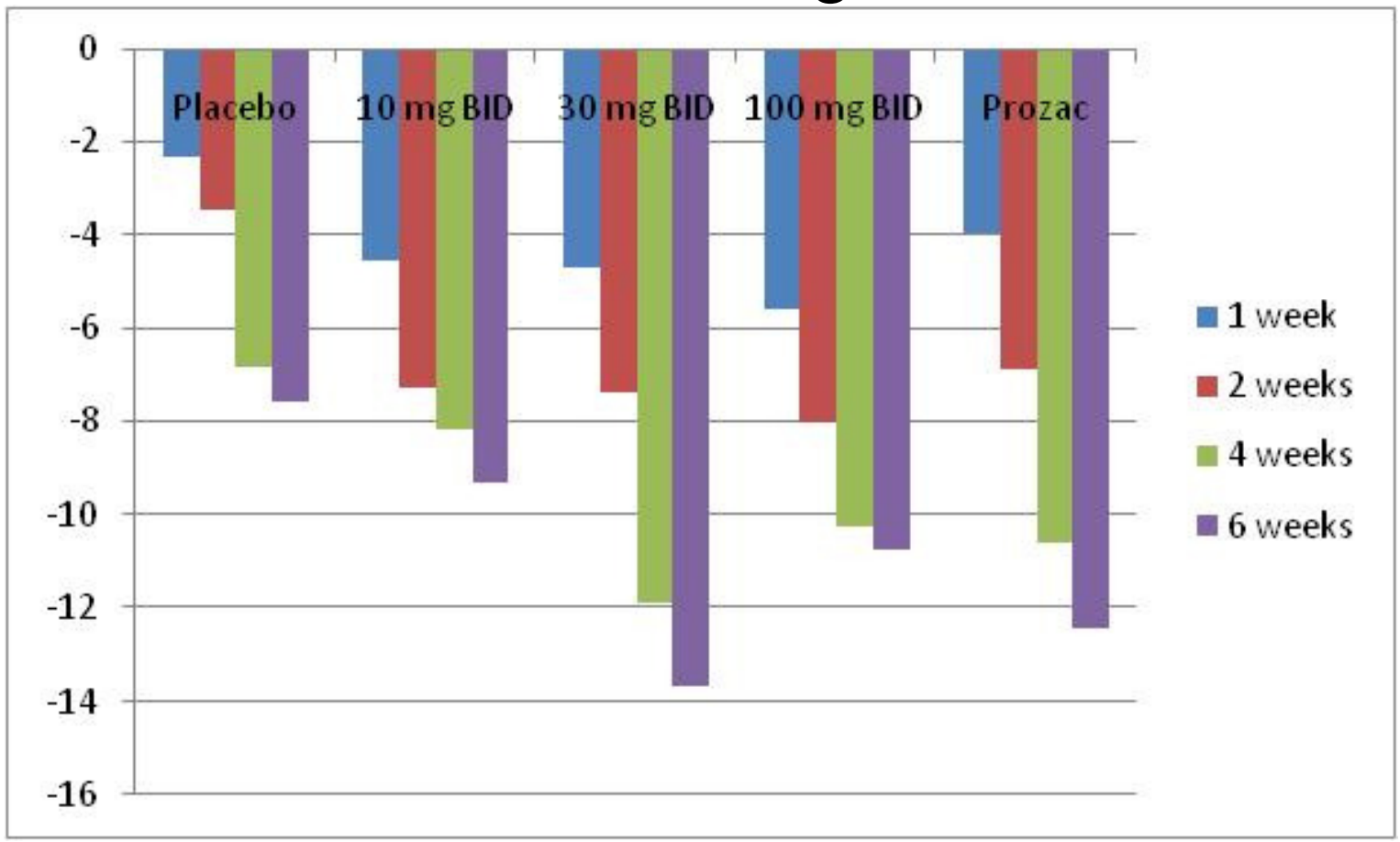
- Unprecedented target
- Black box mechanism
- Unusual dose response (e.g. “U” shaped)
- Negative POM, narrow TI (vs. MTD) or unable to measure pharmacology in phase I
- Drug interactions and QTc prolongation
- Small molecule vs. biologic
- Complicated synthesis for small molecules (COG)
- Dose selection in phase III
- High efficacy hurdle (differentiation needed)

NK-1 (substance P) antagonists for depression…

- Differentiation from SSRIs needed
  - Improved efficacy (better reduction in HAM-D scores) and/or efficacy in resistant patients
  - Better safety profile (sexual side effects, others)
- Pfizer, GSK and Merck all had candidates
  - Efficacy reported in phase II but not superior to SSRIs
  - Different safety issues

NK-1 receptor antagonist in major depressive disorder…

HAM-D Change



Understanding drug development and key risk factors…

Target → Molecule → Translation → Plan → Data → Decisions

- **Unprecedented target**
- **Black box mechanism**
- **Unusual dose response (e.g. "U" shaped)**
- **Negative POM, narrow TI (vs. MTD) or unable to measure pharmacology in phase I**
- **Drug interactions and QTc prolongation**
- **Small molecule vs. biologic**
- **Complicated synthesis for small molecules (COG)**
- **Dose selection in phase III**
- **High efficacy hurdle (differentiation needed)**