Center for Health Policy at BROOKINGS

Improving Productivity in Pharmaceutical Research and Development: The Role of Clinical Pharmacology and Experimental Medicine

Center for Health Policy
The Brookings Institution

The Embassy Row Hotel • Washington, DC
July 28, 2015

Improving Productivity in Pharmaceutical Research & Development

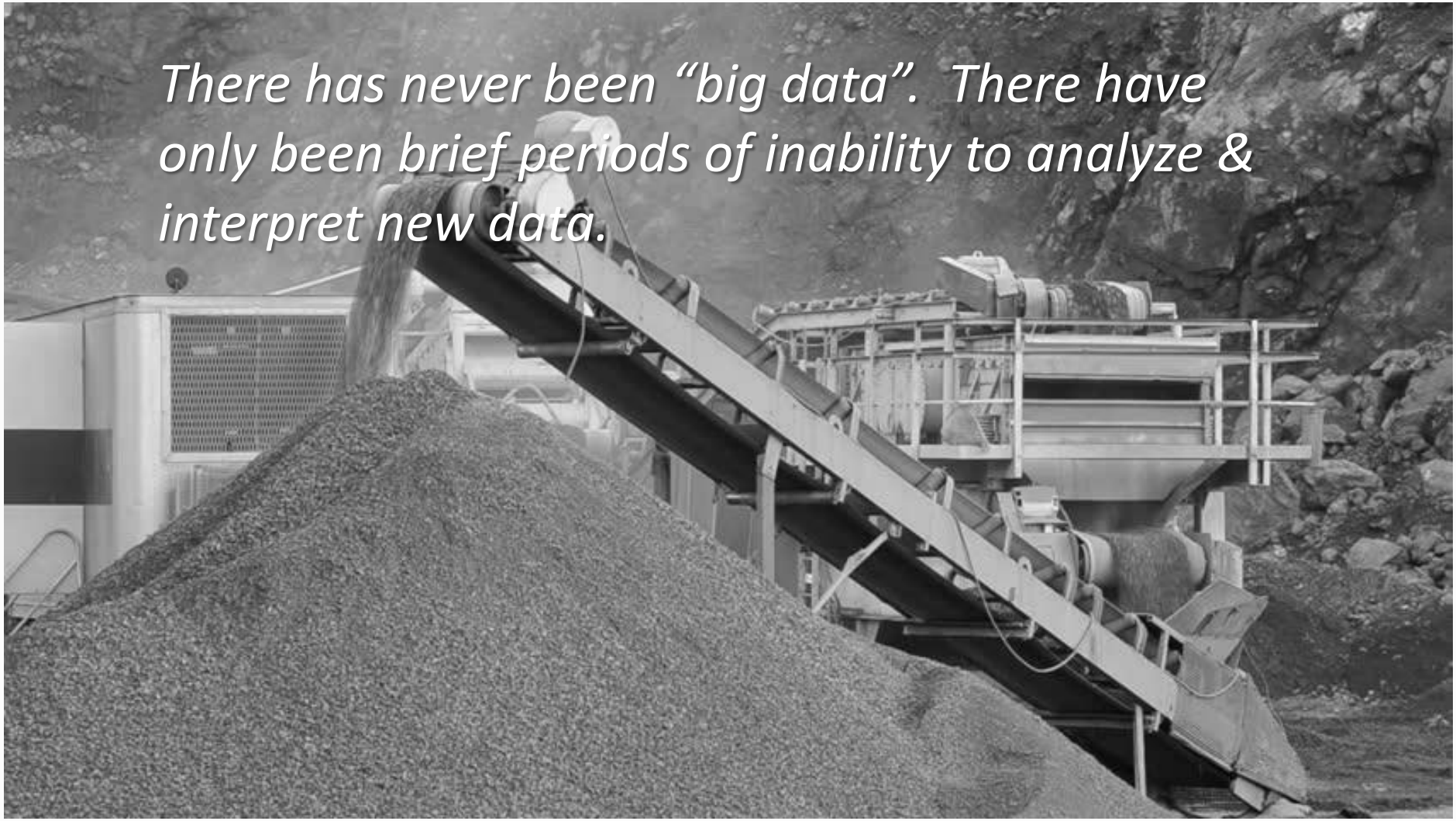
The role of clinical pharmacology and experimental medicine

Mark Rogge, PhD FCP

July 28, 2015

We are at the doorstep of a new era in bringing meaningful new drug treatments to serious unmet needs

- ✓ *Never before has so much knowledge served as the basis for our work in Development*
- ✓ *Never before has such a core mass of computational skill been brought to the characterization of disease progression as it relates to the patient & experimental therapy.*


There has never been "big data". There have only been brief periods of inability to analyze & interpret new data.

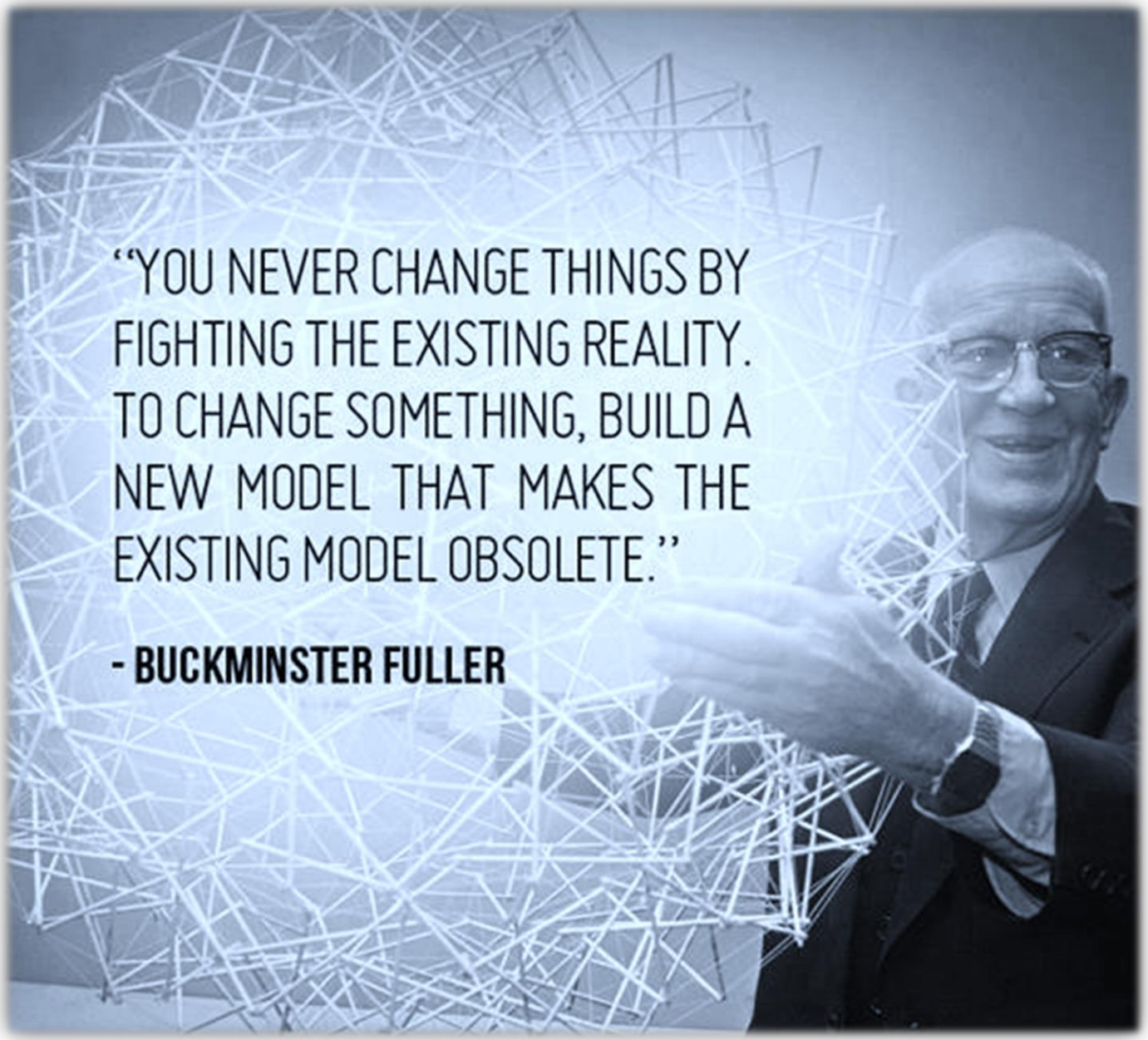
Improving Productivity in Pharmaceutical Research & Development

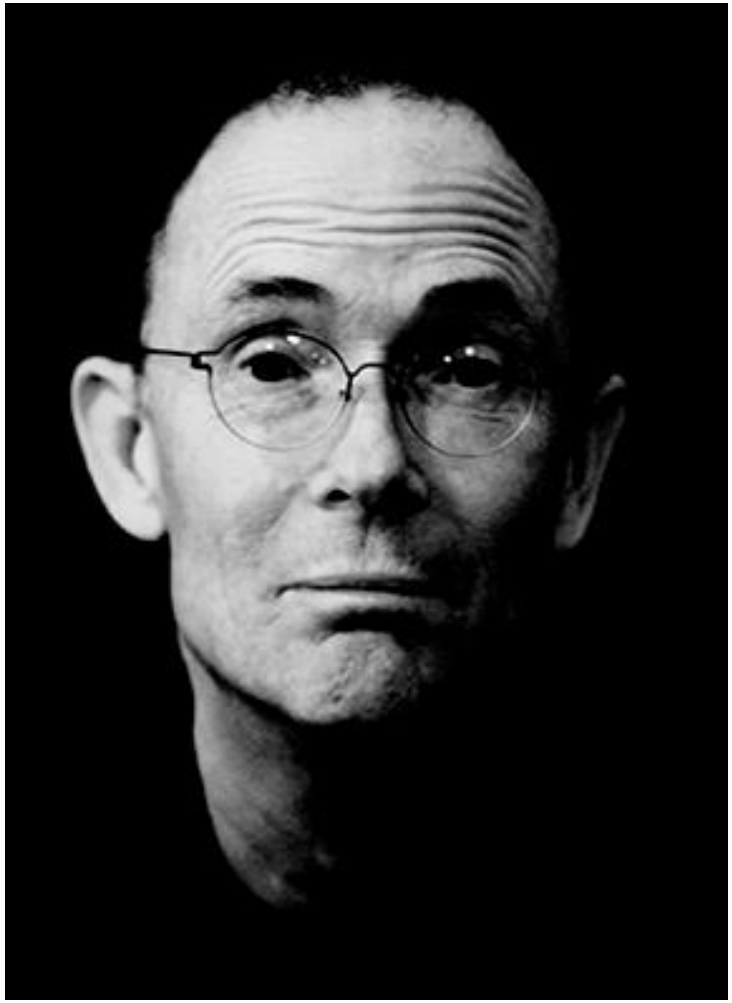
- *Capable Leadership*
- *Target Validation – the extra mile*
- *Sound Dose Regimen Rationale & Appropriate Patient Stratification*

Value-Based Pharma R&D Productivity: Is There A Scalable Model?

Mark Thunecke, IN VIVO 2014.

1. *Leadership has strong understanding of R&D*
2. *Great products first, then profits*
3. *The courage to focus*
4. *Strategic perseverance*
5. *Healthy disrespect for the impossible*


"YOU NEVER CHANGE THINGS BY FIGHTING THE EXISTING REALITY. TO CHANGE SOMETHING, BUILD A NEW MODEL THAT MAKES THE EXISTING MODEL OBSOLETE."
- BUCKMINSTER FULLER

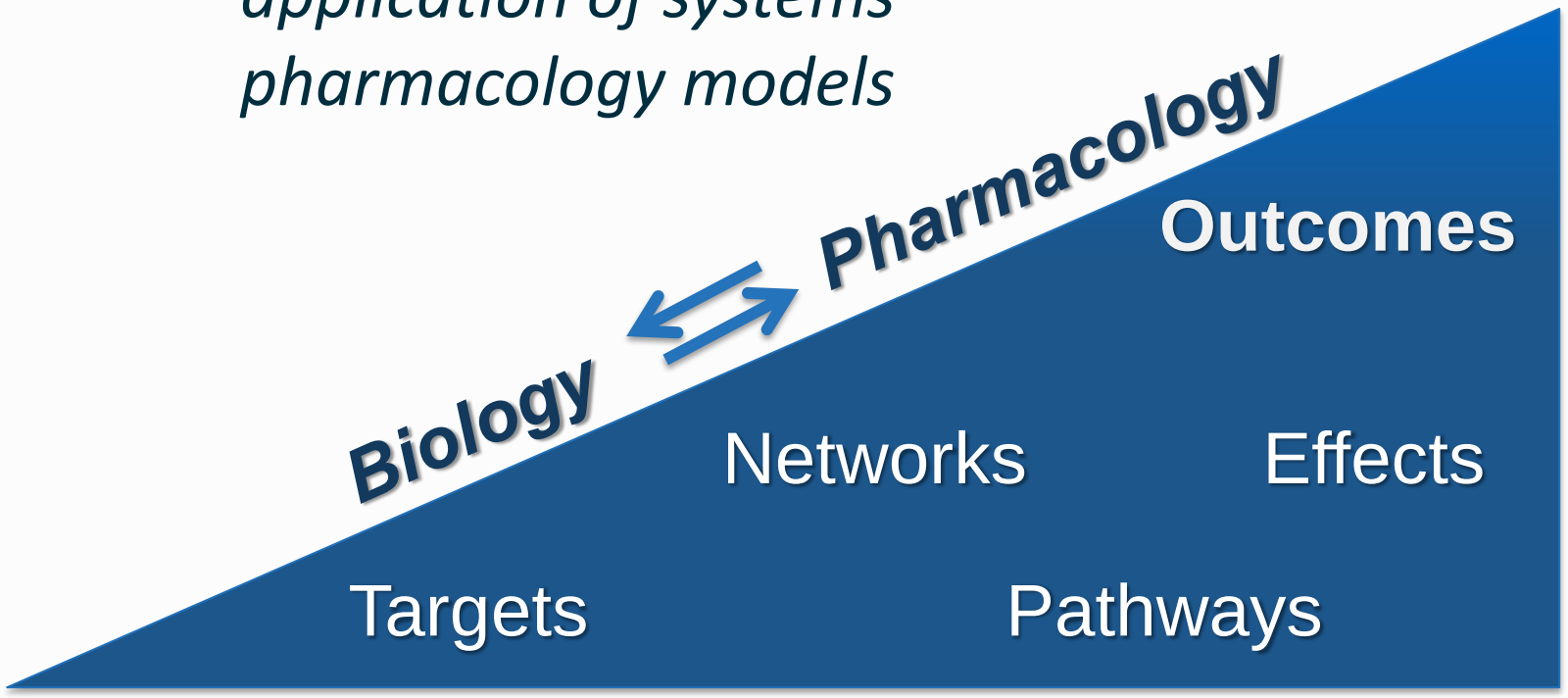


The future is already here — it's just not very evenly distributed.

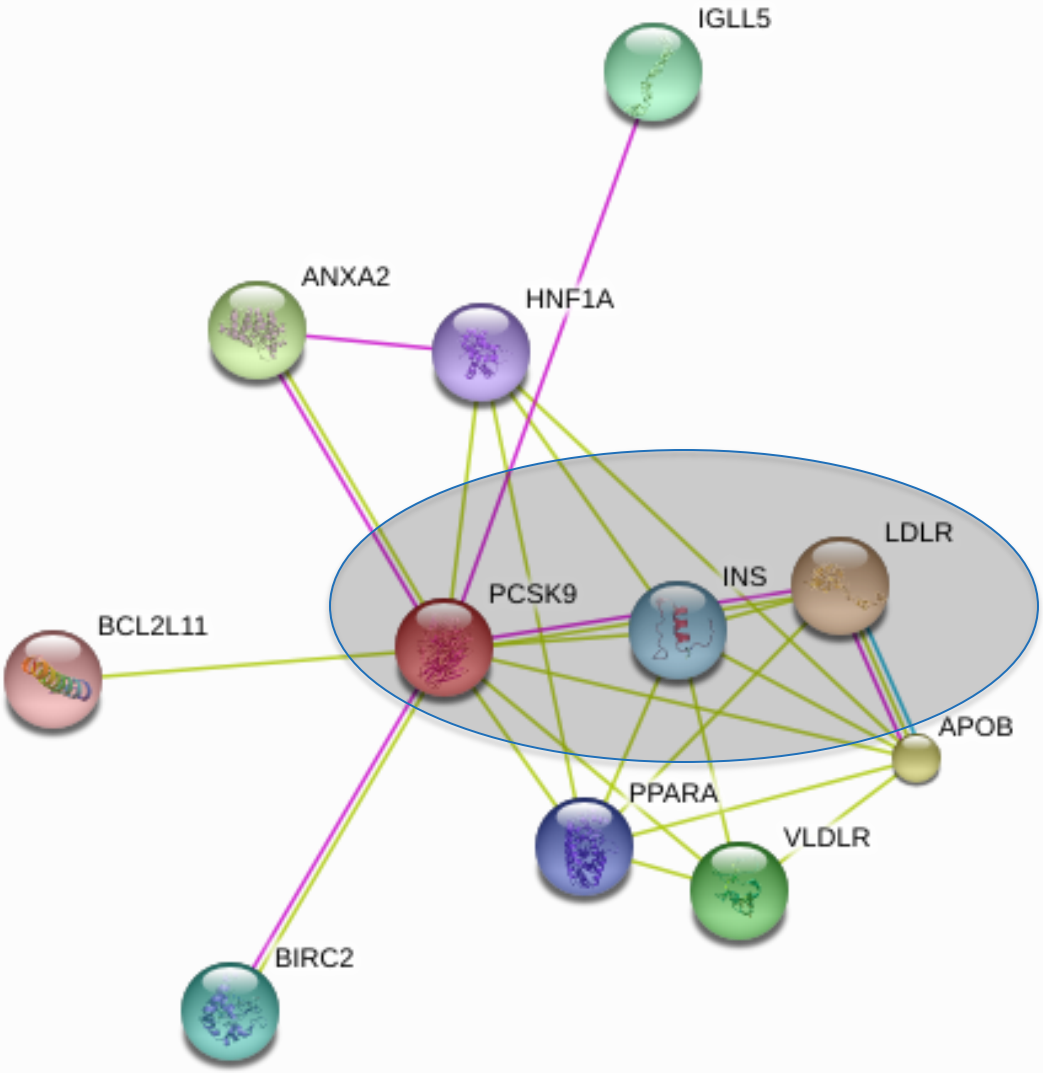
William Ford Gibson
1993

Improving Success

- *Characterization of validated targets*
- *Construction, Qualification & application of systems pharmacology models*

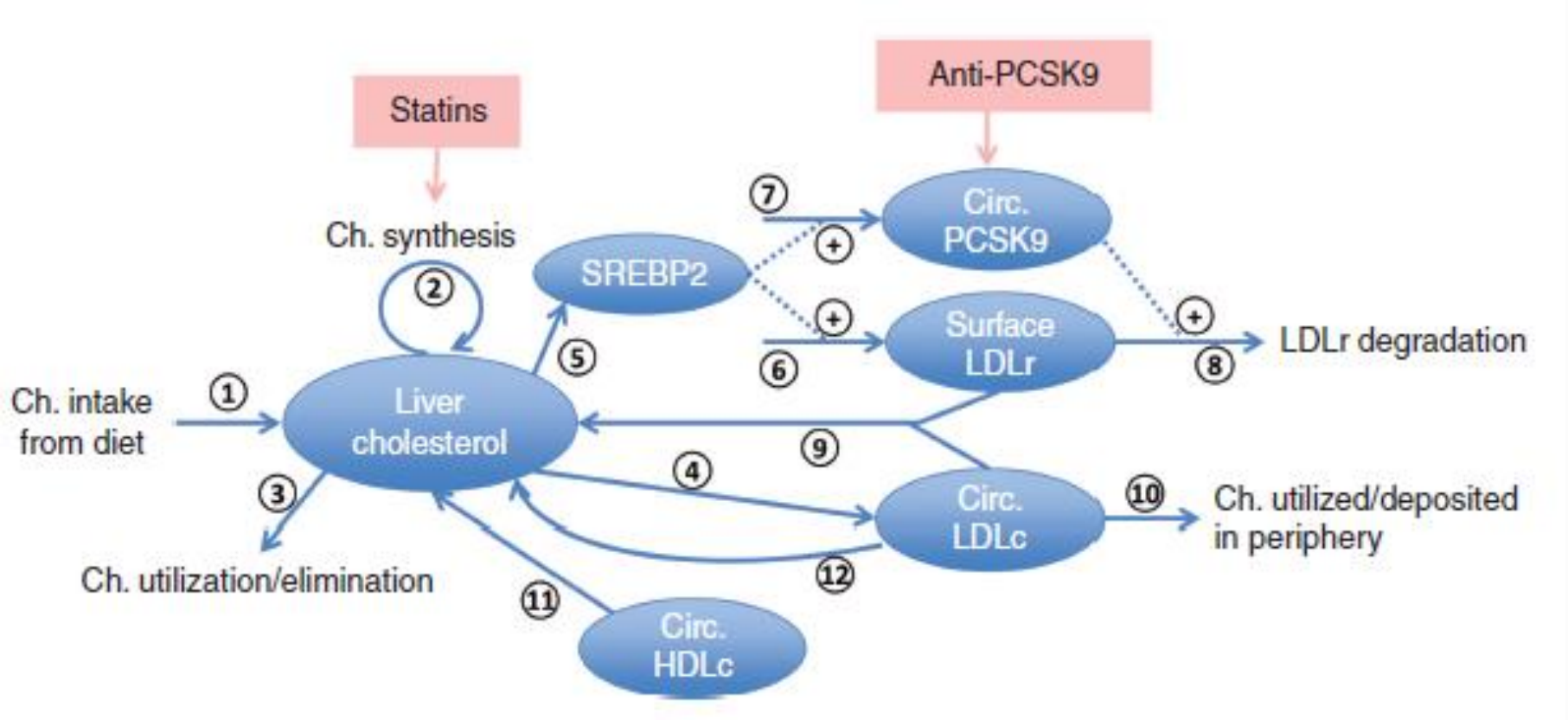


LDL-R Dependence on PCSK9



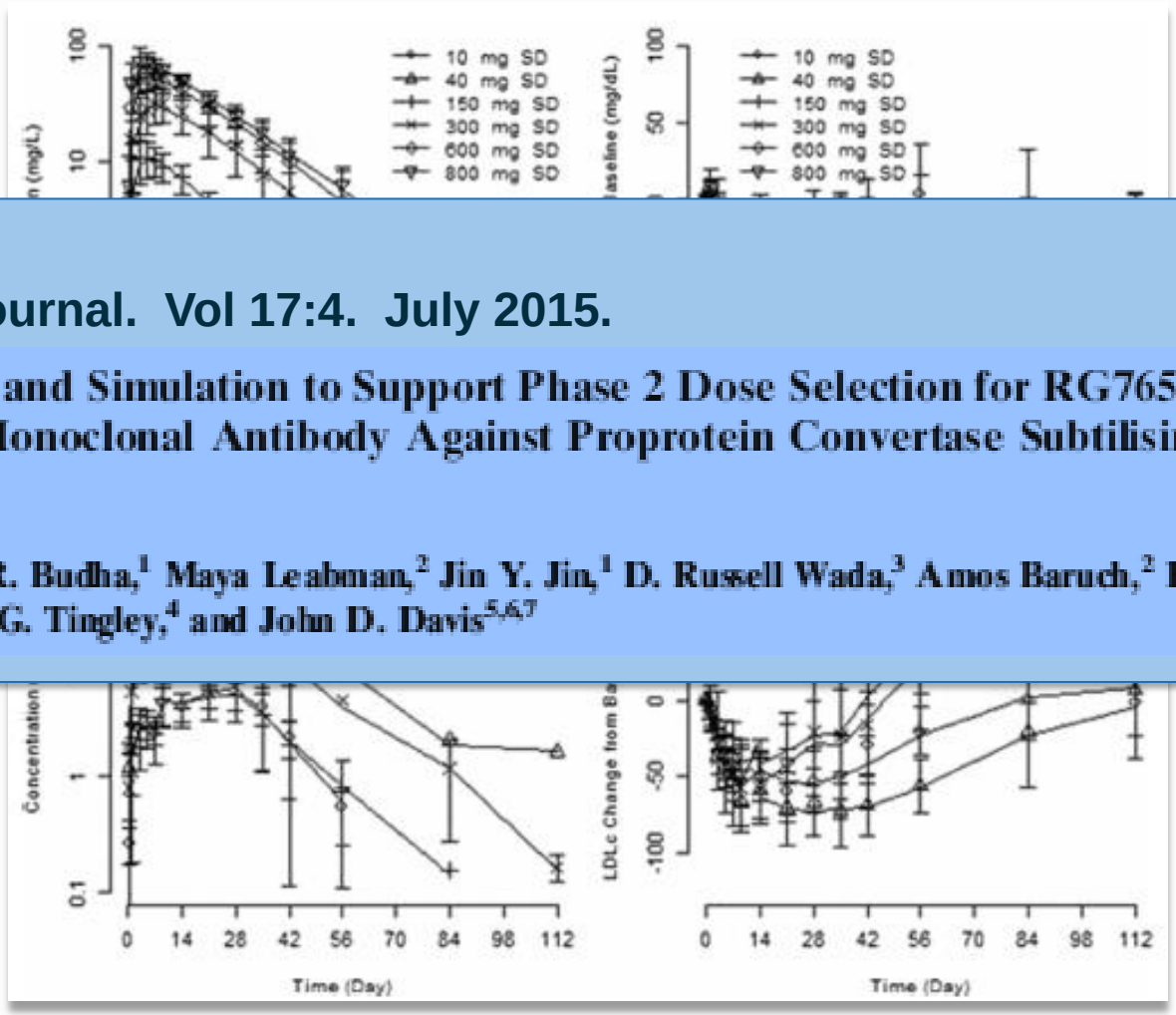
String-db.org

LDL-Cholesterol Modulation via Down-Regulation of LDL-R Clearance



Gadkar et al., 2014

LDL-Cholesterol Modulation via Down-Regulation of LDL-R Clearance



AAPS Journal. Vol 17:4. July 2015.

Modeling and Simulation to Support Phase 2 Dose Selection for RG7652, a Fully Human Monoclonal Antibody Against Proprotein Convertase Subtilisin/Kexin Type 9

Nageshwar R. Budha,[1] Maya Leabman,[2] Jin Y. Jin,[1] D. Russell Wada,[3] Amos Baruch,[2] Kun Peng,[2] Whittemore G. Tingley,[4] and John D. Davis[5,6,7]

Budha et al., 2015

Biogen

My Perspective

- Our understanding of this remarkable wealth of new data is growing into a knowledge base that will form the basis for a new generation of therapeutics.
- Fundamental organizational and operational changes will occur – together, Systems Biology and Pharmacology will become a vital knowledge center of every successful R&D organization.

All views and opinions presented have been those of the presenter and do not necessarily reflect those of Biogen.

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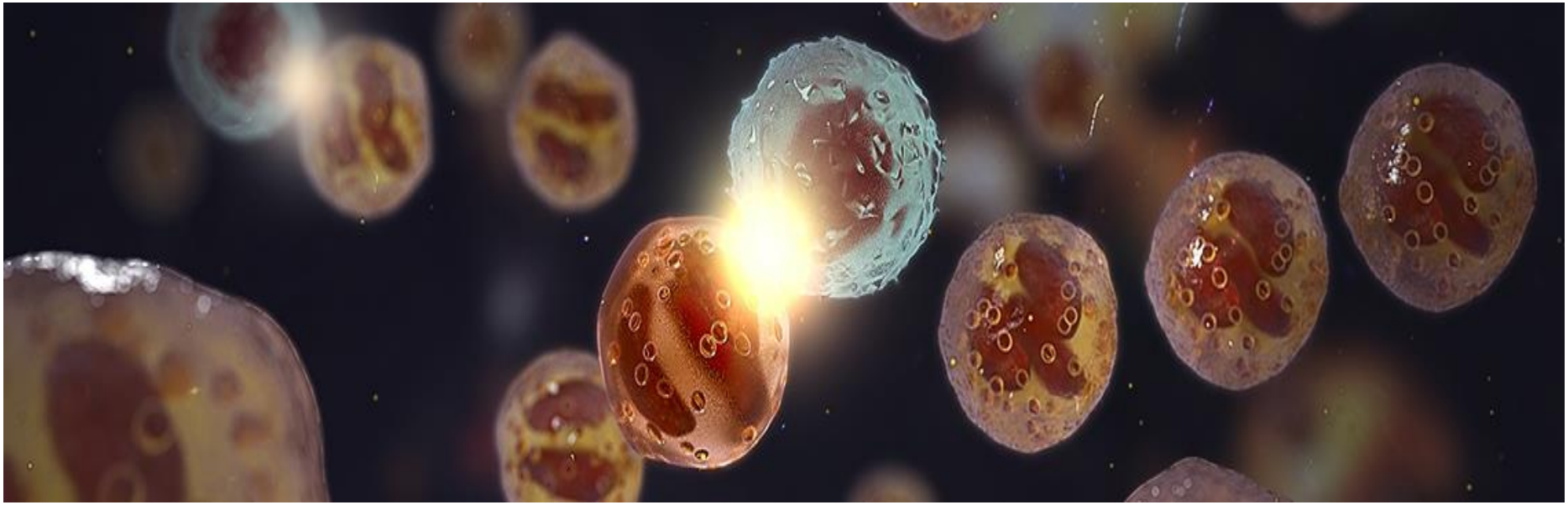
Optimising target and compound selection to enhance early stage decision-making

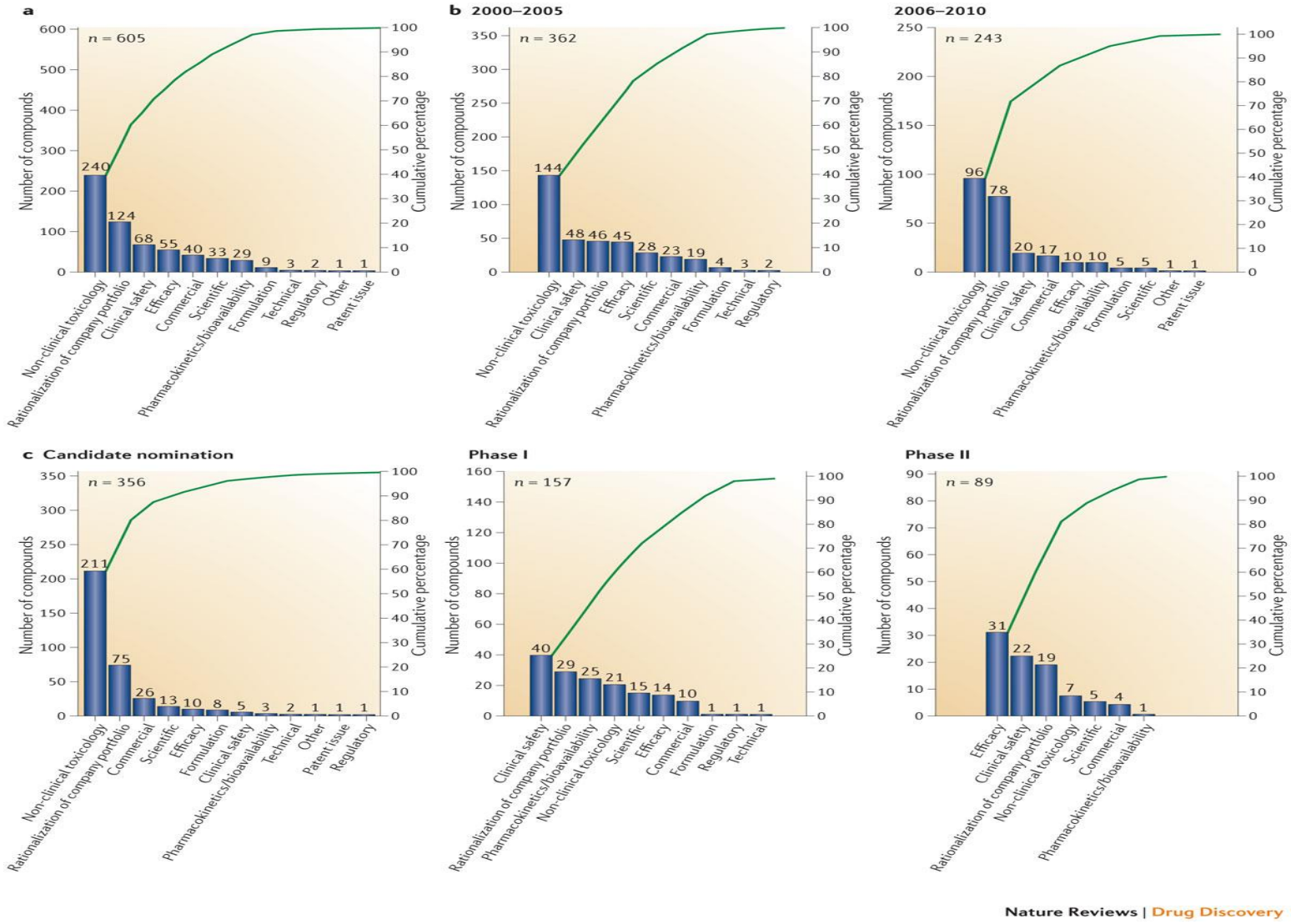
Paul Morgan, Head of Translational Safety, Drug Safety and Metabolism, AstraZeneca, Cambridge, UK

Conference on Improving R&D Productivity – Brookings Institution, Washington

28th July 2015



Reasons for candidate attrition – across 4 Pharma companies



a | Primary cause of failure for terminated compounds. **b** | Differences in the cause of failure for the first half (2000–2005) and second half (2006–2010) of the decade. **c** | Differences in the cause of failure in preclinical, Phase I and Phase II development.

Waring et al, Nature Reviews Drug Discovery, 14: 475-486, June 2015

Response from 2 Pharma Companies

ELSEVIER

Drug Discovery Today

Volume 17, Issues 9–10, May 2012, Pages 419–424

Perspective

Can the flow of medicines be improved? Fundamental pharmacokinetic and pharmacological principles toward improving Phase II survival

Paul Morgan[1], Piet H. Van Der Graaf[1, 2], John Arrowsmith[3], Doug E. Feltner[4], Kira S. Drummond[5], Craig D. Wegner[6], Steve D.A. Street[7]

NATURE REVIEWS | DRUG DISCOVERY VOLUME 13 | JUNE 2014 | 419

PERSPECTIVES

OUTLOOK

Lessons learned from the fate of AstraZeneca's drug pipeline: a five-dimensional framework

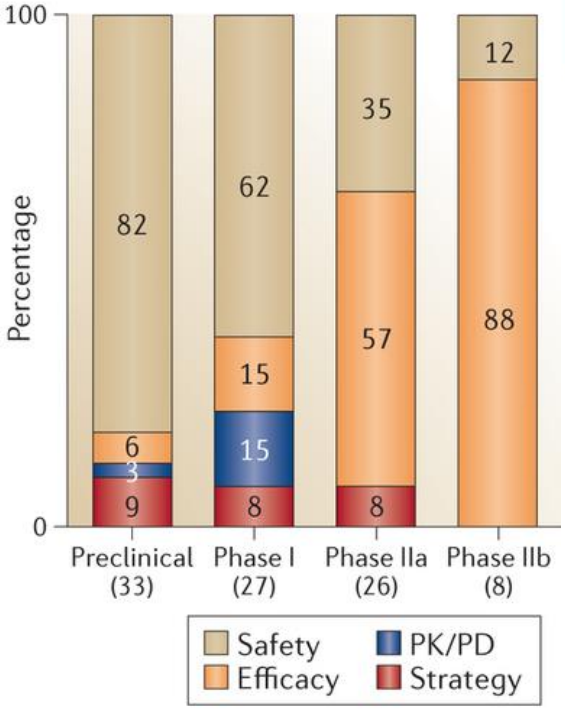
David Cook, Dearg Brown, Robert Alexander, Ruth March, Paul Morgan, Gemma Satterthwaite and Menelas N. Pangalos

This volume-based approach damaged not only the quality and sustainability of R&D pipelines but, more importantly, also the health of the R&D organizations and their underlying scientific curiosity. This is because the focus of scientists and clinicians moved away from the more demanding goal of thoroughly understanding disease pathophysiology and the therapeutic opportunities, and instead moved towards meeting volume-based goals and identifying an unprecedented level of back-up and 'me too' drug candidates. In such an environment,

Why is this important?

Improving success by driving improved candidate quality and decision-making

Drivers of failure



Right target

- Strong link between target and disease
- Differentiated efficacy
- Available and predictive biomarkers

Right tissue

- Adequate bioavailability and tissue exposure
- Definition of PD biomarkers
- Clear understanding of preclinical and clinical PK/PD
- Understanding of drug–drug interactions

Right safety

- Differentiated and clear safety margins
- Understanding of secondary pharmacology risk
- Understanding of reactive metabolites, genotoxicity, drug–drug interactions
- Understanding of target liability

Right patients

- Identification of the most responsive patient population
- Definition of risk–benefit for given population

Right commercial potential

- Differentiated value proposition versus future standard of care
- Focus on market access, payer and provider
- Personalized health-care strategy, including diagnostic and biomarkers

OUTLOOK

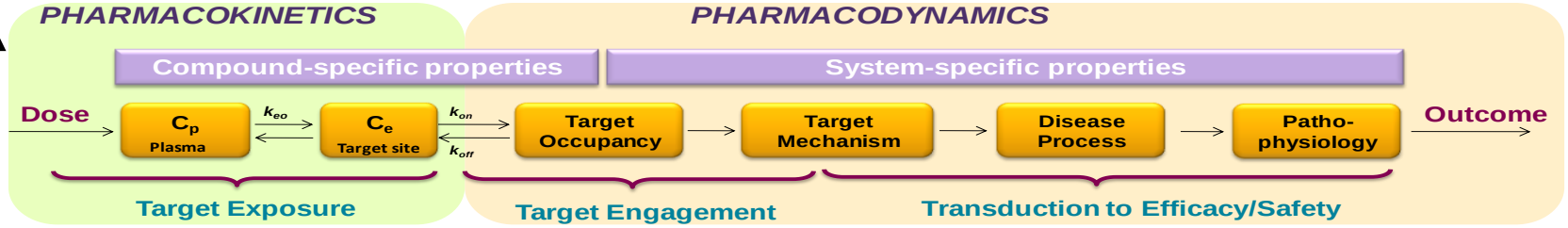
Lessons learned from the fate of AstraZeneca's drug pipeline: a five-dimensional framework

David Cook, Dearg Brown, Robert Alexander, Ruth March, Paul Morgan, Gemma Satterthwaite and Menelas N. Pangalos

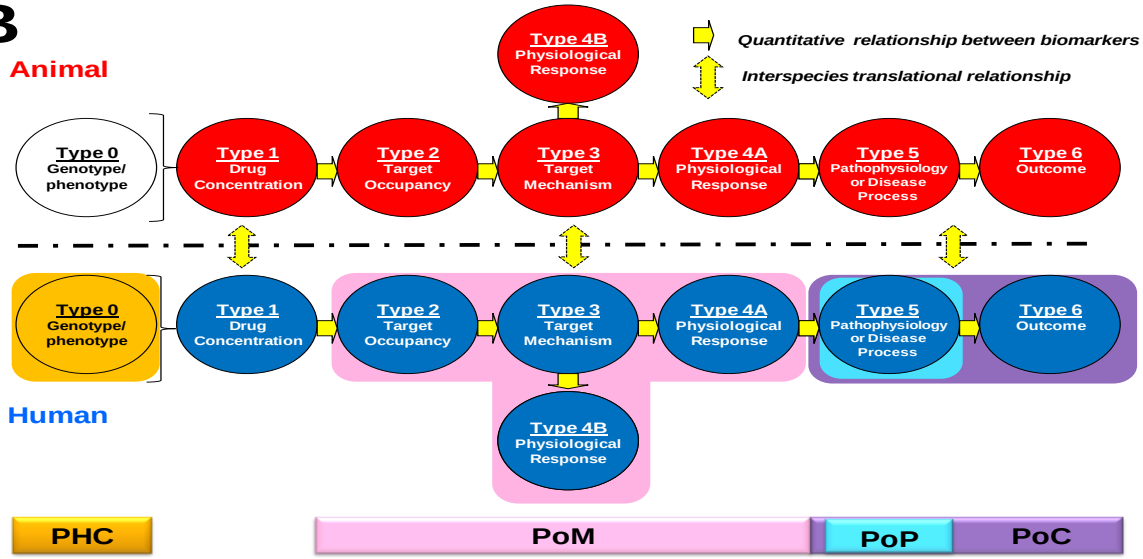
Nature Reviews | Drug Discovery

Quantitative pharmacology relationships and nomenclature

A



B



Type 0	Biomarker that determine the disease state or the potential for therapeutic response or patient stratification (e.g. genotype or phenotype).
Type 1	The pharmacokinetics of the compound typically usually unbound plasma concentrations and/or target site exposure.
Type 2	Target occupancy via a direct measurement of receptor binding.(e.g. PET, autoradiography).
Type 3	An immediate biochemical response as a result of the interaction with the target (e.g. measure of signal transduction or a measure of an enzyme product).
Type 4A	A physiological or tissue response directly linked to the pathophysiology.
Type 4B	Parallel pharmacology driven through the same target but not directly linked to the pathophysiology.(e.g.different tissues such as central vs peripheral)
Type 5	A biomarker of the pathophysiology (e.g. disease marker).
Type 6	Clinical measure of the outcome in a patient population approved by regulators (e.g. pain relief).

C Generic MBDDx aspirations and criteria for Drug discovery phases

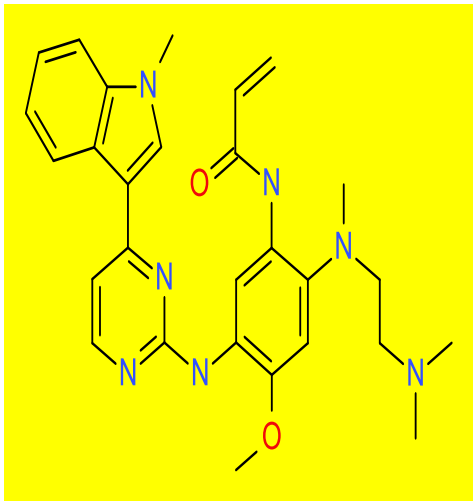
Target Validation (TV)
- Translational plan outlining development and evaluation of appropriate biomarkers to build PKPD understanding.
- If *in vivo* target validation model and a reference compound are available, apply PKPD principles to study design and ensure a sufficient duration and level of systemic unbound exposure relative the *in vitro* potency (also considering target class)

Lead Generation (LG)
- Evaluation and selection of appropriate target engagement biomarker (Type 2, 3 or 4) and optimization of PKPD study design.
- Use reference or lead compounds and target engagement biomarker to establish relationship between *in vivo* and *in vitro* potency.
- Establish the level of target engagement required for meaningful efficacy on the disease (Type 5) biomarker.

Lead optimization (LO) and Candidate selection
- Clinical candidate criteria should be defined at start of LO based on quantitative PKPD relationships established during LG.
- Refinement of key relationships with higher quality compounds.
- Target engagement PKPD as a driver for compound optimization.
- For clinical candidate compound: estimate therapeutic concentration time profile based on the PKPD relationship developed in preclinical species, and translation knowledge like differences PK, target potency and system properties
- Integration of PKPD for safety parameters to assess safety margin.

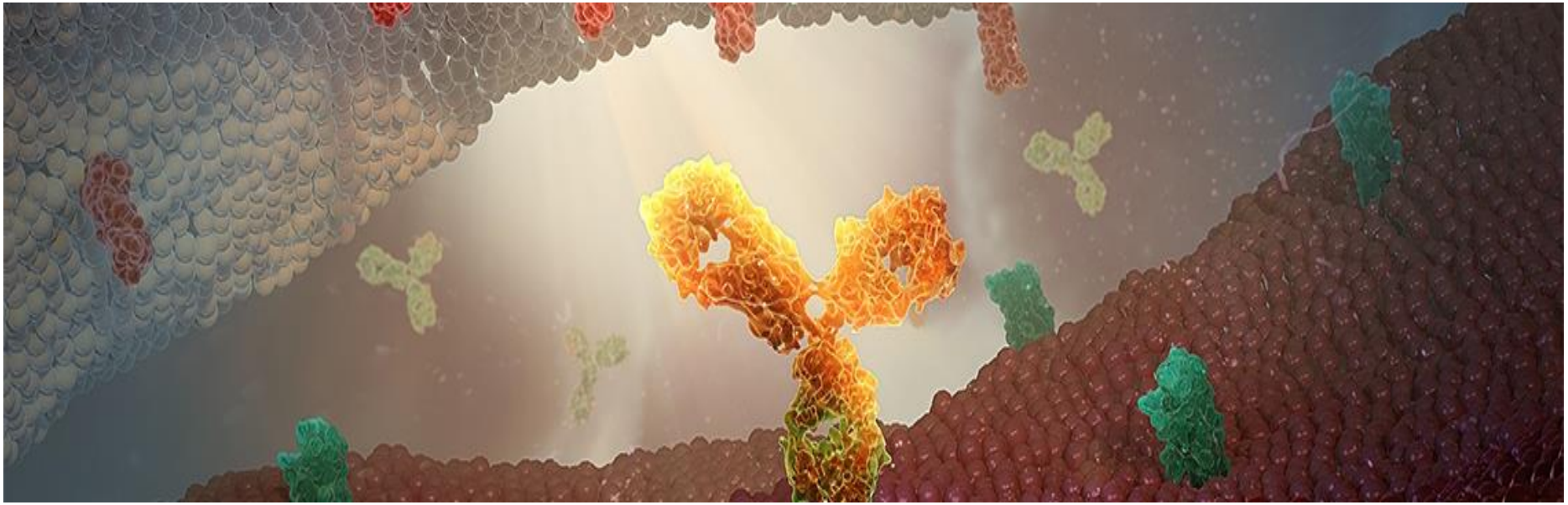
Visser et al, Model-based drug discovery: implementation and impact, Drug Discovery Today, 18: 764-775, 2013

5Rs Case Study: AZD9291, an irreversible inhibitor of EGFR selective for sensitising and T790M resistance mutations



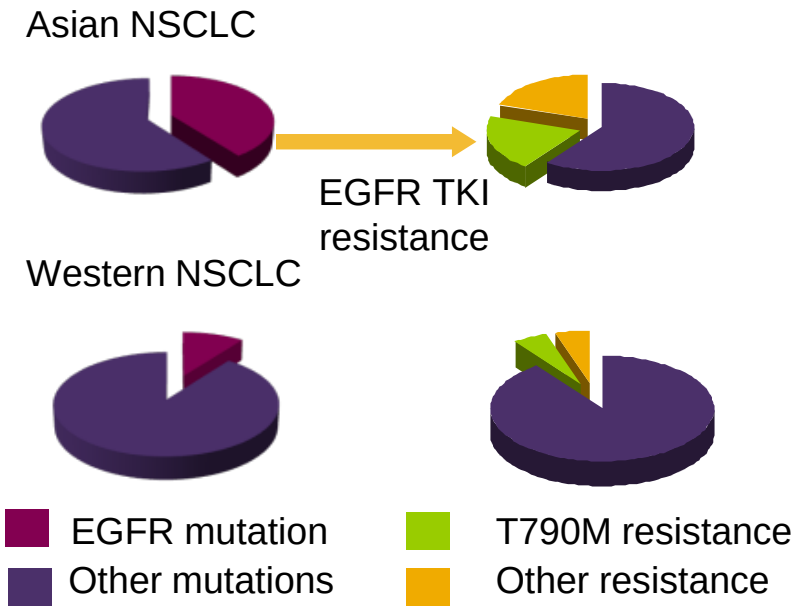
- **Identified as candidate drug in 2012**
- **1st patient dosed in 2013**
- **Designated by FDA as breakthrough therapy in 2014**
- **NDA/MAA filing by end 2Q 2015**

Discovery of a Potent and Selective EGFR Inhibitor (AZD9291) of Both Sensitizing and T790M Resistance Mutations That Spares the Wild Type Form of the Receptor. Finlay et al., J Med Chem. 2014 Oct 23; 57(20): 8249-67

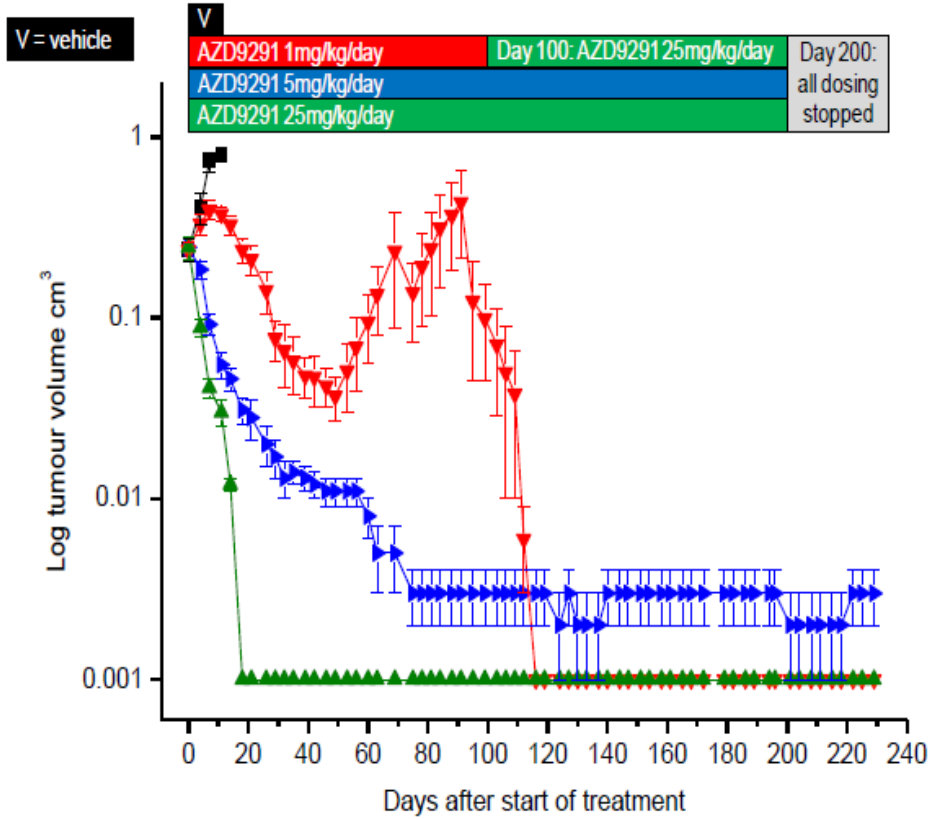


Right Target: optimal potency for T790M and selectivity over WT-EGFR

Sensitising mutant-EGFRm represents ~40% and 10% of NSCLC adenocarcinoma tumours in Asian and Western patients, respectively

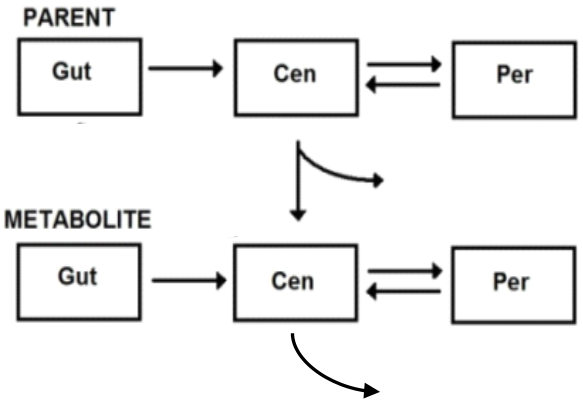


Compd	Coval. binder	EGFRm	T790M	Wild-Type (WT)
gefitinib	No	Active	Inactive	Active
erlotinib	No	Active	Inactive	Active

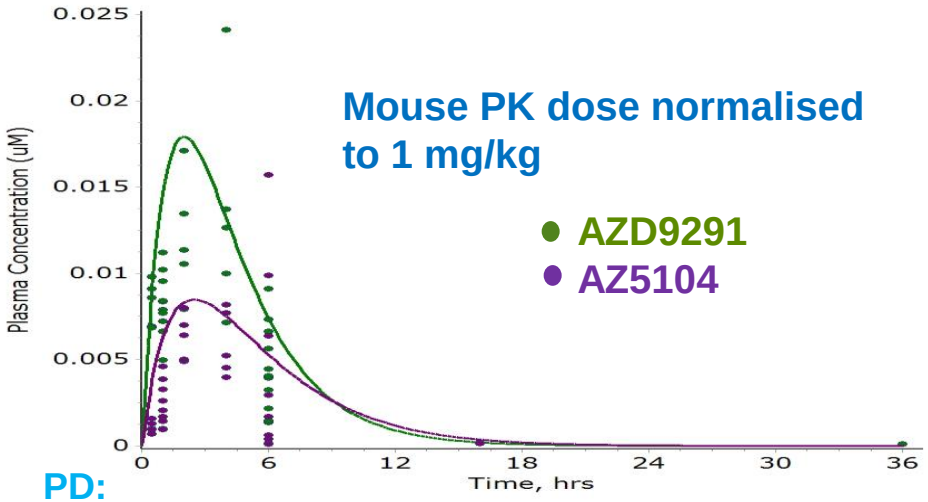


Right Tissue/Exposure: AZD9291 and metabolite PK incorporating irreversible binding and mechanistic biomarker (pEGFR) describes tumour growth inhibition in H1975 (T790M) mouse xenograft

PK model: AZD9291, AZ5104



PK

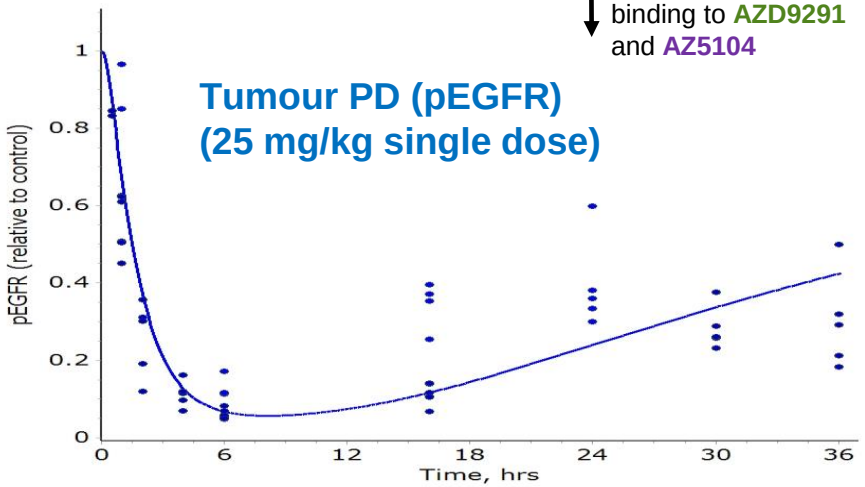


Mouse PK dose normalised to 1 mg/kg

- AZD9291
- AZ5104

PD: Mechanistic Biomarker (pEGFR)

Irreversible binding to **AZD9291** and **AZ5104**



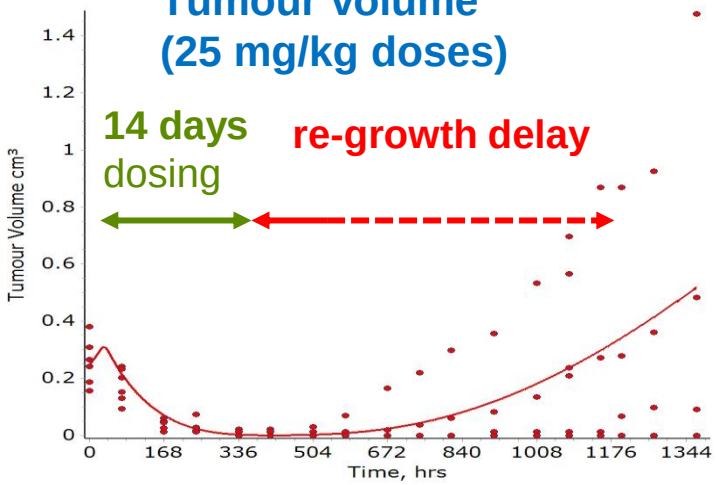
Tumour PD (pEGFR) (25 mg/kg single dose)

Tumor growth inhibition

Tumour volume (25 mg/kg doses)

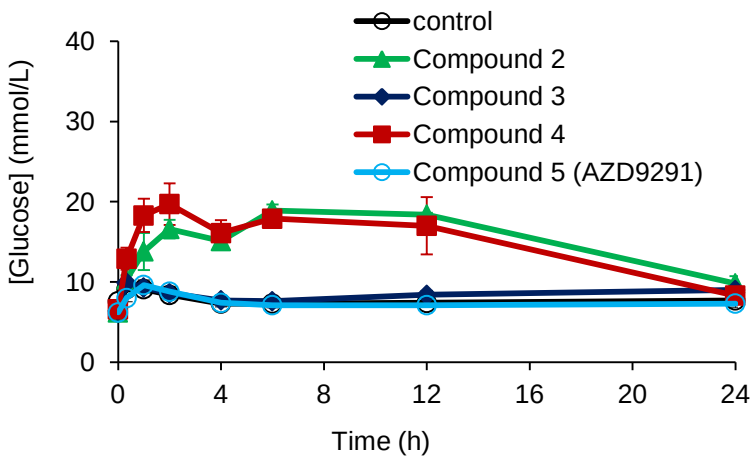
14 days dosing

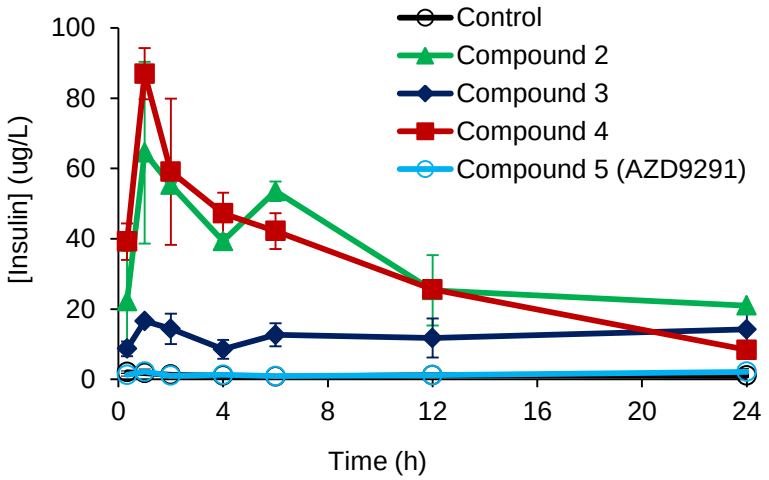
re-growth delay



Right Safety: Insulin Receptor affinity removed from AZD9291 profile – removes potential hyperglycaemia risk

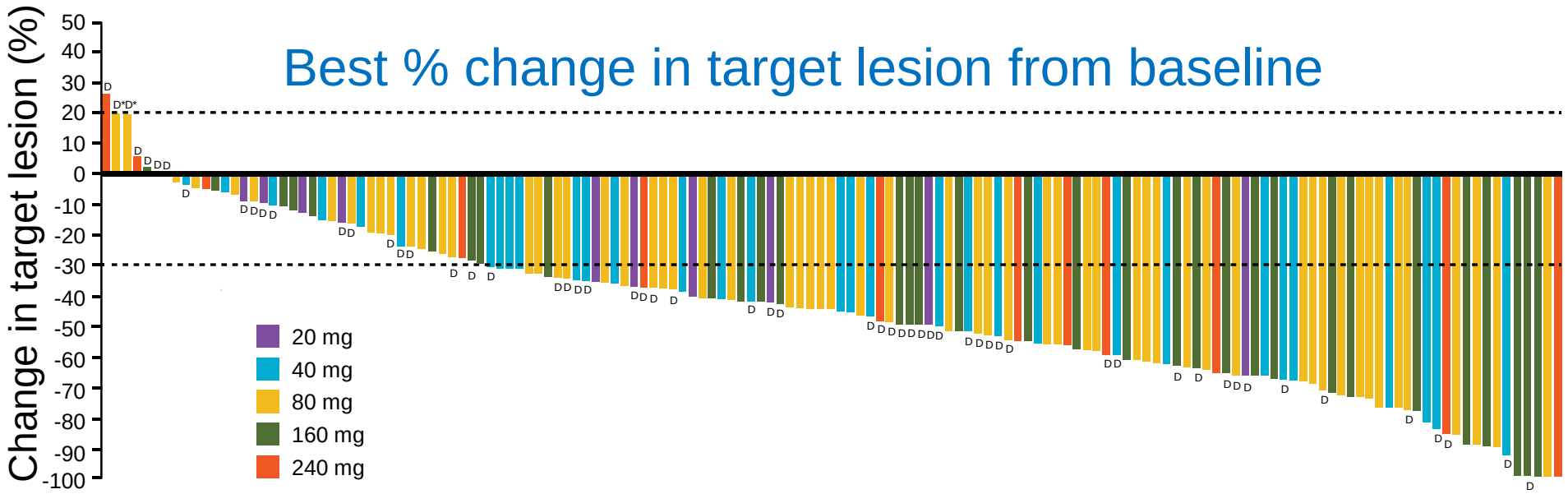
	Compound 1	Compound 2	Compound 3	Compound 4	Compound 5 (AZD9291)
EGFRm+ sensitising mutation cell IC50 (pEGF µM)	0.39	0.016	0.021	0.002	0.017
EGFRm+/T790M double mutation cell IC50 (pEGF µM)	0.091	0.002	0.004	0.0007	0.015
EGFR wild type cell IC50 (pEGFR µM)	23.0	0.36	0.94	0.15	0.48
IR Kinase IC50 (µM)	0.016	0.014	0.022	0.15	0.91
IGFR cell IC50 (pIGFR µM)	0.099	0.16	0.49	0.10	3.3
Ratio SM/IGFR cell selectivity	**0.25**	**10**	**23**	**48**	194





Discovery of a Potent and Selective EGFR Inhibitor (AZD9291) of Both Sensitizing and T790M Resistance Mutations That Spares the Wild Type Form of the Receptor. Finlay et al., J Med Chem. 2014 Oct 23; 57(20): 8249-67

Right Patient: AZD9291 Clinical activity in patients with advanced NSCLC with T790M positive lesions



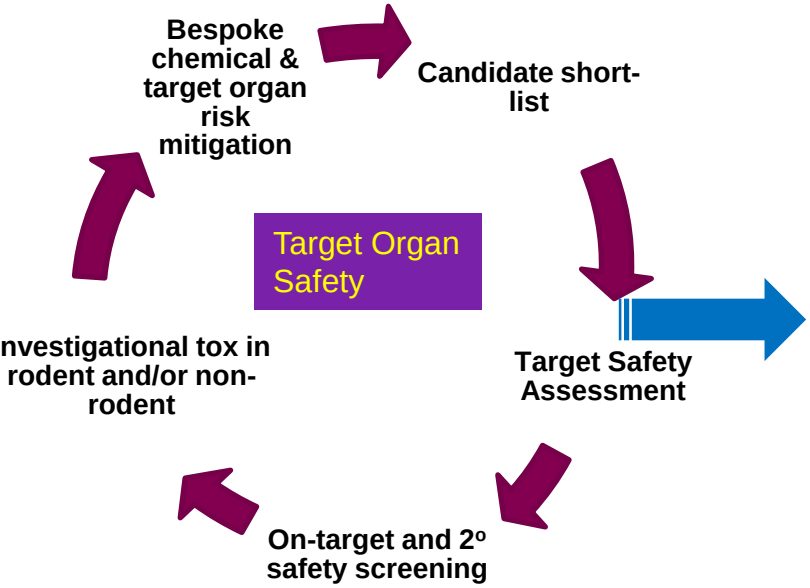
DCR (CR+PR+SD) in patients with centrally tested T790M positive tumours was 90% (141 / 157; 95% CI 84, 94)

	20 mg	40 mg	80 mg	160 mg	240 mg	Total
	10	32	61	41	13	157
ORR (95% CI)	50% (19, 81)	59% (41, 76)	66% (52, 77)	51% (35, 67)	54% (25, 81)	59% (51, 66)

*Imputed values for patients who died within 14 weeks (98 days) of start of treatment and had no evaluable target lesion assessments
Nine patients (seven in the 160 mg cohort) currently have a best overall response of not evaluable, as they have not yet had a 6-week follow-up RECIST assessment
Patients are evaluable for response if they were dosed and had a baseline RECIST assessment. Data cut-off 2 Dec 2014
CI, confidence interval; CR, complete response; D, discontinued; DCR, disease control rate; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease

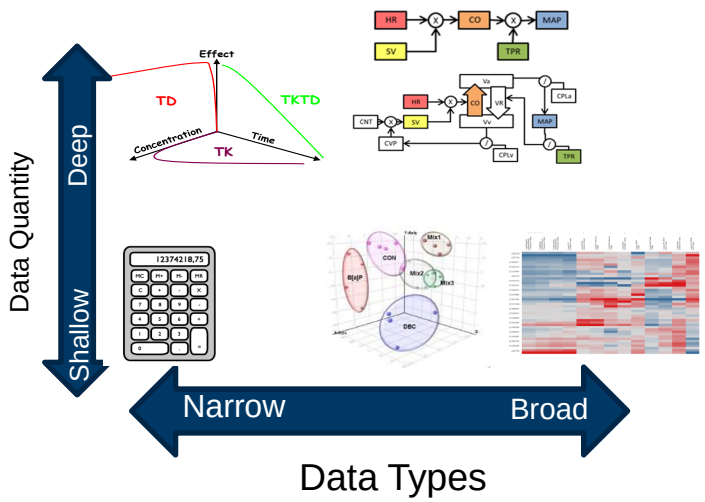
Presented by Pasi A Jänne at the 2015 European Lung Cancer Conference. Ann Oncol 2015; 26(Suppl1): i60, LBA3.

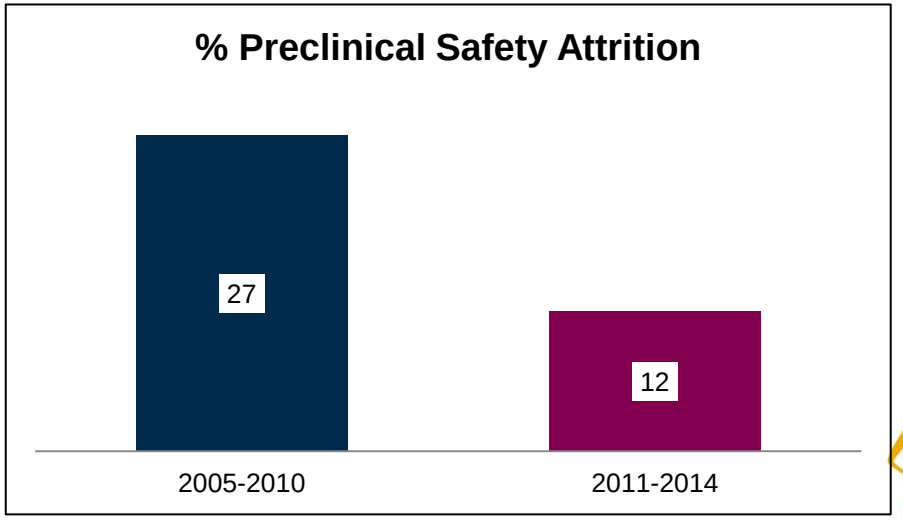
Improvement in preclinical safety attrition: earlier hazard detection, quantitative & translational risk assessment



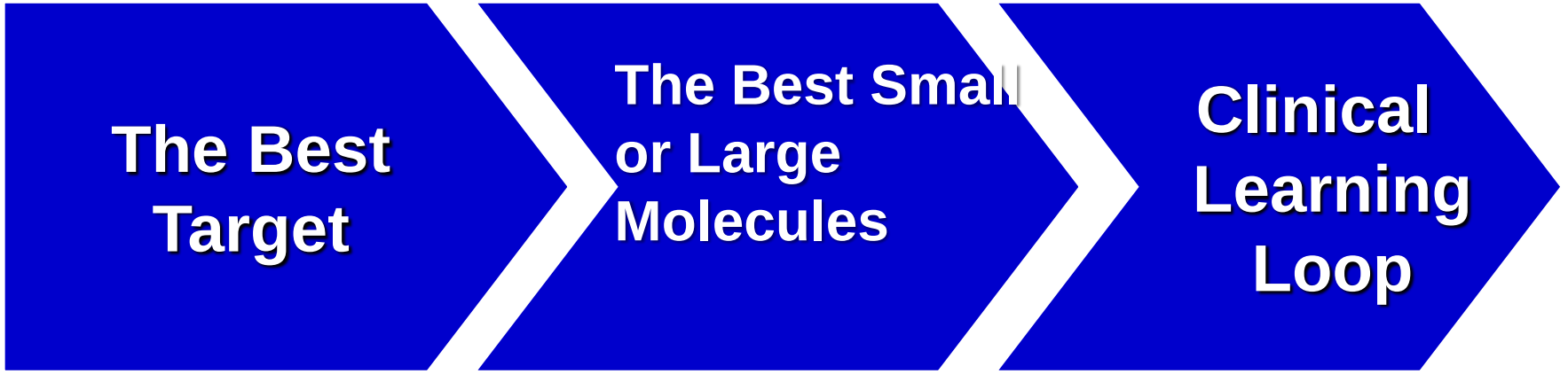
Pre-nom	GLP	Ph1
2 week rodent Control + 3 doses 3M+3F	4 week rodent + recovery. Control + 3 doses	
2 week non-rodent Control + 3 doses	4 week non-rodent + recovery Control + 3 doses	
Non-rodent CV Safety (telemetry)	Safety Pharm package, ie CNS, GI, Resp, Renal	

PK/PD & Systems Pharm





Tackling drug survival: systematic and quantitative approach to key translational knowledge



- Apply fundamental pharmacokinetic-pharmacodynamic principles to choose right combination of target, candidate, efficacy and safety profile
- Evidence-based decision making; generate data/knowledge in preclinical and clinical setting
- Make informed decisions early in development

Acknowledgements

AZ 5Rs framework:
David Cook
Mene Pangalos
Dearg Brown
Will Redfern

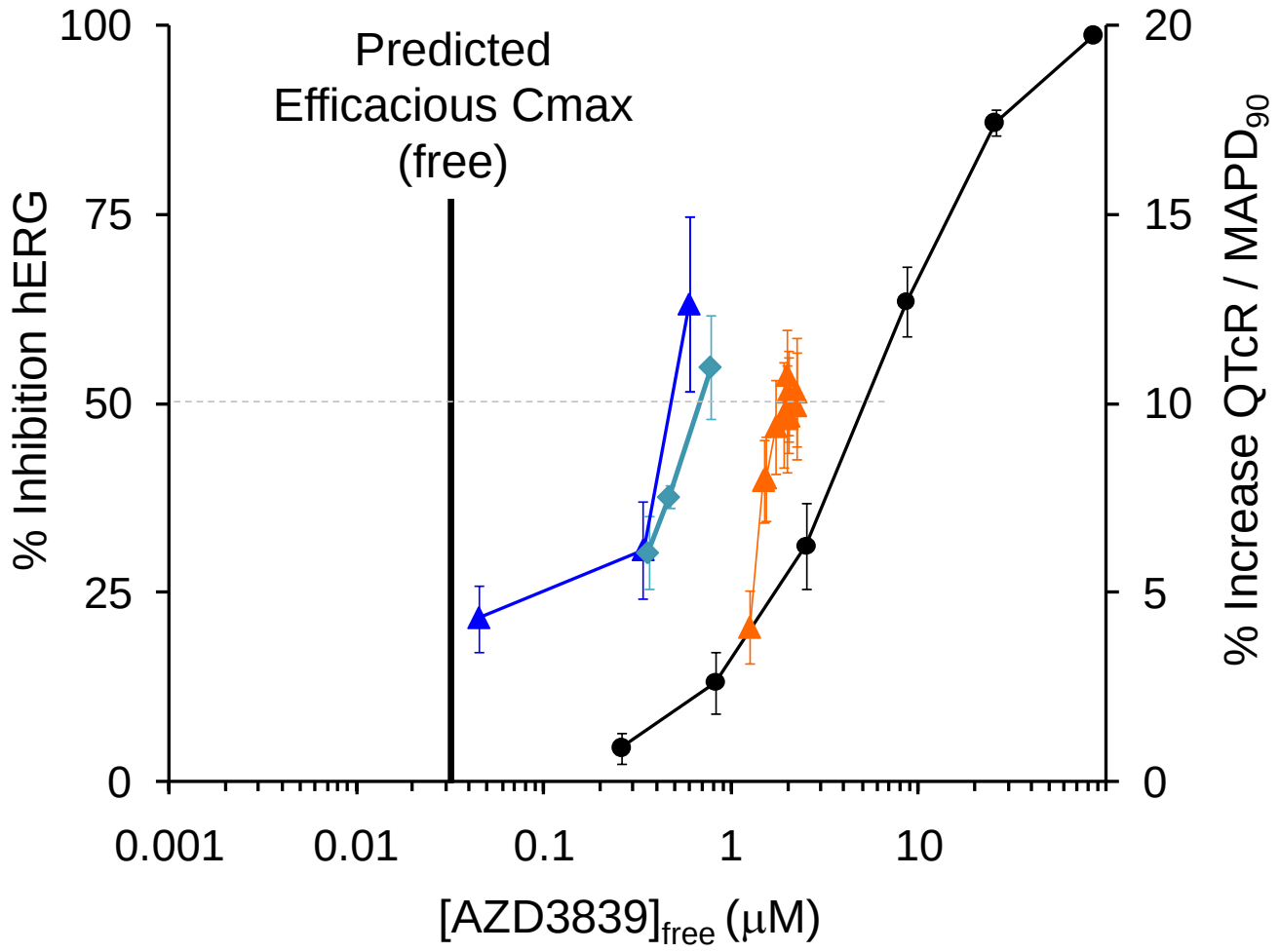
3 Pillars of Survival:
Piet van der Graaf
John Arrowsmith
Charlotte Allerton
Tristan Maurer

Case Studies:
AZD9291 Team
Pete Ballard
Owen Jones
James Yates
Mark Anderton
Stefan Platz
Chris Pollard
Don Stanski

IQ Consortium:
Marcel Hop
Dermot McGinnity

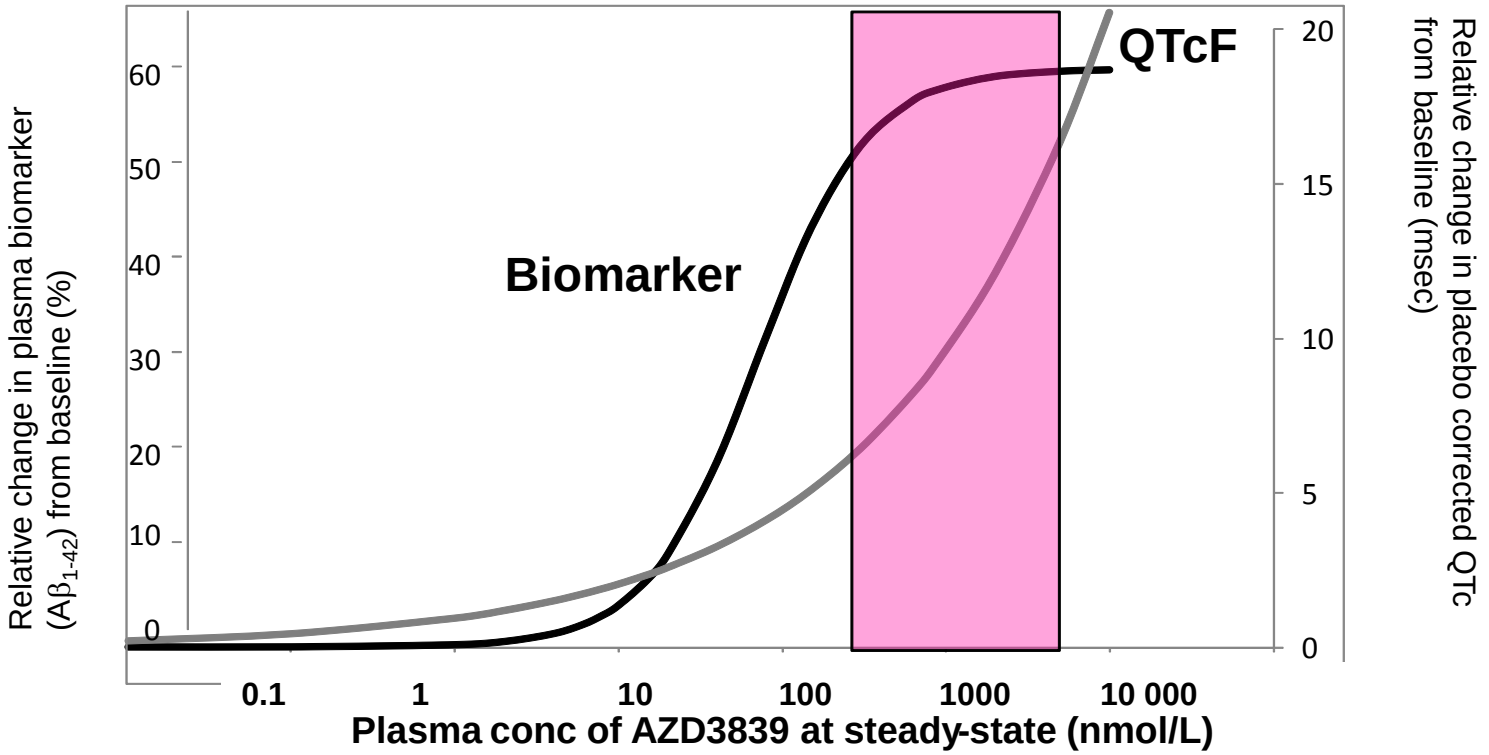
Confidentiality Notice

Case study: Predictive power of integrated risk assessment based on non-clinical CVS studies



- hERG
- Guinea Pig
- Dog – single dose
- Dog – repeat-dose (day 28)

Clinical outcome of QT study confirmed CV risk and low safety margin to efficacy biomarker

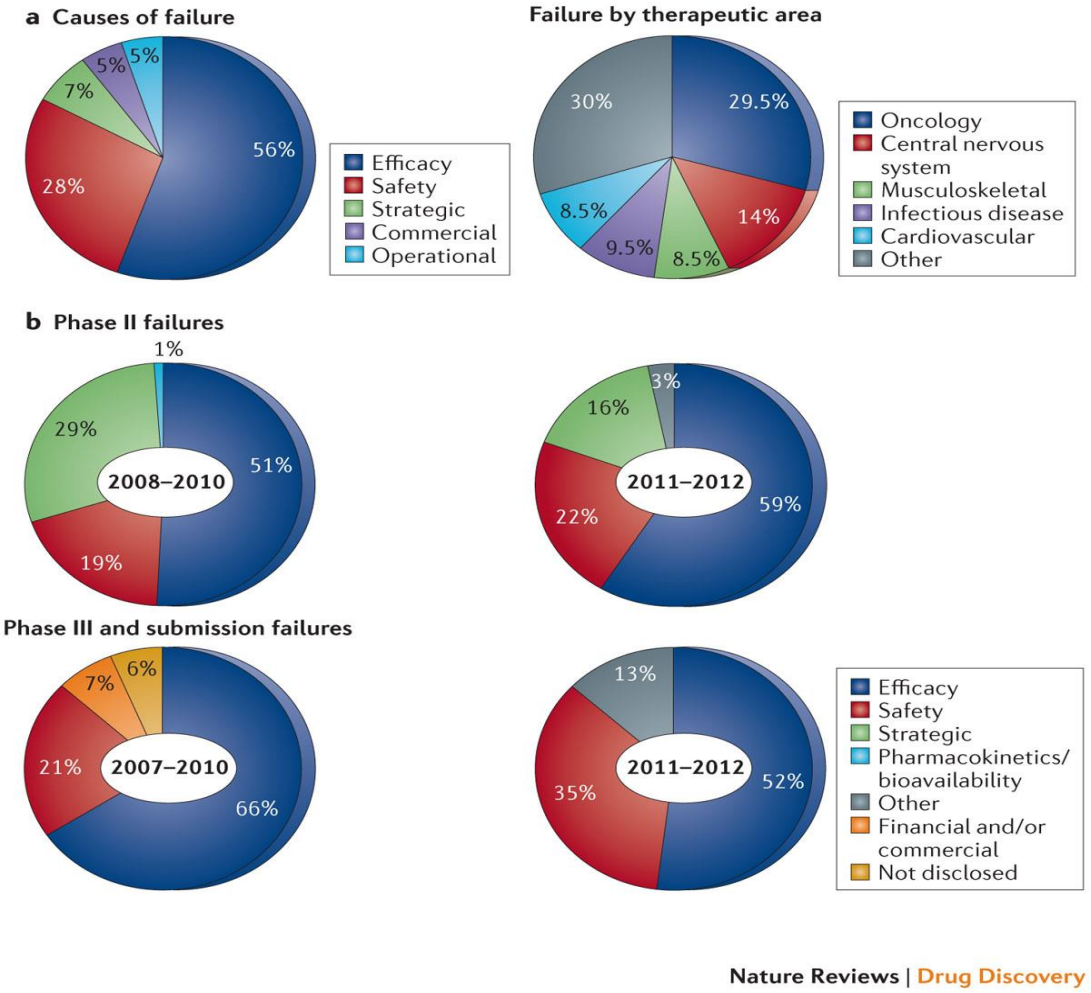


Pre-clincal data indicated QT risk
SAD study ECG monitoing designed accordingly
PK/PD modelling of SAD study QTcF and efficacy biomarker data indicated insufficient safety margin
Compound stopped

Sparve et al, JPET, 2014, 350: 469-72. Prediction and modeling of effects on the QTc interval for clinical safety margin assessment, based on single-ascending-dose study data with AZD3839.

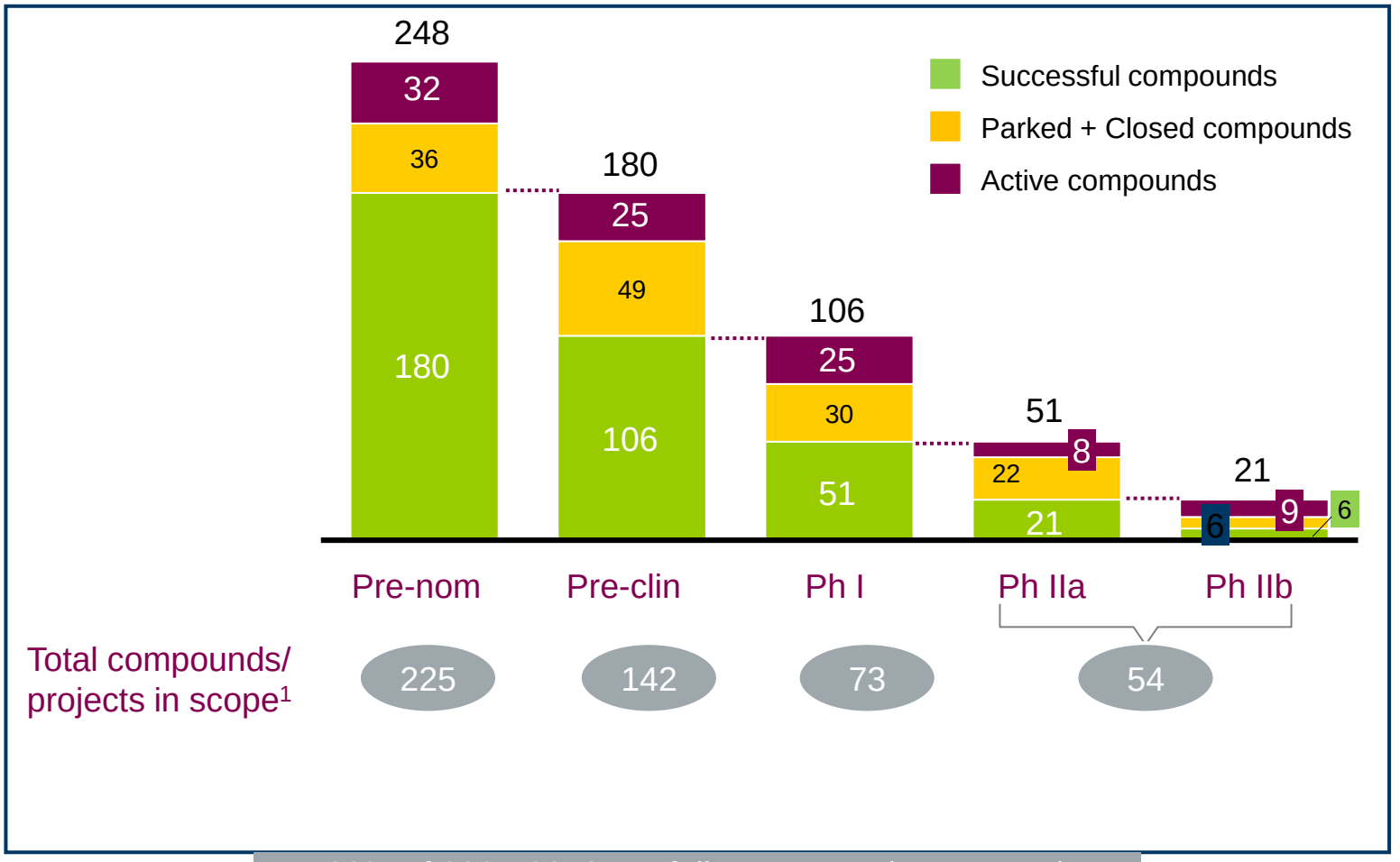
Drug attrition is a major cause of R&D productivity challenge

- 148 failures b/n Ph2 and submission in 2011-12



Arrowsmith and Miller, Trial Watch: Phase II and III attrition rates 2011-2012. Nature Reviews Drug Discovery, 12, 569, 2013

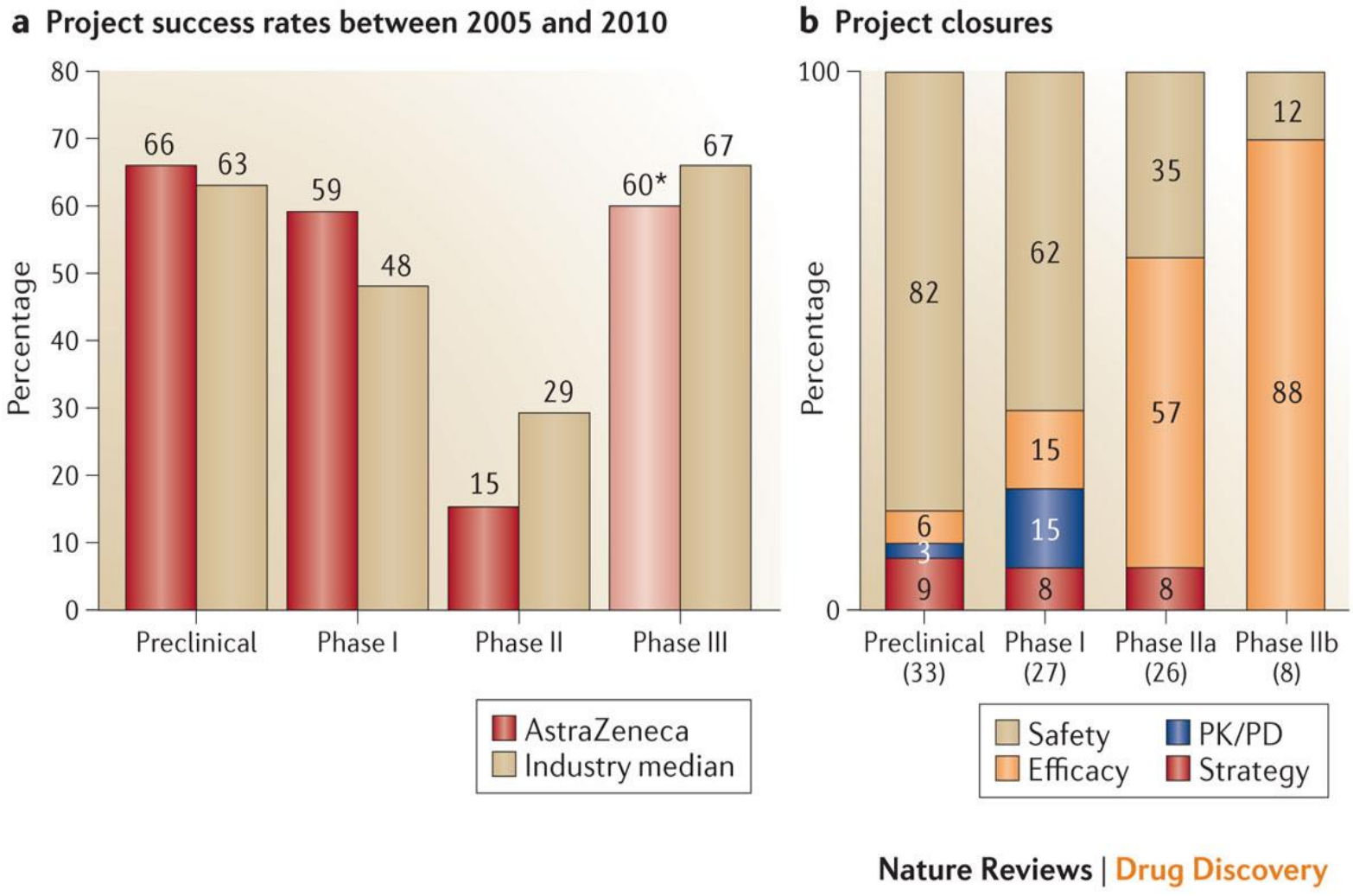
Comprehensive approach to assess full 2005-10 AZ iMed portfolio



- > 80% of 2005-2010 portfolio compounds assessed
- Compounds assessed in each phase separately

1 Compounds / projects excluded for a variety of reasons, for example, investigational compounds, biologics, old projects, or data not readily available; Active projects were not included in Pre-clinical and Phase I analyses

Overview of AZ project success rate and reasons for closure



Cook et al, Lessons learnt from the fate of AstraZeneca's drug pipeline: a five dimensional framework. Nature Reviews Drug Discovery, 13, 419-431, 2014

Safety-related attrition is a major cause of drug attrition

Type of adverse findings:	Preclinical	Nonclinical	Nonclinical	Nonclinical		Phase I-III	Phase I-III	Phase I-III	Phase I-II
Information:	Causes of attrition	Causes of attrition	Causes of attrition	Causes of attrition		Causes of attrition	Causes of attrition	Causes of attrition	Causes of attrition
Source:	ABPI (2008) Unpublished	BMS (Car, 2006)	GSK (2011) Unpublished	AZ (NRDD 2014)		Olson et al. (2000)	ABPI (2008) Unpublished	DIA Daily Jan-Dec 2010	AZ (NRDD 2014)
Sample size:	156 CDs stopped	88 CDs stopped	UNKNOWN	48 CDs stopped		82 CDs stopped	63 CDs stopped	18 CDs delayed/stopped	33 CDs stopped
Cardiovascular:	24%	27%	40%	17%		21%	35%	22%	24%
Hepatotoxicity:	15%	8%	10%	14%		21%	29%	11%	14%
Nervous system:	12%	14%	8%	7%		21%	2%	22%	38%
Immunotox; photosensitivity:	7%	7%	4%	0%		11%	10%	22%	3%
Renal:	6%	2%	4%	8%		9%	5%	0%	10%
Gastrointestinal:	5%	3%	8%	3%		5%	2%	11%	10%
Haematology/ Bone marrow:	3%	7%	4%	2%		4%	3%	0%	0%
Reprotox:	9%	13%	7%	7%		1%	5%	0%	0%
Musculoskeletal; Connective tissue	8%	4%	6%	12%		1%	5%	6%	3%
Genetic tox:	5%	5%	4%	10%		0%	0%	0%	3%
Respiratory:	1%	2%	0%	8%		0%	2%	6%	3%
Carcinogenicity:	0%	3%	0%	0%		0%	3%	6%	0%
Other:	4%	0%	4%	11%		4%	2%	11%	3%

The various toxicity domains have been ranked first by contribution to attrition due to clinical findings, then by nonclinical findings.

Courtesy of Will Redfern, AZ

0% 1-9% 10-19% >20%

5-Dimensional framework used for project assessment

Cook et al, Lessons learned from the fate of AstraZeneca drug pipeline: a five-dimensional framework, NRDD, 16 May 2014

Right target

- Strong link between target and disease
- Differentiating efficacy
- Available and predictive biomarkers

Right tissue

- Adequate bioavailability and tissue exposure
- Definition of PD biomarkers
- Clear understanding of preclinical and clinical PK-PD

Right safety

- Differentiated and clear safety margins
- Understanding secondary pharmacology risk
- Reactive metabolites, Gentox, Drug-drug interactions
- Understanding of target liability

Right patients

- Identification of most responsive patient population
- Definition of risk/benefit for given population

Right commercial

- Differentiated value proposition vs. future standard of care
- Market access/payer/provider focus
- Personalised healthcare strategy including diagnostic/biomarkers

5Rs Portfolio Review – Project deep dives

Data collection

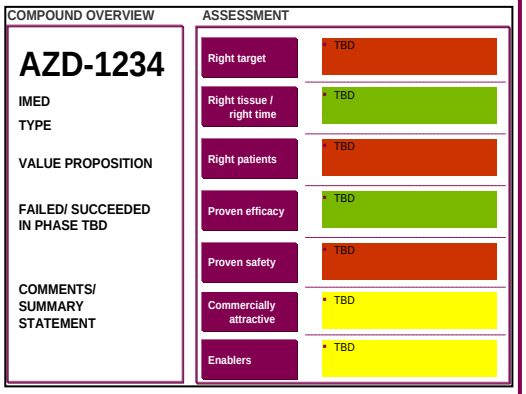
1a Fill in 'agnostic' survey (200 questions)

AZD-1234					
#	Question	Options			
1.	Was there preclinical evidence of **target validation** for the anticipated lead indication?	X			
2.	Was there evidence of **adequate binding** to pharmacological target?		X		
3.	**Efficacy biomarkers** – what were they measuring?			X	
...	..	...	...	...	...
198.	Efficacy biomarkers – what were they measuring?	X			
199.	Efficacy biomarkers – what were they measuring?				
200.	Efficacy biomarkers – what were they measuring?				

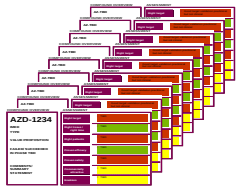
1b Interview sessions for additional information

Data analyses

2a Create a draft evaluation of the project



2b Finalize project evaluations in working sessions



End products

3 Distil end products

- Root causes …
- Predictors …
- Recommendations …

3 Basic Principles of Survival in Phase 2

~45 Phase 2 studies, conducted between 2005 & 2009 within Pfizer, were analyzed in depth
Outcome of termination or progression to Phase 3 was compared with confidence in PKPD relationship and confidence in testing the mechanism

Analysis identified 3 basic principles of survival which, when all three were present, was highly predictive of success in Phase 2 for this cohort

Morgan et al, Can the flow of medicines be improved? Fundamental pharmacokinetic and pharmacological principles towards improving Phase 2 survival. Drug Discovery Today: 2012, 17, 419-424

3 Basic Principles of Phase 2 Survival

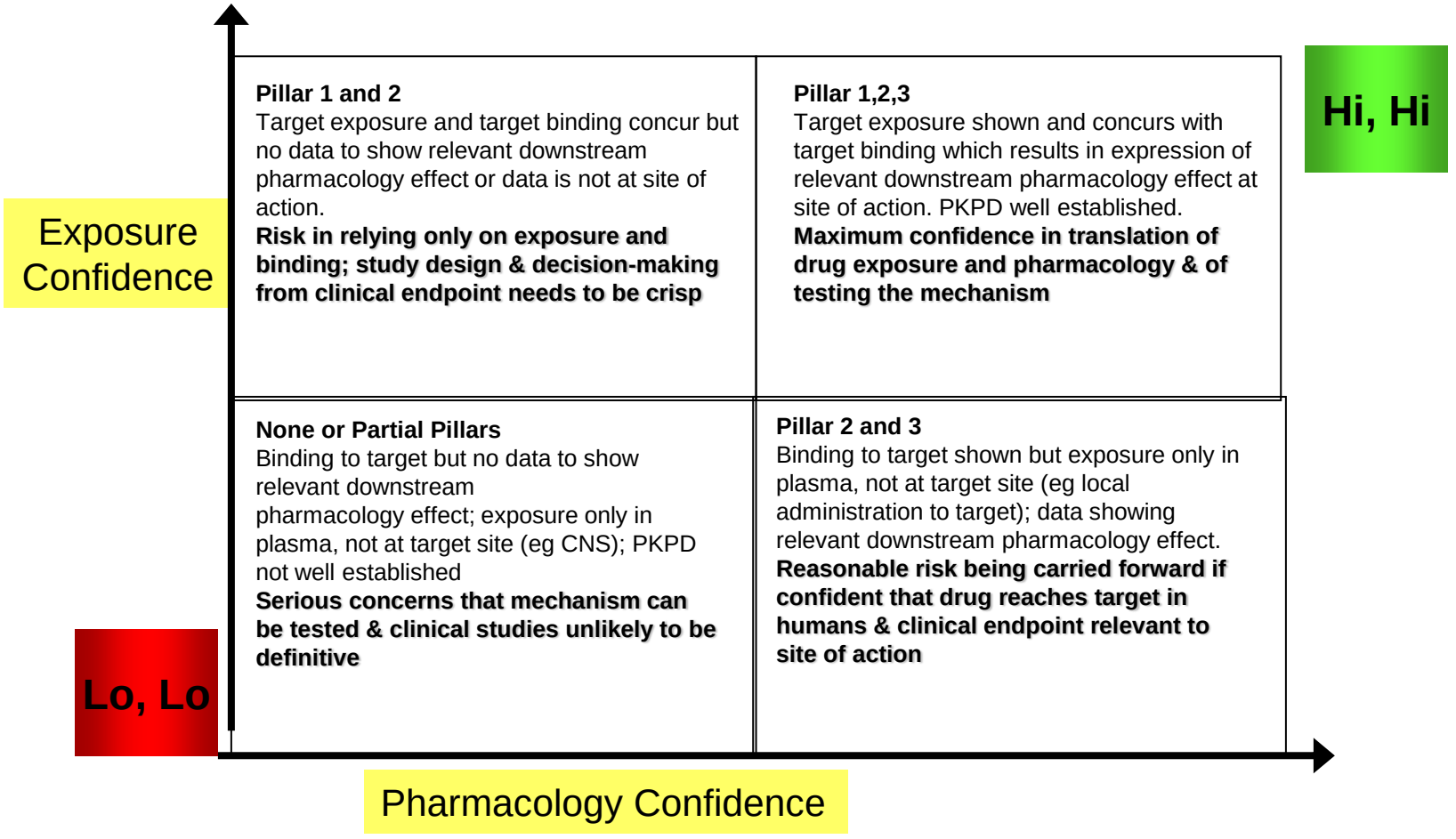
1. Exposure at the target site of action as expected for pharmacological activity.

2. Binding to the pharmacological target as expected for its mode of action.

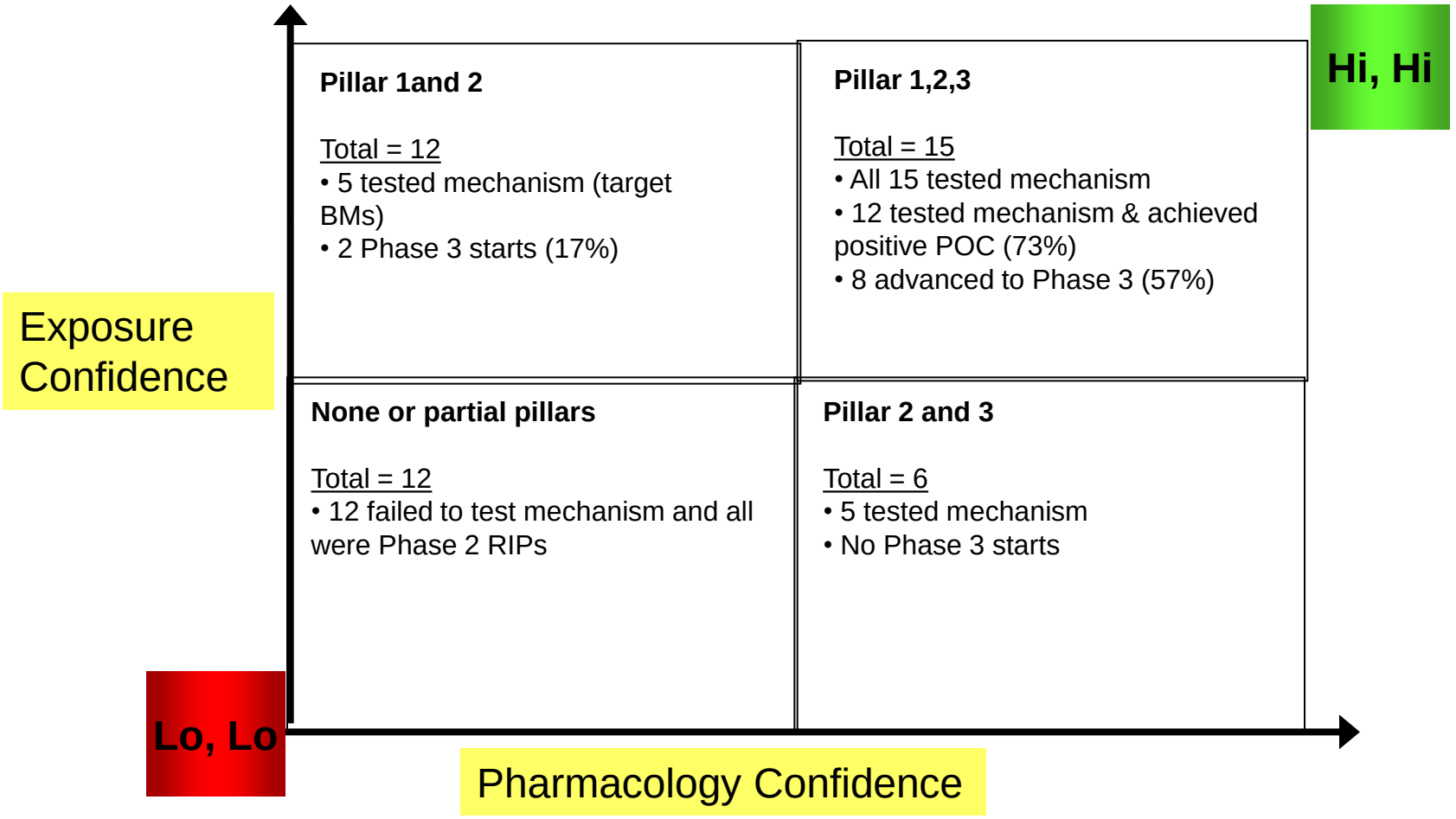
3. Expression of pharmacological activity commensurate with the demonstrated target exposure and target binding.

Risk Management with respect to enabling Proof of Mechanism

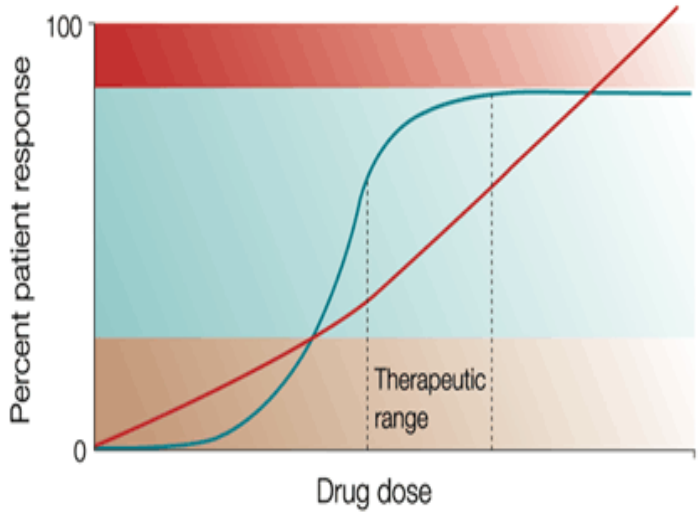
Data and knowledge around the 3 principles can be used to assess risk being carried forward and to inform appropriate clinical study design for testing the mechanism



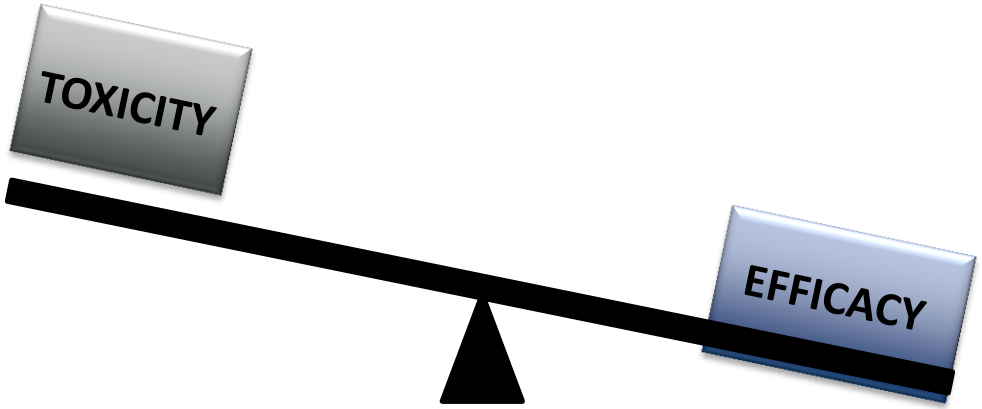
Alignment with 3 principles for 45 Phase 2 projects



Oncology agents frequently limited by on target toxicities



Nature Reviews Cancer 1, 99-108 (November 2001)



Drugs in oncology are often inherently cytotoxic

Toxicity (on target) and efficacy closely linked

Narrow therapeutic window

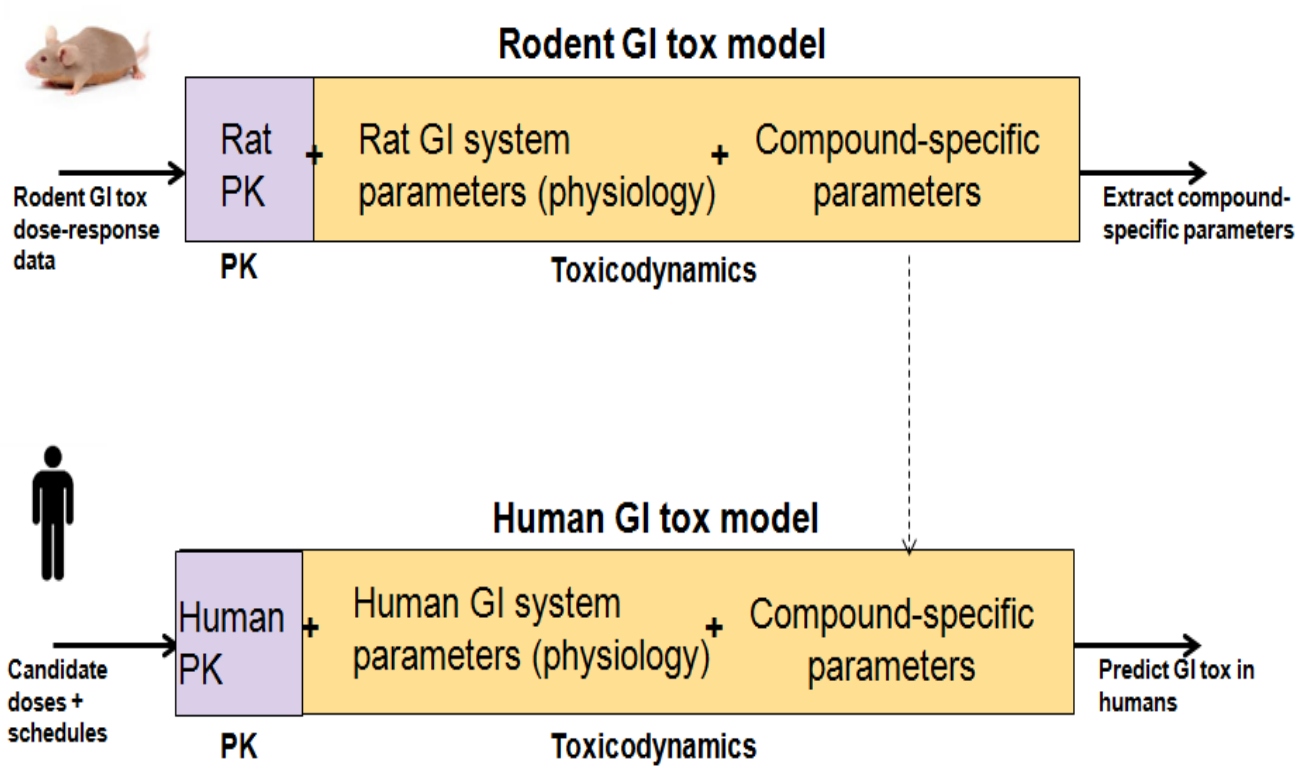
Success depends on maximizing exposure and minimizing toxicity

Table 2 Incidence of drug-induced diarrhea in phase I–III studies of molecular-targeted cancer drugs.

Drug	Incidence of diarrhea (%)	Reference
Erlotinib	55 (6% grade 3–5) 68 (12% grade 3–4)[a]	Shepherd *et al.* (2005)[2] Herbst *et al.* (2005)[65]
Gefitinib	40–60 (8% grade 2) 58 (3% grade 3–4)[a]	Fukuoka *et al.* (2003)[3] Herbst *et al.* (2004)[66]
Lapatinib	40 (10% grade 3) 60 (13% grade 3–4)	Burrhis *et al.* (2005)[24] Geyer *et al.* (2006)[67]
HKI-272	84	Wong *et al.* (2006)[19]
Sorafenib	33 (24% grade 2–3)	Escudier *et al.* (2005)[10]
Sunitinib	20 (grade 2–3)	Motzer *et al.* (2006)[11]
Imatinib	45	Demetri *et al.* (2002)[14]
Flavopiridol	50	Liu *et al.* (2004)[15]
Bortezomib	32 (8% grade 3–4) 29 (9% grade 3–4)	Fanucchi *et al.* (2003)[34]

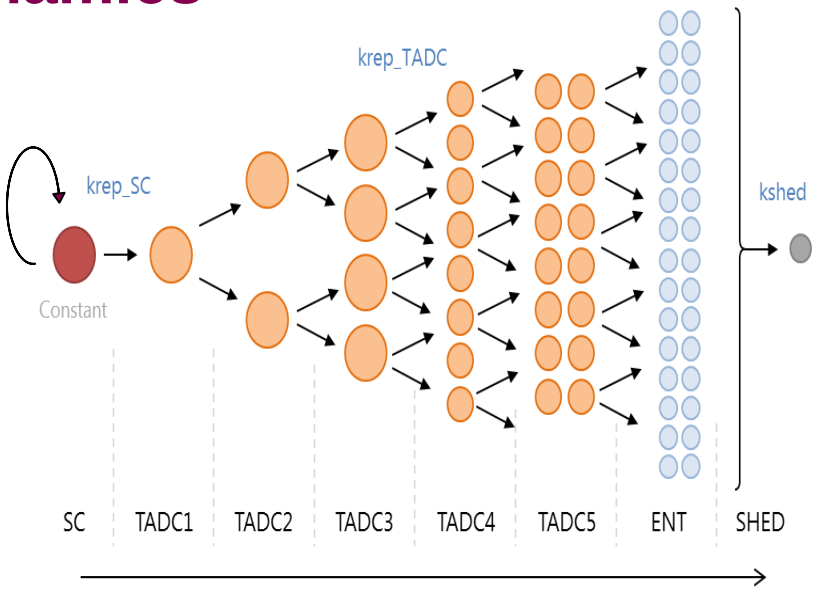
[a]Drug used in combination with cytotoxic chemotherapy.

Right Safety: PBPK – Systems Toxicology approach would address safety related risks early in drug discovery and would inform clinical dose and scheduling options

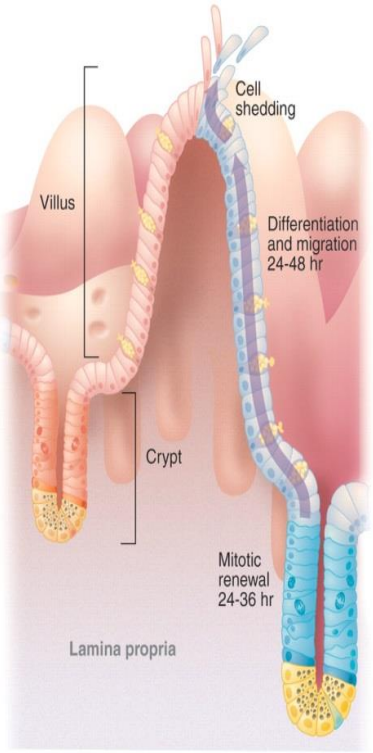


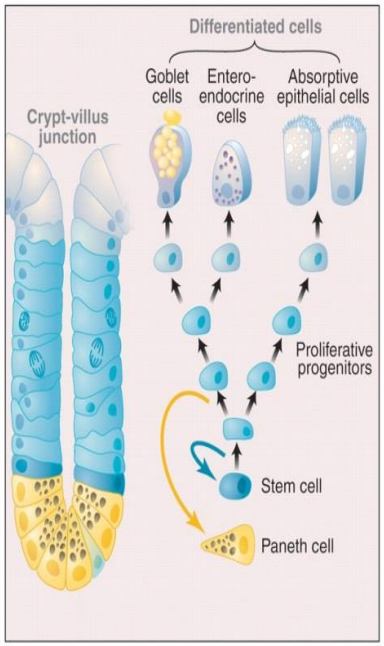
Build model of intestinal cell dynamics

Model Structure



Biological Understanding

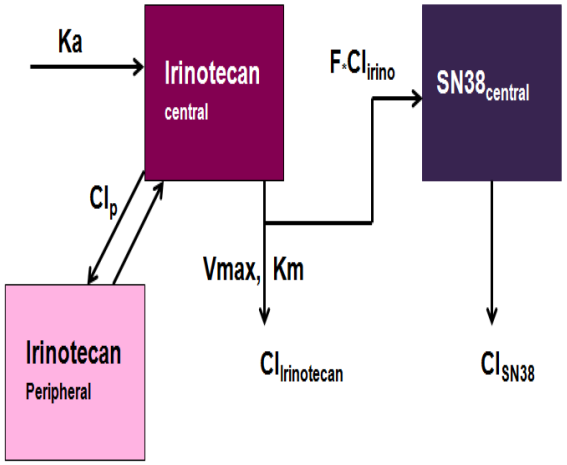




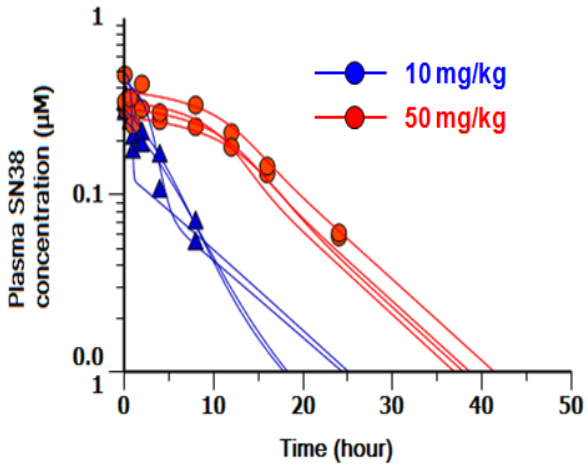
Parameter	Rodent Model	Human Model
Stem Cells/Crypt	10	10
Stem cell doubling time	16 hrs	72 hrs
TADC doubling time	12 hrs	32 hrs
Shedding rate	0.45 /day	0.2 /day
# of Transit compartments	4	5
# of Crypts feeding each	7	7

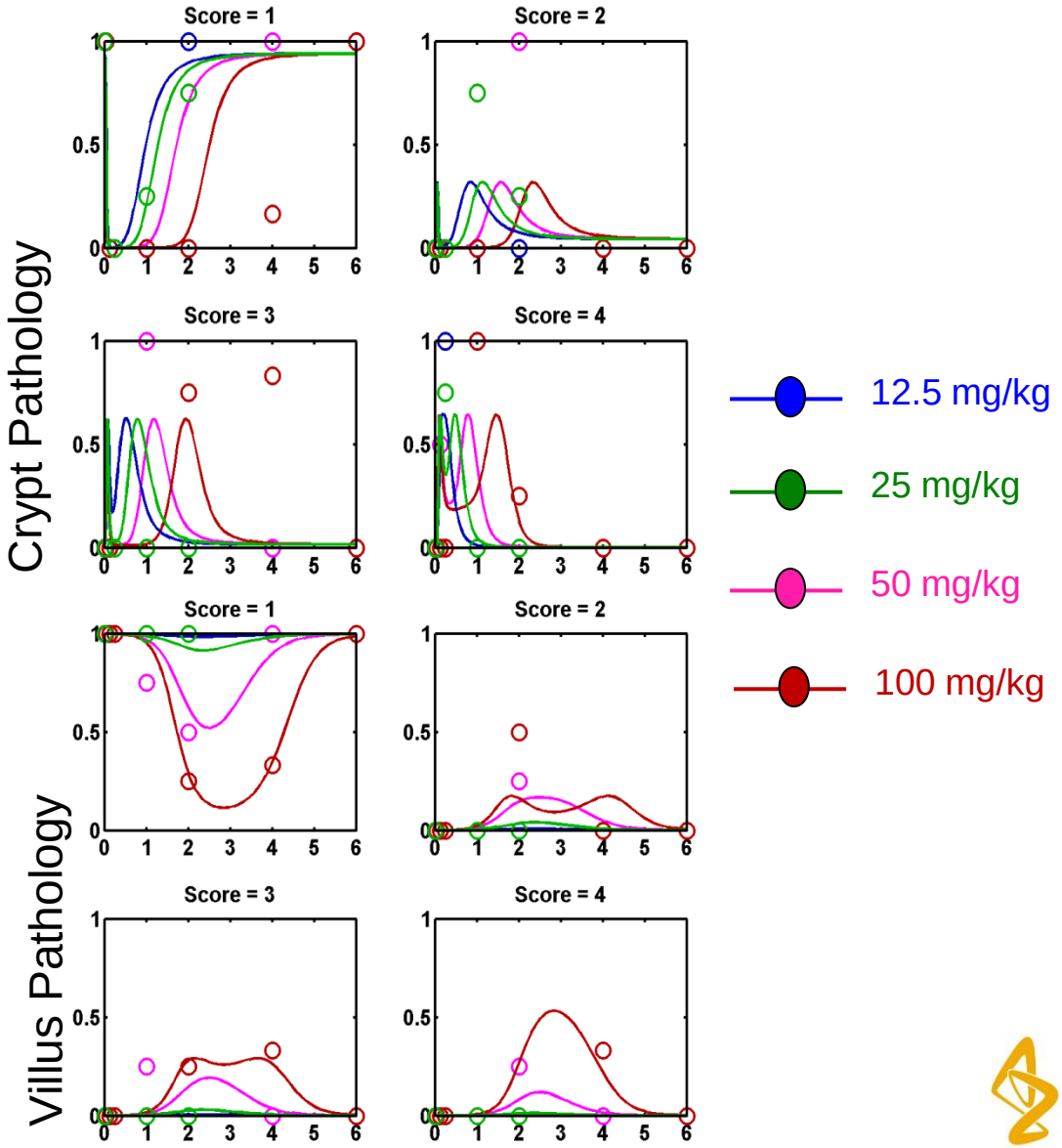
Testing model in rat: fitting irinotecan PK and g.i. toxicity

PK model for non-linear Irinotecan /SN38 in rats

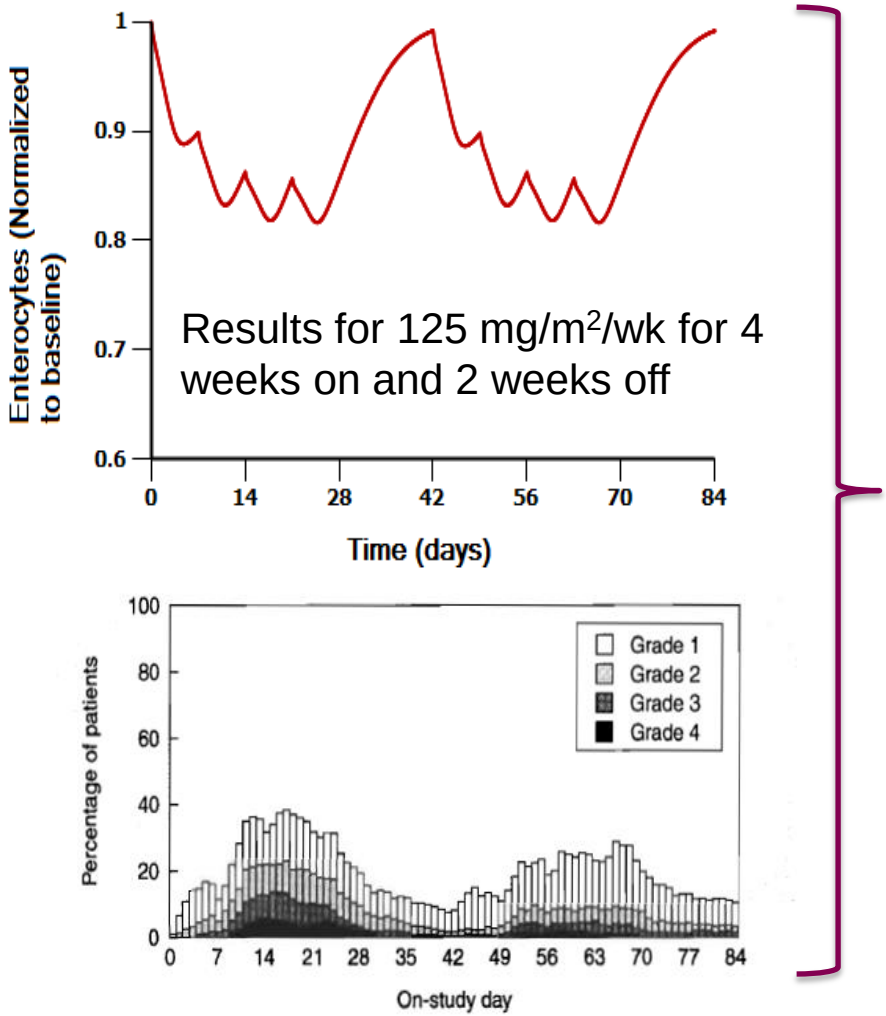


Model fits (lines) to rat PK data (markers)

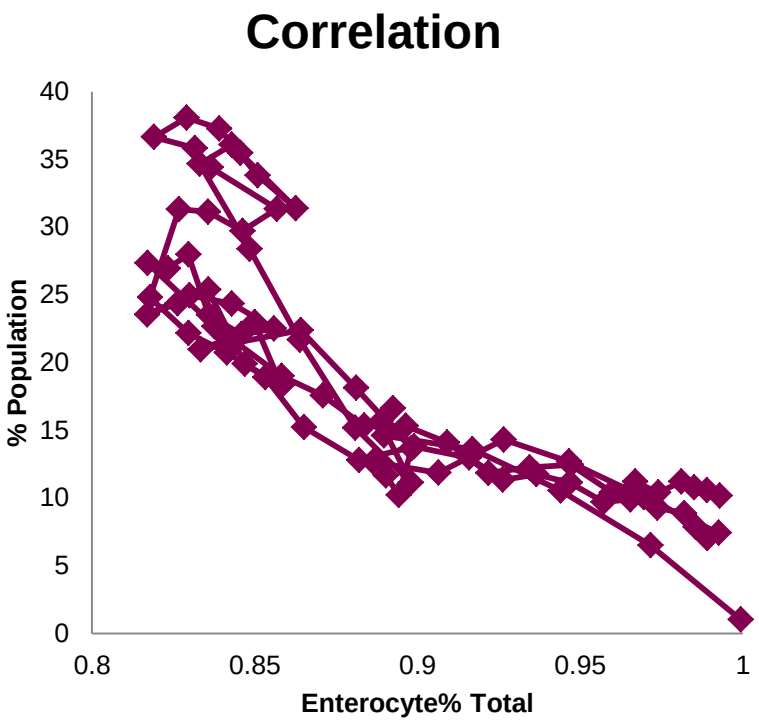




Simulation of human GI toxicity

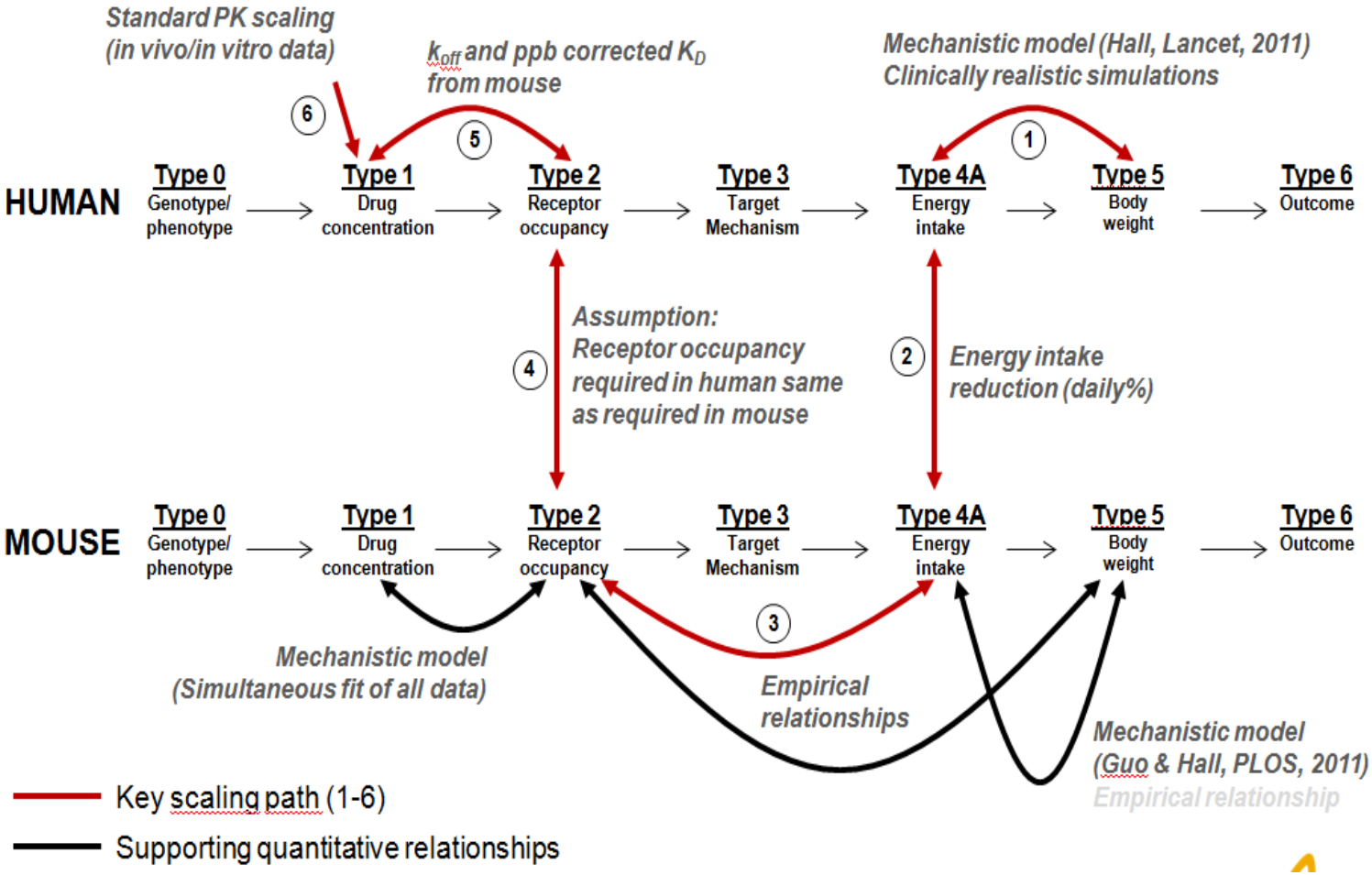


Hecht, Gastrointestinal toxicity of Irinotecan, Oncology, 1998



Courtesy of Harish Shankaran and Jay Mettetal; manuscript in preparation

Right Target and Right Tissue: Quantitative modelling approach for compounds affecting body composition



Gennemark P, et al. A modeling approach for compounds affecting body composition . Journal of Pharmacokinet & Pharmacodynamics, 40(6):651-67, 2013.

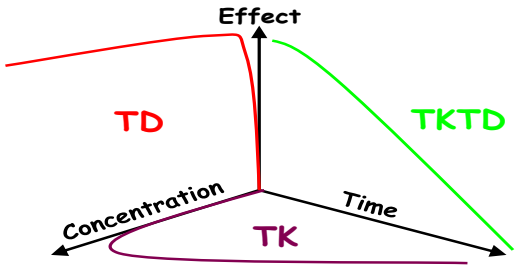
Modelling and Informatics Approaches inPreclinical Safety

Fit for purpose

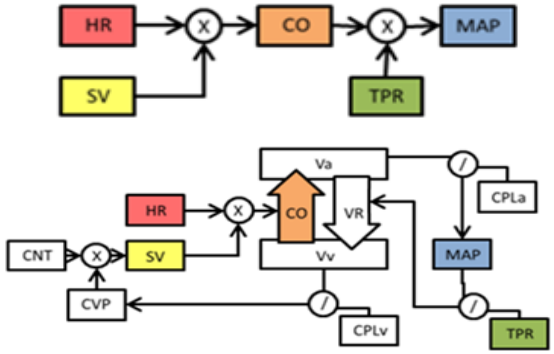
Data Quantity

Deep

Shallow

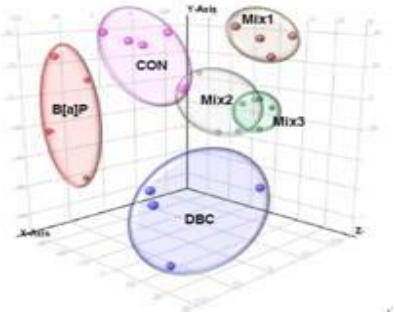


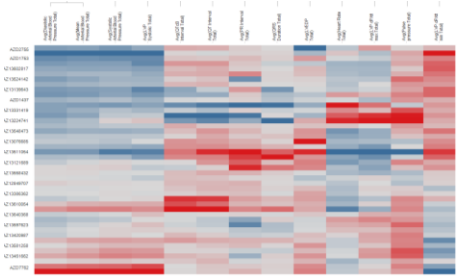
PK/PD &
Empirical models



Systems Pharmacology/
Mechanism based models

"Old Fashioned Elbow Grease"





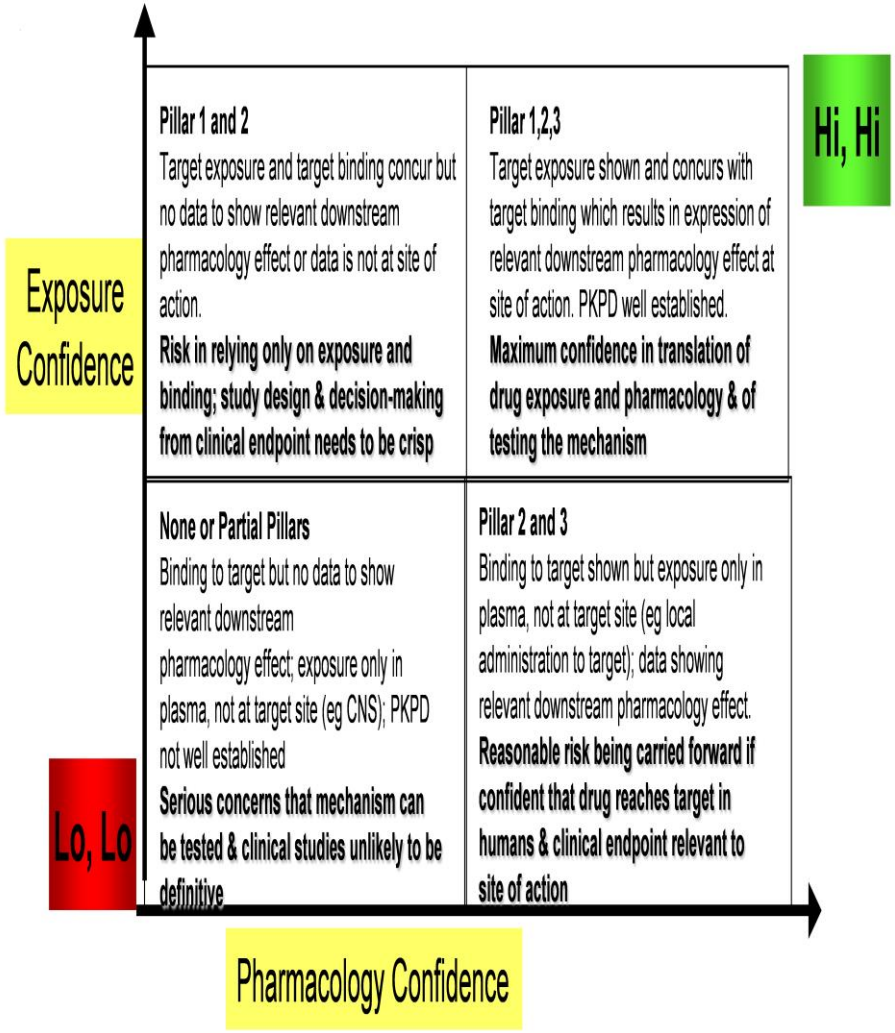
Informatics &
"Big Data" Approaches

Narrow

Broad

Data Types

3 Pillars of Survival and 5Rs framework



Right target

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- Differentiating efficacy
- Available and predictive biomarkers

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Center for Health Policy at BROOKINGS

Improving Productivity in Pharmaceutical Research and Development: The Role of Clinical Pharmacology and Experimental Medicine

Center for Health Policy
The Brookings Institution

The Embassy Row Hotel • Washington, DC
July 28, 2015

Department of Pharmacology Physiology

DISCOVER DEVELOP DELIVER

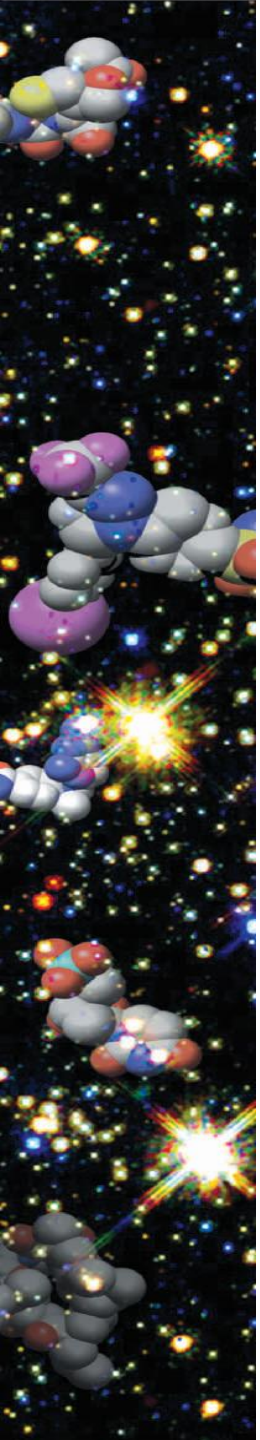
Optimizing Target and Compound Selection to Enhance Early Stage Decision-Making

Brookings Institute Conference on Improving Pharmaceutical Research and Development

James E. Barrett, Ph.D.
Professor and Chair

DREXEL UNIVERSITY Clinical and Translational Research Institute

DREXEL UNIVERSITY College of Medicine
Department of Pharmacology and Physiology



General Outline

- Target Identification and Validation
  - Backdrop
  - Challenges
- Optimizing Approaches
- Future Directions
- Conclusions

Target Identification and Validation on the Translational Continuum

Basic Research	Exploratory	Discovery	Preclinical	Phase 1	Phase 2	Phase 3
Target ID • Genetic screening • TxP profiling • Epidemiology	**Target Validation** • Animal models • Cellular assays • Human tissue profiling	**Target Prosecution** • Assay Development • HTS/Lead ID • Lead Optimization	**Cmpd De-Risking** • Safety • Toxicology • PK/PD modeling • Biomarkers	**Proof of Mechanism** • Safety • Tolerability • Exposure to target • Target Engagement • Evidence of pharm • ESOE studies	**Proof of Concept** • Efficacy • Safety • Biomarker • ESOE	**Pivotal Trails** • Efficacy • Safety

Regulatory
Approval

Patients

Translational
"Valley of Death"

Potentially Face a delay of between 10-15 years.

Is poor research the cause of the declining productivity of the pharmaceutical industry? An industry in need of a paradigm shift

Frank Sams-Dodd[1,2]

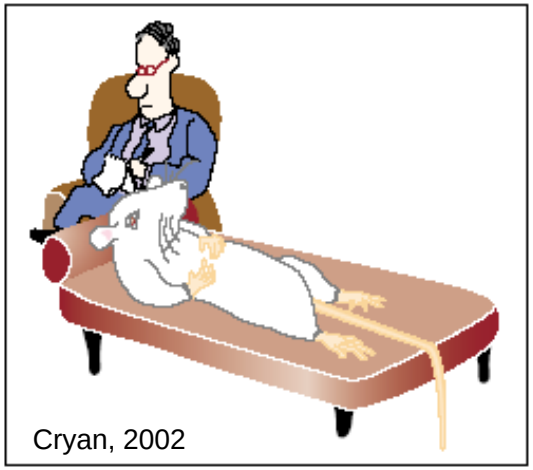
"There is growing acceptance that a … *fundamental paradigm shift* is required if we are to accept that ***drug discovery is [at present] the art of developing effective treatments against diseases we do not fully understand using drugs we do not fully know how they work***."

For the past 20 years ***target-based drug discovery*** *has been the main research paradigm used by the pharmaceutical industry* and billions of dollars have been invested into this approach … recent industry data strongly indicate that the *target-based approach is* ***not an effective drug discovery paradigm*** and is likely to be the cause of the productivity crisis … from a theoretical and scientific perspective the target-based approach appears sound, so why is it not more successful?

Drug Discovery Today, 2013

Lessons learned from the fate of AZ's Drug Pipeline – Retrospective Analysis

- The five most important determinants of project success and pipeline quality – 5 R's
  - ***The right target***
  - The right patient
  - The right tissue
  - The right safety
  - The right commercial potential



- Plus the 6th factor – THE RIGHT CULTURE

Cook et al., 2014, Nat. Rev. Drug Discov.

What is a drug target?

A native protein in the body whose activity is modified by a drug, resulting in a therapeutically relevant response.

The definition of a drug target can be relative as well as elusive:

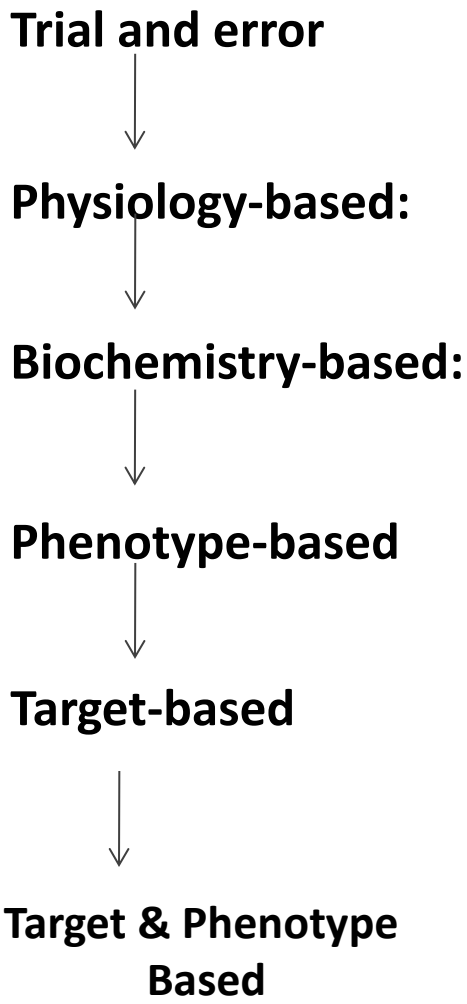
- The target may be a drug target in one tissue, but not in another.
- The target may be a drug target in one age group, but not another.
- The target may be a drug target in one gender, but not the other.
- The expression, activity, and structure of target may change over the during the course of a pathological process.
- The structure/function of target may be altered by drug treatment.
- The target may not be involved in the disease process.

Some 'myths' about drug targets

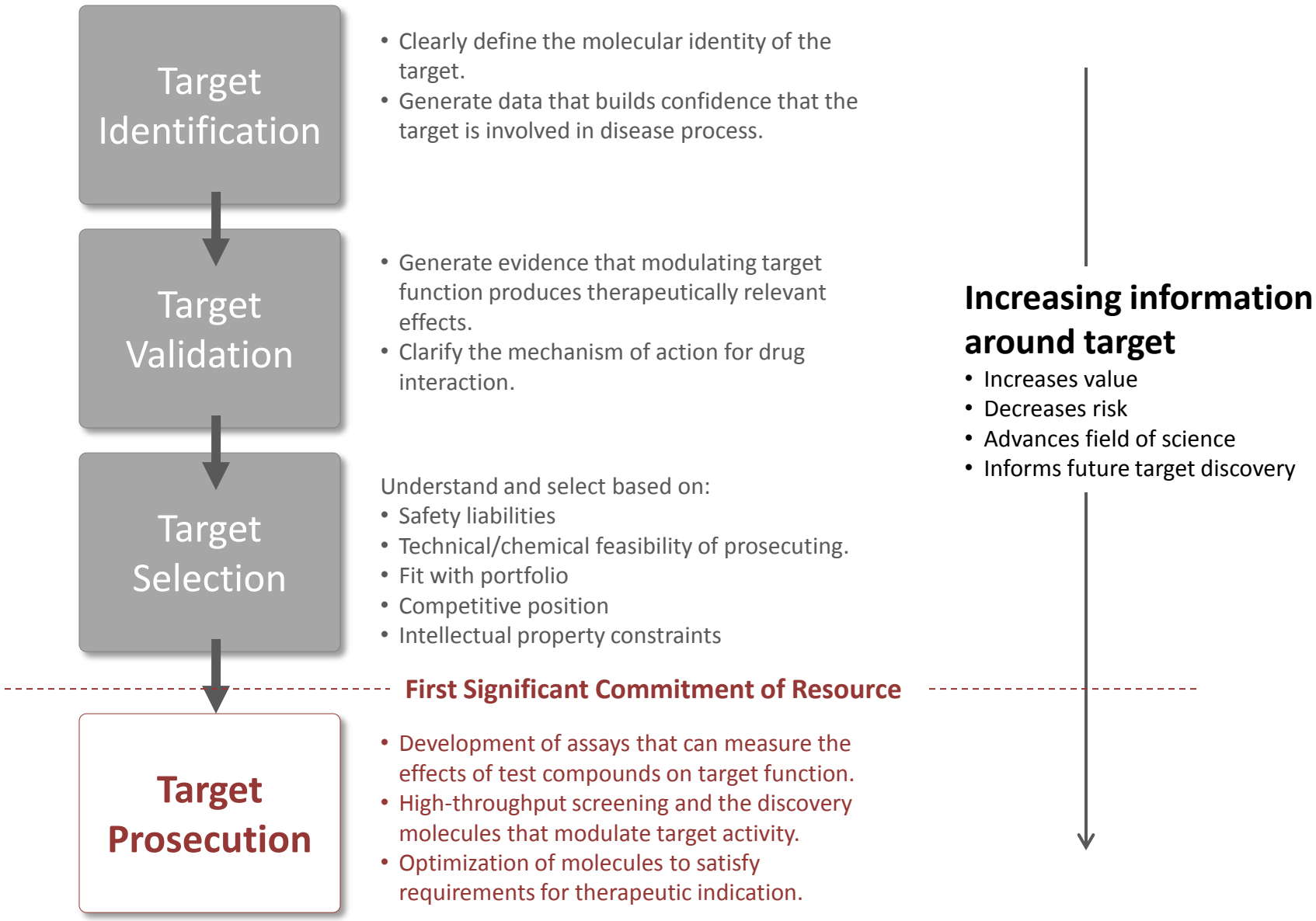
Most disorders can be treated by focusing on a single target

Approaches to target identification and validation are similar across therapeutic areas or diseases

Evolution of Research Strategy underlying Drug Discovery

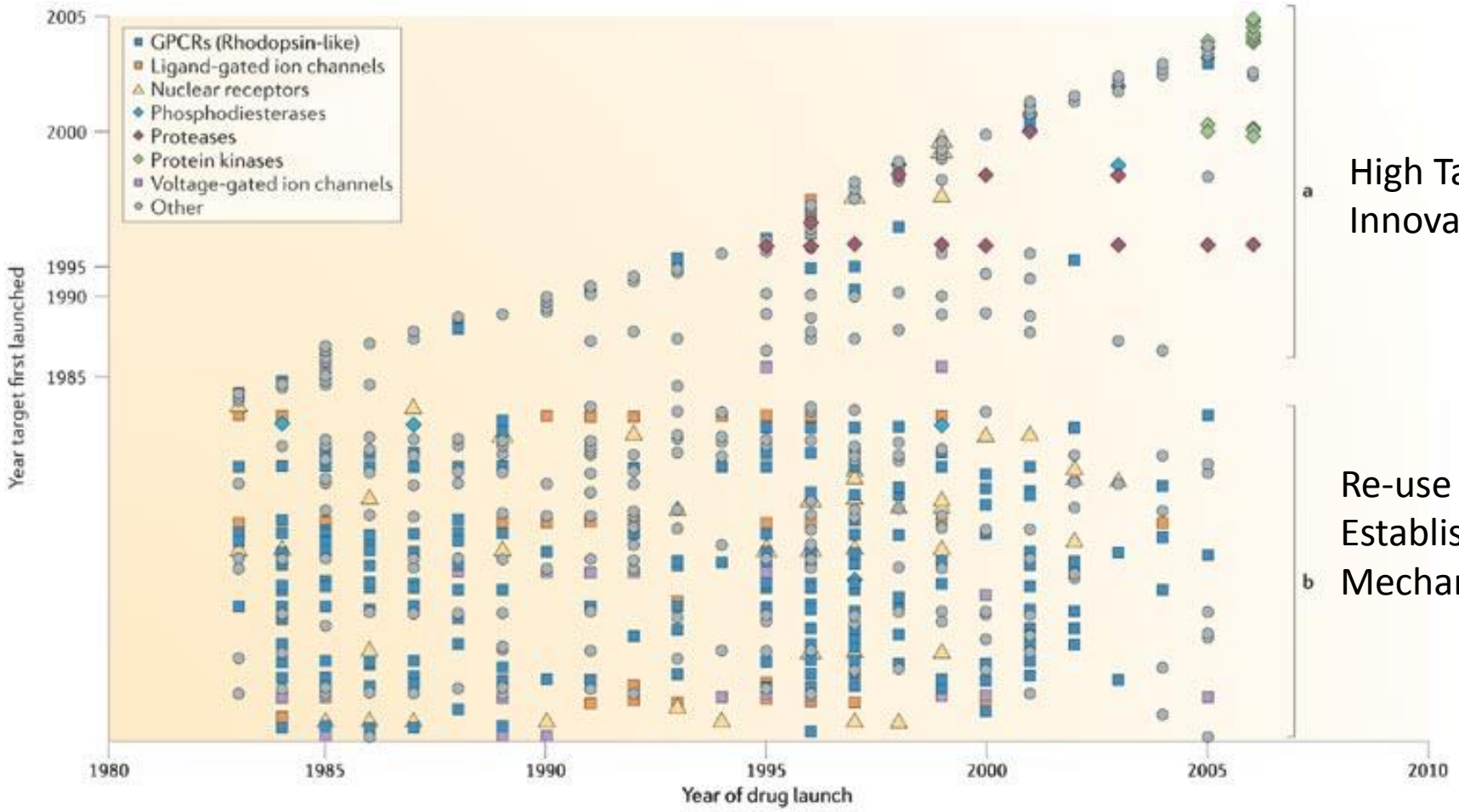


Basic Logic of Target-based Discovery



R. Ring, Unpublished

Rate of Target Innovation



High Target Innovation

Re-use of Established Mechanisms

Overington et al., 2006

Novelty in the Pharmaceutical Target Landscape

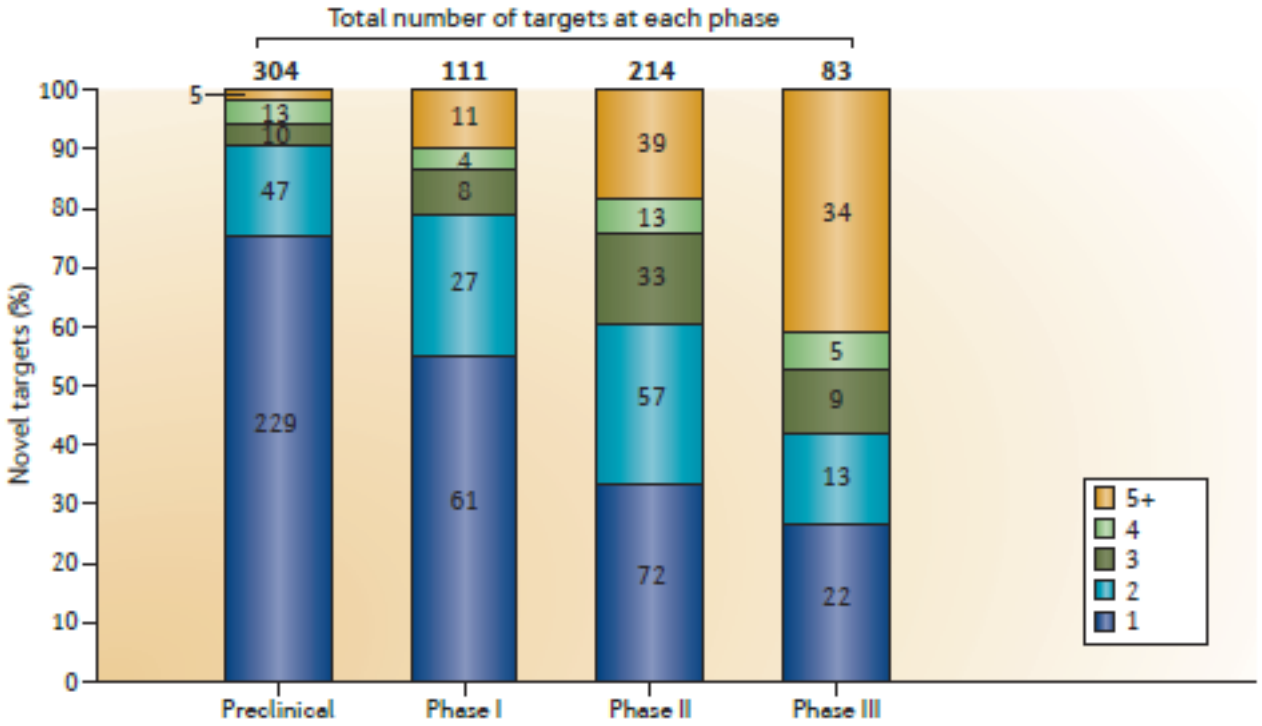
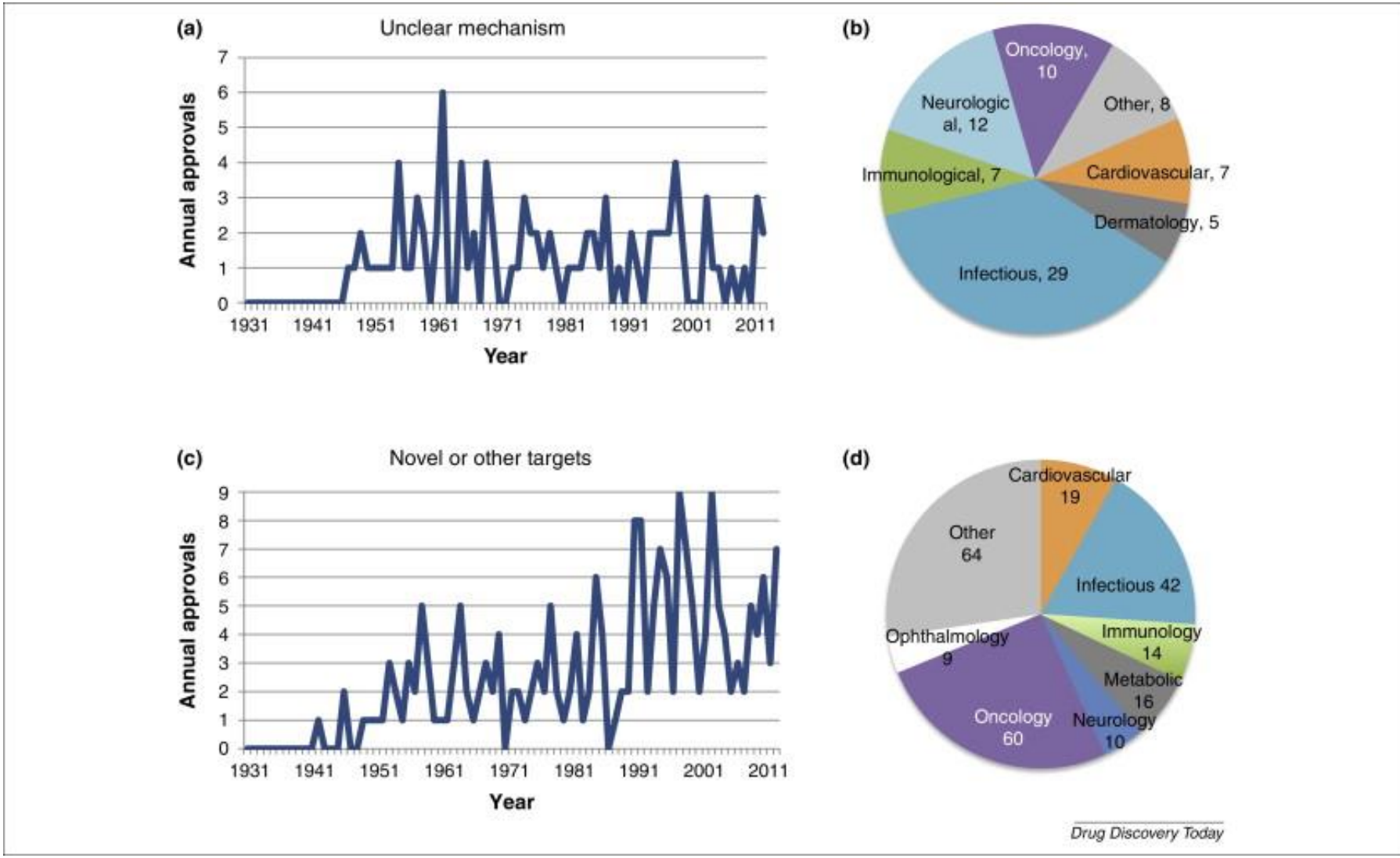


Figure 2 | **Competition on novel targets by latest development phase.** All of the novel targets are categorized by the latest phase of any project associated with them and tabulated by the amount of competition on each target. Thus, 75% of preclinical targets have no competition, but as evidence around the target increases, so does competition. The actual number of novel targets is shown at the top of the graph. Data are from Citeline's Pharmaprojects, 2013.

Agarwal et al., Nat. Rev. Drug Discov. 2013

Ambiguity and Novelty in Drug Targeting



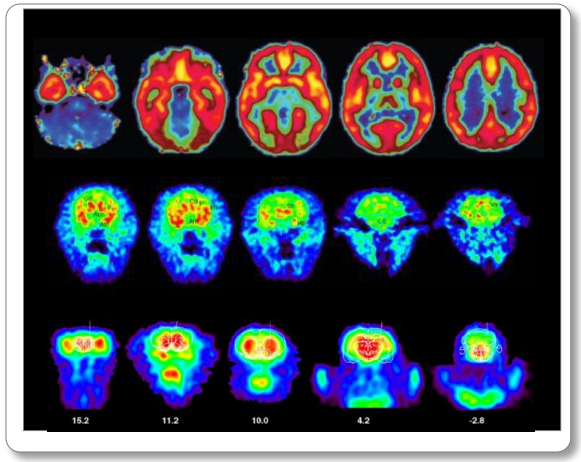
Kinch et al. 2015

Target Identification:

Additional information gathered during target identification phase:

- **Distribution of target in tissues, cell types, and/or biological fluids.**
  - Identify possible side effect liabilities.
  - Understand the safety concerns up front and plan for mitigation.
- **Understanding of homologies with other targets**.
  - Define the goals for selectivity when entering drug discovery and design.
  - Basic understanding of the side effect liabilities with nearest neighbors.
- **Understanding of species differences in target.**
  - Confirm and understand expression in species used for validation studies and program prosecution (tissues, cell types, fluids).
  - Understand species homologies (sequence, function, pharmacology).

- *Information used to understand risk of pursuing target.*
- *Aids in selecting relevant validation models.*
- *Defines early de-risking strategies for target prosecution.*
- *Increases value.*



R. Ring, Unpublished

New Target Validation:

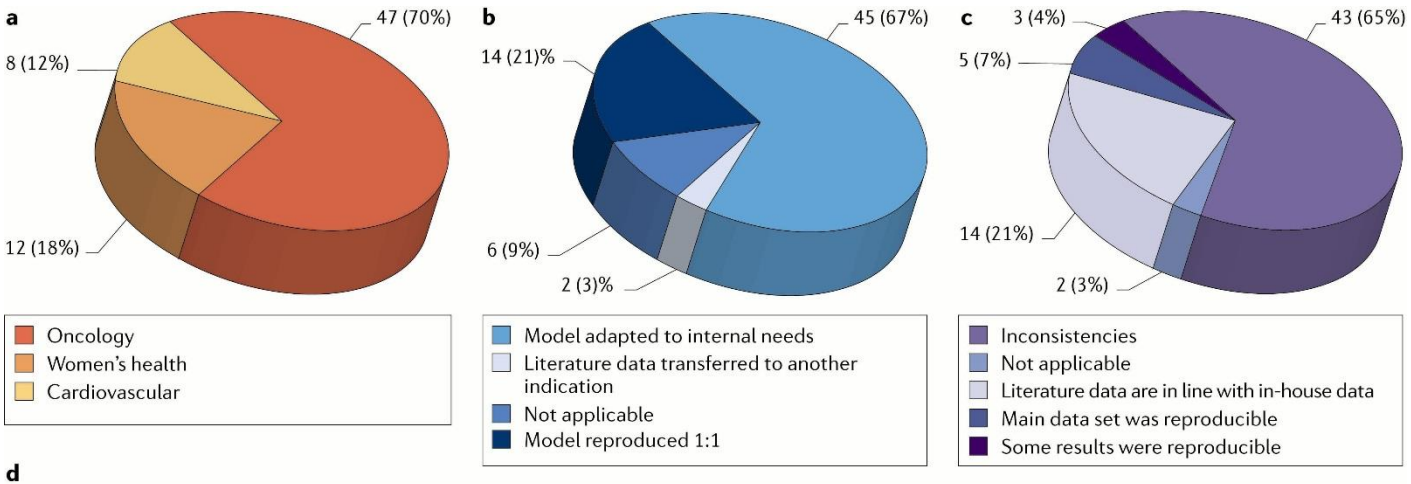
The majority of target validation efforts are focused on demonstrating that the modulation of target function produces a biologically relevant effects in model systems. Initial evaluation frequently involves:

- Modulation of a disease-relevant phenotype in animal models.
  - Behavior
  - Body weight
  - Body temperature
  - Structure
- Modulation of a specific biology in predictive models of drug action.
- Modulation of cellular function(s) in vitro
  - Biochemical endpoints relevant to signal transduction.
  - Electrophysiology
  - Apoptotic processes

"A target is not validated until a drug works in the clinic"

Inconvenient Truths about Validation: Need for Replication

Validity of published data on potential targets is crucial for drug companies when deciding to start novel projects



d

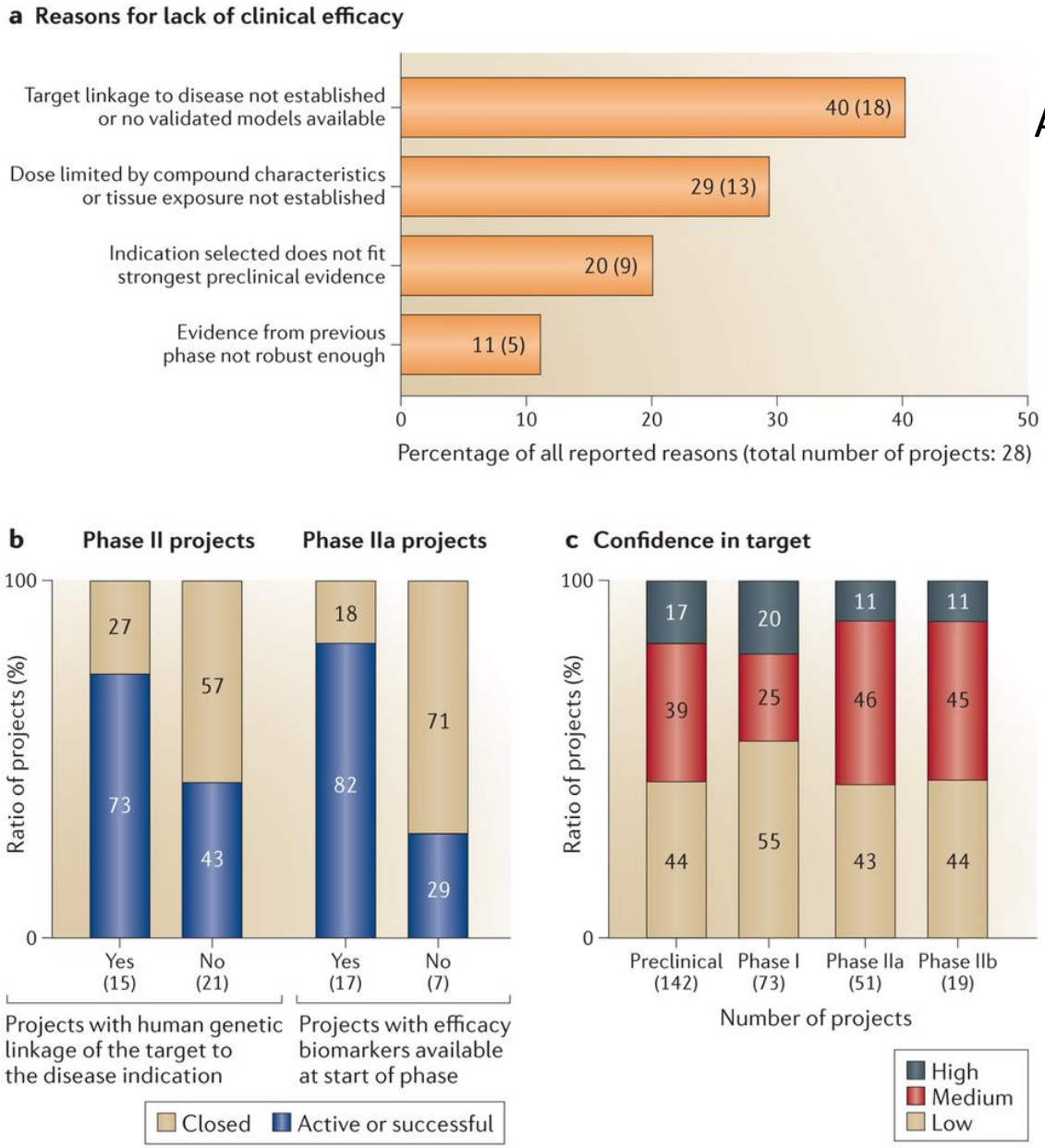
	Model reproduced 1:1	Model adapted to internal needs (cell line, assays)	Literature data transferred to another indication	Not applicable
In-house data in line with published results	1 (7%)	12 (86%)	0	1 (7%)
Inconsistencies that led to project termination	11 (26%)	26 (60%)	2 (5%)	4 (9%)

Prinz, Schlange, & Asadullah Nature Reviews Drug Discovery 2011

Nature Reviews | Drug Discovery

- 2/3 of published data were not reproducible or had inconsistencies that lead to prolonged delays or termination of projects.
- Reproducibility does not correlate with journal impact factors.
- Unspoken Rule (Venture Capital Perspective): 50% of published studies cannot be repeated with similar conclusions in industry labs.
- Likely Explanations:
  - Inappropriate statistical analysis of results
  - Immense competition among labs and pressure to publish.
  - Bias towards the publication of positive results.
- **Estimated that prevalence of irreproducible preclinical research results in ~$28B in US Alone (Freedman et al. PLOS Biology, 2015)**

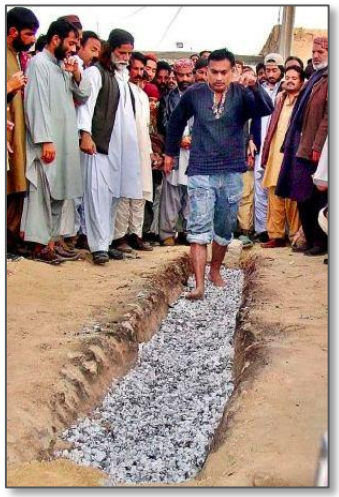
Analysis of AZ Project Closures Due to Efficacy Issues



- 40% lacked data demonstrating linkage of target to the disease
- Lack of access to a well-validated animal model
- 73% of targets with some genetic linkage to the disease were ongoing or successful in Phase II
- Projects with efficacy biomarkers at the start of Phase IIa were more successful or ongoing (82 vs 29%)

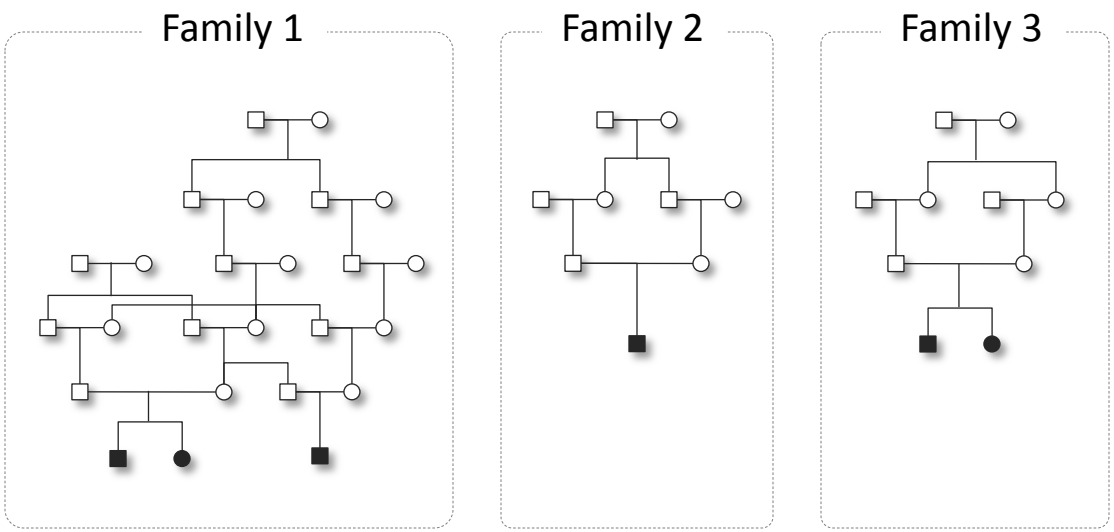
Cook et al., 2014

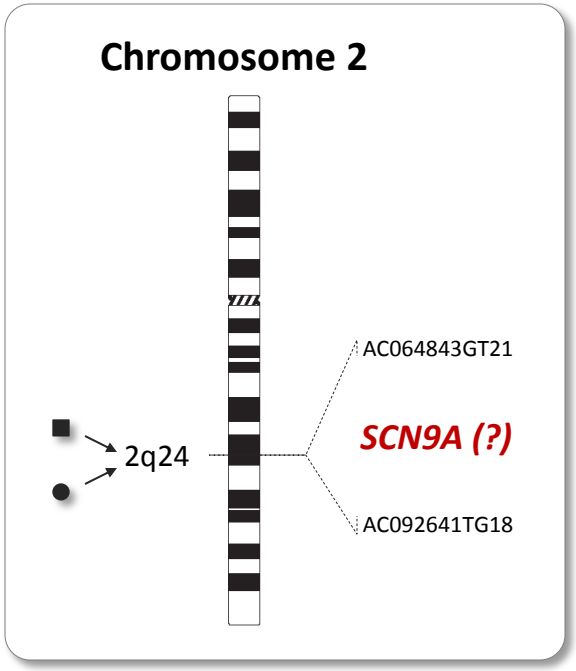
Target ID/Validation Case Study: Nav 1.7 (*SCN9A*)



- Index case: 10 yr old street performer, Northern Pakistan
- Died jumping of a house roof.
- Congenital inability to perceive any form of pain.
- All other sensory modalities (PNS and CNS) normal. Could feel pressure, warm, cold etc.

Sodium Channelopathy





Cox et al Nature 2006

Phenotype-based versus Target-Based Drug Discovery

ACS Chemical Neuroscience

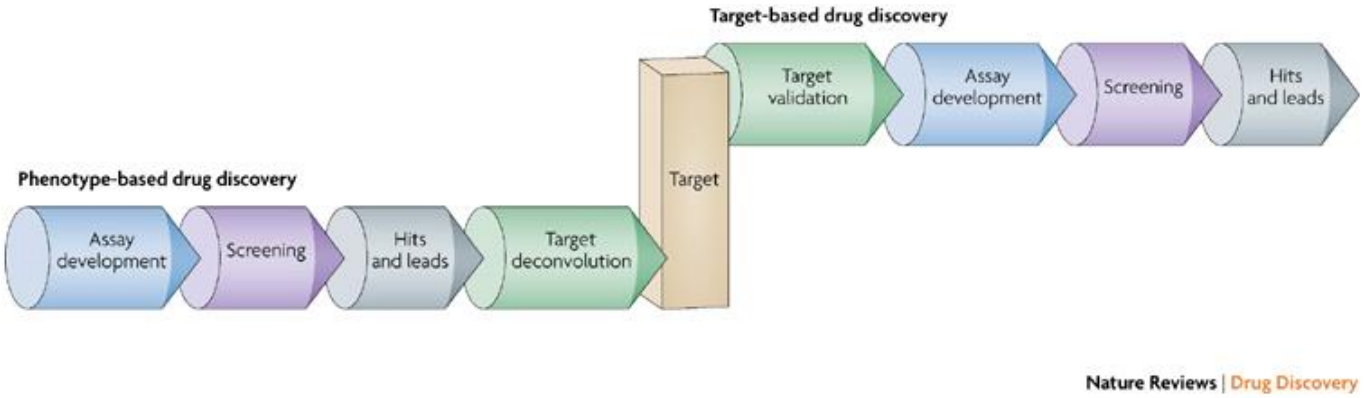
Review

pubs.acs.org/chemneuro

Back to the Future with Phenotypic Screening

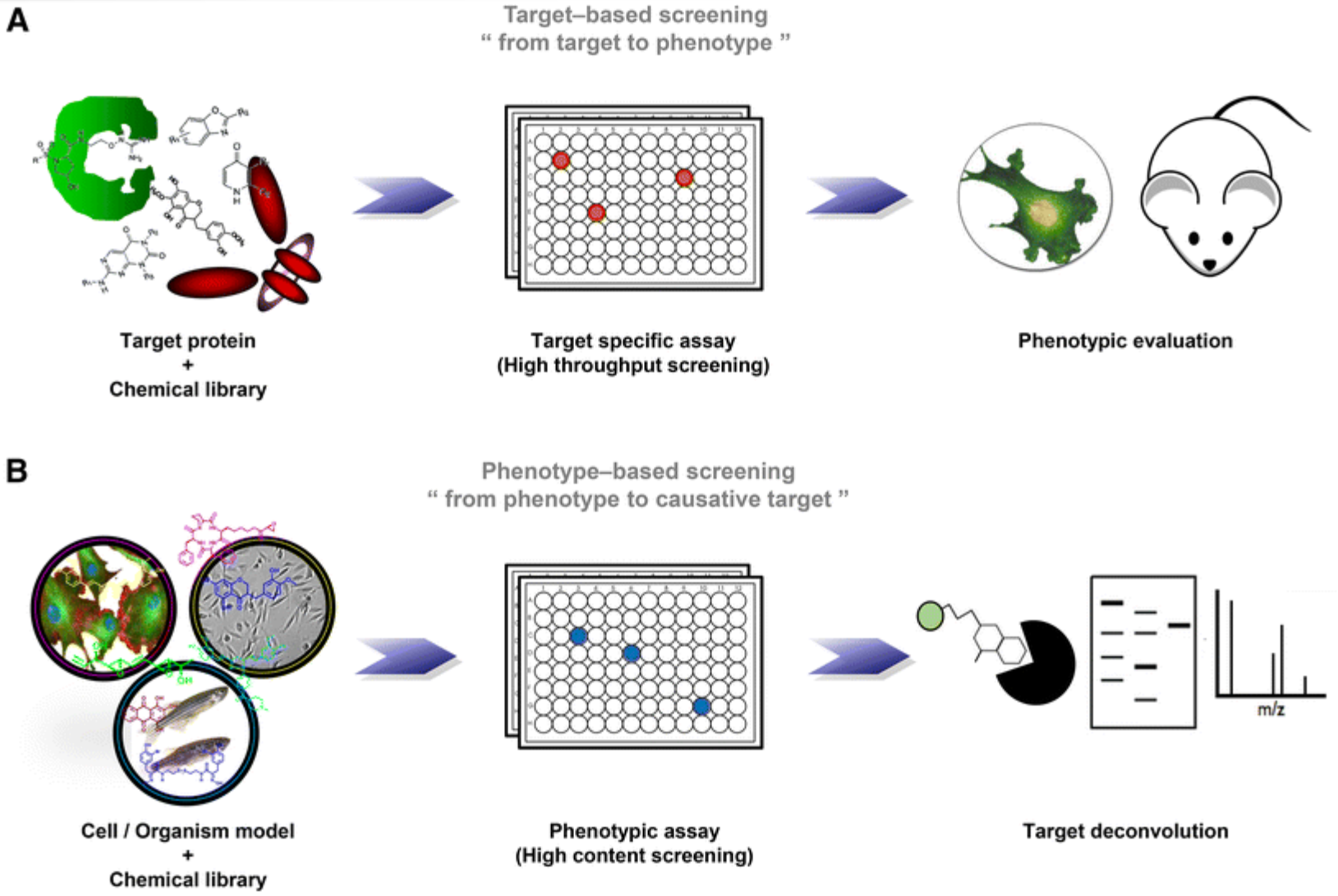
Marguerite Prior,*,† Chandramouli Chiruta,† Antonio Currais, Josh Goldberg, Justin Ramsey, Richard Dargusch, Pamela A. Maher, and David Schubert

Cellular Neurobiology Laboratory, The Salk Institute for Biological Studies, La Jolla, California 92037-1002, United States



Terstappen et al., Nat. Rev. Drug Disc., 2007

Target deconvolution: The heart of chemical biology and drug discovery

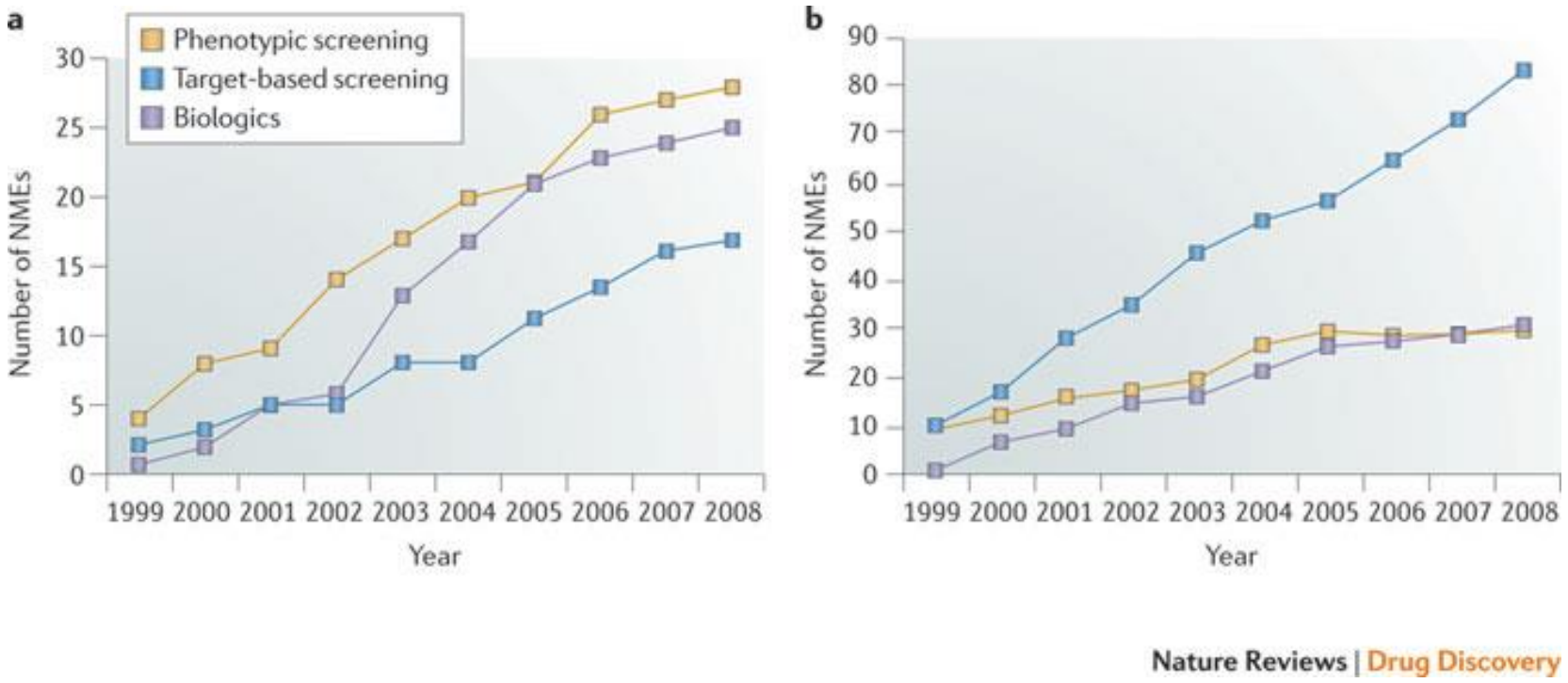


Jung and Kwon, Arch. Pharm. Res., 2015

Cumulative Distribution of New Drugs by Discovery Strategy

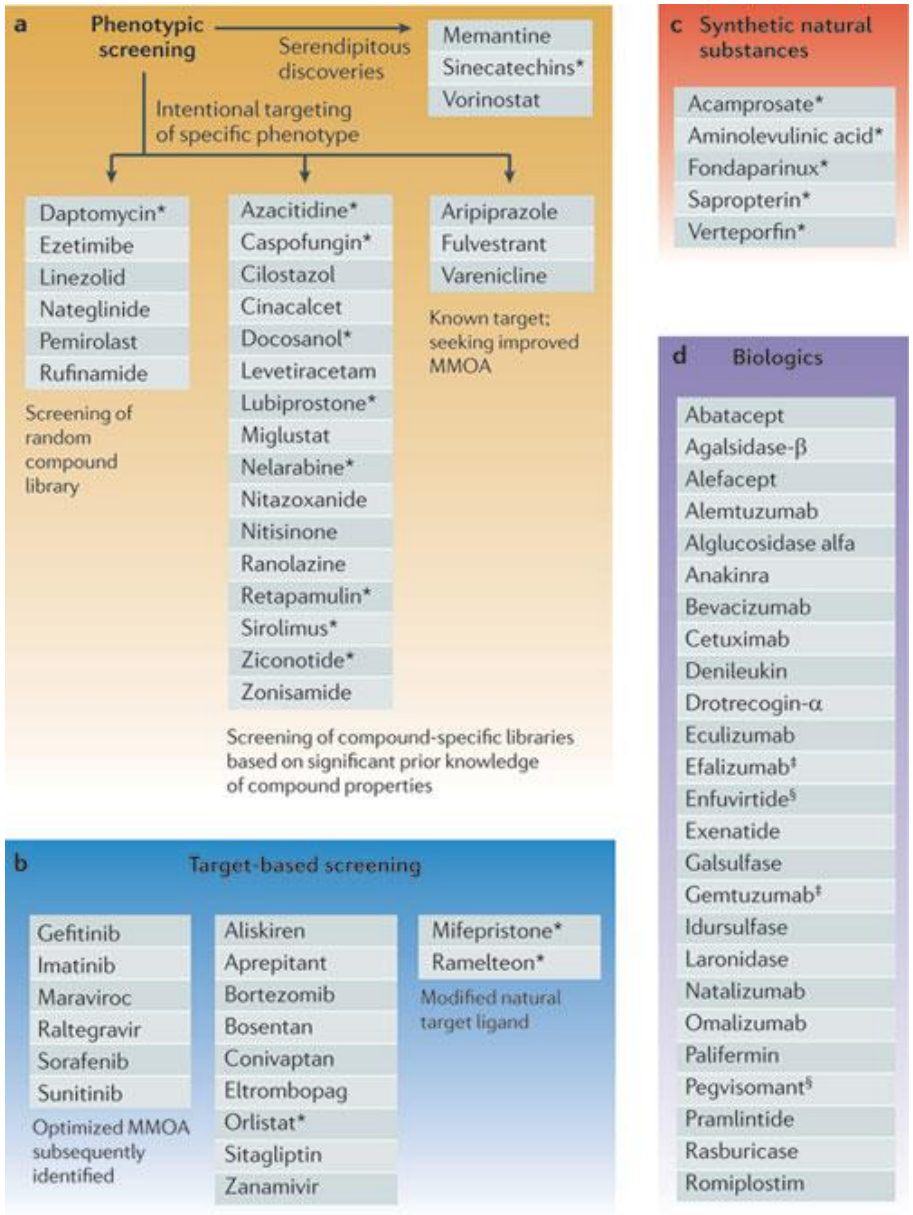
First in Class

Follower Drugs

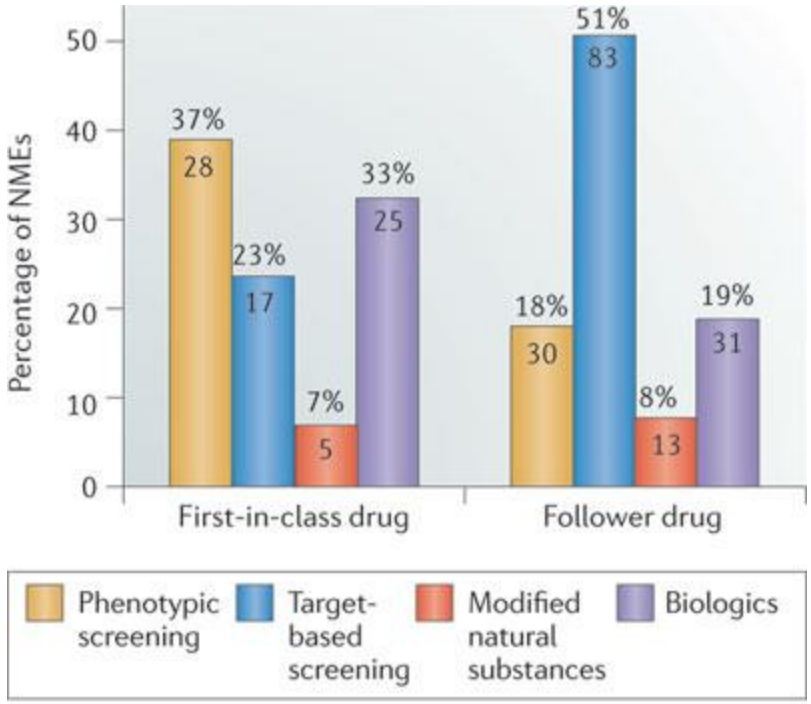


Swinney et al., Nat. Rev. Drug Discov., 2011

Phenotypic vs. Target-Based Drug Discovery for First-in-Class Medicines



New Drug Discovery Strategies



Swinney and Anthony, 2011

Biomarkers & Bioinformatics

Box 1 | **Biomarkers Definitions Working Group**[11]

Biological marker (biomarker)
A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention.

Clinical endpoint
A characteristic or variable that reflects how a patient feels or functions, or how long a patient survives.

Surrogate endpoint
A biomarker intended to substitute for a clinical endpoint. A clinical investigator uses epidemiological, therapeutic, pathophysiological, or other scientific evidence to select a surrogate endpoint that is expected to predict clinical benefit, harm, or lack of benefit or harm.

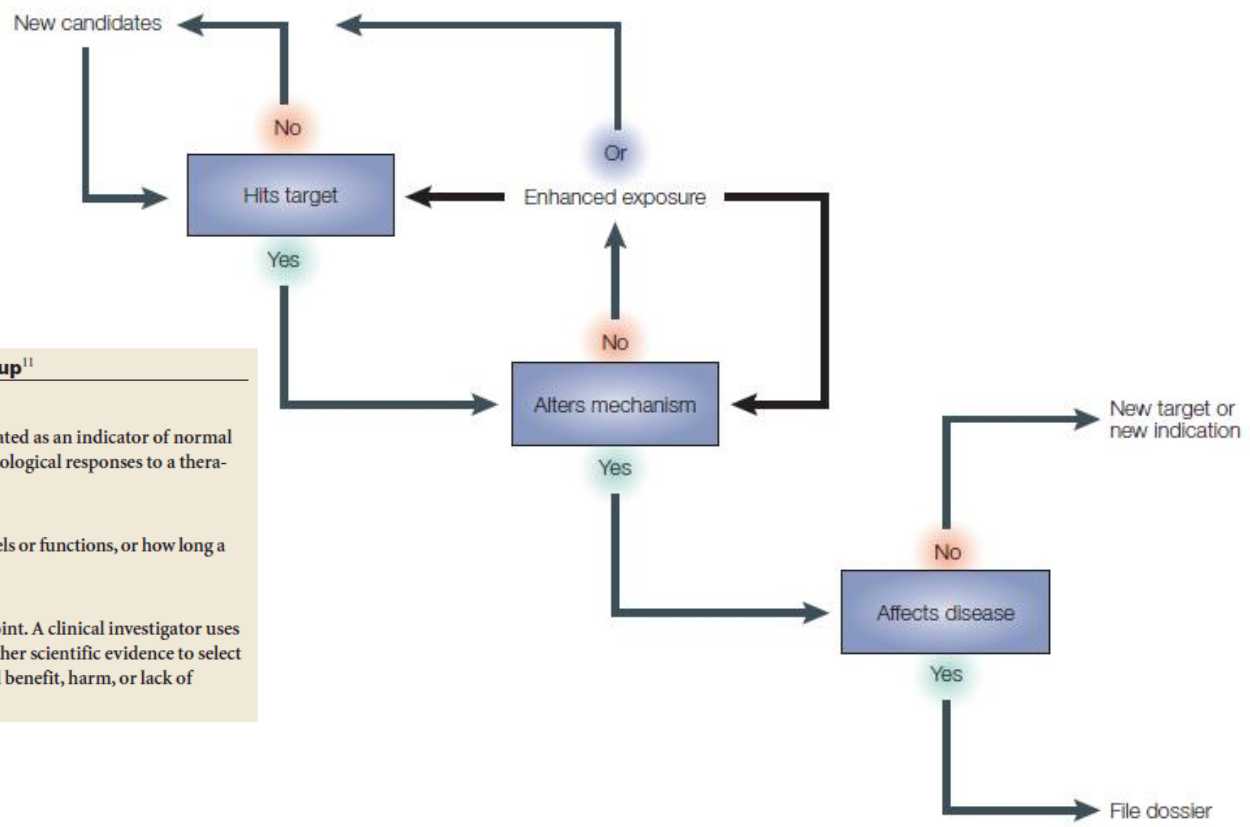


Figure 2 | **Biomarker categories: target, mechanism and clinical.** Biomarkers can be categorized into three distinct categories on the basis of their contribution to the logic of a clinical plan. Although they seem to parallel the three phases of drug development, the objective is to deploy them as early as possible, first to confirm hitting the target and then to test two concepts, namely, that hitting this target alters the pathophysiological mechanism and altering this mechanism affects clinical status.

Challenges of Pain Models

- Pain is a subjective, multidimensional experience
  - Sensory, emotional and cognitive components
  - Difficult to incorporate into a single animal model
  - Pain is clinically heterogeneous
  - Many preclinical models assess pain using reflex assays – not the case clinically
- Complex pathophysiology – acute and chronic
- “CNS plasticity” – central reorganization
- Substrates for pain likely involve a number of pathways and mechanisms – neuroinflammatory, channels, cytokines, GPCRs – likely not a single-target approach
- Number of significant clinical failures
  - NK-1 Antagonists

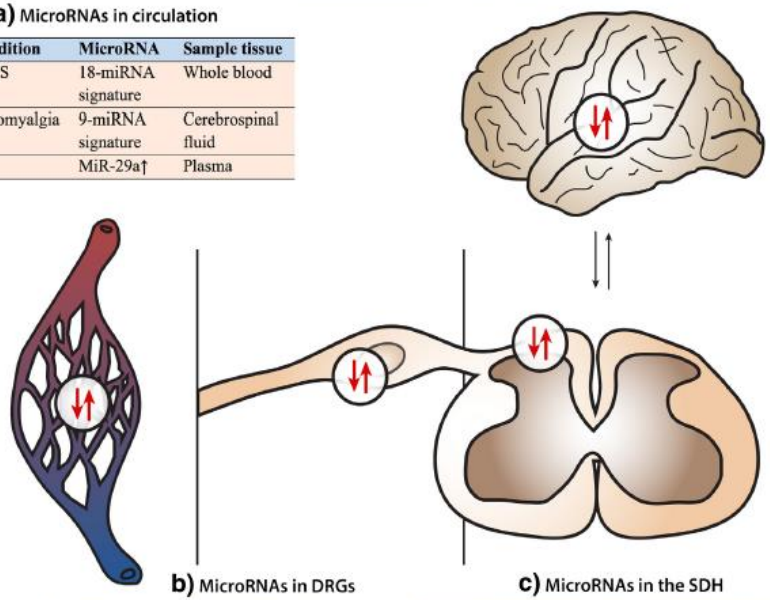
MicroRNAs as Biomarkers of Pain Conditions

d) MicroRNAs in the brain

Condition	MicroRNA	Gene target
Inflammatory pain	MiR-200b, MiR-429↓	DNMT3a
Neuropathic pain	MiR-155↓	C/EBP*↑

a) MicroRNAs in circulation

Condition	MicroRNA	Sample tissue
CRPS	18-miRNA signature	Whole blood
Fibromyalgia	9-miRNA signature	Cerebrospinal fluid
IBS	MiR-29a↑	Plasma



b) MicroRNAs in DRGs

Condition	MicroRNA	Gene target
Inflammatory pain	MiR-134↑	MOR1
Neuropathic pain	MiR-183↓	CACNA1D*

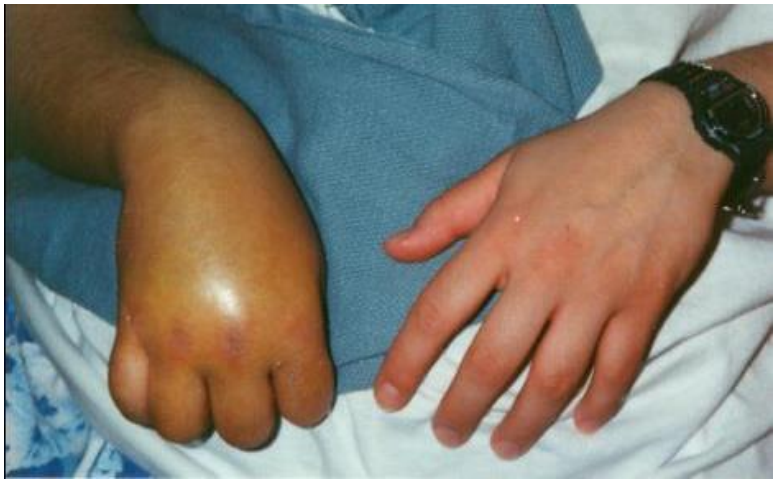
c) MicroRNAs in the SDH

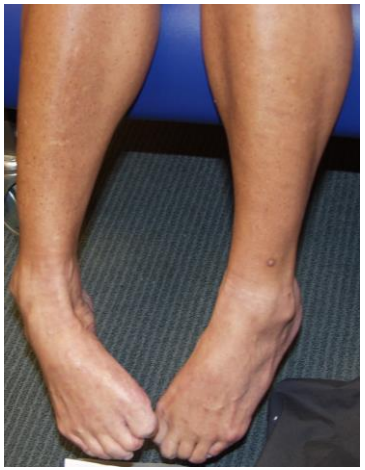
Condition	MicroRNA	Gene target
Inflammatory pain	MiR-181a↑	GABRA1
	MiR-124↓	MECP2
Neuropathic pain	MiR-29a↓	CACNA1C
	MiR-23b↓	NOX4

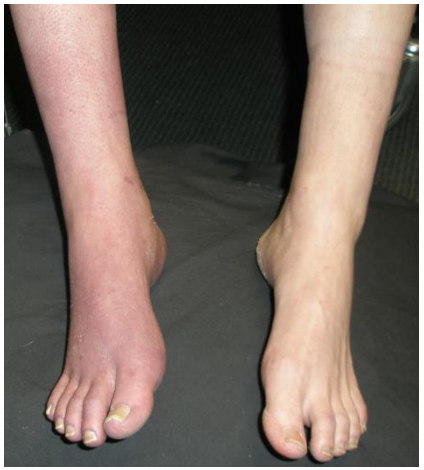
- MicroRNAs are emerging as pivotal players in pain
- Represent potential biomarkers and therapeutic targets
- Have the potential to engage multiple targets

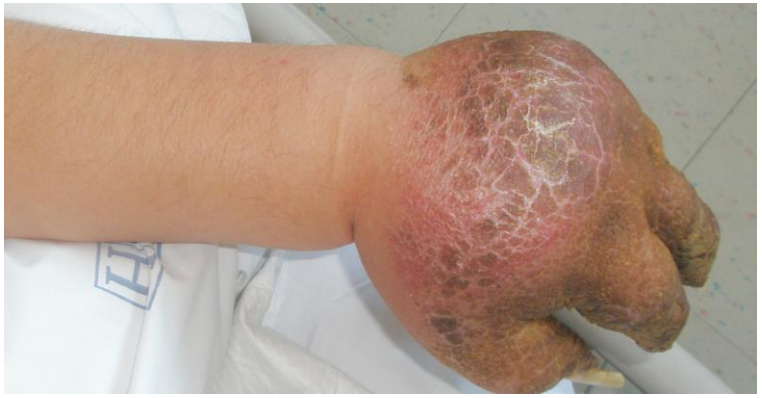
Andersen et al., 2014

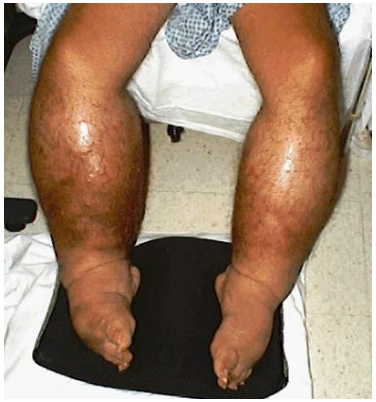
Features of CRPS – Edema, color change, dystonia

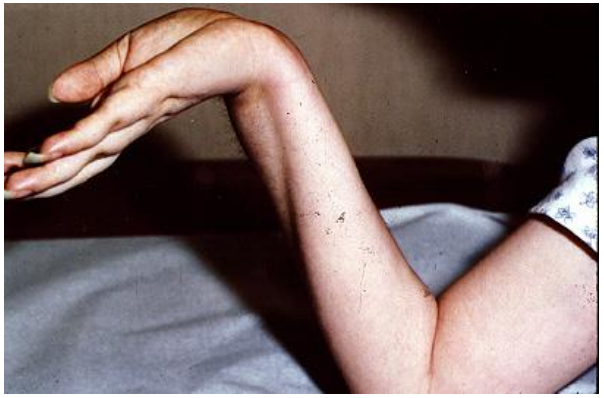












Bioinformatics prediction indicates putative miR-939 binding sites in mRNAs involved in pain and inflammation

Bioinformatics prediction by TargetScan and/or miRBase

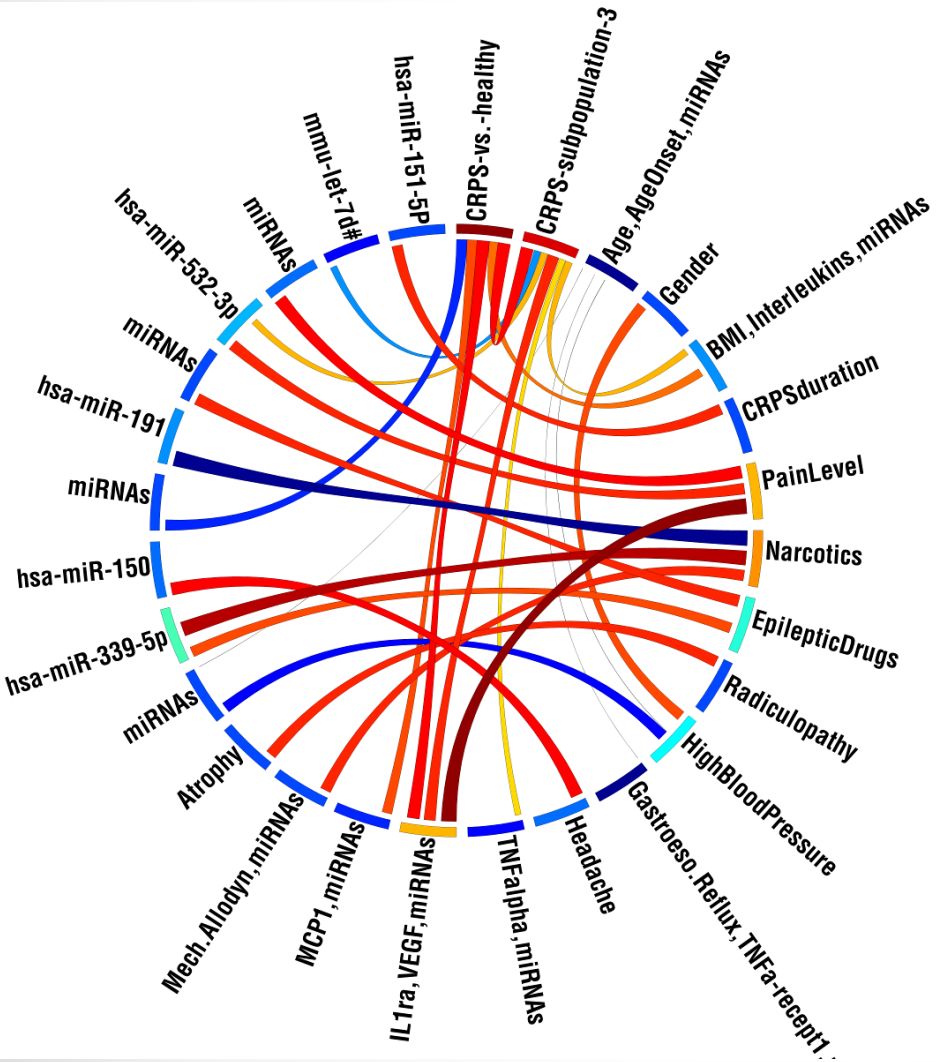
TNF-α	**tumor necrosis factor alpha**
TNFAIP1	**Tumor necrosis factor alpha induced protein 1**
iNOS	**Inducible nitric oxide synthase**
VEGFA	**vascular endothelial growth factor A**
IL-6	**interleukin-6**
NFκB	**nuclear factor kappa B**
SCN4a	**Sodium channel, voltage-gated, type IV, alpha subunit**
OPRM1	**opioid receptor mu -1**

Rationale: Modulating the levels of one miRNA capable of targeting several genes and can amplify a pro-inflammatory signal transduction cascade

Ajit et al., Unpublished

DREXEL UNIVERSITY College of Medicine
Department of Pharmacology and Physiology

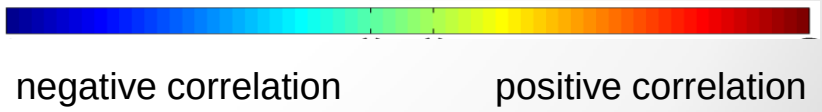
Circos diagram showing the correlation of selected parameters and miRNAs



The nodes along the circle are colored by the total strength of correlation of the corresponding variable

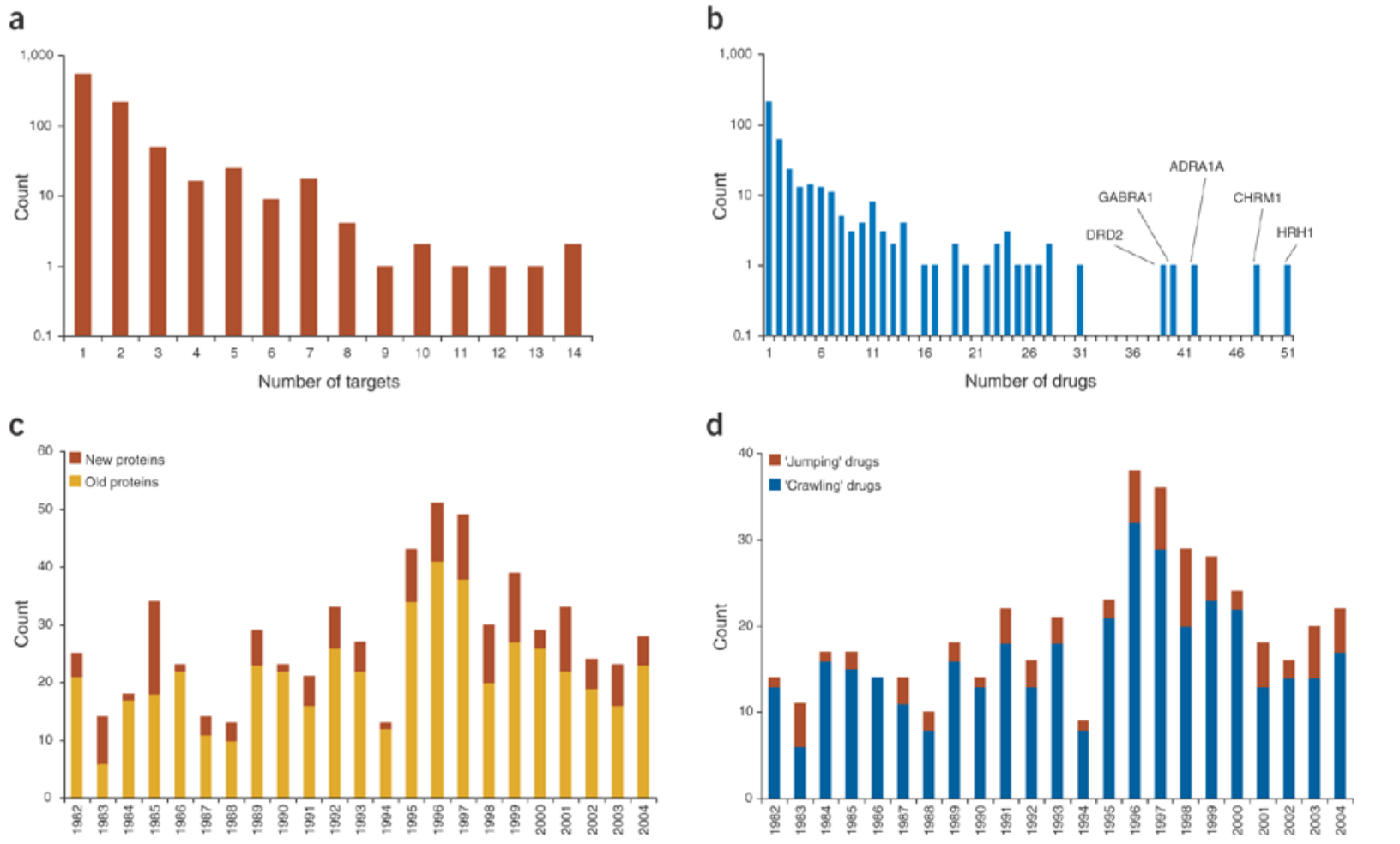
Strong negative correlations shown in dark blue (e.g., narcotics vs. hsa-miR-191).

Strong positive correlations are shown in dark red (e.g., pain level vs. "IL1Ra, VEGF, miRNAs")



Orlova et al. 2011

Distribution of Drugs and Drug Targets



Yildrum et al., 2007. Nat Rev. Drug Discov.

Polypharmacology

"The experimental and computational tools of systems biology, network pharmacology and chemical biology offer hope that combinations of two or more targets can be identified which when modulated would be predicted to lead to a greater beneficial effect on disease compared with targeting a single protein".

J.G. Cumming et al. Potential strategies for increasing drug-discovery productivity. Future Med. Chem. 2014, ***6****: 515-527.*

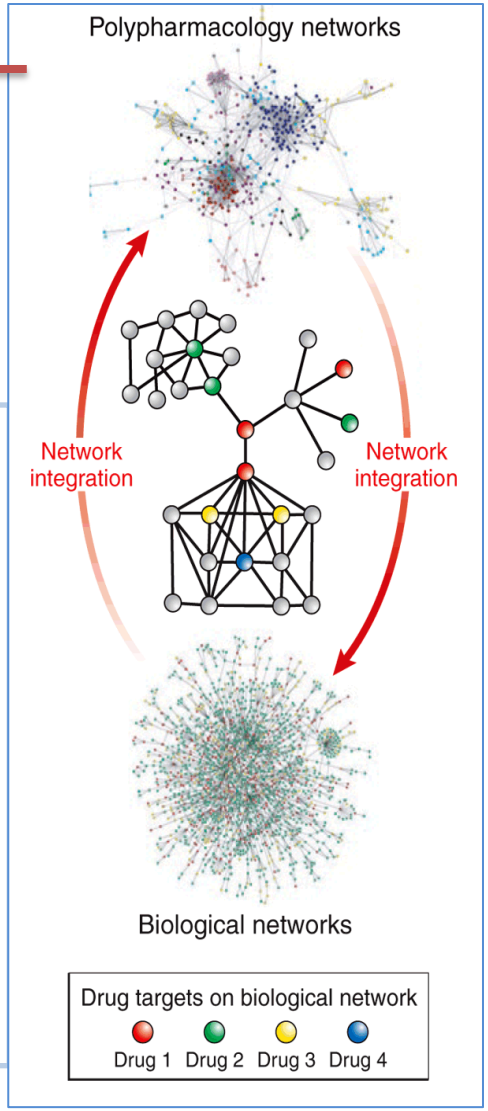
Multi-target Approaches, Systems and Network Pharmacology

Multitarget drug discovery projects in CNS diseases: quantitative systems pharmacology as a possible path forward

Hugo Geerts & Ludo Kennis, 2014 Future Medicinal Chemistry

Systems Pharmacology: An opinion on how how to turn the impossible into grand challenges Hans V. Westerhoff[1,2,3,*], Shintaro Nakayama[2], Thierry D.G.A. Mondeel[1], Matteo Barberis[1]

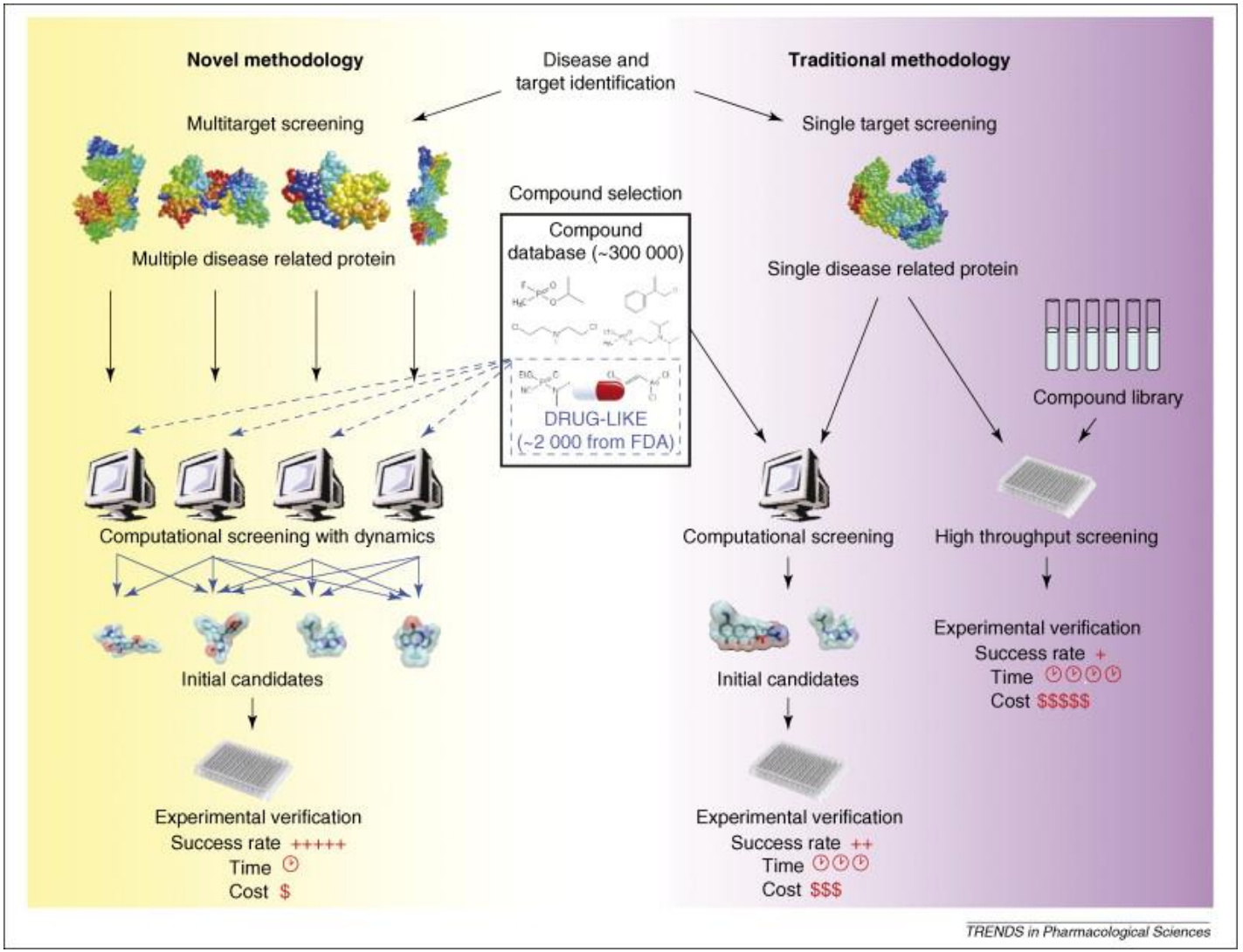
A pharmacology that hits single disease-causing molecules with a Single drug … is not going to be effective … a great many diseases are systems biology diseases; complex networks of some hundred thousand types of molecule, determine the functions that constitute human health, through nonlinear interactions. Malfunctions are caused by a variety of molecular failures at the same time; rarely the same variety in different individuals … Few molecules cause disease single-handedly and few drugs will cure the disease all by themselves.



Drug Discovery Today: Technologies, 2015

Hopkins Nat. Biotech., 2007

Computational Multi-target Screening



Jenwitheesuk et al., 2008

ACS Medicinal Chemistry Letters

Viewpoint

pubs.acs.org/acsmedchemlett

Four Lessons from Global Health Drug Discovery: Medicine for an Ailing Industry?

Richard L. Elliott*

Bill & Melinda Gates Foundation, P.O. Box 23350, Seattle, Washington 98102, United States

ABSTRACT: In recent years, the pharmaceutical industry has faced many challenges to its business model, undergoing tremendous change and turmoil to survive. Are there any lessons to be drawn from drug discovery focused on Global Health, where there is little market incentive?

Yogi Berra: "We made too many wrong mistakes"

Richard L. Elliott: "We are not very good at picking drug targets"

Lesson #1: Go after compounds, not targets.

Lesson #2: Some things, such as chemical libraries and HTS hits should be pre-competitive.

Lesson # 3: Be open-minded and not afraid to take risks.

Lesson #4: Have a long-term strategic vision and stick with it.

General Conclusions

- Drug discovery and development starts with identification of the target
- There are a variety of ways to attempt to validate the target and increase the probability of success
- Target-based approaches along with phenotypic approaches both provide valuable information
- Most diseases and disorders are complex and single target approaches are not always viable or successful; means to develop multi-targeted approaches using computational and network biology are of growing importance
- Complex, heterogeneous diseases and disorders require a systems biology approach. There is patient heterogeneity, different etiology diverse comorbidities - all requiring the need for more integrative approaches to understanding the pathophysiology and the appication of effective pharmacology

Thank you!

May you live a long pain-free life

Center for Health Policy at BROOKINGS

Improving Productivity in Pharmaceutical Research and Development: The Role of Clinical Pharmacology and Experimental Medicine

Center for Health Policy
The Brookings Institution

The Embassy Row Hotel • Washington, DC
July 28, 2015

Optimizing Target & Compound Selection- Nonclinical Safety Perspective

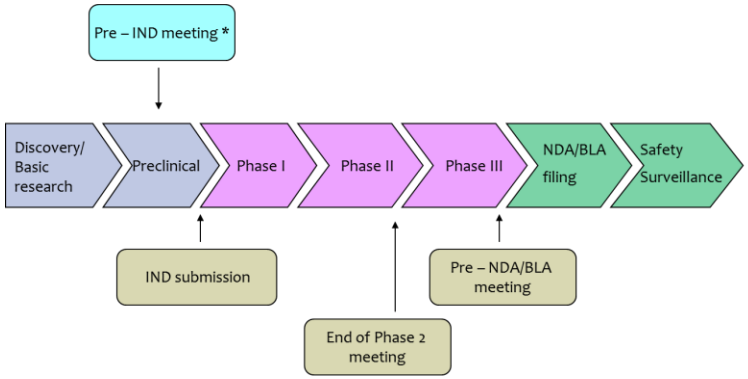
Karen Davis-Bruno PhD

FDA/CDER/OND

Associate Director Pharmacology & Toxicology

Supportive Nonclinical Studies

- Pharmacology/Safety pharmacology
- Repeat dose toxicity (rodent, non-rodent)
  - Test species based on human PD/PK similarity
- Genotoxicity (in vitro, in vivo)
- Developmental & Reproductive (DART)
  - Fertility
  - Embryo-fetal developmental
  - Pre-/Post-natal development
- Carcinogenicity



Adequate Nonclinical Studies Provide

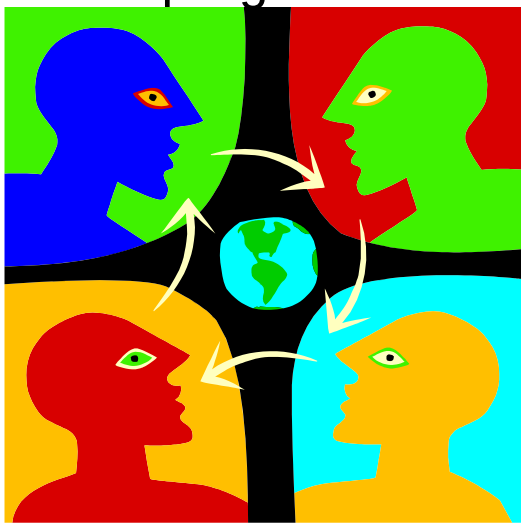
- Understanding of MOA
- Establish exposure (dose) response relationship
- Relationship to duration & extent of systemic exposure
- Identification of target organs & characterization of toxic effects
- Assess potential reversibility of toxic effects
- Extrapolate to potential human risk
- Estimate safe starting dose/regimen, route for clinical trials including FIH [21 CFR 312.23(a)(8)]
- Identify parameters for clinical safety monitoring & guide patient eligibility
- Assist in management of risk

Nonclinical Paradigm Shift

- From observational/reactive approach
  - Animal toxicity to mechanistic risk assessment
  - Selection for safety (no risk approach)
  - Limited candidate selection for development
- Into an integrative predictive/proactive approach
  - MOA/-Omics/in silico/in vitro/in vivo
  - Verify and confirm approach to risk assessment
  - Management of product risk

Changing the nonclinical development paradigm

- Reinforce knowledge of efficacy:
  - Pharmacodynamics
    - Biology-receptors/signal transduction cascades (cross talk), molecular target involvement in disease, disease progression & human variability
  - Pharmacokinetics
    - Target distribution
    - Exposure (dose) response
- Reinforce knowledge of safety:
    - Understand species differences
    - Models with improved human predictivity
- Improve multidisciplinary interactions cross-talk & advances



❖ Personalized medicine experience: Humans don't always predict humans because they differ in their response to therapeutics

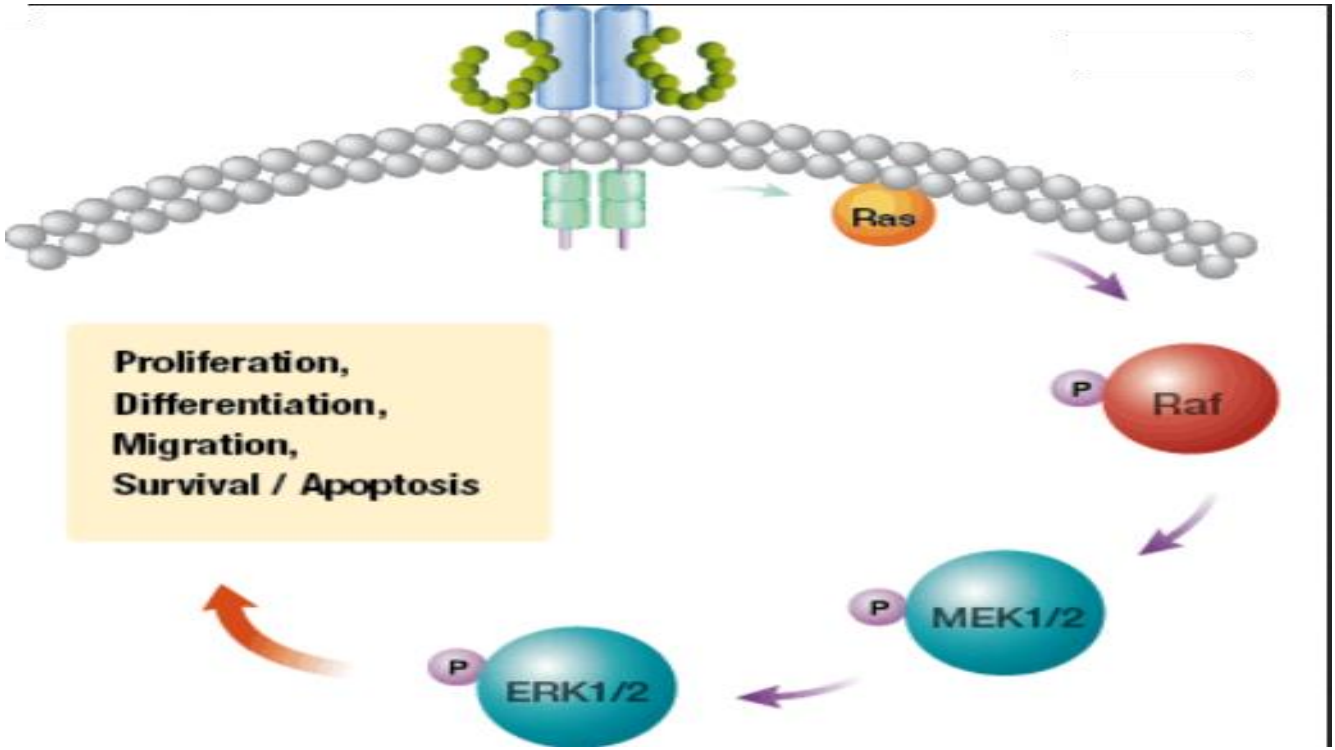
High Attrition Rates-Why?

- Insufficient screening for lead candidates
- Inadequate clinical paradigms
- Inadequate predictivity of POC/safety from nonclinical models
  - Healthy, normal animal model used for predictivity
  - Susceptibility/sensitivity of model & patient population
    - Comorbidities e.g. contractility, cardiomyopathy not readily identified
- Customize tox studies to better address these factors
    - Better use of secondary pharm follow-up MOA
- Effective management of risk rather than predictivity for no risk
    - More candidates for development, less attrition

Case Study-Anti-Cancer MEK Inhibitors

Ras proteins can activate signaling pathways that lead to cell proliferation, differentiation, migration, survival, and apoptosis.

Researchers are testing drugs that target the MEK protein, which acts downstream from Ras, to disrupt cancer cell growth and survival.



Useful mechanism for developing oncology drugs

Risk/Benefit MEK Inhibitors

- Kinase inhibitors CV adverse effects despite favorable anti-cancer risk/benefit
  - Age, co-morbidity risk of CV events
- Use of secondary pharmacology
  - MEK I associated with HF
  - Normal animal model for general toxicity
    - *Don't incorporate comorbidity factor of concern*
  - Normotensive Wistar rat + MEK I results in LVF decrement by echocardiography but variable response
  - Spontaneously hypertensive rat (SHR) have a decrement in LV ejection fraction at baseline compared to Wistar + MEK I results in robust, uniform ↓ LVF
  - If hypertension is a ppt factor for ↓LVF induced by MEK I can you control BP and avoid ΔLVF?
    - Lisinopril (ACE I) will normalize BP in SHR & prevent ↓LVF

Center for Health Policy at BROOKINGS

Improving Productivity in Pharmaceutical Research and Development: The Role of Clinical Pharmacology and Experimental Medicine

Center for Health Policy
The Brookings Institution

The Embassy Row Hotel • Washington, DC
July 28, 2015

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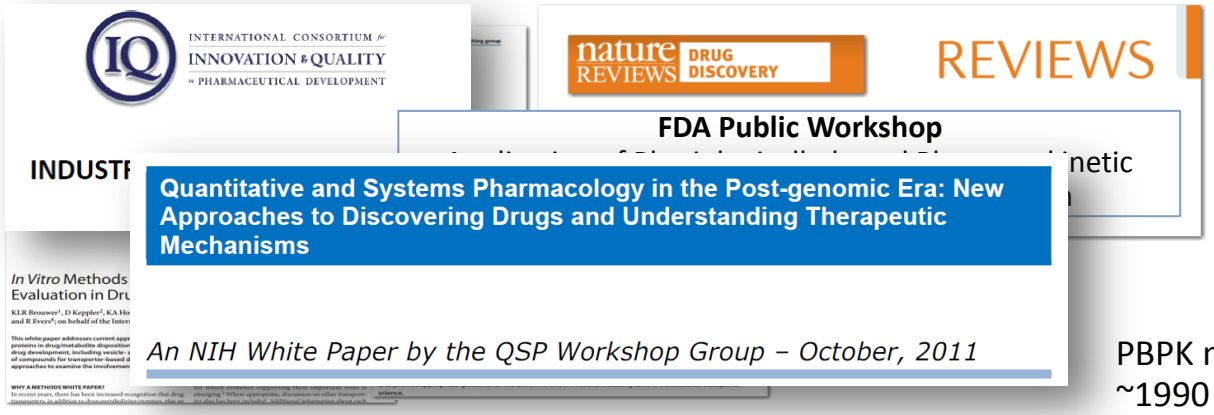
Optimizing Target and Compound Selection to Enhance Early Stage Decision-Making

Volker Fischer

July, 2015

Progress in Science and Technology Enables Mechanistic Understanding and Quantitative Translational Modeling and Decisions



Human Hepatocytes ~1985

Recombinant Enzymes ~1988

PBPK modeling ~1990

1st DDI Guidance 1996

SimCYP DDI modeling ~2000

MS in DMPK ~1990

LIMS

Basic Robotics

Electronic Lab Notebooks

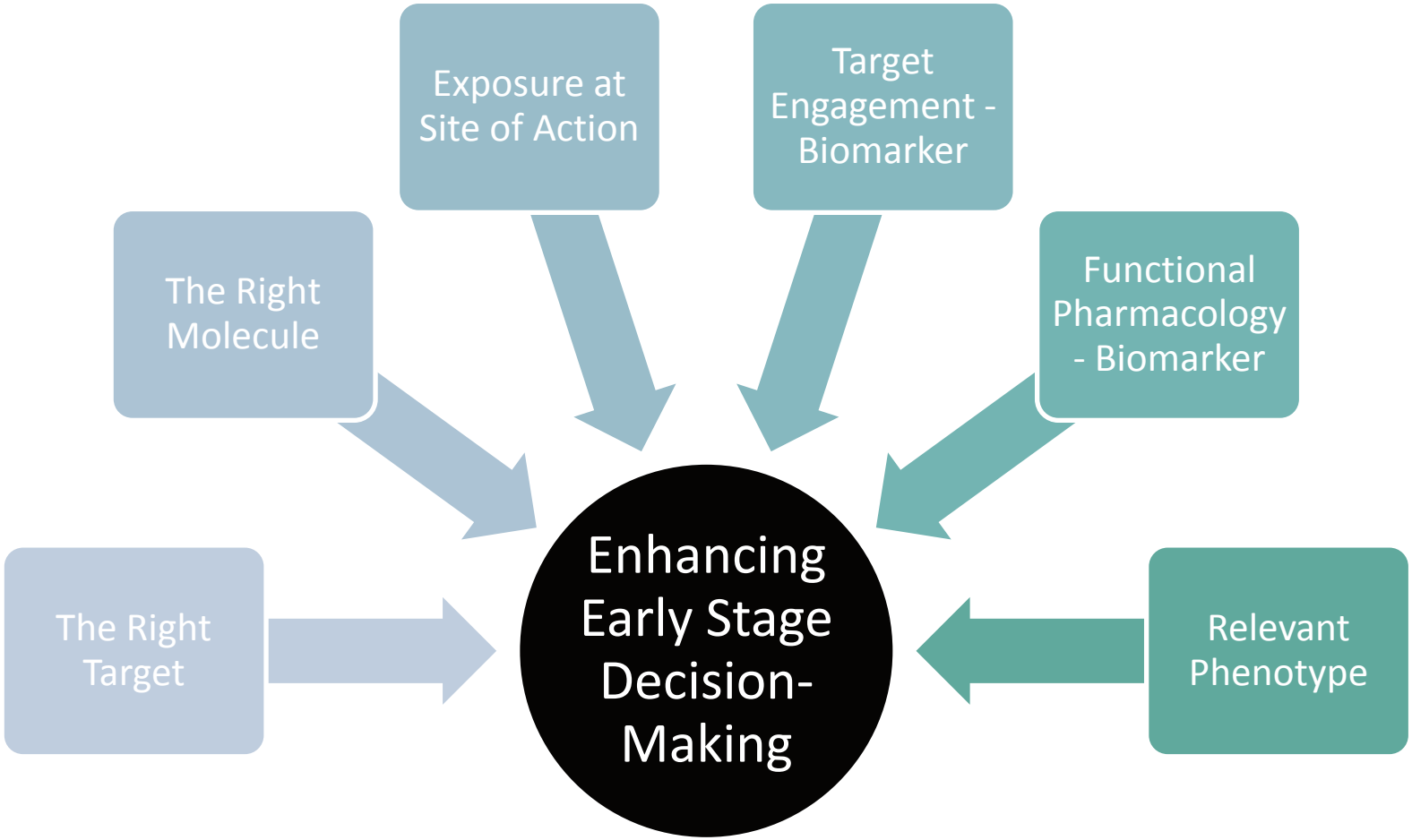
Transporter quantification and scaling

DDI Guidance incl Transporter 2012

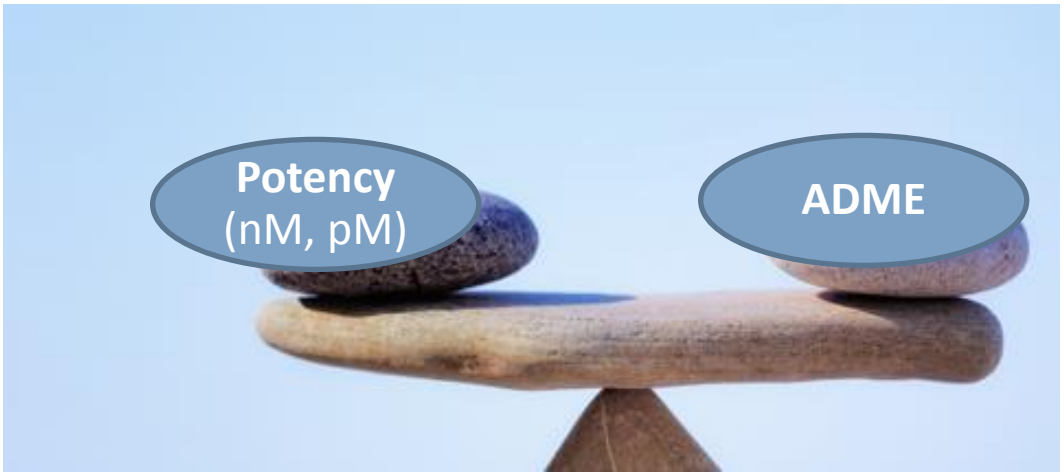
PBPK Guidance in progress

QSP emerging across pharma

Key Scientific Questions for Early Decision-Making



The Right Compound – Balancing Potency and ADME for Lowest Dose



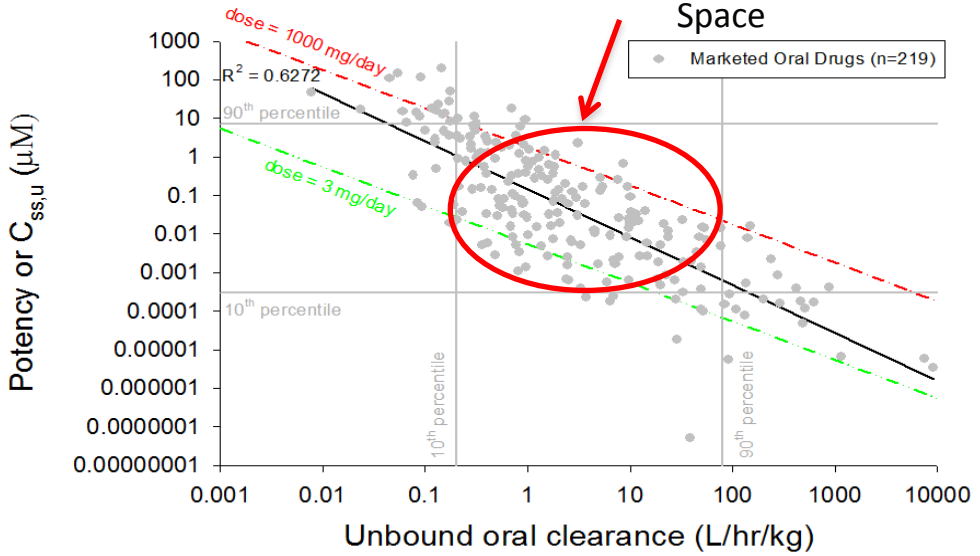
$$\text{Efficacious dose} \propto \frac{AUC_{eff,u} \times CL_{int,u} \times \text{target tissue impairment}}{f_a \times f_g}$$

High Throughput Screen:

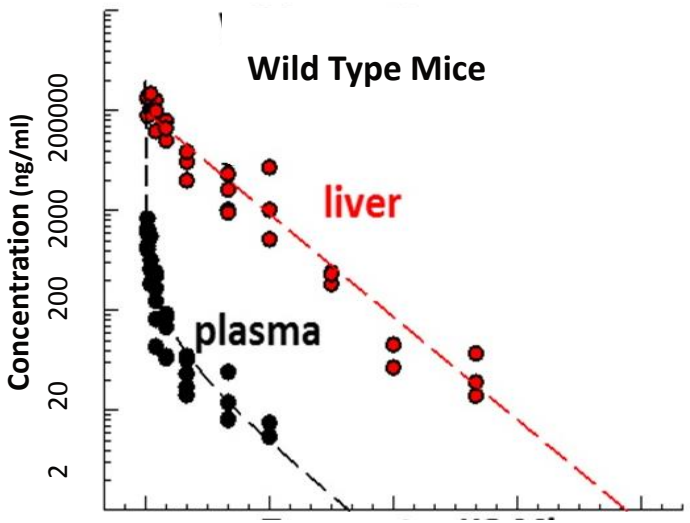
- **Dissolution**
- **Permeability**
- **Unbound Clearance**

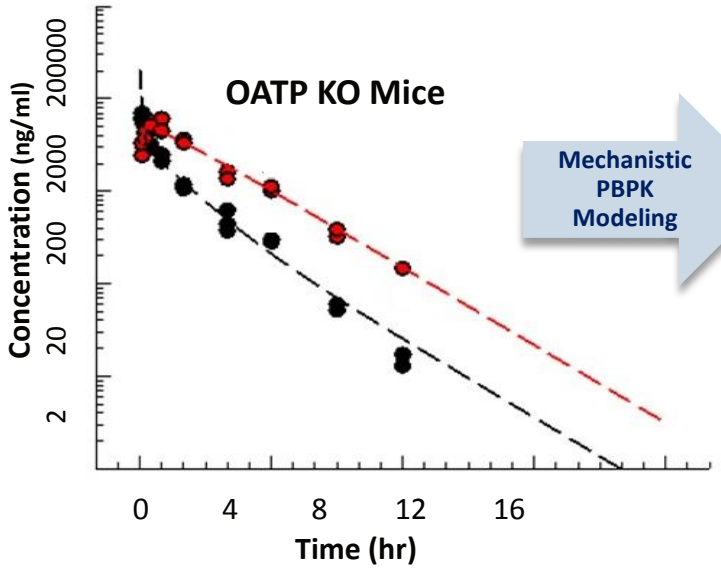
- Increased productivity due to standardized work-flow
- More compounds in drug-like space
  - 2009-2010= 62%
  - 2011-2013= **86%**

Established Biopharmaceutical Space

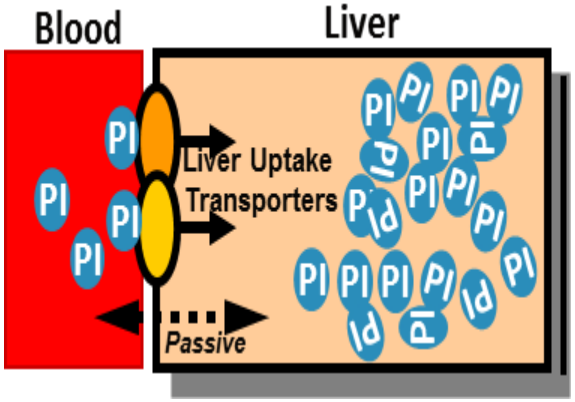


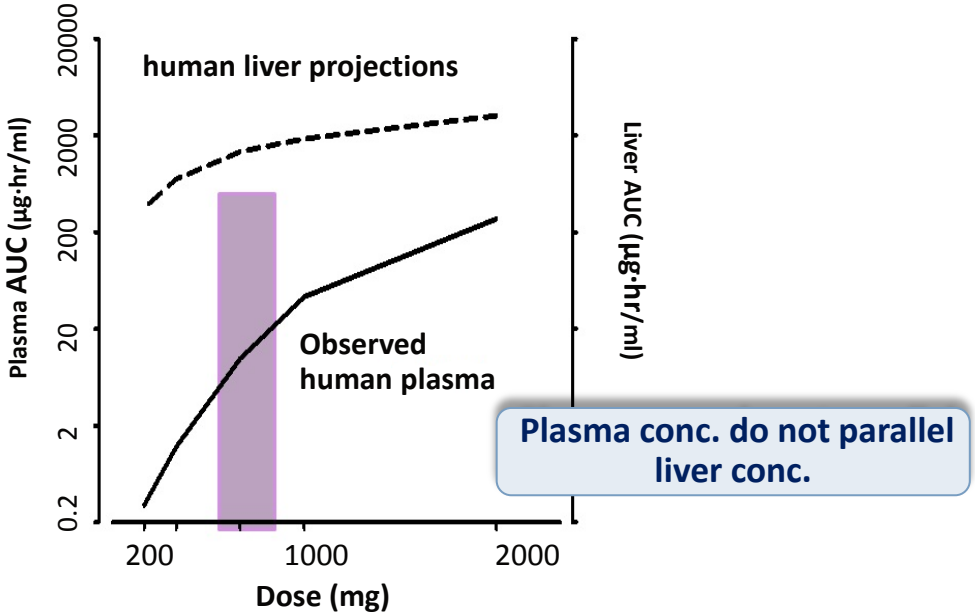
Exposure at Site of Action – Human Dose Predictions by PBPK Based on Projected Liver Concentrations





Mechanistic PBPK Modeling

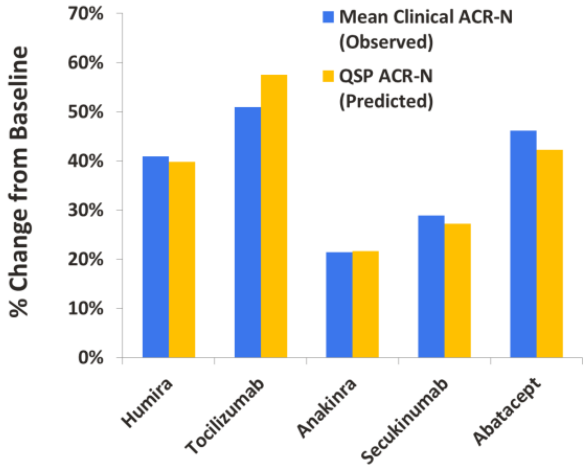




Plasma conc. do not parallel liver conc.

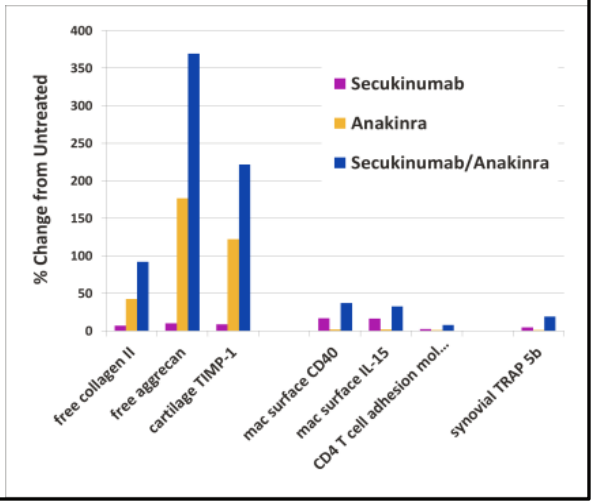
The Right Target and Target Engagement – Identification of Potential Synergy and Biomarkers of Combination Therapy by Quantitative Systems Pharmacology (QSP). IL-1β/IL-17 Case Study.

Model Qualification

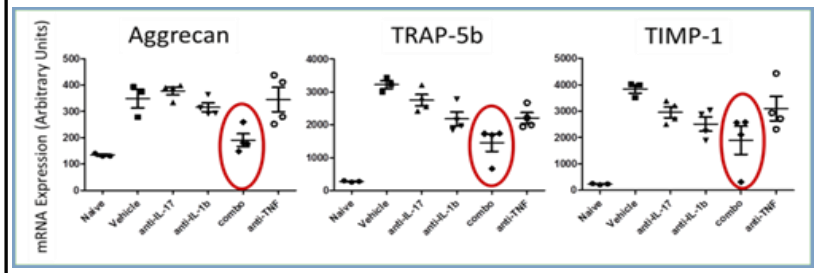


Biomarker Identification:

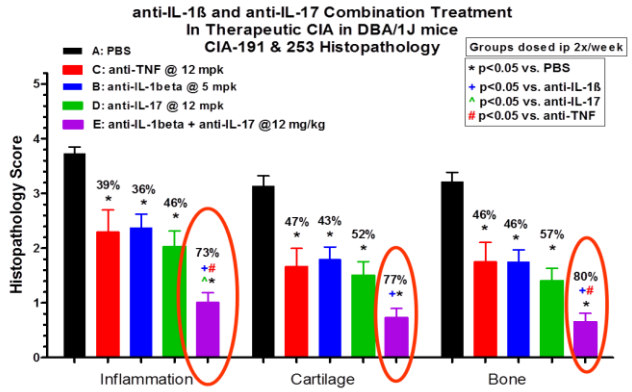
-free collagen,
-free aggrecan
-TIMP-1



Gene expression in DBA-1 CIA mice



In Vivo Pharmacology: Combination shows significant effect on inflammation, cartilage and bone

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Center for Health Policy at BROOKINGS

Improving Productivity in Pharmaceutical Research and Development: The Role of Clinical Pharmacology and Experimental Medicine

Center for Health Policy
The Brookings Institution

The Embassy Row Hotel • Washington, DC
July 28, 2015

Improving productivity in pharmaceutical research an development
Brookings, Washington DC, 28th July 2015

Session 1: Optimizing target and compound selection to enhance early stage decision-making

PERSPECTIVE

Piet van der Graaf

Editor-in-Chief
CPT: Pharmacometrics & Systems Pharmacology

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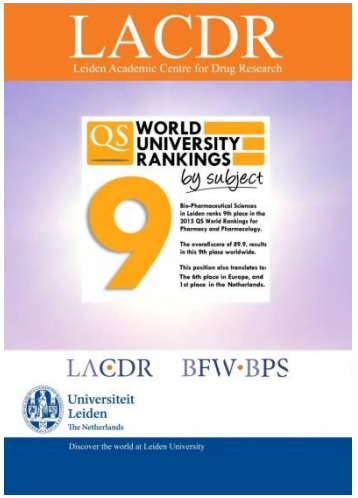
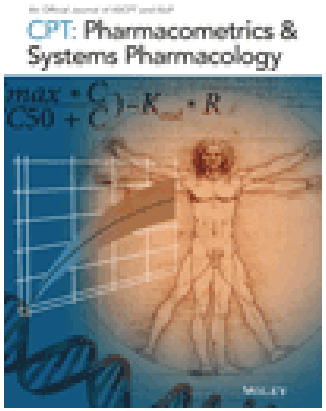
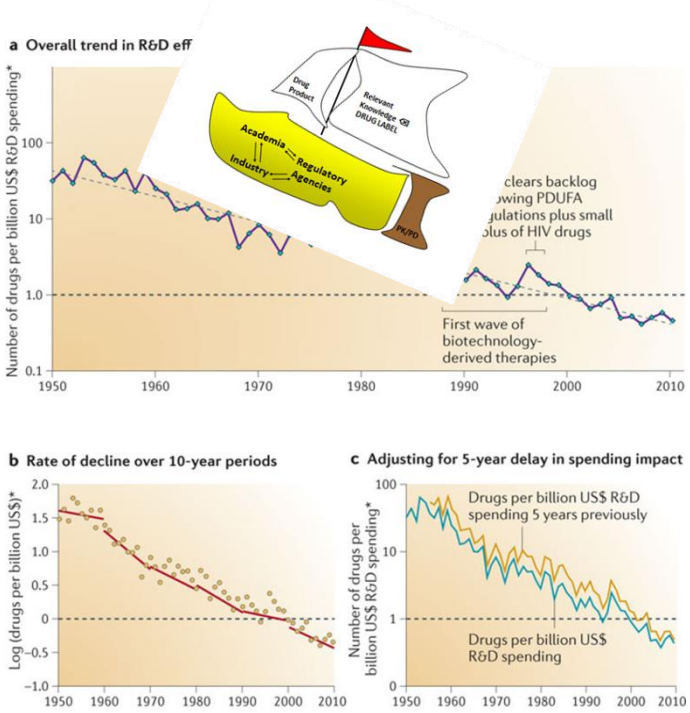




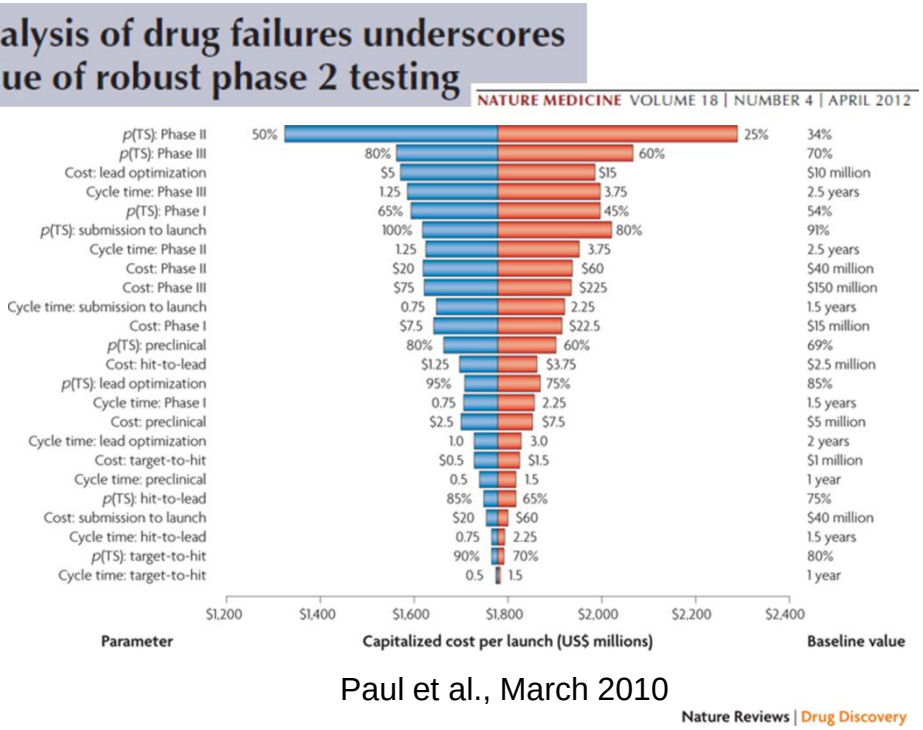
LACDR

XenologiQ

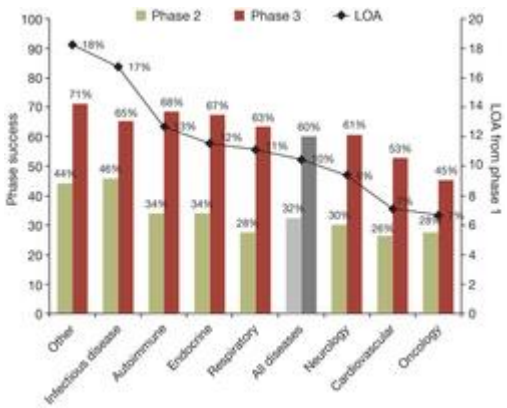
piet@xenologiq.com



Scannell et al.
Nature Reviews Drug Discovery 11, 191-200 (March 2012)



Paul et al., March 2010



Hay et al., Nature Biotech. 2014

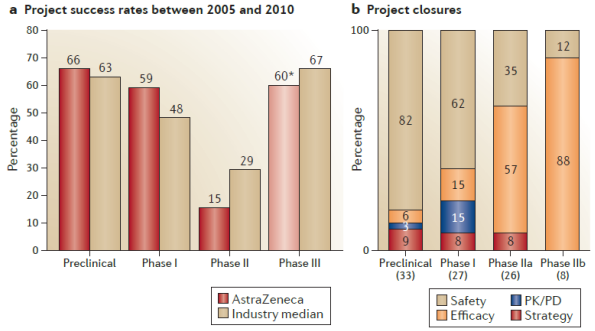
NATURE REVIEWS | DRUG DISCOVERY

OUTLOOK

VOLUME 13 | JUNE 2014 | 419

Lessons learned from the fate of AstraZeneca's drug pipeline: a five-dimensional framework

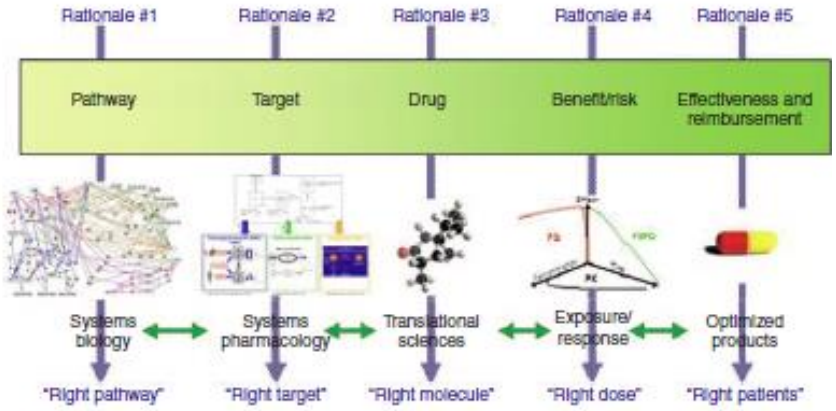
David Cook, Dearg Brown, Robert Alexander, Ruth March, Paul Morgan, Gemma Satterthwaite and Menelas N. Pangalos



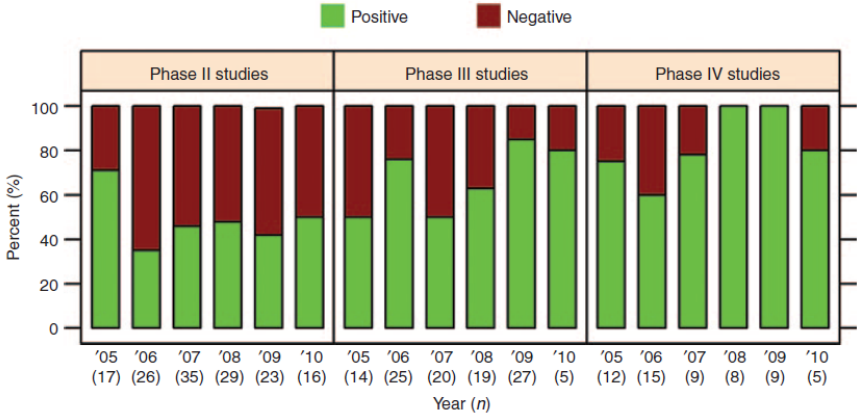
VOLUME 93 NUMBER 6 | JUNE 2013 | www.nature.com/cpt

Model-Based Drug Development: A Rational Approach to Efficiently Accelerate Drug Development

PA Milligan[1], MJ Brown[2], B Marchant[3,10], SW Martin[1], PH van der Graaf[4,1], N Benson[4,11], G Nucci[5], DJ Nichols[5], RA Boyd[6], JW Mandema[7], S Krishnaswami[6], S Zwillich[8], D Gruben[2], RJ Anziano[2], TC Stock[9] and RL Lalonde[6]



The evolution of model-based drug development (MBDD). Adapted from ref. 2.



Can the flow of medicines be improved? Fundamental pharmacokinetic and pharmacological principles toward improving Phase II survival

Drug Discovery Today • Volume 17, Numbers 9/10 • May 2012

Paul Morgan[1], Piet H. Van Der Graaf[1,2], piet.van.der.graaf@pfizer.com, John Arrowsmith[3], Doug E. Feltner[4], Kira S. Drummond[5], Craig D. Wegner[6] and Steve D.A. Street[7]

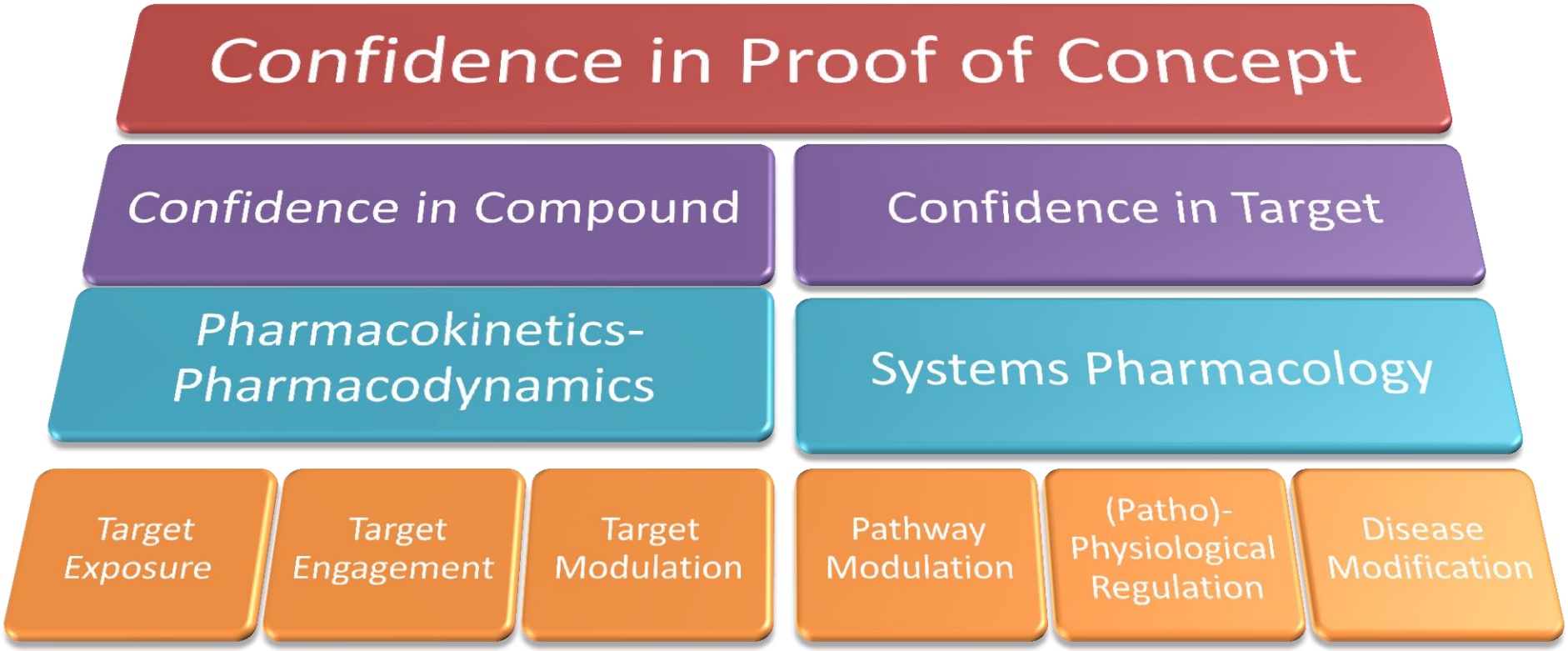
Definition of the three Pillars of survival

For a development candidate to have potential to elicit the desired effect over the necessary period of time, three fundamental elements need to be demonstrated:

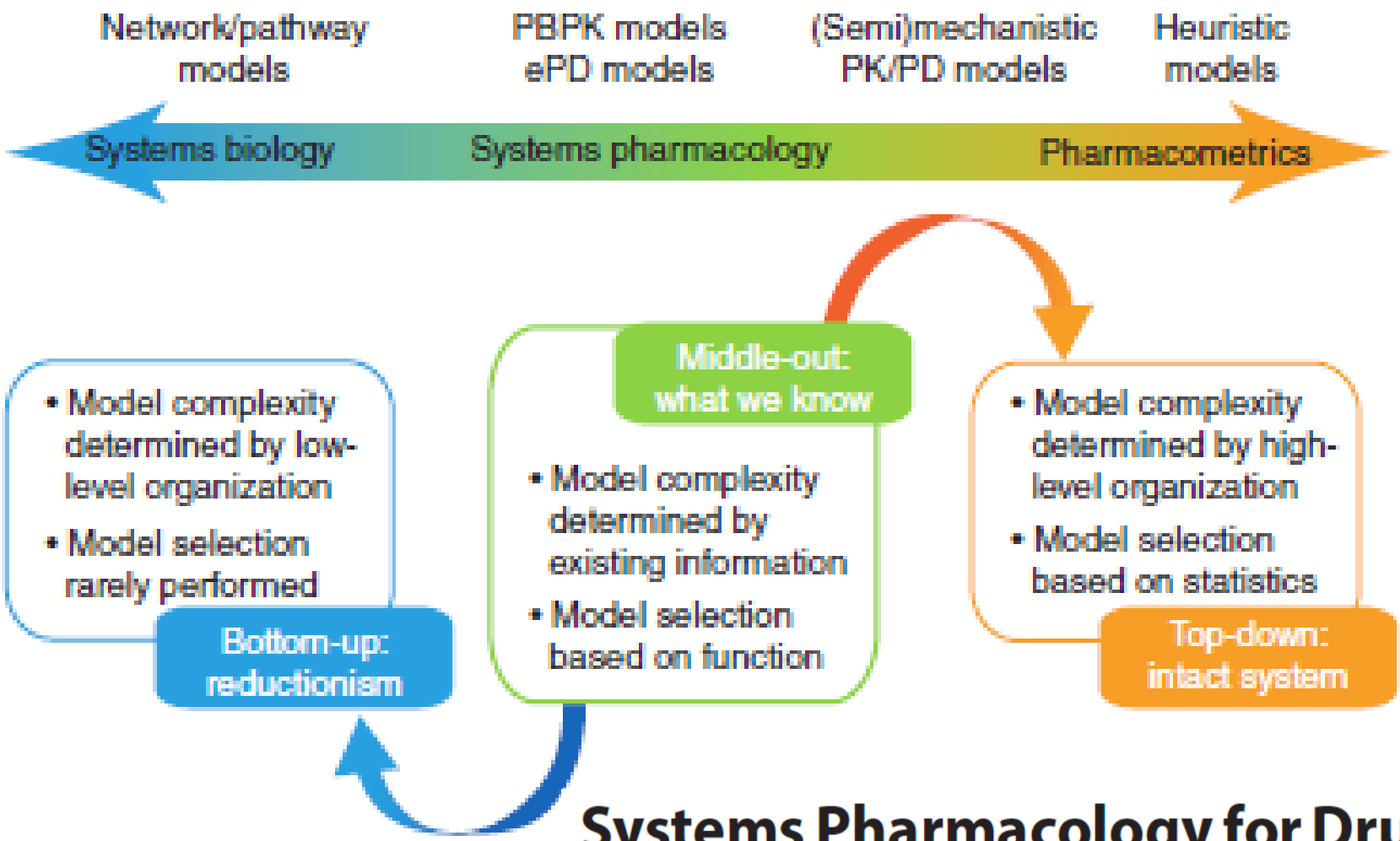
i. Exposure at the target site of action over a desired period of time
ii. Binding to the pharmacological target as expected for its mode of action
iii. Expression of pharmacological activity commensurate with the demonstrated target exposure and target binding

QSP CONGRESS EUROPE 2015

Translational PKPD and Systems Pharmacology to improve Phase 2 success



Vicini & Van Der Graaf CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 93 NUMBER 5 | MAY 2013



Systems Pharmacology for Drug Discovery and Development: Paradigm Shift or Flash in the Pan?

P Vicini[1] and PH van der Graaf[2,3]

QSP IMPLEMENTATION: Some Points for discussion

1. Why, What & When:
   - Define the question and potential impact
   - Scope and Timing

2. How:
   - Training and Education
   - New data requirements
     - *Biomarkers*
     - *Biomeasures*
   - Model validation
   - (Precompetitive) collaboration
     - *Models*
     - *Databases*

QSP IMPLEMENTATION: Some Points for discussion

1. Why, What & When:
   - Define the question and potential impact
   - Scope and Timing

2. How:
   - Training and Education

Mathematical Pharmacology
from 30 Nov 2015 through 4 Dec 2015

Venue: Lorentz Center@Snellius

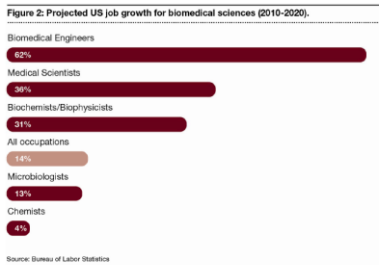
Lorentz center

- **Description and aim** of the workshop
- **Registration** form
- **Participants**
- Scientific organizers:
  Gianne Derks (Guildford, United Kingdom)
  Pinky Dua (Cambridge, United Kingdom)
  Piet Hein van der Graaf (Leiden, The Netherlands)
  Coen van Hasselt (Leiden, The Netherlands)
  Vivi Rottschäfer (Leiden, The Netherlands)
- Workshop Coordinator: **Aimée Reinards,** Tel: 071 5275400

Organizational Log-in (restricted)

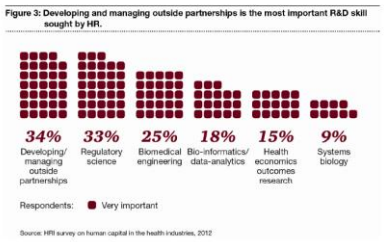
PwC Health Research Institute

New chemistry:
Getting the biopharmaceutical talent formula right



PwC Health Research Institute – New chemistry: Getting the biopharmaceutical talent formula right
Chart Pack

The life sciences industry is looking for new skills among scientists.



PwC Health Research Institute – New chemistry: Getting the biopharmaceutical talent formula right
Chart Pack

http://www.pwc.com/us/newchemistry

From: owner-nmusers@globomaxnm.com on behalf of Graaf, P.H. van der <p.vandergraaf@lacdr.leidenuniv.nl>
To: nmusers@globomaxnm.com
Cc:
Subject: [NMusers] OPENINGS IN COMPUTATIONAL DRUG DISCOVERY & DEVELOPMENT AT LACDR

LACDR

The Leiden Academic Centre for Drug Research (LACDR) is a leading institute dedicated to cutting-edge research and education in drug discovery and development. In the 2015 QS World University R
worldwide in the field of Pharmacy and Pharmacology. LACDR has a world-leading reputation in the field of translational, mechanism-based pharmacokinetic-pharmacodynamic (PKPD) modelling as well as
the areas of systems pharmacology, metabolomics, medicinal chemistry, biology and toxicology. Building on this basis we are expanding further into computational areas related to Pharmacology, Bio
bedside". In light of this strategic growth in Computational Drug Discovery & Development, we are continuously looking for top talent to strengthen our research and education and currently have the follow

ASSISTANT PROFESSOR COMPUTATIONAL SYSTEMS PHARMACOLOGY

http://werkenbij.leidenuniv.nl/vacatures/wetenschappelijke-functies/15-207-vacature-universiteit-leiden-assistant-professor-computational-systems-pharmacology.html

POSTDOC COMPUTATIONAL BIOLOGY

http://werkenbij.leidenuniv.nl/vacatures/wetenschappelijke-functies/15-194-vacature-universiteit-leiden-postdoc-in-computational-biology.html

POSTDOC MATHEMATICAL PHARMACOLOGY

http://werkenbij.leidenuniv.nl/vacatures/wetenschappelijke-functies/15-169-vacature-universiteit-leiden-postdoc-mathematical-pharmacology.html

POSTDOC QUANTITATIVE CLINICAL PHARMACOLOGY

http://werkenbij.leidenuniv.nl/vacatures/wetenschappelijke-functies/15-212-vacature-universitei-leiden-postdoc-quantitative-clinical-pharmacology.html

PHD COMPUTATIONAL BIOLOGY

http://werkenbij.leidenuniv.nl/vacatures/phd-posities/15-193-vacature-universiteit-leiden-phd-candidate-in-computational-biology.html

PHD QUANTITATIVE CLINICAL PHARMACOLOGY

http://werkenbij.leidenuniv.nl/vacatures/phd-posities/15-213-vacature-universiteit-leiden-phd-candidate-in-quantitative-clinical-pharmacology.html

PHD COMPUTATIONAL CHEMISTRY

http://werkenbij.leidenuniv.nl/vacatures/phd-posities/15-209-vacature-universiteit-leiden-phd-candidate-computational-chemistry.html

QSP IMPLEMENTATION: Some Points for discussion

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     - *Biomarkers*
     - *Biomeasures*

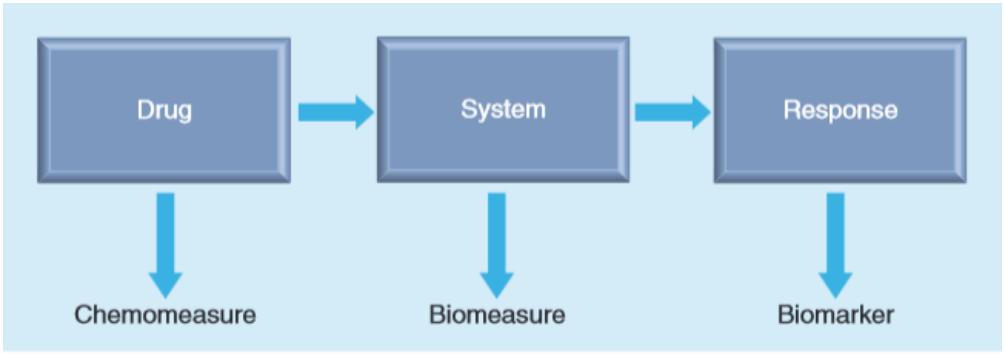
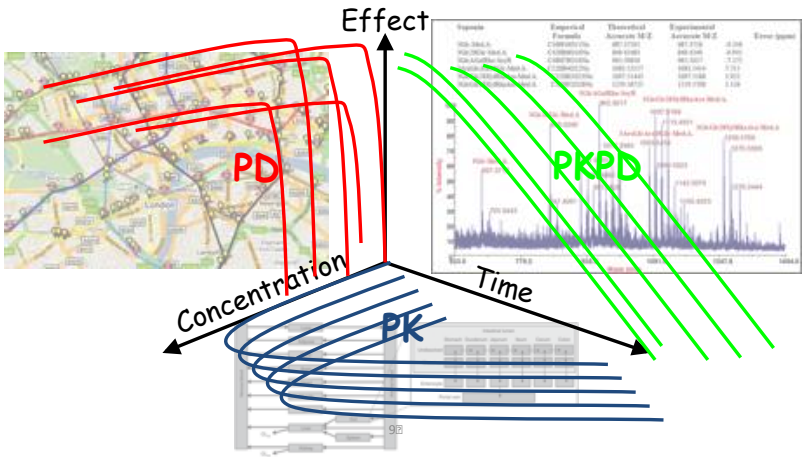


Figure 1. Three types of measures underpinning the development of

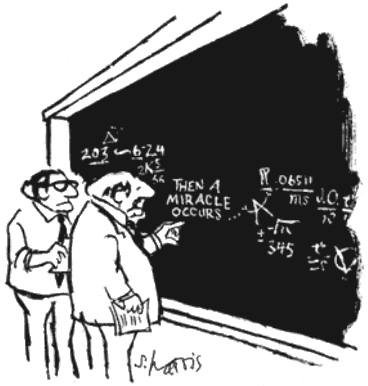
Bioanalysis (2012) 4(10), 1143–1145

Multivariate PBPK-PD



QSP IMPL “Validating” Systems Pharmacology Models? ssion

1. Why,
   - De
   - Sc
2. How:
   - Tra
   - Ne
   -
   - Biomeasures
   - Model validation
   - (Precompetitive) collaboration
     - *Models*
     - *Databases*



Models are psychologically most appealing when they succeed, but logically strongest when they fail

After Yates (1978), *Am. J. Physiol.* 3, R159-160

…all models are wrong, but some are useful

Wrong models are most useful?

Citation: CPT Pharmacometrics Syst. Pharmacol. (2014) 3, e101; doi:10.1038/psp.2013.77

www.nature.com/psp

PERSPECTIVE

Evaluating Systems Pharmacology Models Is Different From Evaluating Standard Pharmacokinetic–Pharmacodynamic Models

B Agoram[1]

Based on the author's recent experience, there appears to be some confusion regarding the steps required to qualify a systems pharmacology model as adequate for the intended purpose. This manuscript outlines the model evaluation approach used in the author's recent publication[1] on the systems pharmacology of a 5-lipoxygenase inhibitor and is an attempt to generate discussion on this topic within the pharmacometrics and systems pharmacology community.

CPT Pharmacometrics Syst. Pharmacol. (2014) **3**, e101; doi:10.1038/psp.2013.77; published online 19 February 2014

Citation: CPT: Pharmacometrics & Systems Pharmacology (2013) 2, e48; doi:10.1038/psp.2013.28

www.nature.com/psp

COMMENTARY

Negative Modeling Results: A Dime a Dozen or a Stepping Stone to Scientific Discovery?

B Hendriks[1]

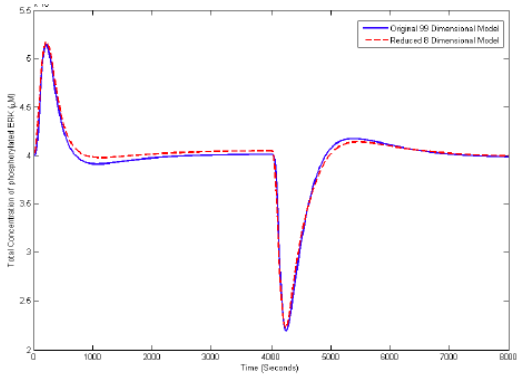
CPT: Pharmacometrics & Systems Pharmacology (2013) **2**, e48; doi:10.1038/psp.2013.28; advance online publication 12 June 2013

Systems pharmacology models, in general, tend to span multiple timescales bridging detailed mechanism with higher level responses or functional outputs. These features serve to put systems pharmacology models in a separate class that brings with it specific challenges, particularly in evaluating such work. When models are constructed on well-understood mechanisms but fail to match experimental data, in what cases should “negative modeling results” be considered scientific findings?

Summary of PhD Research

Tom Snowden

Supervisors: PH van der Graaf & MJ Tindall



QSP IMPLEMENTATION

Need for (precompetitive) collaboration

MODELS

REVIEW

The impact of mathematical modeling on the understanding of diabetes and related complications

I Ajmera[1,2], M Swat[1], C Laibe[1], N Le Novère[1,3] and V Chelliah[1]

Diabetes is a chronic and complex multifactorial disease caused by persistent hyperglycemia and for which underlying pathogenesis is still not completely understood. The mathematical modeling of glucose homeostasis, diabetic condition, and its associated complications is rapidly growing and provides new insights into the underlying mechanisms involved. Here, we discuss contributions to the diabetes modeling field over the past five decades, highlighting the areas where more focused research is required.

CPT: Pharmacometrics & Systems Pharmacology (2013) **2**, e54; doi:10.1038/psp.2013.30; advance online publication 10 July 2013

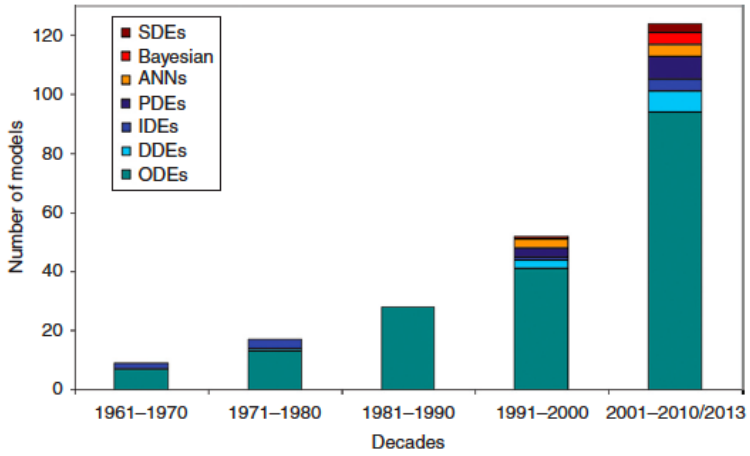


Figure 2 Modeling approaches vs. the number of models in relation to diabetes and associated complications, over the past five decades. There has been a significant increase in the number of models, as well as in the diversity of the modeling approaches applied toward addressing diabetes. ANNs, artificial neural networks; DDEs, delay differential equations; IDEs, integro-differential equations; ODEs, ordinary differential equations; PDEs, partial differential equations; SDEs, stochastic differential equations.

DATABASES

CPT: Pharmacometrics & Systems Pharmacology
An Official Journal of ASCPT and ISoP
Open Access

Article

Database -
A New Article Type in *CPT: Pharmacometrics & Systems Pharmacology*

Lang Li[1] and Piet H. van der Graaf[2]

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Center for Computational Biology and Bioinformatics, Department of Medical and Molecular Genetics, School of Medicine, Indiana University, Indianapolis, 46202, U.S.A.
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CPT: Pharmacometrics & Systems Pharmacology
An Official Journal of ASCPT and ISoP
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Citation: CPT Pharmacometrics Syst. Pharmacol. (2015) 00, 00; doi:10.1002/psp4.55

DATABASE

Organ Impairment—Drug–Drug Interaction Database: A Tool for Evaluating the Impact of Renal or Hepatic Impairment and Pharmacologic Inhibition on the Systemic Exposure of Drugs

CK Yeung[1,2], K Yoshida[3], M Kusama[4], H Zhang[3], I Ragueneau-Majlessi[2*], S Argon[2], L Li[3], P Chang[3], CD Le[3], P Zhao[3], L Zhang[3], Y Sugiyama[4] and S-M Huang[3*]

The organ impairment and drug–drug interaction (OI-DDI) database is the first rigorously assembled database of pharmacokinetic drug exposure data from publicly available renal and hepatic impairment studies presented together with the maximum change in drug exposure from drug interaction inhibition studies. The database was used to conduct a systematic comparison of the effect of renal/hepatic impairment and pharmacologic inhibition on drug exposure. Additional applications are feasible with the public availability of this database.

CPT Pharmacometrics Syst. Pharmacol. (2015) **00**, 00; doi:10.1002/psp4.55; published online on 0 Month 2015.

LACDR

Additional Material

Precompetitive Collaboration: Development of a Translational Systems Pharmacology Model for hERG-induced QT Prolongation

- Largest cross-company PKPD meta-analysis of placebo and reference agent data

- Demonstrates impact of preclinical PKPD in CV safety testing quantitatively:
  - High degree of cross-company conistency
  - 2 x more efficient
  - >>> reduction of false positives

- QT_CSP model established:
  - Scales in vitro→ preclinical in vivo → human
  - Scales to special populations (i.e. pediatrics)

Contents lists available at ScienceDirect

Journal of Pharmacological and Toxicological Methods

journal homepage: www.elsevier.com/locate/jpharmtox

Original article

Sensitivity of pharmacokinetic–pharmacodynamic analysis for detecting small magnitudes of QTc prolongation in preclinical safety testing

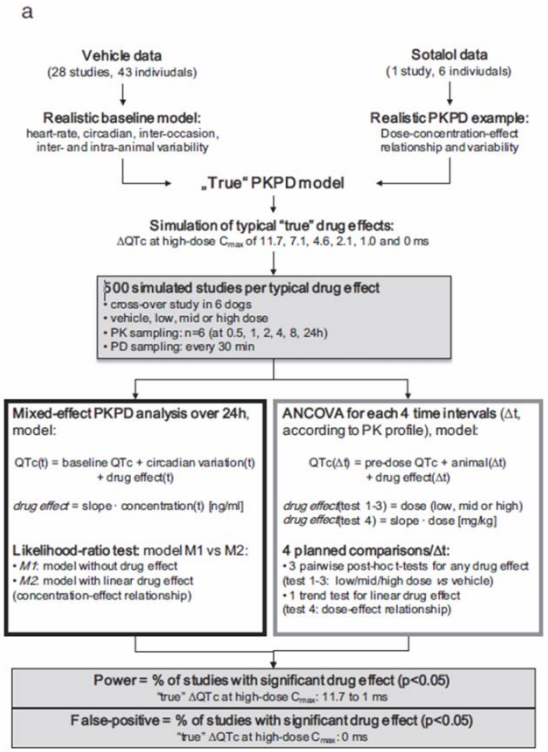
Verena Gotta [a], Frank Cools [b], Karel van Ammel [b], David J. Gallacher [b], Sandra A.G. Visser [c], Frederick Sannajust [d], Pierre Morissette [d], Meindert Danhof [a], Piet H. van der Graaf [a,*]

[a] Systems Pharmacology, Leiden Academic Center of Drug Research (LACDR), Leiden University, Leiden, The Netherlands
[b] Global Safety Pharmacology, Janssen Research & Development, Janssen Pharmaceutica NV, Beerse, Belgium
[c] Quantitative Pharmacology and Pharmacometrics, Merck Research Laboratories, Merck & Co., Inc., Upper Gwynedd, PA, US
[d] SALAR, Safety and Exploratory Pharmacology Department, Merck Research Laboratories, Merck & Co., Inc., West Point, PA,

Table 1
Study data characteristics (conscious telemetered dog).

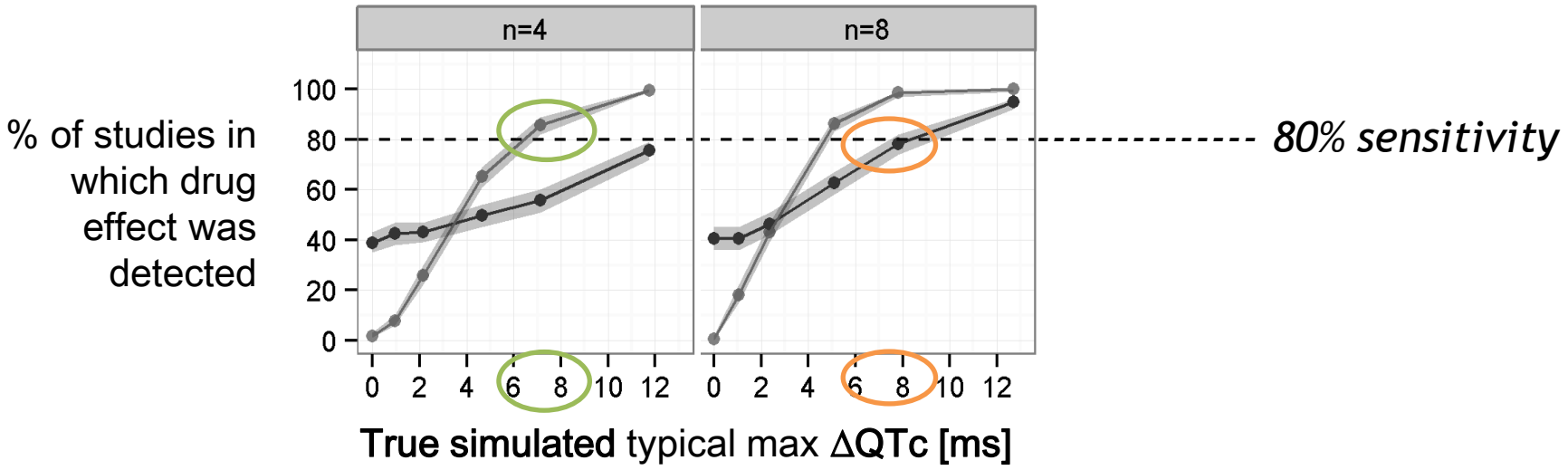
	Vehicle study data	Sotalol study data
Number of studies	28	1
Study durations [h]	22 (1.83–502)	23.5
Total number of individuals	43	6
Individuals per study (n studies)	6 (n = 18), 4 (n = 3), 2 (n = 2), 1 (n = 5)	
Studies per individual (n individuals)	1 (n = 10), 2 (n = 14), 3 to 8 (n = 19)	
Breed	Beagle dogs (CEDS, Mezilles, France)	Beagle dogs (CEDS, Mezilles, France)
Gender	Female	Female
Body weight [kg] median (range)	12.4 ± 0.9 (10.5–16.9)	12.0 (11.3–13.5)
Animal condition (number of studies)	Freely moving (18) Slinged (10)	Freely moving
Drug dose [mg/kg]	NA (only vehicle)	vehicle, 4, 8, 32 (administration in Latin-square design)
Route of administration	Oral: 23, i.v.: 3, s.c.: 2	oral
ECG sampling	Every 30 min[a]	Every 5 min[b]
PK sampling	NA (only vehicle)	12 samples, at 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 23 h

[a] Median over 10 consecutive beats, RR sampled 1–5 min before QT (average beat method) or median over 10 or 20 min as defined in the study protocol (Notocord-hem, KRN42a, Notocord, France).
[b] Median over 5 min (Notocord-hem, KRN42a, Notocord, France).



M&S impact in drug discovery & early development:
Doubling efficiency of *in vivo* resources

- **80% sensitivity** to detect **ΔQTc of 6-8 ms**
  - **PKPD (n=4)**
  - **ANCOVA (n=8)**
  - False positive rate: 1% (vs 39% ANCOVA)



Simplifying PKPD for routine application

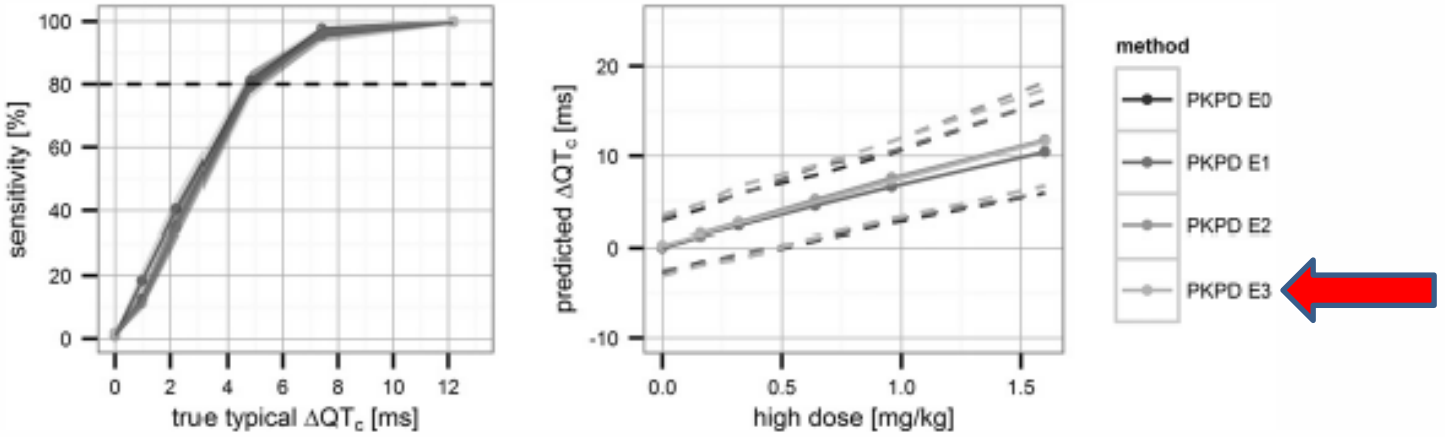
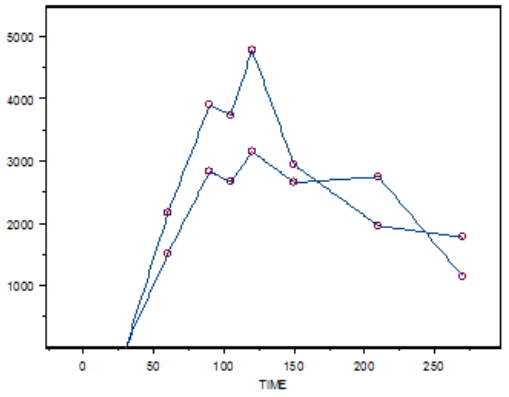


Fig. 4. Left: Sensitivity estimates (dots) with 95% Wilson confidence intervals (shaded areas) resulting from different PKPD analyses (all from the same original simulation scenario S0: n = 6 animals, terminal half-life = 6 h, individual QTc reporting every 30 min). Right: median effect predictions (dots) and 95% prediction intervals (dashed lines) at high-dose. E0: original analysis, i.e. concentration = individual model-based PK predictions (from 1-compartment model), E1: same as E0, but ignoring circadian variation, E2: concentration = typical model-based PK predictions (from 2-compartment model), E3: no PK modeling, concentration–individual interpolated concentrations.

Problem statement and Justification

- Frequently encounter issue that a PKPD model needs to be developed/simulated in the absence of a PK model:
  - PK data cannot be described by regular model:
    - Unusual profiles
    - Noisy/erratic data
  - PK profile generated by PBPK model:
    - May need PBPK output as input for PKPD simulations, however:
      - Subtle profile cannot be fitted by standard 1,2,3,..compartment model
- Often only interested in PK as input for PKPD:
  - Good description of individual profiles more relevant than actual (population) PK parameter estimates

'Connecting the dots' Expected result



British Journal of Pharmacology

DOI:10.1111/bph.13218
www.brjpharmacol.org

RESEARCH PAPER

Inter-study variability of preclinical *in vivo* safety studies and translational exposure–QTc relationships – a PKPD meta-analysis

V Gotta[1], F Cools[2], K van Ammel[2], D J Gallacher[2], S A G Visser[3], F Sannajust[4], P Morissette[4], M Danhof[1] and P H van der Graaf[1]

[1]*Systems Pharmacology, Leiden Academic Center of Drug Research (LACDR), Leiden University, Leiden, The Netherlands,* [2]*Global Safety Pharmacology, Janssen Research & Development, Janssen Pharmaceutica NV, Beerse, Belgium,* [3]*Quantitative Pharmacology and Pharmacometrics/Merck Research Laboratories, and* [4]*SALAR-Safety and Exploratory Pharmacology Department/Merck Research Laboratories, Merck & Co., Inc., Upper Gwynedd, PA, USA*

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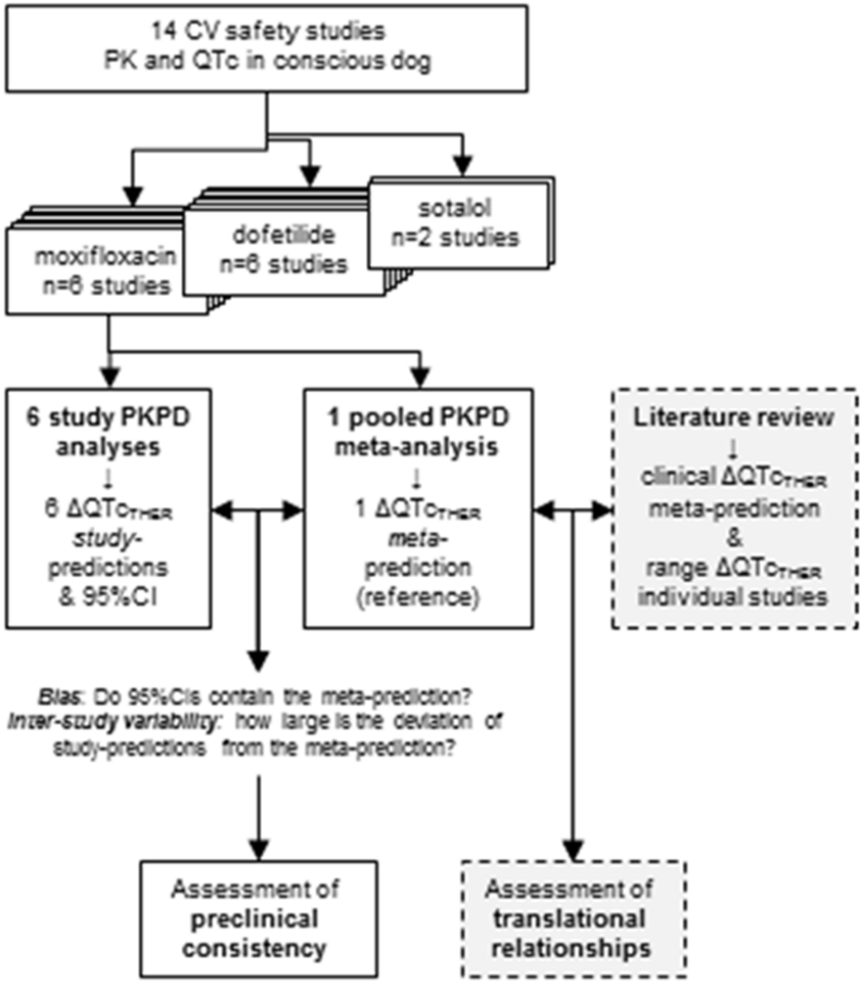
Received
11 March 2015
Revised
7 May 2015
Accepted
5 June 2015



A systems pharmacology model to explain developmental differences in sensitivity to drug-induced QT prolongation

Verena Gotta, Marc Pfister, John van den Anker, Piet H. van der Graaf

[1]*Systems Pharmacology, Leiden Academic Center of Drug Research (LACDR), Leiden University, Leiden, The Netherlands.*

[2]*University Children's Hospital Basel, University of Basel, Basel, Switzerland*

European Society for Developmental Perinatal and Pediatric Pharmacology (ESDPPP), Belgrade, 23-26th June 2015

1.1. Estimation of system-specific transduction parameters for translational preclinical–clinical scaling *(dofetilide)*

- maximal $\Delta QTc_{\%}$ via hERG-block: $E_{m,human} = E_{m,dog} = 28\%$ **from baseline**
- transducer ratio τ: $\tau_{human} = 2.4 \cdot \tau_{dog}$

Interpretation of τ : τ ~ hERG-channel/I_{kr}-density, and
$1/\tau$ ~ %hERG/I_{kr}-block leading to half-maximal ΔQTc

→ Equal $\Delta QTc_{\%}$ achieved in human at 60% lower hERG-block than in dog ($1/\tau = 26\%$ in human vs 62% in dog), explained by a **2.4 x higher hERG-channel density in human and/or I_{kr}-net contribution to cardiac repolarization**.

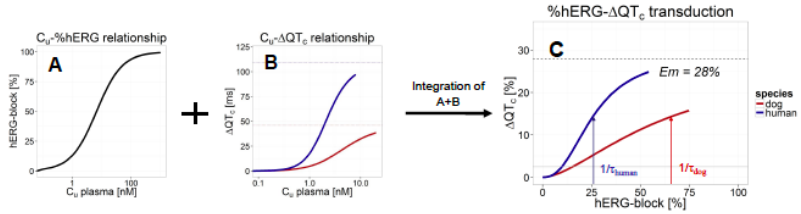


Fig.1: Pharmacodynamics of dofetilide in preclinical (consious dog[4]) and clinical setting (healthy men[5]). **A**: %hERG-block (from *in vitro* binding kinetic experiments) and **B:** ΔQTc (from *in vivo* studies). **C**: estimated transduction of hERG-block. C_u: unbound plasma concentration.

1.2. External evaluation of translational predictions *(sotalol & moxifloxacin)*

Good clinical predictions in adults and children were obtained (*<5-10 ms prediction discrepancy from clinical regression model until ΔQTc of 35 ms*). However, QTc- effects in neonates were under-predicted (*>20 ms prediction discrepancy*).

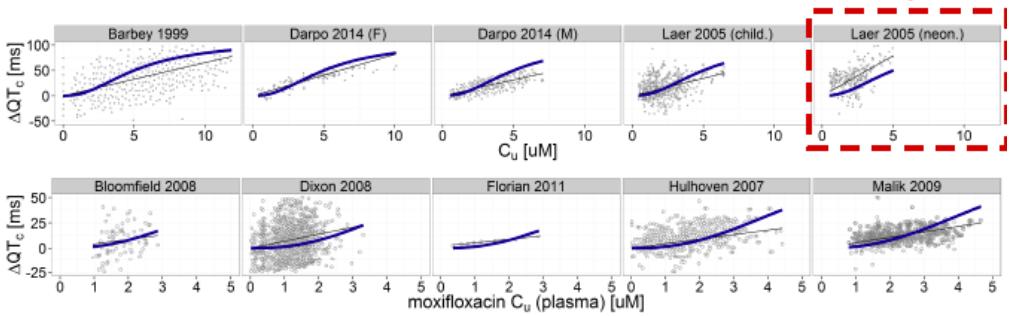


Fig.2: Translational predictions from preclinical data and system-specific scaling parameters only *(blue lines)* are contrasted with reported clinical ΔQTc from indicated references (*grey dots:* digitized observations. *black lines:* predictions from respective clinical regression model).

2. Refinement of system-specific transduction parameters for neonates

Re-estimated transducer ratio: $\tau_{neonates} = 1.77 \cdot \tau_{children}$

→ Higher sensitivity of neonates to drug-induced ΔQTc explained by a **1.77 x higher hERG-channel density and/or I_{kr}-net contribution to cardiac repolarization** than in older children (≈ adults), resulting in equal $\Delta QTc_{\%}$ at 43% lower hERG-block.

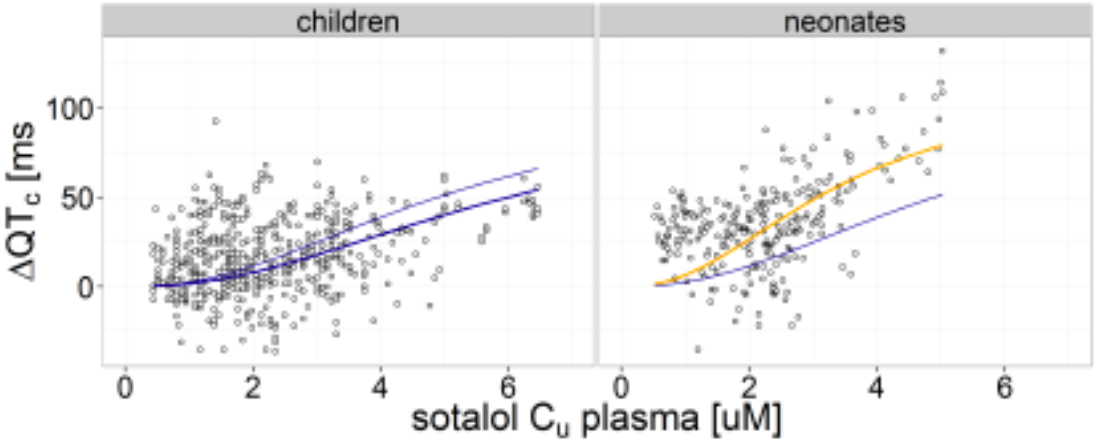


Fig.3: Observed pediatric ΔQTc (*dots,* digitized from Läer et al.[6]) after sotalol administration, contrasted with translational predictions for adults (*thin blue lines*) and refined predictions for children (***thick blue line***) and neonates (***orange line***). ΔQTc-pharmacodynamics in children and adults was very similar.

Center for Health Policy at BROOKINGS

Improving Productivity in Pharmaceutical Research and Development: The Role of Clinical Pharmacology and Experimental Medicine

Center for Health Policy
The Brookings Institution

The Embassy Row Hotel • Washington, DC
July 28, 2015

The Right Dose for the Right Patient: Challenges and Opportunities in Dose Optimization

Vikram Sinha, PhD

Conference on Improving R&D Productivity

Brookings Institution, Washington DC

July 28th 2015

Director, Division of Pharmacometrics
Office of Clinical Pharmacology
Office of Translational Sciences
CDER, USFDA

Disclosures and Acknowledgements

- Disclosures
  - The views expressed in this presentation are that of the speaker and do not reflect the official policy of the FDA. No official endorsement by the FDA is intended nor should be inferred.

- Contributors to the concept and content presented today
  - Division of Pharmacometrics
  - Office of Clinical Pharmacology and Office of Biostatistics
  - Examples - Review Teams; Publically disclosed

Session Goals

- Emphasize the importance of proper dose finding and dose-(exposure)- response characterization for successful drug development,
  - ➢ Approval, labelling, and lifecycle management of medicinal products;
  - ➢ Discuss key challenges and actions

Outline

I. Challenges

II. Frame-work for Dose-Response – ICHE4, exposure-response, evidence of effectiveness

III. Trends in approval, labelling and life-cycle management

IV. Actions

Challenges

1. Optimal dose not a requirement by law
2. Development cost, cycle times (benefit of "learning" phase)
3. Disease specific considerations in benefit/risk assessments and dose selection

- **Can conduct adequate dose response studies** however, dose selection "criteria" can vary which is the larger issue

4. Methodology – exploratory vs. confirmatory

Why invest in Dose Response?

- Conducting confirmatory phase III trials is expensive

- Identifying "right" dose is and should be the key goal of every clinical development program:

– too high a dose can result in unacceptable toxicity

– too low a dose decreases chance of showing efficacy

- **Two main goals in early development:**

– proof-of-concept (PoC) – any evidence of treatment effect

– dose-selection – which dose(s) to take into phase III?

– minimum effective dose (MED), maximum safe dose (MSD)

by pairwise comparison of doses or. documenting change in slope with changes in concentration

- Develop a framework for regulatory decisions and dose optimization

Guidance on Dose Response

ICH E4 [Dose-Response Information to Support Drug Registration, 1994] links dose response to safe and effective use of drugs

FDA 2004 [Exposure Response Analysis] speaks to linking concentration and response

Other Guidance also refer to assessment of DR

Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products - 1998

Therapeutic Area – Current Trends (1 of 2)

Therapeutic Area	Phase 2	Phase 3	PMC/PMR	# of Strengths	Derived dose
Anti-Infective	2	1	rare	1	
Antiviral	3	1	rare	1	
Transplant	2	1	rare	1	
CadioRenal	3	1-2	rare	>=1	Yes
Neurology	3	2	occasional	>=1	
Psychiatry	2-3	2	occasional	>=2	Yes
Anesthesia	2	1	rare	1	
Metabolism	3	1-2	rare	1	Yes
Endocrinology	2-3	1-2	rare	>=1	
Pulmonary	3	2	rare	1	
Rheumatology	3	1-2	rare	1-2	

# of strengths: Dose level approved

Therapeutic Area – Current Trends (2 of 2)

Therapeutic Area	Phase 2	Phase 3	PMC/PMR	# of Strengths	Derived dose
Dermatology	2	1-2	rare	1	
Gastroenterology	3	1-2	rare	2	
Bone	2	1	rare	1	
Reproductive	3	1-2	rare	1	
Urologic	2	1-2	rare	1	
Oncology	<=2	1	often	1	
Hematology	2	1	occasional	1	

18 Therapeutic Divisions

Spectrum of:

- Acute vs. Chronic Indications
- Benefit-Risk Assessment
- Unmet medical need differs

Is uniformity feasible or should we strive towards efficient and informative trial designs and analysis approaches tailored for specific therapeutic areas ?

Recent Advisory Committee Meeting (2 of 2)

Metabolic and Endocrine

Parathyroid Hormone (Ind. Hypoparathyroidism) – Sep, 2014

Review - A system pharmacology approach applied to recommend an alternate dosing regimen

Dermatology

Secukinumab (Ind. Psoriasis) – October, 2014

Review - Exposure Response analysis suggested a need for a higher dose in subjects with higher body weight

Recent Advisory Committee Meeting (2 of 2)

Oncology/Hematology

Panobinostat (Ind. Multiple Myeloma) – Nov, 2014

Review - Dose –Safety (no concentrations) assessing dose reductions relative to efficacy – overall benefit-risk assessment

Cardio-Renal

Edoxaban (Ind. Stroke Reduction Atrial Fibrillation) – Oct, 2014

Review - Exposure Response and need for a dose adjustment in subjects with normal renal function

Approvals

NME (Indication)	Dose Optimization
Pasireotide (Cushings)	Lower starting dose was approved based on interpolation of ER of efficacy and safety
Eliglustat (Gaucher's)	A fixed dose approved; studies were titration designs; label also included dosing in poor metabolizers of CYP2D6.
Nalexogol (Constipation)	ER for efficacy and safety was used to gain approval of lower dose in a population who could not tolerate a higher dose

Greater flexibility with individualization with more than one strength?

Actions

- Expect good rationale to support dose selection for phase 3 trials
  - Dose finding phase 2 (early) trials to cover full dose-response range and/or use model based approaches
- More therapeutic areas target the minimum dose with near maximum efficacy – move towards rational dose selection
- Efficient and informative trial designs/analysis approaches tailored for specific therapeutic areas

Science of applying quantitative principles to the interpretation of pharmacological observations

- A multidisciplinary approach that combines the *quantitative* relationships between diseases, drug characteristics, and individual variability

- Integrates and quantifies dose-exposure-response knowledge
  - Disease progression
  - Time course of concentration (PK) – biomarker and relationships to outcomes
  - Dose (Exposure)-response

➢ Used to inform/confirm subsequent trial design and dose regimen selection.

Evidence Generation: Dose Selection

This is the target

	Scenario 1	Scenario 2	Scenario 3	Scenario 4
MTD Determination	✓	✓	✓	✓
Modeling and simulation to design trials			✓	✓
Assessing efficacy of lower doses /alternate regimens			✓	✓
Exposure-response (efficacy and safety) based dose justification: IND stage		✓	✓	✓
Covariate based dosing in registration trials	✓	✓	✓	✓
Exposure-response (efficacy and safety) based dose justification: NDA/BLA				

Thank you!

Center for Health Policy at BROOKINGS

Improving Productivity in Pharmaceutical Research and Development: The Role of Clinical Pharmacology and Experimental Medicine

Center for Health Policy
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The Embassy Row Hotel • Washington, DC
July 28, 2015

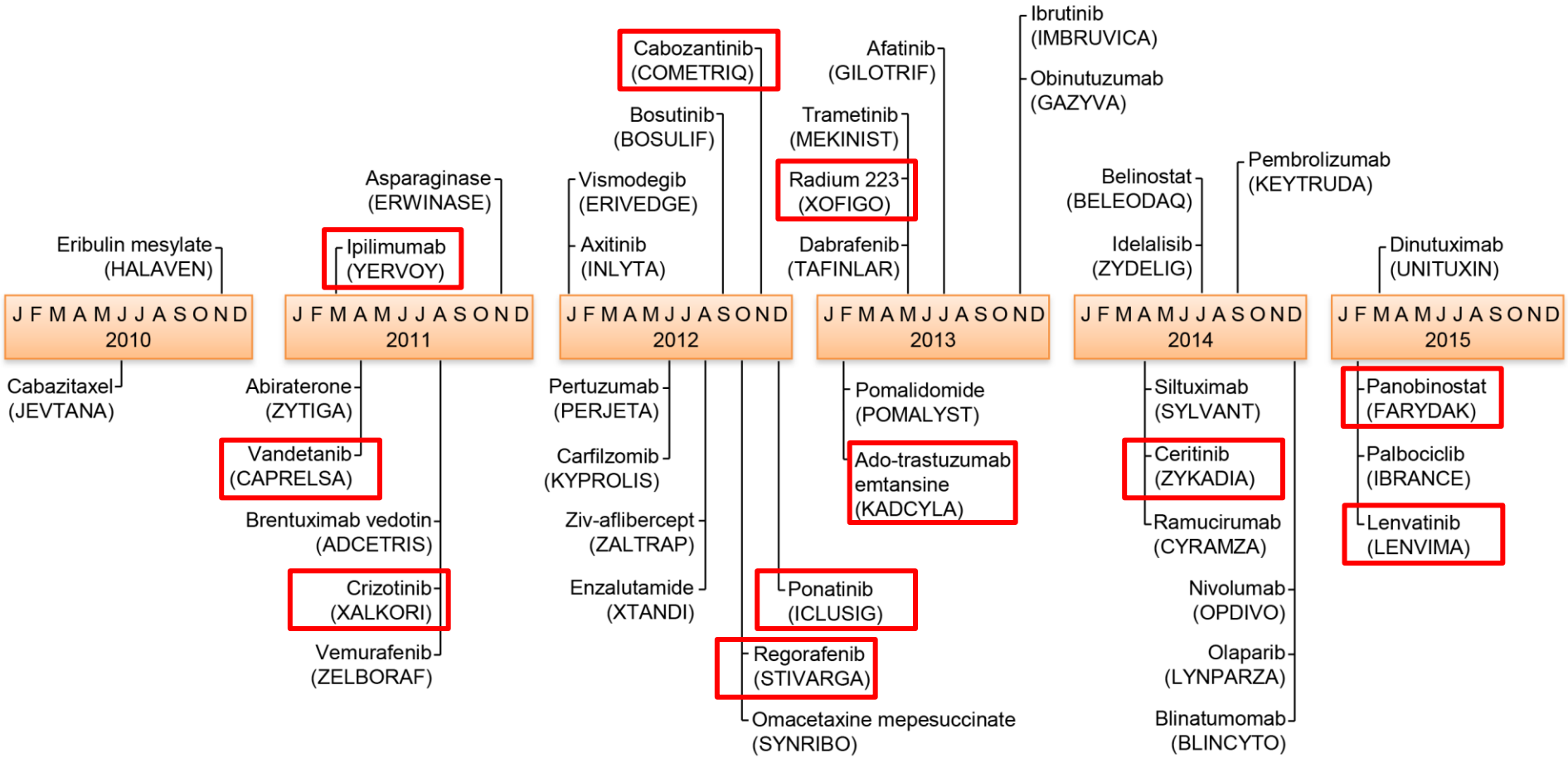
Improving Productivity in Oncology: Opportunities for Dose Optimization

Amita Joshi, Ph.D.
Senior Director, Head of Clinical Pharmacology
Genentech

Presentation co-authors: Bert Lum, Dana Lu, Sandhya Girish, Jin Jin

Brookings Conference, July 28 2015, Washington DC

Oncology Drugs approved by US FDA from 2010 – Q1 2015
(Survey by the Genentech dose optimization working group)



11/41 (~27%) drugs

Dose optimization PMR/PMCs by FDA

Oncology Drugs approved by US FDA from 2010 – Q1 2015
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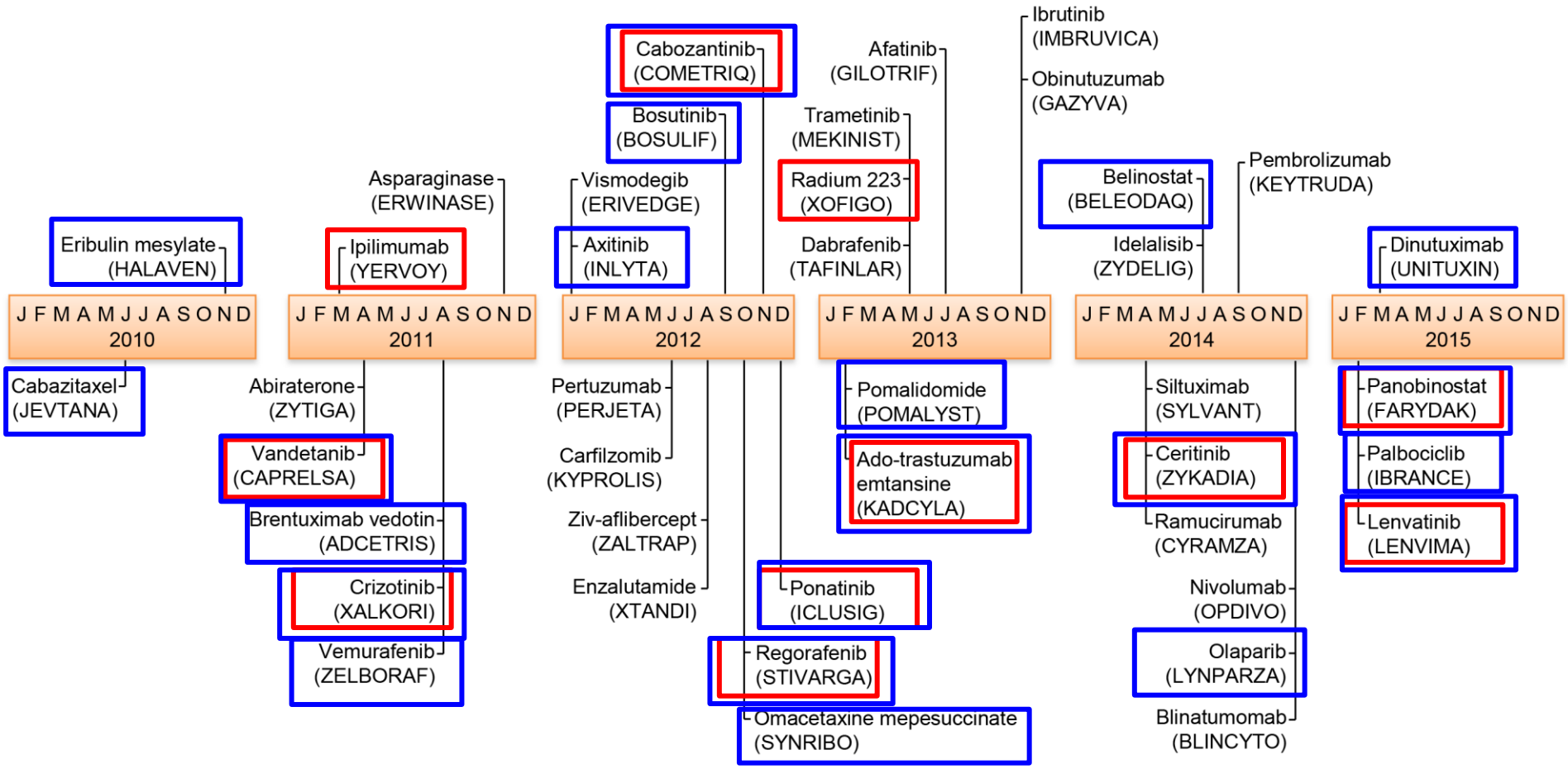


11/41 (~27%) drugs

Dose optimization PMR/PMCs by FDA

21/41 (~51%) drugs

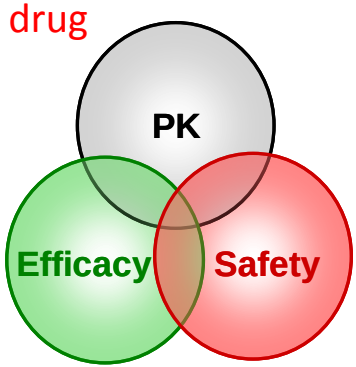
Developed at MTD dose

9/21 (~43%) drugs developed at MTD have dose optimization PMR/PMC issued by FDA

How Can Clinical Pharmacology Improve Productivity and Success in Oncology?

- **Study designs aspects need to evolve to improve speed and success**
  - Study multiple doses and schedules in Phase II to understand dose-response better
  - Adaptive designs to efficiently identify optimal doses ✔
  - Collection of tumor biopsies, tumor based biomarkers and PK in trials
  - Use of surrogate endpoints
  - Understanding and leverage early/late endpoint relationship

- **Need better prediction tools for PK, Safety and Efficacy to optimally predict the Therapeutic Window**
  - Use of translational and clinical PKPD to pick doses and/or schedules ✔
  - Test multiple dose-schedules in the clinic simultaneously ✔
  - Use of tumor biomarkers and PKPD for picking the optimal biological dose ✔
  - For single arm studies, use of literature based meta analyses to benchmark test drug with standard of care safety ✔
  - Concentration-R analyses to reveal balance between efficacy and safety
  - Systems Pharmacology tools to inform dose/AE relationship ✔

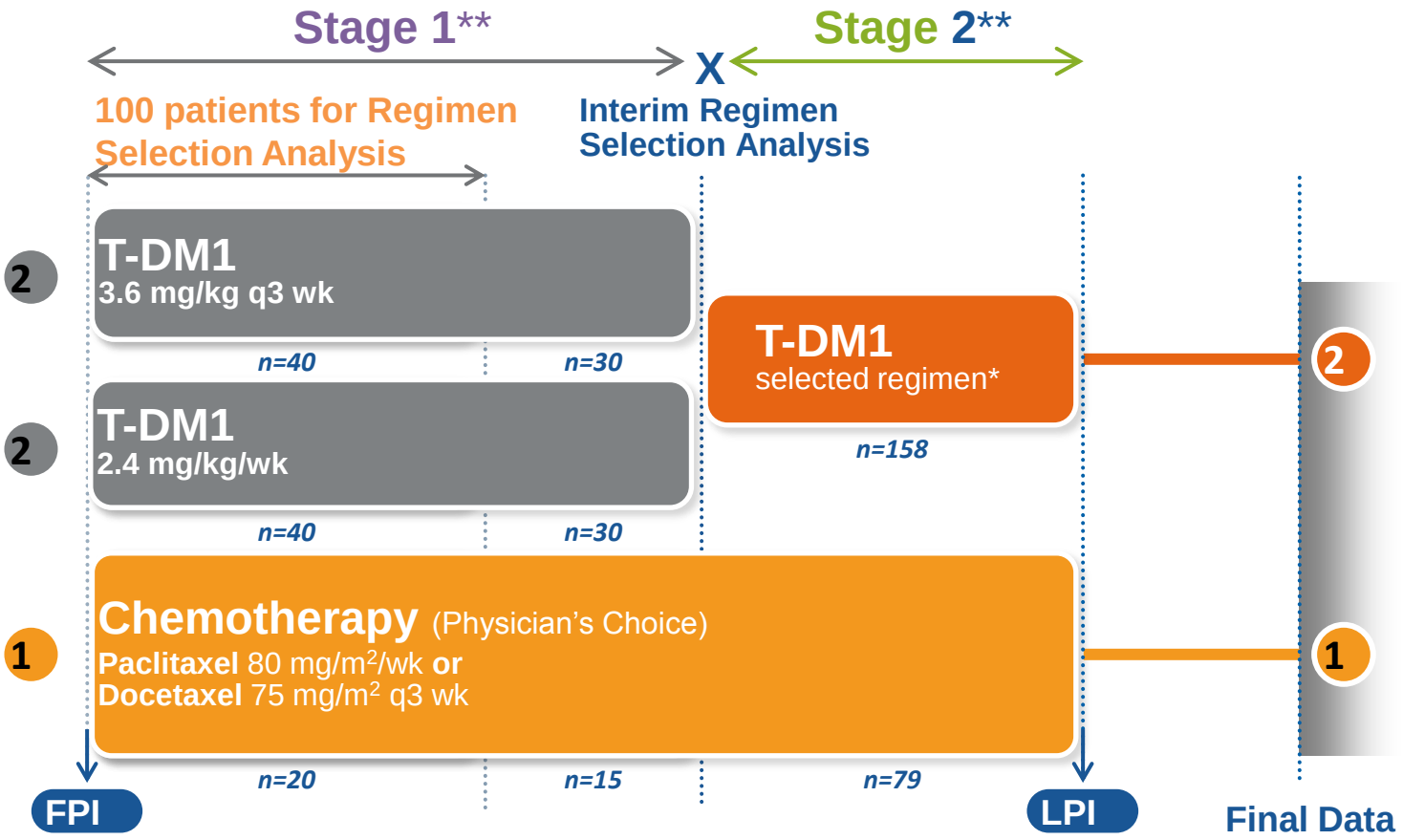


Case Study: Adaptive Designs to Efficiently Identify Doses

Challenge: Unknown exposure and efficacy of T-DM1 in Gastric Cancer

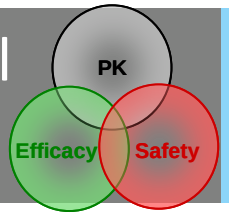
Opportunity: **Adaptive Phase II/III design trial** to pick optimal regimen for Phase III

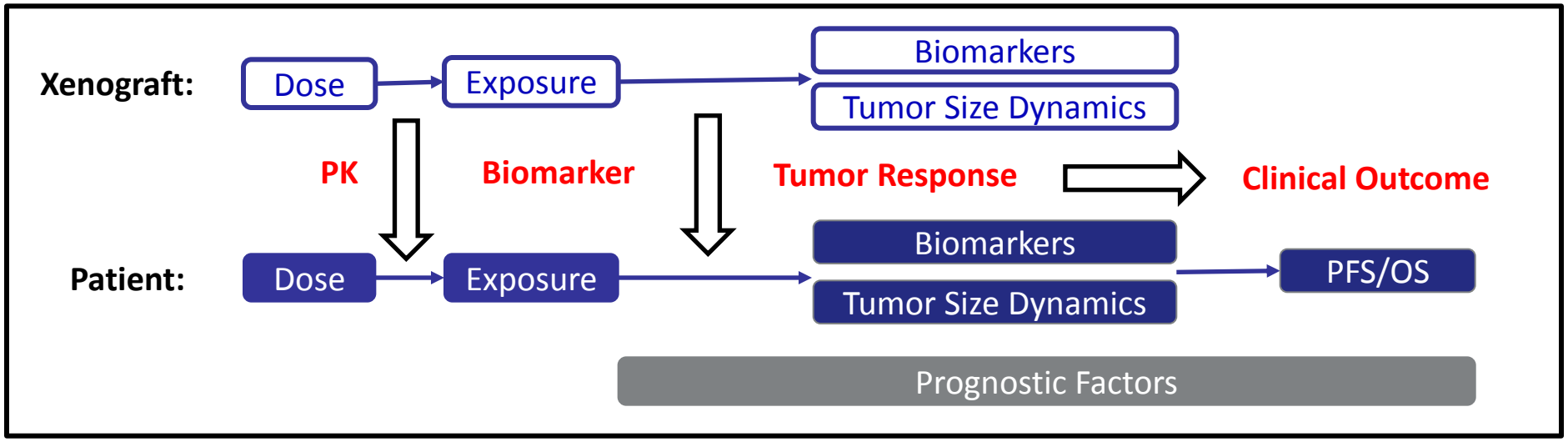
Population:
2L HER2+ AGC
Prior chemo ± prior HER2 tx
PS 0-1
Total n=412 (Stage 1 + 2)



Sandhya Girish, Amit Garg

Dose Optimization Strategy in Oncology- Translational Approaches Using Biomarkers or Tumor Dynamics





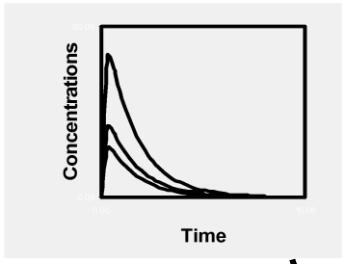
- **Preclinical-to-clinical translation**
  - Homogeneous xenograft vs. heterogeneous patients
  - Resistance development
- **Early-to-late clinical translation**
  - Predictive biomarkers
  - Translation of early tumor response to long-term efficacy

- **PK:**
  - High PK variability in oncology patients
  - Dose adjustment based on intrinsic/extrinsic factors
- **Biomarker:**
  - Demonstration of pathway inhibition
  - Dosing justification based on target-specific or indication-specific biomarkers
- **Clinical efficacy/safety:**
  - Optimize therapeutic window

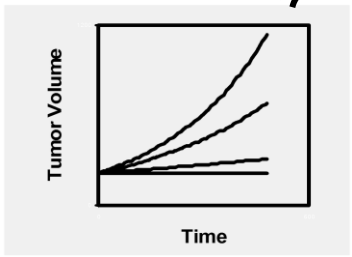
***Opportunity* for Translational approaches and innovative trial design**

Translational PKPD Approach- Tumor Size Dynamics

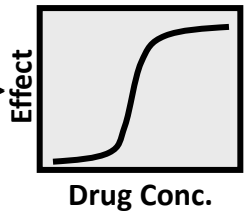
STAGE 1 – Fitting (Mouse)
Mouse PK



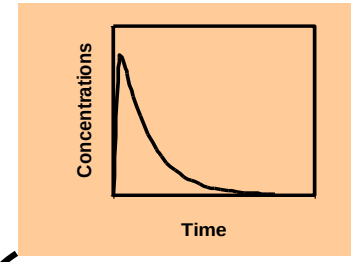
Mouse Efficacy



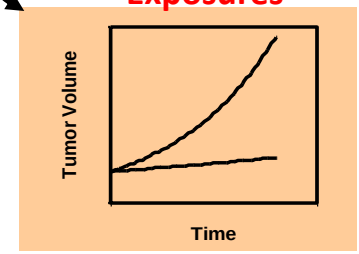
Conc. vs. Effect



STAGE 2 – Simulation (Human)
Human PK



%TGI at Clinical Exposures

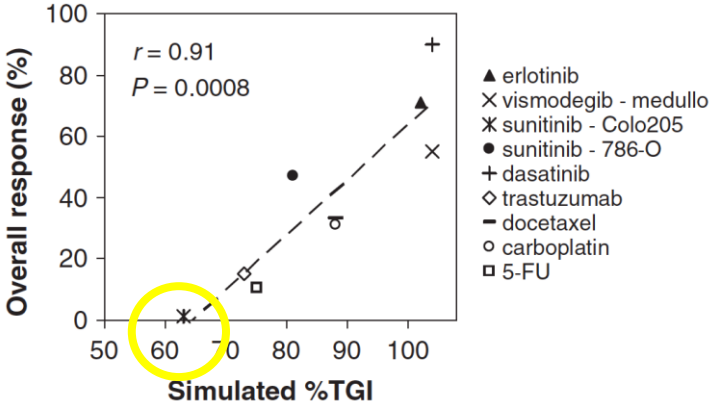


TGI: tumor growth inhibition

- Mouse PKPD model to correlate drug concentration and anti-tumor response

- Use of human PK to correct for inter-species difference in drug exposure
- Correction for inter-species difference in protein binding or target binding
- Assume same PD parameters in mouse and human

Rational of the PKPD Approach



- Retrospective analysis of 8 anti-cancer agents suggested good correlation between simulated xenograft TGI driven by human PK and clinical response provided disease relevant xenograft tumor models are employed.
- This analysis suggests >60% TGI in preclinical models, at clinically relevant exposures, are more likely to lead to clinical response

Opportunity: **Approach provides early guidance on target efficacious exposures in patients based on disease relevant xenograft tumor models**

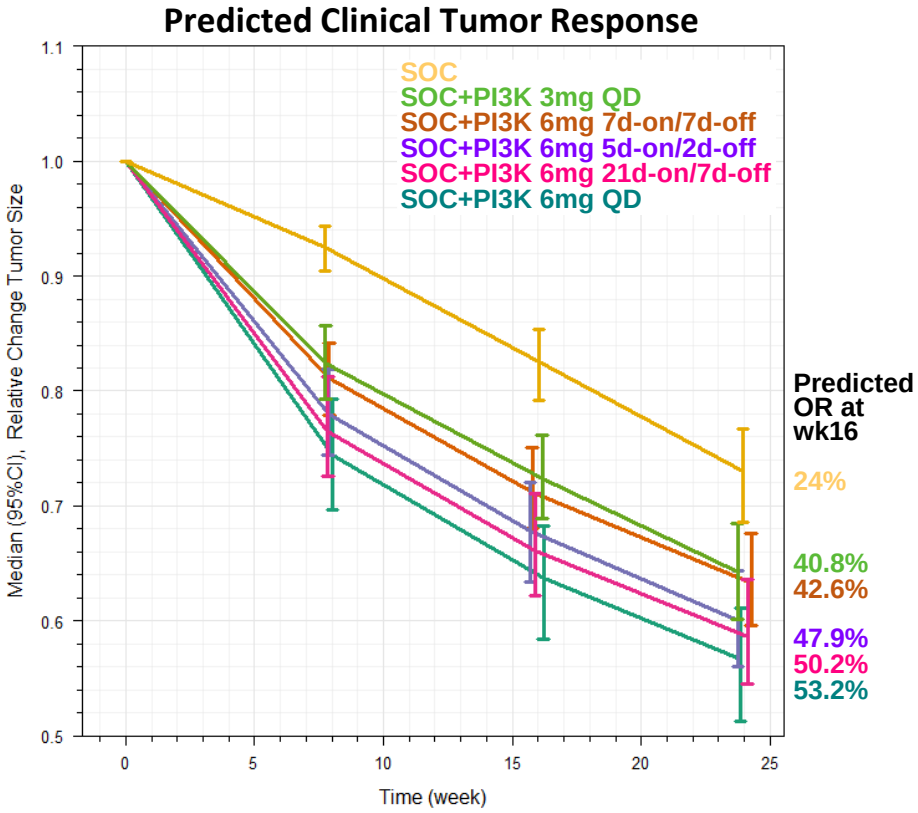
Wong H et al. Clin Cancer Res. 2012. 18: 3846-3855

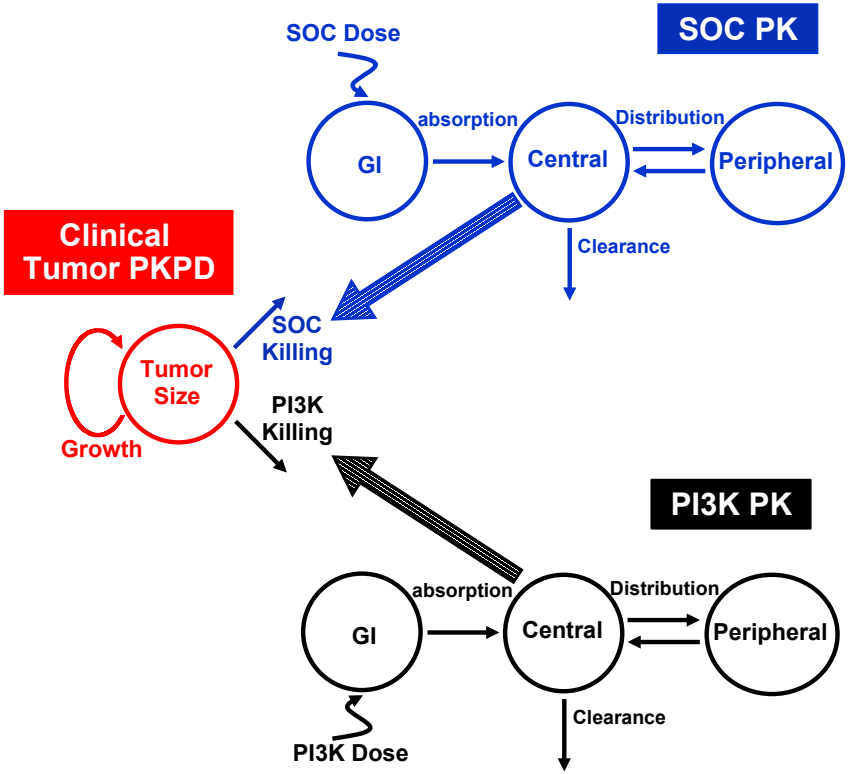
Case Study: Use of Translational and Clinical PKPD to Pick Dose-schedules

Challenge: Team considering alternate dose/schedule for tolerability

Opportunity: Identify regimens which give acceptable **degrees of predicted tumor inhibition**

SOC+NME Clinical PKPD





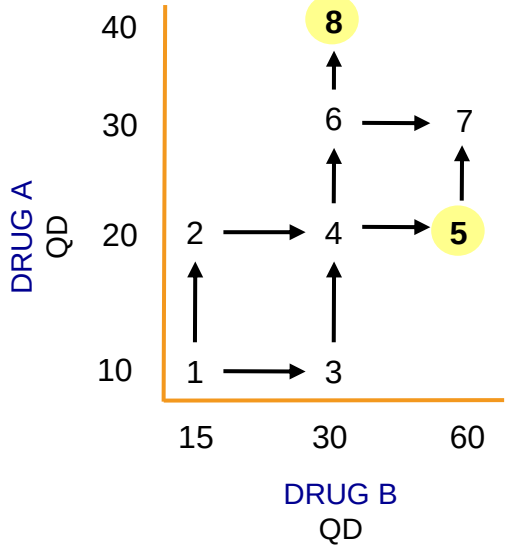
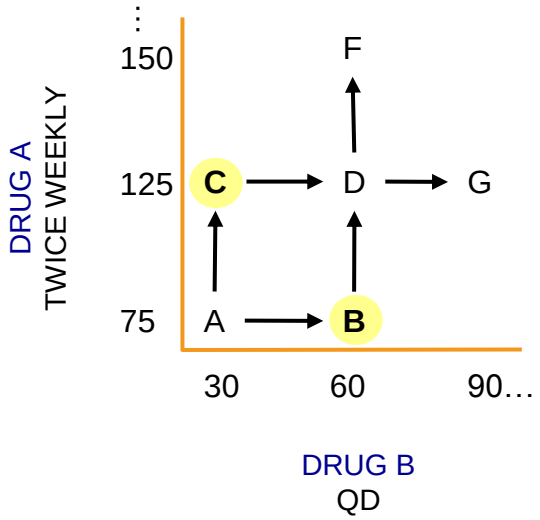
Clinical PKPD of longitudinal tumor response suggested low risk of losing efficacy with intermittent PI3K dosing, which can be investigated as alternative dosing option to potentially mitigate safety risk.

Lu T, Claret L, Bruno R, Ware J, Jin J et al.

Case Study: Test Multiple Dose-Schedules in the Clinic Simultaneously

Challenge: What dose schedule allows maximizing doses of Drug A in a A+B combination?

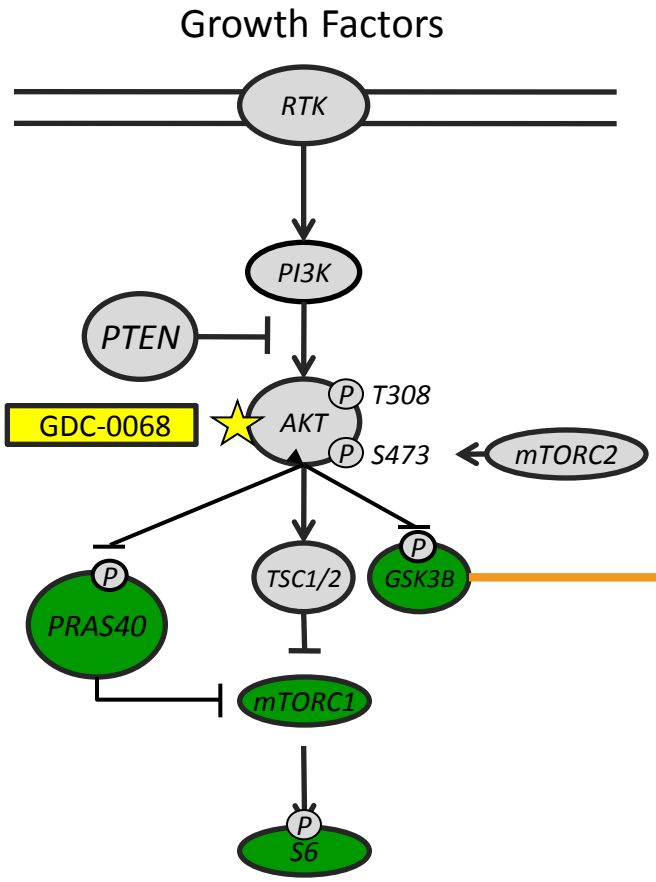
Opportunity: Phase 1b studies with parallel exploration of daily dosing and intermittent dosing schedule revealed that **intermittent dosing had better tolerability** profile for Drug A

	Daily Dosing	Intermittent Dosing
Dose Escalation Schema		
	3+3 study design, PK sample collection, tumor assessments q8 weeks,	
Expansion Cohorts	• Chose MTD (DL 8) as higher dose of Drug A could be administered	• Intermittent dosing for Drug A to allow higher doses to be delivered.

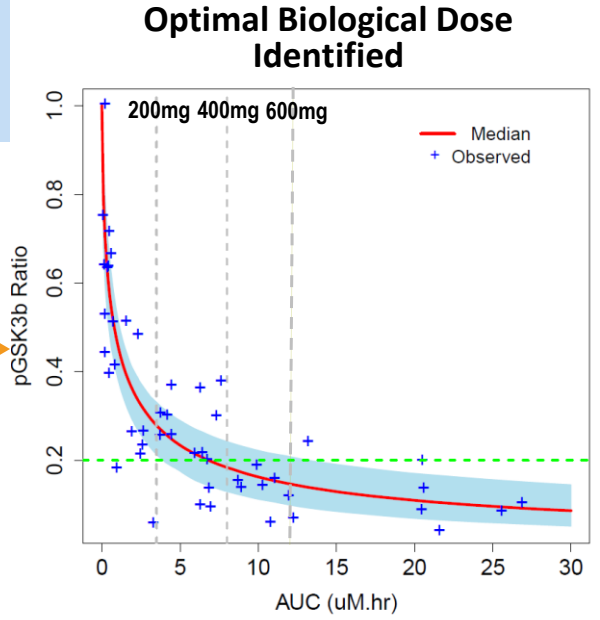
Case Study: Use of Tumor Biomarkers and PKPD for Picking the Optimal Biological Dose

Challenge: What doses are likely to be effective?

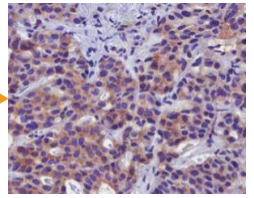
Opportunity: Dose justification based on **target specific biomarker response and PKPD**



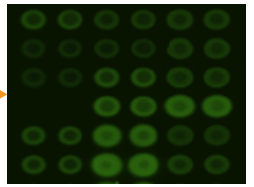
PRP



Core Biopsies



pPRAS40 IHC



RPPA: 40 phospho-proteins

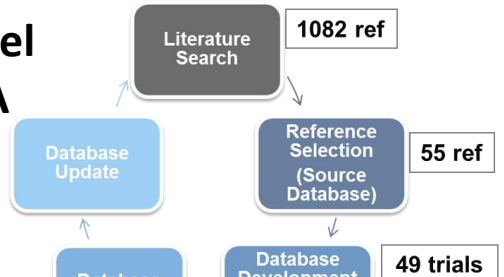
Yan et al, CCR 2013

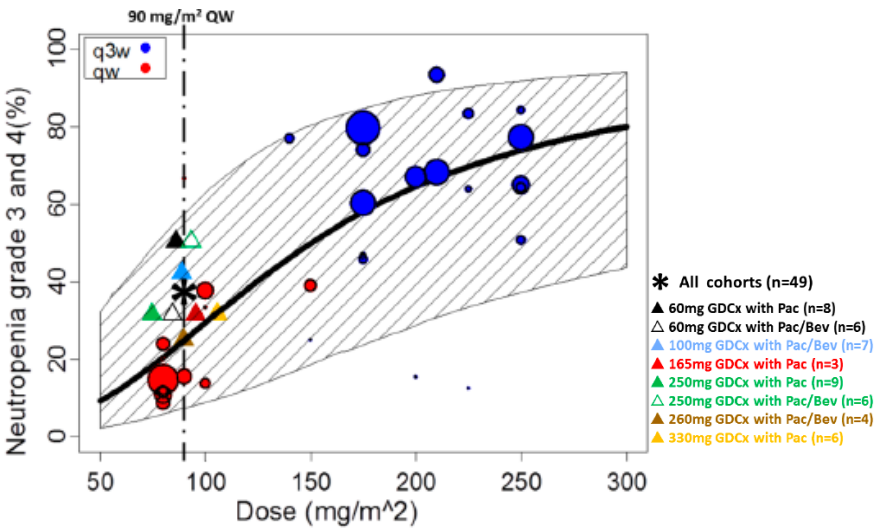
Case Study: For Single Arm Studies, use of Literature Based Meta Analyses to Benchmark Test Drug with SOC Safety

Challenge: Interpretation of combo tolerability **without control arm in study**

Opportunity: Maximize learning from historical single agent data

Paclitaxel MBMA

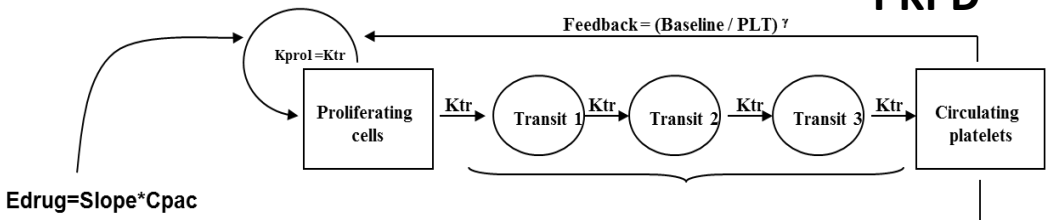


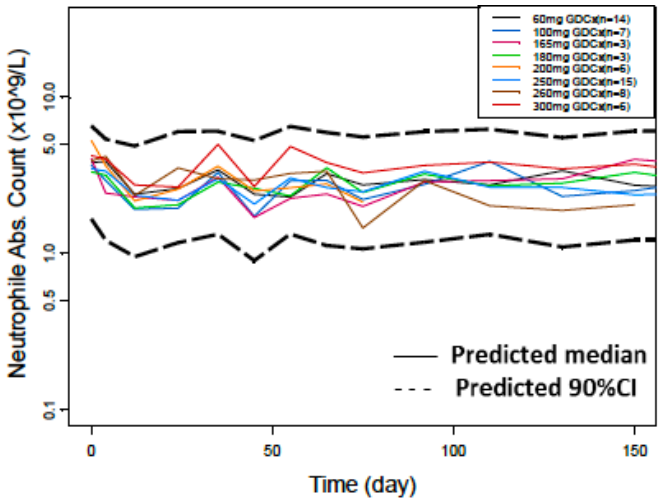


Lu D et al. CPT:PSP. 2014

Lu T, Lu D, Ware J, Dresser M, Jin JY et al. 2013 ACoP

PKPD

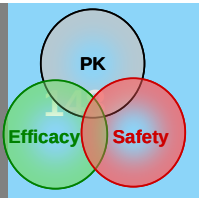




Neutropenia incidence rate and neutrophil counts time profiles in NME+PAC combo was consistent with historical Paclitaxel monotherapy based on literature database MBMA and PKPD.

Friberg L et al. JCO. 2002

Case Study: Systems Pharmacology Tools to inform Dose/Biomarker/AE Relationship



Opportunity: **Quantitative Systems Pharmacology to inform combo dose/regimen**

Dose → Exposure

PK MODELS

Biomarkers (PD, Efficacy, Safety)

Tumor Size Dynamics

OUTCOME MODELS

PFS/OS

Tox

QUANTITATIVE SYSTEMS MODELS

Target Modulation

PI3Ki

RAFi

MEKi

RTKs, Shc,Grb,Sos, PI3K, RAS, PIP3,PDK1, PTEN, RAF, AKT, MEK, FOXO, ERK, mTOR, GLUT, RSKs, 4EBP, p70S6K, GSK, p21, p27, s6, CDK, cyclins, Bcl-2 Family

f(x)

Downstream Biology & Markers

Blood Glucose (Hyperglycemia)

Tumor Growth

Prolif

BRAF PIK3CA

Apop

ADC

Courtesy of Saroja Ramanujan

Conclusions

- Identification of the “optimal dose” is a primary challenge and uncertainty in drug development and provides opportunity to improve success in cancer drug development.
  - Approximately 30% of oncology drug approvals have dose-related PMR/PMC activities.
- Case examples presented today illustrate clinical pharmacology and translational strategies and methodologies implemented in our oncology drug development efforts in two broad areas to improve identification of the optimal dose-
  - Adaptive trial designs that allow the efficient study and identification of doses and schedules
  - Translational investigations and modeling approaches that use biomarkers or tumor dynamics to guide-
    - Preclinical-to-clinical translation: Identification of doses and schedules which are predicted to have activity as single agents or in combination regimens at relevant human PK exposure.
    - Early-to-late-clinical translation: Integrated PK, PD and biomarker assessments to optimize the dose-schedule and therapeutic window of single agents or combination regimens.
    - Trial design: Rational and more efficient design of phase 1b studies which allow simultaneous testing of multiple dose-schedules
- Adoption of Clinical Pharmacology strategies which integrate study design, translational tools, effective PK and drug activity measurements, and application of modeling and simulation throughout the development cycle of a drug will assist in reducing the uncertainty in the identification of the optimal dose and value of a medicinal product.

Acknowledgments

Clinical Pharmacology and M&S
Bert Lum, Dana Lu, Sandhya Girish
Jin Jin (co-authors)
Luna Musib
Nageshwar Budha
Joseph Ware
Mark Dresser

Quantitative Systems Pharmacology
Saroja Ramanujan

Pharsight/Certera
Rene Bruno
Laurent Claret

Oncology Biomarkers and Diagnostics
Yibing Yang
Mark Lackner
Garret Hampton

DMPK
Harvey Wong
Laurent Salphati
Edna Choo
Marcel Hop

Oncology Clinical Science
Iris Chan
Premal Patel
Mika Derynck
Stuart Lutzker

Center for Health Policy at BROOKINGS

Improving Productivity in Pharmaceutical Research and Development: The Role of Clinical Pharmacology and Experimental Medicine

Center for Health Policy
The Brookings Institution

The Embassy Row Hotel • Washington, DC
July 28, 2015

Rationale for dosing strategies: the apixaban case

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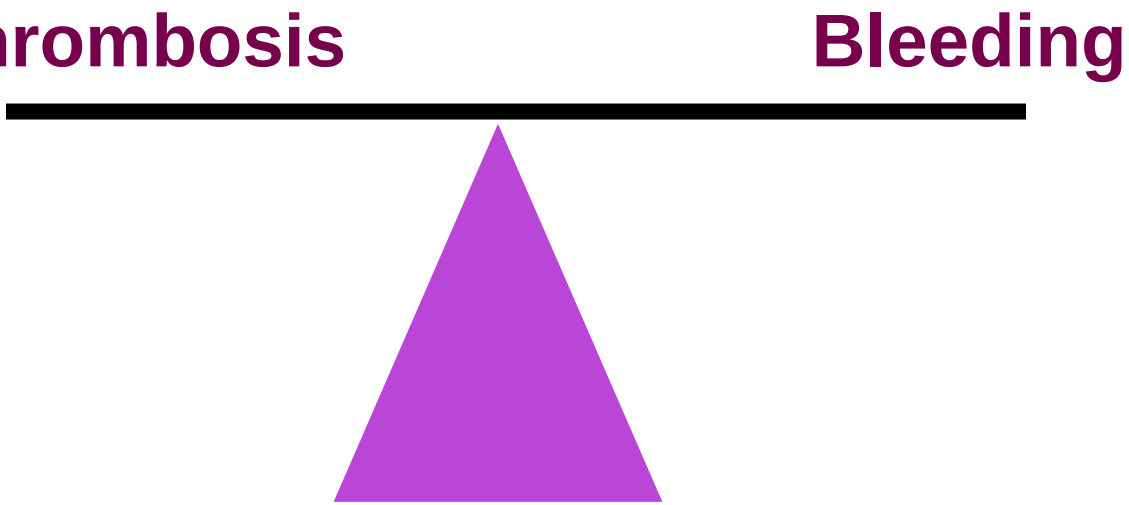
Group Director
Clinical Pharmacology and Pharmacometrics
Bristol-Myers Squibb
July 28, 2015

Bristol-Myers Squibb

Disclosures

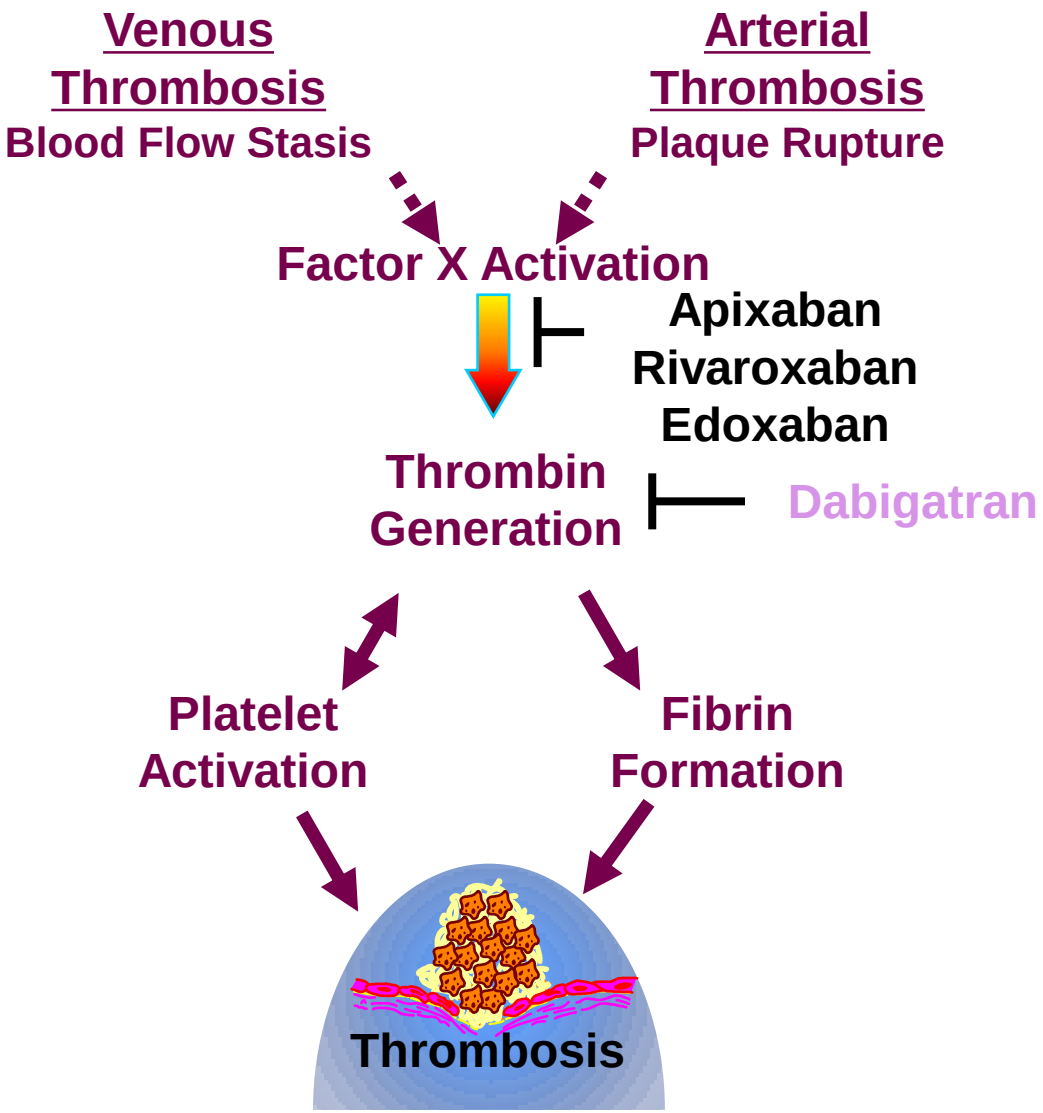
Full-time employee of Bristol-Myers Squibb

The therapeutic balance in anticoagulation



Dose and dose regimen of apixaban intended to optimize the balance of efficacy and safety for each target population

Apixaban, a rationally designed Factor Xa inhibitor



Designed to have:

- Low metabolic clearance[1]
- Small volume of distribution[1]
- Multiple elimination pathways[2]

Profile well suited for an elderly population

1. Pinto et al. *J Med Chem*. 2007;50(22):5339–56.
2. Apixaban SmPC. Available at http://www.ema.europa.eu

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Clinical pharmacology profile of apixaban

Rapidly absorbed with oral bioavailability ~50%[1]

- **No effect of food, gastric pH[2], or therapeutic dose**

Half-life ~12 hours[1]

Multiple routes of elimination[1]

- **Filtered by the kidneys (27%), metabolized by multiple Cytochrome P450 (CYP) enzymes including CYP3A4, also secreted directly into the gastrointestinal (GI) tract**

No active metabolites of apixaban[1]

Limited influence of demographics and disease

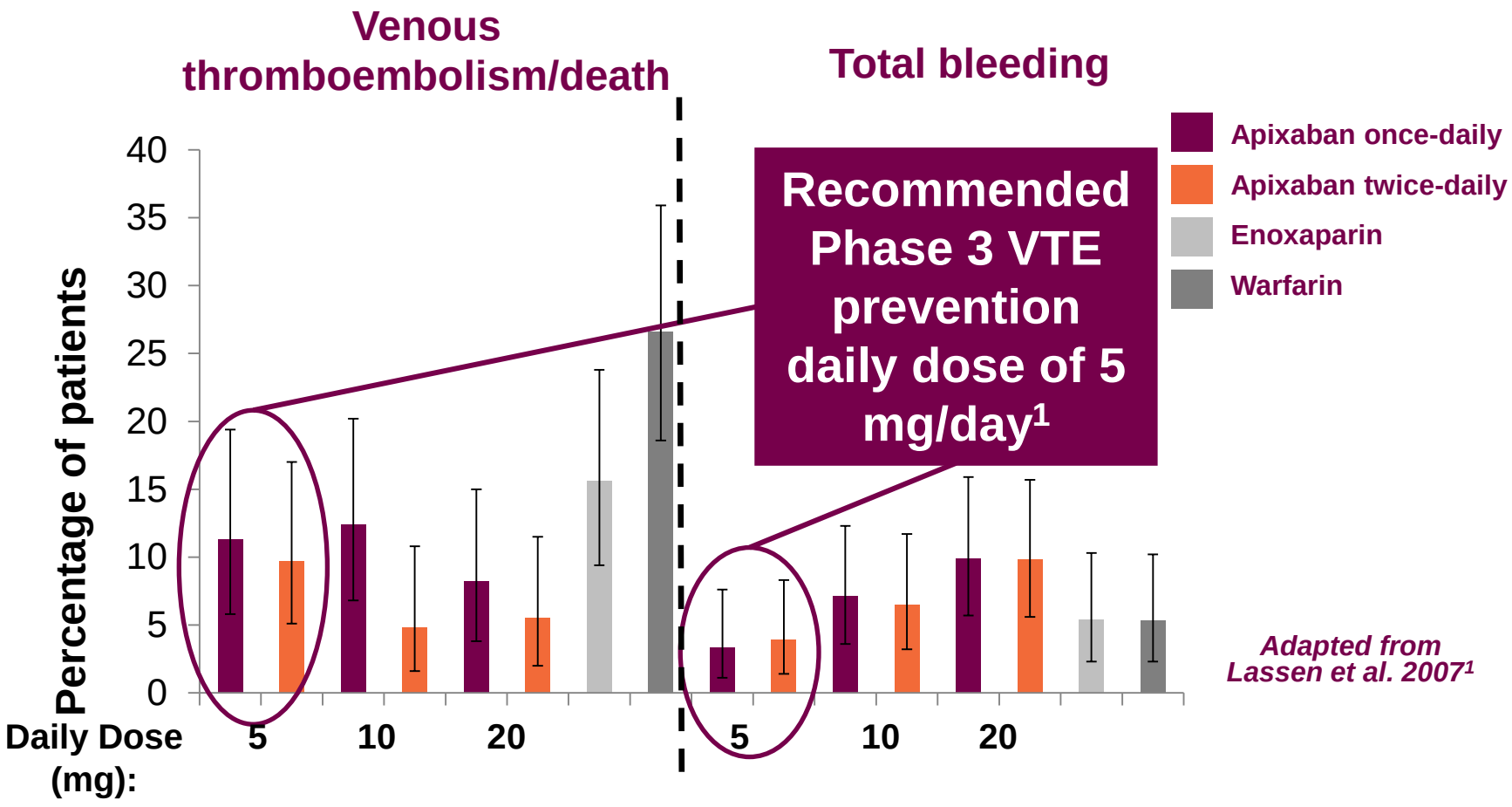
- **Pharmacokinetics (PK) of apixaban are similar in healthy White/Caucasian, Asian and Black/African American subjects[1]**

Limited potential for drug-drug interactions[1]

. Apixaban SmPC. Available at http://www.ema.europa.eu.

2. Upreti et al. *Clin Pharmacol*. 2013; 5: 59–66.

APROPOS study – daily dose selection for venous thromboembolism (VTE) prevention after total knee replacement (n=1,217)[1]



Adapted from Lassen et al. 2007[1]

This is a dose ranging PK/PD study and shown for illustrative purposes only. Only the 2.5mg BD dose of apixaban is licensed for VTE prophylaxis after elective TKR.

PD: pharmacodynamics; TKR: total knee replacement

1. Lassen et al. *J Thromb Haemost* 2007;5:2368–75.

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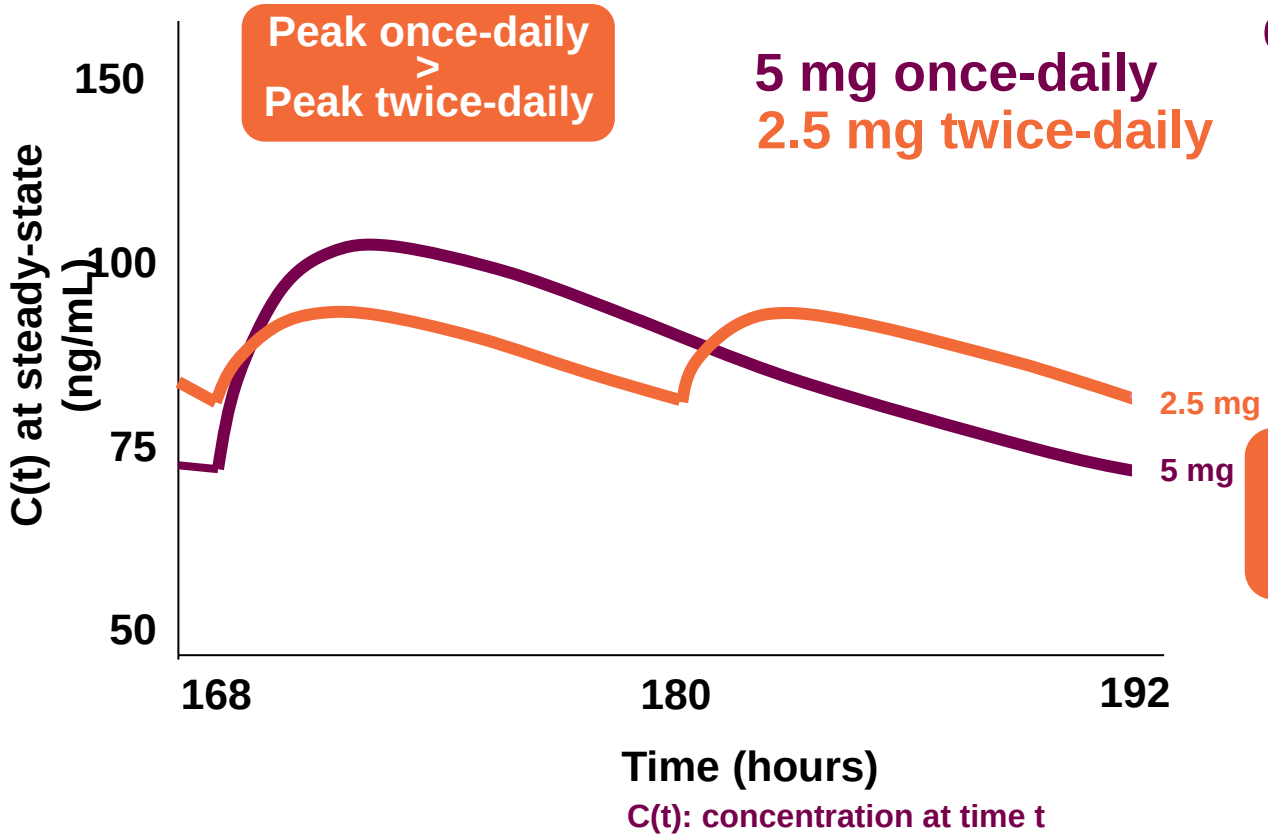
APROPOS: Pharmacokinetic modelling to justify the twice-daily or once-daily regimen[1]



- Hypothesis in favour of a twice-daily dose regimen
  - Lower peak to reduce bleeding risk
  - Higher trough to improve efficacy

Adapted from Leil et al. 2010[1]

This is a PK study shown for illustrative purposes only. The 5mg once daily dose of apixaban is not licensed

1. Leil et al. *Clin Pharmacol Ther* 2010;88:375–82

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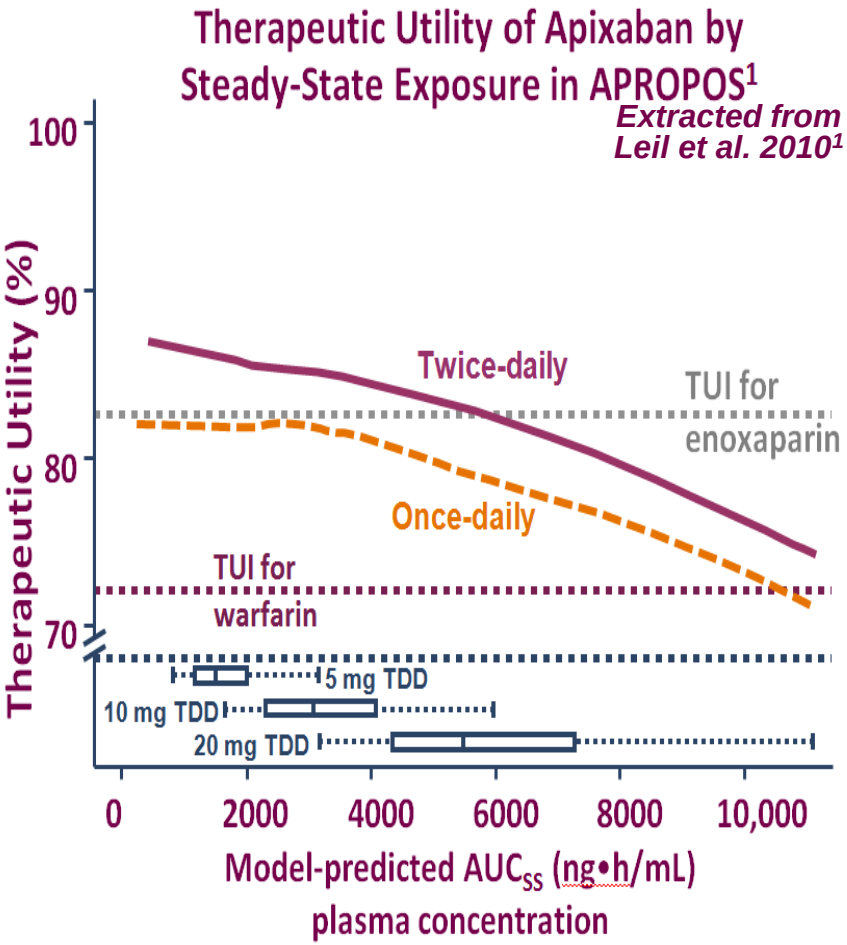
The choice of the apixaban twice-daily dosing regimen in all studied indications is based on a clear rationale



Twice-daily dosing provided greater therapeutic utility (a combined measure of efficacy and safety) than once-daily dosing at all doses studied[1]

- **The 2.5mg twice-daily dose was chosen for testing in phase III VTE prevention trials[1,2]**

Twice-daily dosing was selected to maximize efficacy without increasing bleeding risk

AUC_{SS}: area under the curve at steady state; DVT: deep vein thrombosis; TDD: total daily dose; TUI: therapeutic utility index

1. Leil TA et al. *Clin Pharm Ther*. 2010;88(3):375–82.
2. Lopes RD et al. *Am Heart J*. 2010;159(3):331–39.

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Apixaban phase 3 dose selection for non-valvular atrial fibrillation (NVAF)

Select NVAF daily dose	10 mg daily dose
↓	↓
Select once-daily vs. twice-daily	Twice-daily
↓	↓
Select 1 vs. 2 doses	One dose (5 mg twice daily)
↓	↓
Dosage adjustment	Algorithm

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Dose reduction algorithm in NVAF
5 mg twice-daily → 2.5 mg twice-daily

For prevention of stroke or systemic embolism in patients with NVAF, a single dose of an anticoagulant is unlikely to be appropriate for all patients

For apixaban, no single factor (e.g. age, body weight or gender) has a major impact on apixaban exposure or bleeding risk[1]

Without dose adjustment, exposure increase from a combination of factors may produce less than optimal benefit-risk profile

Therefore, patients satisfying at least 2 of the following 3 criteria were given 2.5 mg twice-daily at randomization (and thereafter):[2,3]

- Age ≥ 80 yrs
- Body weight ≤ 60 kg
- Serum creatinine ≥ 1.5 mg/dL (133 µmol/L)*

***Note: Per the SmPC, patients with the exclusive criterion of severe renal impairment (CrCl 15–29 ml/min) should also receive the lower dose of apixaban 2.5 mg twice daily. This new criterion differs from the trial conduct**

1. Leil et al. *Clin Pharmacol Ther* 2010;88:375–82.
2. Granger et al. *N Engl J Med* 2011;365:981–92.
3. Connolly et al. *N Engl J Med* 2011;364:806–17.

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Apixaban trials for stroke prevention in NVAF: ARISTOTLE and AVERROES

Documented NVAF + risk factor(s) for stroke

ARISTOTLE

***Apixaban versus* warfarin**

(n=18,201)

AVERROES

***Apixaban versus* ASA**

(n=5,599)

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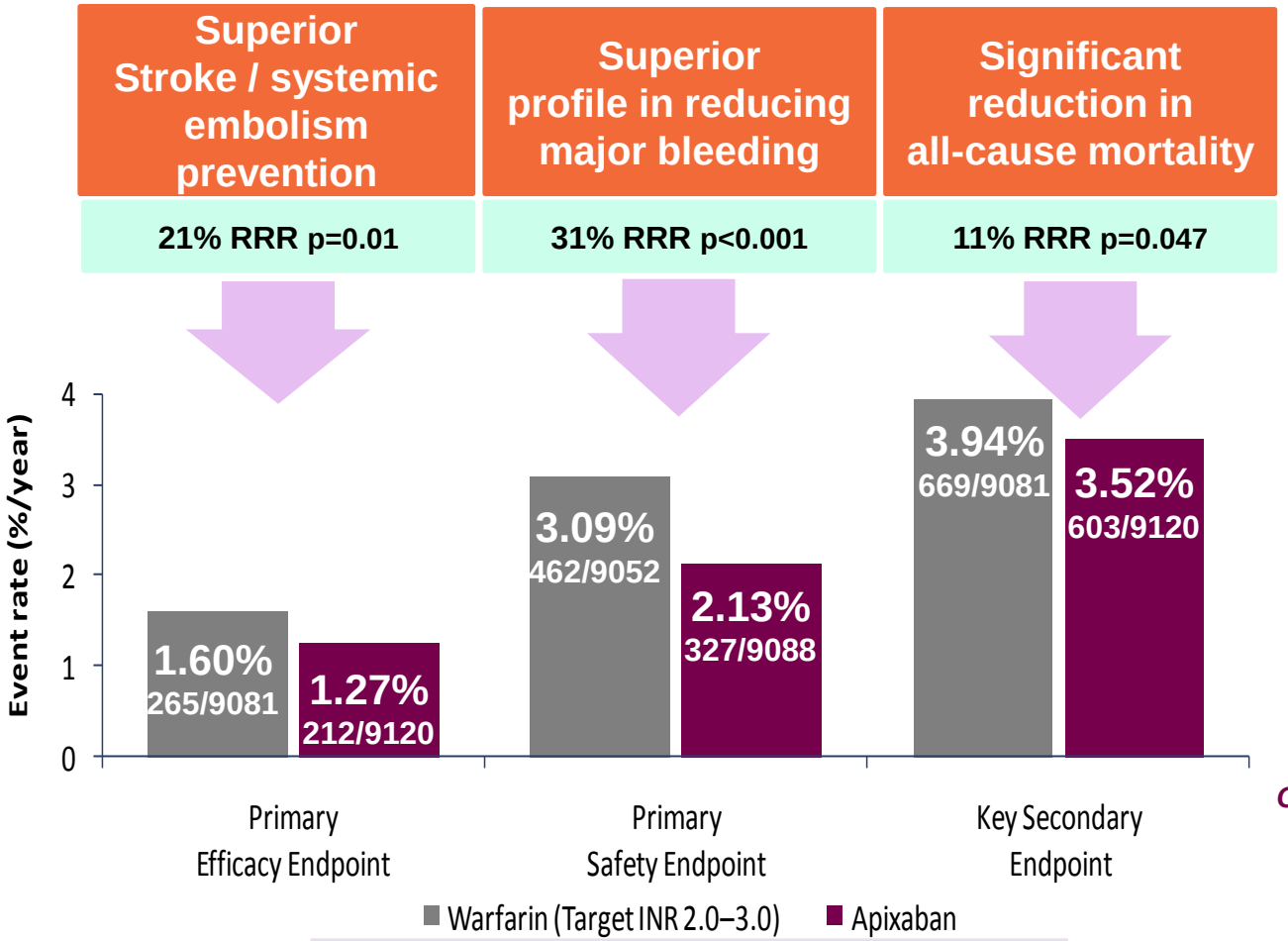
ARISTOTLE: Apixaban has demonstrated superiority vs. warfarin in the following key outcomes[1]



Created from Granger et al. 2011[1]

Median duration of follow-up 1.8 years

INR: international normalised ratio;
RRR: relative risk reduction

1. Granger et al. N Engl J Med 2011;365:981–92.

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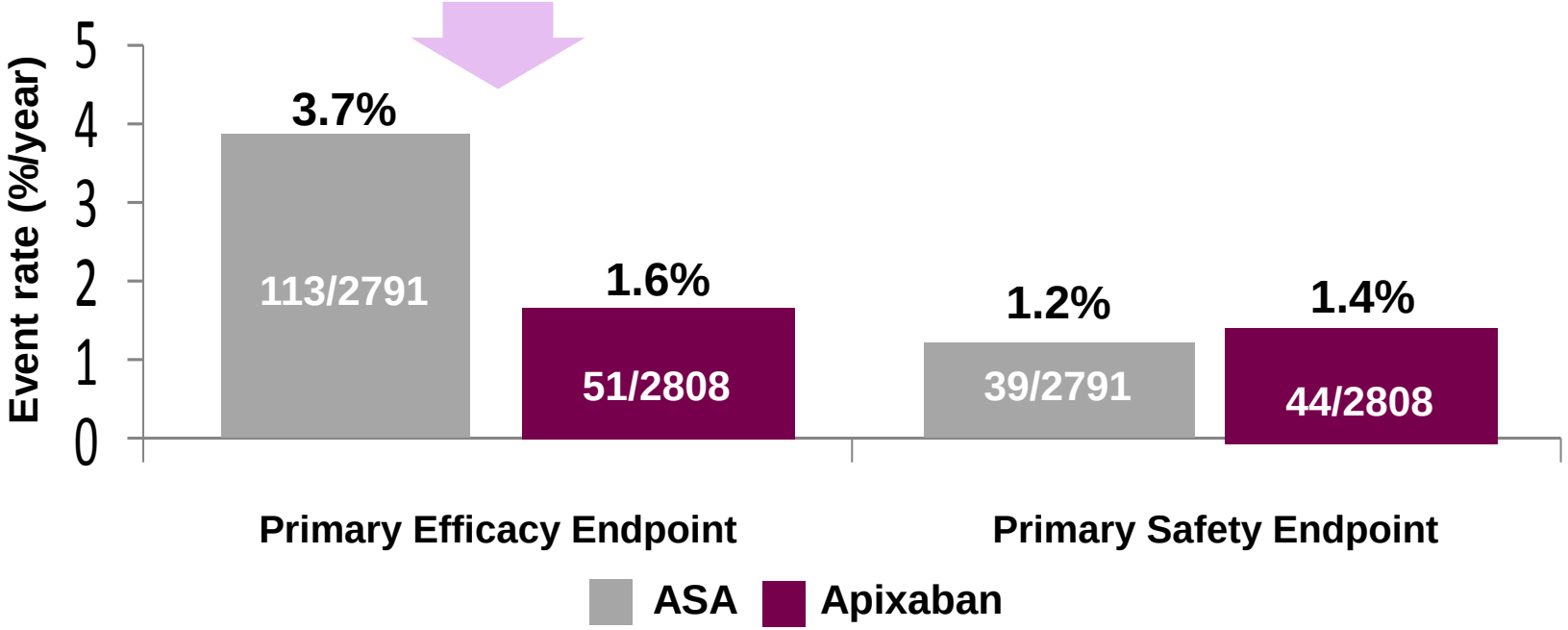
AVERROES: apixaban demonstrated superior efficacy *vs.* ASA without significantly increasing the risk of major bleeding[1]

Stroke / Systemic Embolism

55% RRR
2.1% ARR
p<0.001

Major Bleeding

No significant difference
p=0.57



Mean duration of follow-up 1.1 year

ARR: absolute risk reduction;
RRR: relative risk reduction

1. Connolly et al. *N Engl J Med*. 2011;364:806–17.

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Rationale for apixaban dosing strategies: conclusions

Apixaban is a rationally designed Factor Xa inhibitor

- Choice for twice-daily dosing was based on clear rationale[1]
- Choice for twice-daily dosing also reflects greater priority placed on clinical outcomes than on convenience

Decisions during clinical development led to favourable outcomes for apixaban in:

- VTE prevention after Total Knee Replacement (ADVANCE-2)[2]
- VTE prevention after Total Hip Replacement (ADVANCE-3)[3]
- Stroke prevention in NVAF (ARISTOTLE)[4]
- Stroke prevention in NVAF in patients unsuitable to warfarin (AVERROES)[5]
- Initial and long-term treatment of VTE (AMPLIFY)[6]
- Extended treatment and prevention of VTE (AMPLIFY-EXT)[7]

Overall: twice-daily dosing delivered beneficial therapeutic balance between efficacy and safety across registered indications[1]

1. Leil TA et al. *Clin Pharm Ther*. 2010;88(3):375–382. 2. Lassen et al. *N Engl J Med* 2010;363:2487–98; 3. Lassen et al. *Lancet* 2010;375:807–15; 4. Agnelli et al. *N Engl J Med* 2013;369:799–808; 5. Agnelli *et al. N Engl J Med* 2013; 368:699–708; 6. Granger et al. *N Engl J Med* 2011;365:981–92; 7. Connolly et al. *N Engl J Med* 2011;364:806–17.

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Acknowledgements

Members of the BMS-Pfizer Alliance Team

Rebecca Boyd

Wonkyung Byon

Charles Frost

Margarida Geraldes

Elora Gupta

Michael Hanna

Robert Knabb

Puneet Mohan

Frank LaCreta

John H. Lawrence

Tarek Leil

Yan Song

Junyuan Wang

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Center for Health Policy at BROOKINGS

Improving Productivity in Pharmaceutical Research and Development: The Role of Clinical Pharmacology and Experimental Medicine

Center for Health Policy
The Brookings Institution

The Embassy Row Hotel • Washington, DC
July 28, 2015

Center for Health Policy at Brookings Institution

Improving Productivity in Pharmaceutical Research and Development: The Role of Clinical Pharmacology and Experimental Medicine

A clinician's perspective on the right dose for the right patient: Challenges and Opportunities in Dose Optimization

Michael Maitland, MD PhD
Asst. Professor
Committee on Clinical Pharmacology and Pharmacogenomics
Department of Medicine, Section of Hematology/Oncology
July 28, 2015

Comments

1. **High impact from concentrated resources**
2. **Time-to-market vs. knowledgebase**
3. **Real patient-level impact**
4. **From sub-populations to patients**
5. **C&O in pre-competitive, off-label, and outcomes studies**

Department of Medicine Annual Report 2014

Precision Medicine TODAY

THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES

Emerging concepts in developing treatments with better therapeutic index

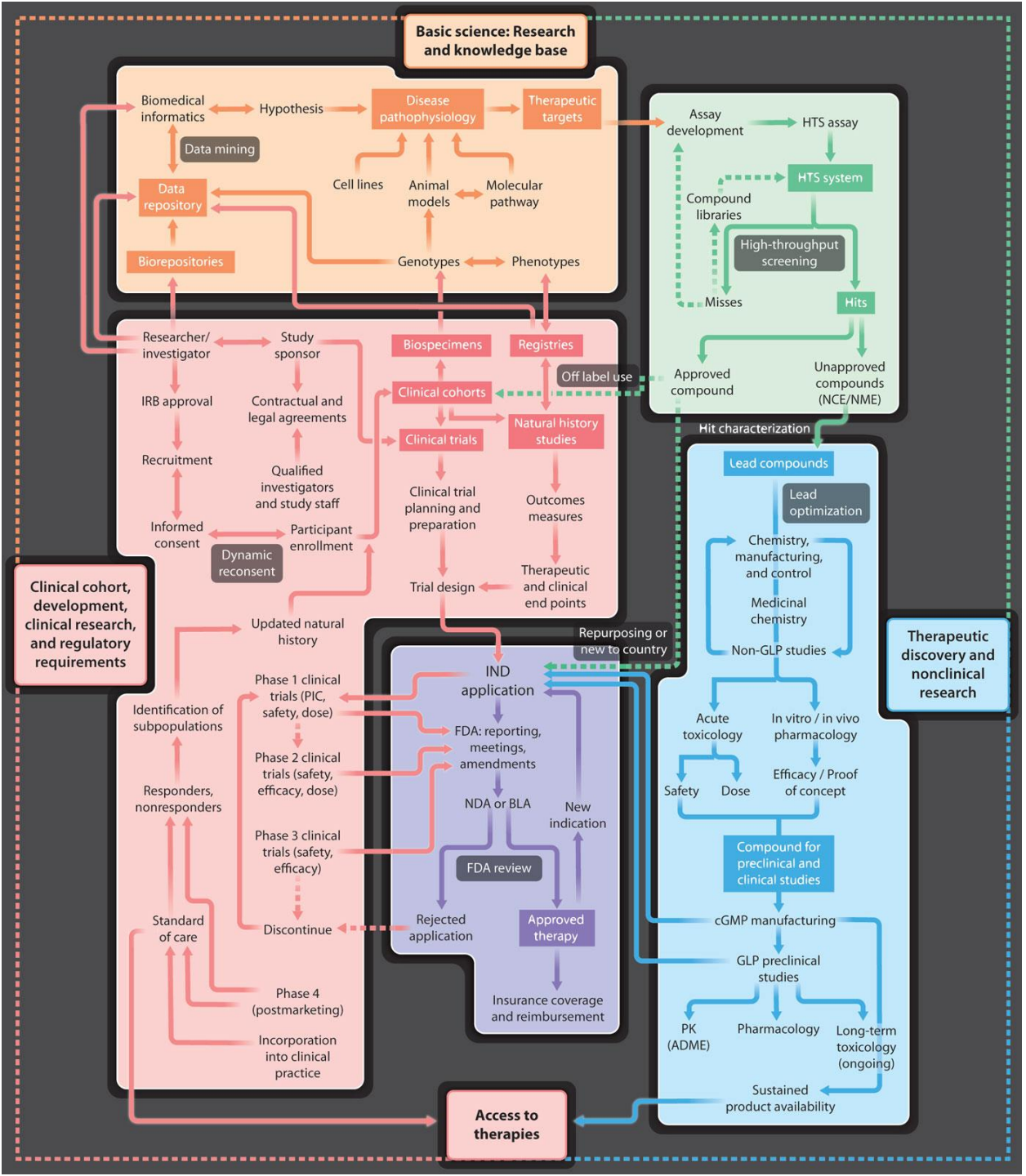


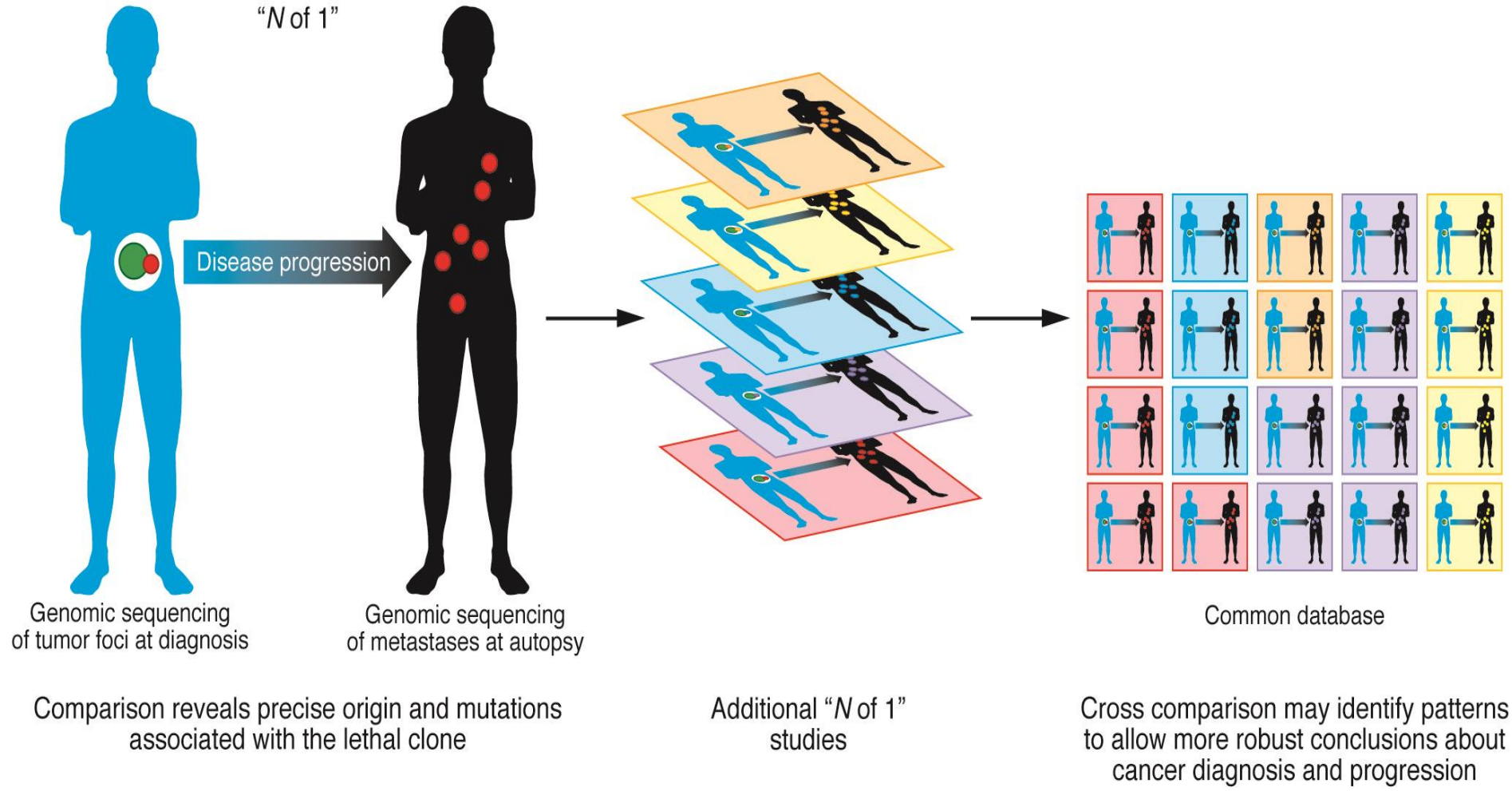
Fig. 1. Using NETS to catch new therapies.

Kristin Baxter et al., Sci Transl Med 2013;5:171

JCI The Journal of Clinical Investigation

Emerging concepts in developing treatments with better therapeutic index

Brannon & Sawyers *J Clin Inv* '13



Center for Health Policy at BROOKINGS

Improving Productivity in Pharmaceutical Research and Development: The Role of Clinical Pharmacology and Experimental Medicine

Center for Health Policy
The Brookings Institution

The Embassy Row Hotel • Washington, DC
July 28, 2015

Precision Medicine: Trial Enrichment, Biomarker Science, and Mechanistic Reasoning to Optimize Patient Selection

Mike Pacanowski
Associate Director for Genomics and Targeted Therapy
CDER/OTS/OCP

This presentation reflects the views of the presenter and is not be construed to represent FDA's policies or positions.

Goal

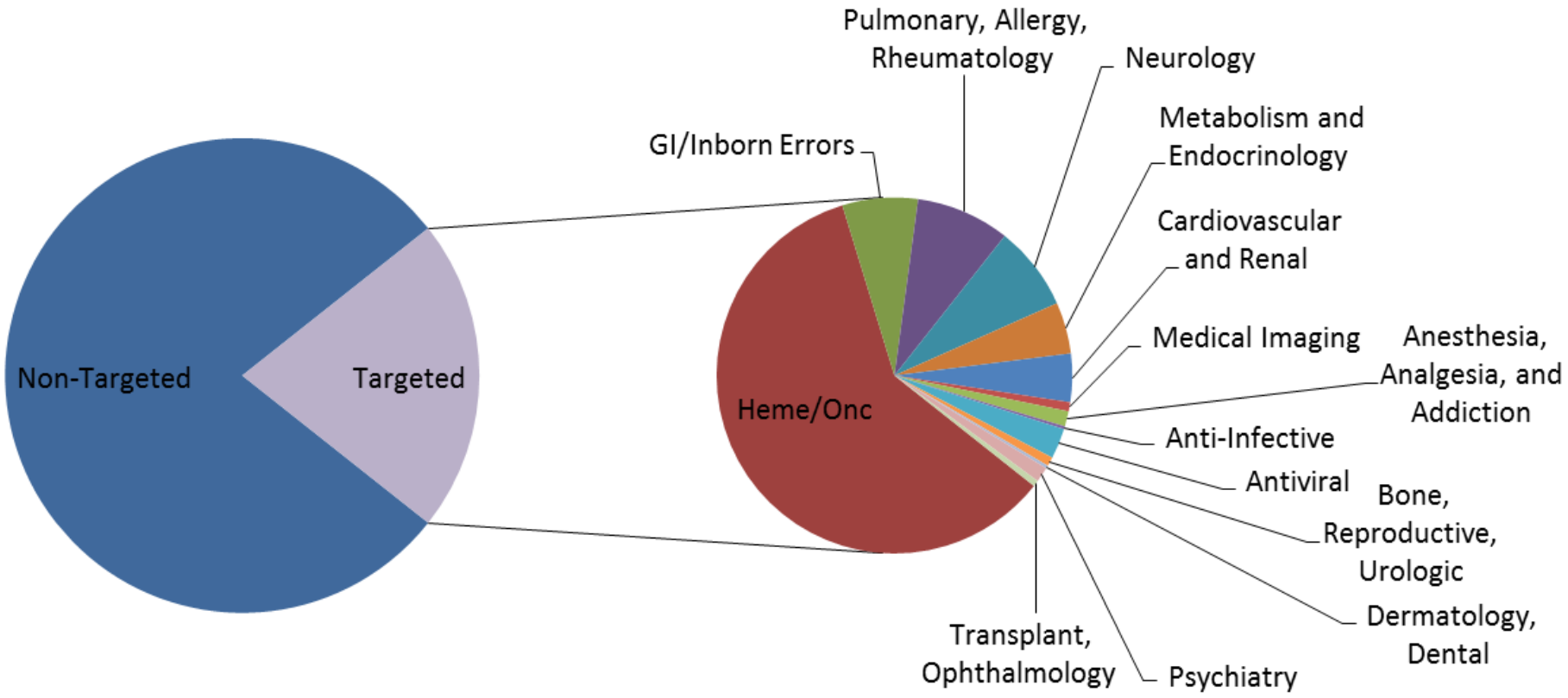
- Identify best design practices for early-phase trials to enable late-phase enrichment strategies that reduce attrition and improve benefit/risk assessments for individual patients

Precision Medicines

- Drug or biologic intended for use in only a subset of patients with a disease who are identified by a genomic, proteomic, or other specific biomarker
- Biomarkers may have diagnostic, prognostic, predictive, or other value; reasonable expectation that the pharmacology of the drug depends on the biomarker
- Targeted strategy may stem from mechanistic relationship to well-understood biomarker, or evidence for differential effects in experimental studies or clinical trials

PMID: 23571772

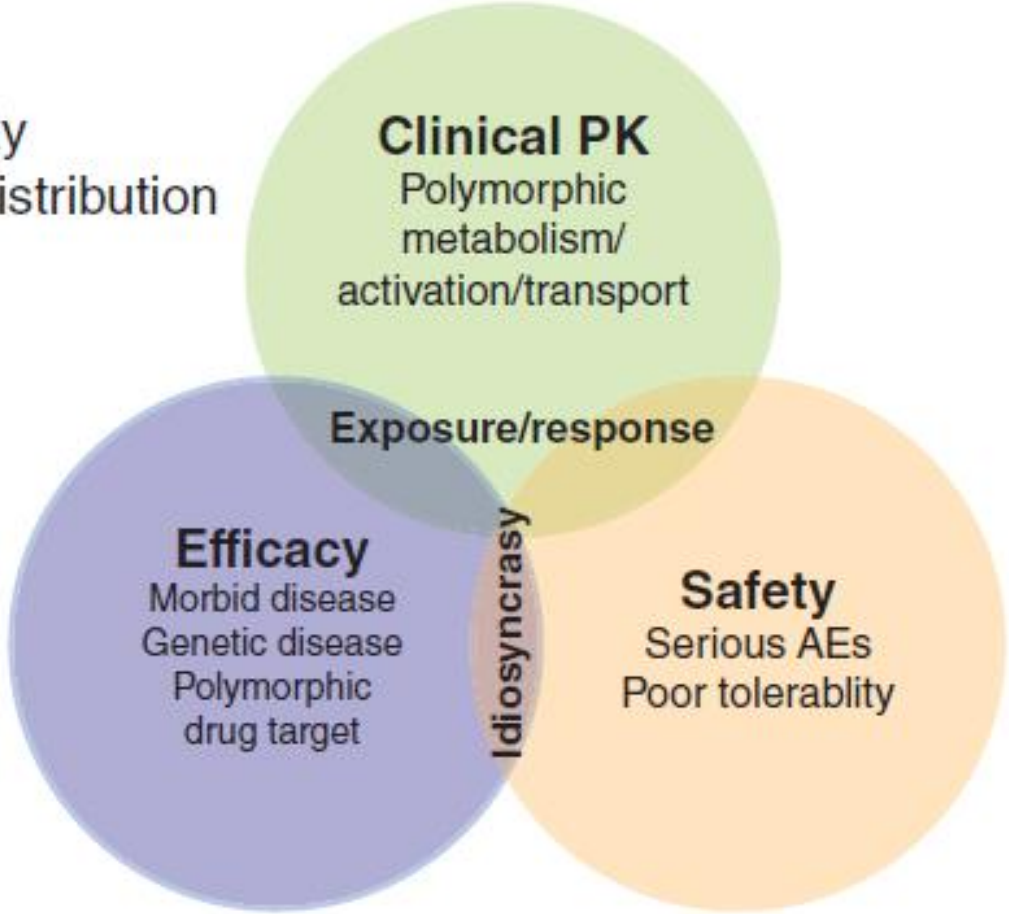
Investigational Drug Landscape



Estimated volume of meeting packages and protocols with biomarker-based objectives (e.g., enrichment, stratification, endpoints) based on ~1700 electronic submissions, May 2014-Mar 2015

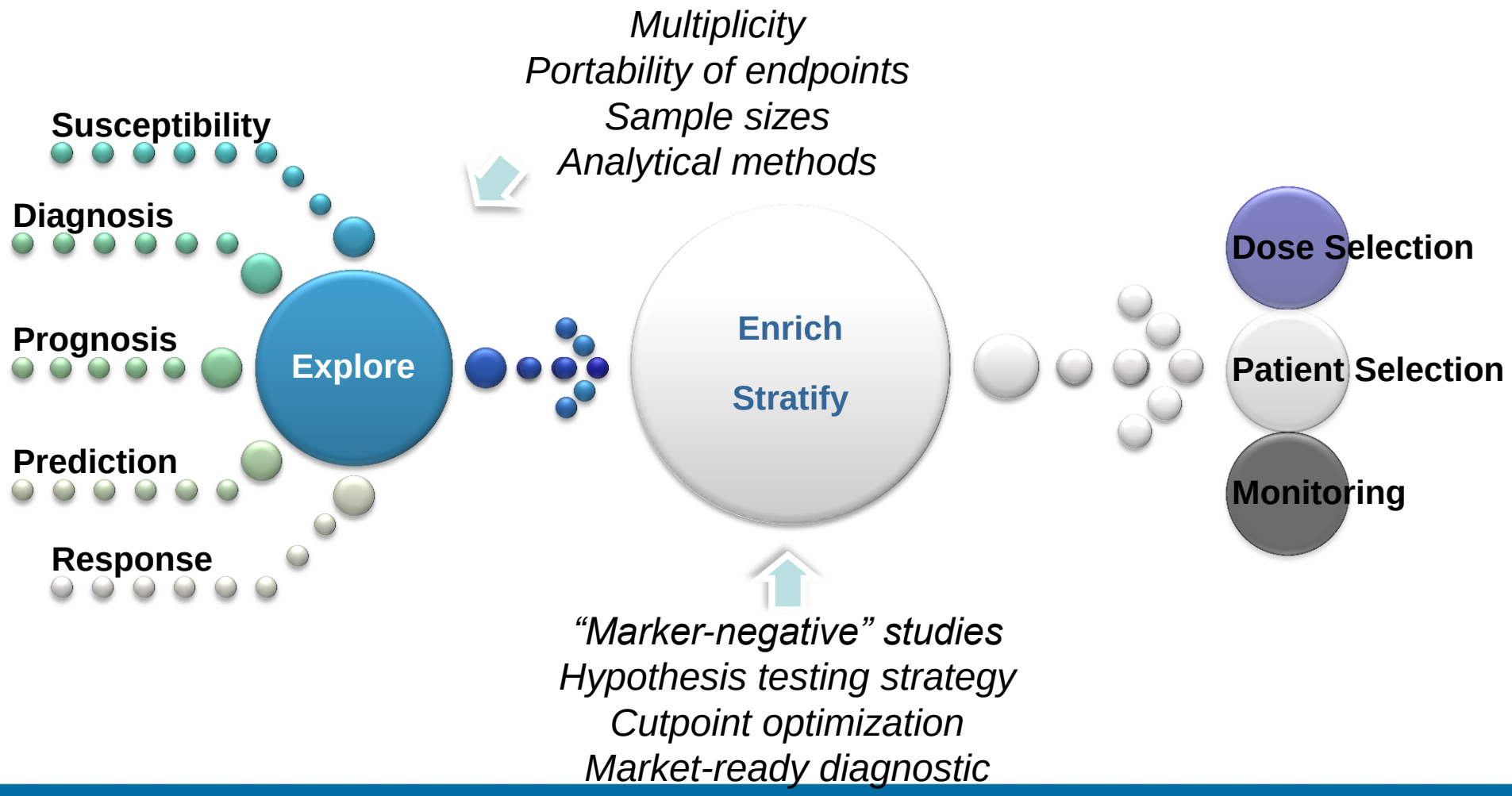
Suitable Candidates for Targeted Development

High variablity
Multimodal distribution
Race effects
Outliers



PMID: 24548989; see Guidance for Industry – Clinical Pharmacogenomics

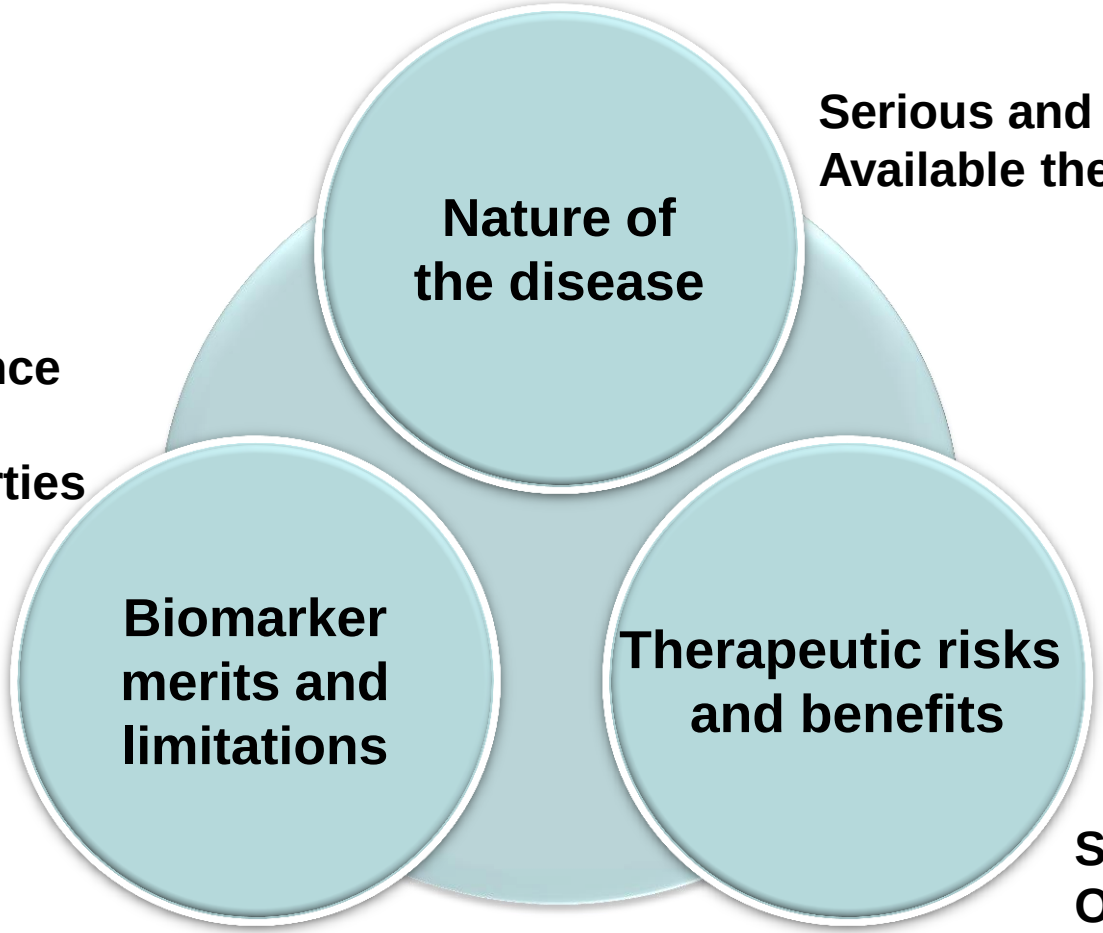
Patient Selection Biomarkers in Clinical Drug Development



Targeted Development Approaches

- Ideally, codevelopment planned from outset
  - Suitable for known predictive/prognostic biomarkers, clear differences in the drug target
- Typically, strategy established at EOP2 junction
  - Based on early trials fit to find large biomarker effects
  - Gain some evidence of predictive value
- Exceptionally, discovered in late-phases or post-approval
  - Certainty, and compelling shift in risk/benefit
  - Complete, high-quality data are essential
  - Pro-/retrospective approaches require careful planning

Appropriateness of Biomarker-Based Indications



Serious and life-threatening
Available therapies

Medical relevance
Utility
Intrinsic properties

Safety profile
Overall benefit

Idealized Development Scenario

	Phase 1: Safety>PK>PD (BA, E/R, DDI, QT, Food)					**Post-Marketing:** Efficacy Safety PK
		Phase 2: PK/PD>Safety>Efficacy				
				Phase 3: Efficacy>Safety>PK/PD		
Learn	*ADME*	*ADME, Target, Disease*	*Omics*			
Confirm			*ADME, Target, Disease*	*Omics +/–*		*Omics –*
Apply	*ADME, Target, Disease*	*ADME, Target, Disease*		*ADME, Target, Disease*	*Omics +*	*Omics –*

Points to Consider

- Proactively manage exposure and response variability
- Exploit known biology for “quick[er] win” or “fast[er] fail”
- Design trials that are fit to identify predictive biomarkers

- Challenges
  - What is needed to build confidence with limited data?
  - Best way to develop around known liabilities?
  - How will (un)expected findings affect the program?
  - When to commit resources to assay development?
  - Best approach integrate hypotheses in late-phase trials?

PMID: 20168317

Center for Health Policy at BROOKINGS

Improving Productivity in Pharmaceutical Research and Development: The Role of Clinical Pharmacology and Experimental Medicine

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Aducanumab (BIIB037), an Anti-Amyloid Beta Monoclonal Antibody, in Patients With Prodromal or Mild Alzheimer's Disease

Brookings, Washington, DC

July 28, 2015

Vissia Viglietta MD, PhD

Biogen, Cambridge MA

Alzheimer's Disease: The stats

In 2013, 15.5 million family & friends provided 17.7 billion hours of unpaid care to those with Alzheimer's disease and other dementias

Alzheimer's disease (AD) accounts for 60–70% of all dementia diagnoses

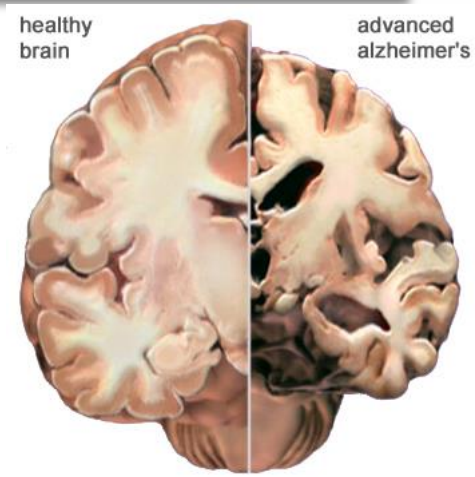
~ 5 million in the U.S. are living with AD
By 2050, up to 16 million

Median survival after diagnosis is 8.5 years
AD is the sixth leading cause of death in the U.S.

Over $600B in global healthcare spend
AD is the most expensive condition in the U.S.

Alzheimer's disease

Plaques & tangles



- Pathological hallmarks
  - Amyloid-β (Aβ) plaques
  - Neurofibrillary tangles
- Inflammatory processes likely play role
- Associated with
  - Brain atrophy
  - Neurochemical changes
  - Neuronal loss

Biogen

The Amyloid Hypothesis

- Alzheimer's disease is characterized by the aggregation of Aβ peptides in the form of Aβ plaques, one of the hallmark neuropathological features of the disease

- Aβ peptide is produced by sequential processing of amyloid precursor protein (APP) in the amyloidogenic pathway

- Aβ peptides self aggregate into various forms, including soluble monomers and oligomers, and insoluble fibrils and amyloid plaques

- Clearance pathways for brain Aβ include receptor-mediated transport across the blood-brain barrier and enzymatic degradation

- Accumulation of Aβ production within the Alzheimer's disease may result from either overproduction and/or impaired clearance

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However, the road to drug development in AD has been paved with high profile failures

Trial Design Issues

- Earlier AD trials did not screen patients for amyloid plaque; patients enrolled without Alzheimer's (e.g Roche's gantenerumab in prodromal patients)
  - Bapi Ph3 6.5% ApoE4 carriers, 36% ApoE4 non-carriers not meeting SUVR cut off for positivity (PIB)
  - Sola Ph3 6.6% ApoE4 carriers, 32.8% ApoE4 non-carriers not meeting SUVR cut off for positivity (AV45)
- Patients enrolled with moderate Alzheimer's; too progressed to benefit from therapy (e.g. Lilly's solanezumab trial in moderate)

Dose Effect

- Adverse event of ARIA limited ability to push dose high enough for efficacy (e.g. Pfizer's/J&J's bapineuzumab)

The industry has learned from these failures and incorporated learnings into the newer DMT clinical trials underway

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Aducanumab Background

- Human monoclonal antibody selective for aggregated forms of beta-amyloid, including soluble oligomers and insoluble fibrils
- In Tg2576 mouse model of AD:
  - Dose-dependent reduction of Aβ with chronic dosing[1]
  - Microglia-mediated phagocytosis of amyloid plaques[2]
- A single ascending dose study[3] of aducanumab demonstrated acceptable safety and tolerability in mild-to-moderate subjects with AD at doses up to 30 mg/kg

Biogen

1. Bussiere et al. ADPD 2013; 2. Nitsch et al. Geneva/Springfield symposium 2014;. 3. Sevigny et al. ADPD 2013.

Key Elements of Study Design

Population

- Prodromal or mild AD
- MMSE ≥20
- Stable concomitant medications
- **Positive amyloid PET scan**

Dose Escalation Design

1 & 3 mg/kg: placebo (Arms 1-3)

10 mg/kg: placebo (Arms 4-5)

6 mg/kg: placebo (Arms 6-7)

Titration: placebo (Arms 8-9)

- Planned sample size **188** subjects
- Randomization 3:1 active vs placebo
- Planned enrollment 30 subjects per active arm
- Stratified by ApoE ε4 status
- Dose escalation based on independent DMC review of safety, tolerability and PK data

Endpoints

Primary

- Safety and tolerability

Secondary

- Serum PK
- Anti-aducanumab antibodies
- Amyloid PET, change from baseline to Week 26

Exploratory

- CDR-sb, MMSE
- Amyloid PET, change from baseline to Week 54

Prodromal AD: MMSE 24-30; spontaneous memory complaint; total free recall score ≤27 on FCSRT; global CDR score 0.5; absence of significant levels of impairment in other cognitive domains; essentially preserved activities of daily living and absence of dementia

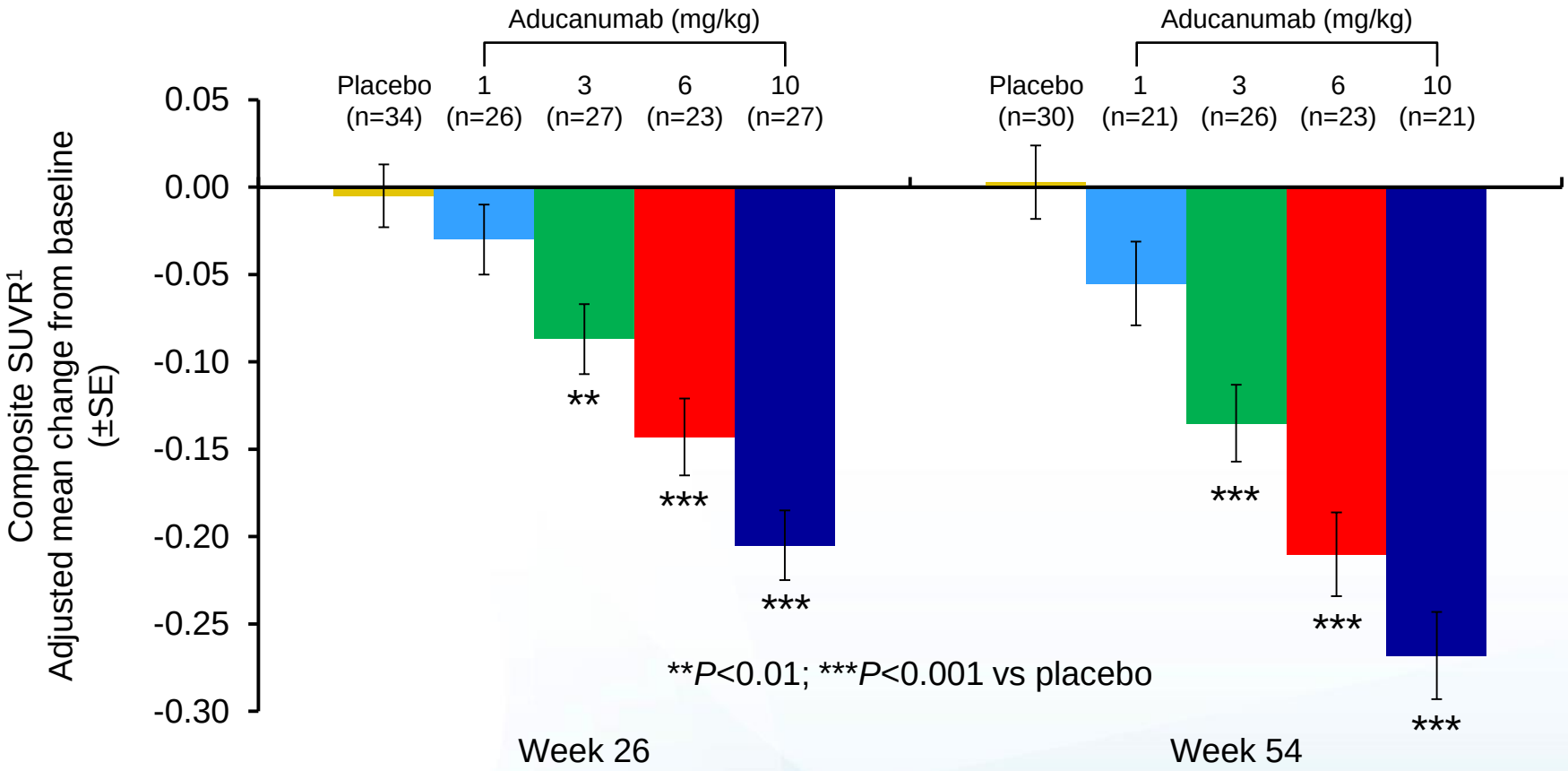
Mild AD: MMSE 20-26; global CDR 0.5 or 1.0; meeting NIA-AA core clinical criteria for probable AD

Baseline Disease Characteristics

		Aducanumab			
	Placebo (n=40)	1 mg/kg (n=31)	3 mg/kg (n=32)	6 mg/kg (n=30)	10 mg/kg (n=32)
Age years, mean	72.8	72.6	70.5	73.3	73.7
ApoE ε4, n (%)					
Carriers	26 (65)	19 (61)	21 (66)	21 (70)	20 (63)
Non-carriers	14 (35)	12 (39)	11 (34)	9 (30)	12 (38)
Clinical stage, n (%)					
Prodromal	19 (48)	10 (32)	14 (44)	12 (40)	13 (41)
Mild	21 (53)	21 (68)	18 (56)	18 (60)	19 (59)
MMSE, mean ± SD	24.7 ± 3.6	23.6 ± 3.3	23.2 ± 4.2	24.4 ± 2.9	24.8 ± 3.1
Global CDR, n (%)					
0.5	34 (85)	22 (71)	22 (69)	25 (83)	24 (75)
1	6 (15)	9 (29)	10 (31)	5 (17)	8 (25)
CDR-sb, mean ± SD	2.66 ± 1.50	3.40 ± 1.76	3.50 ± 2.06	3.32 ± 1.54	3.14 ± 1.71
PET SUVR, mean	1.441	1.441	1.464	1.429	1.441
AD medications use,[a] n (%)	24 (60)	19 (61)	28 (88)	20 (67)	17 (53)

CDR-sb, Clinical Dementia Rating sum of boxes; [a]Cholinesterase inhibitors and/or memantine

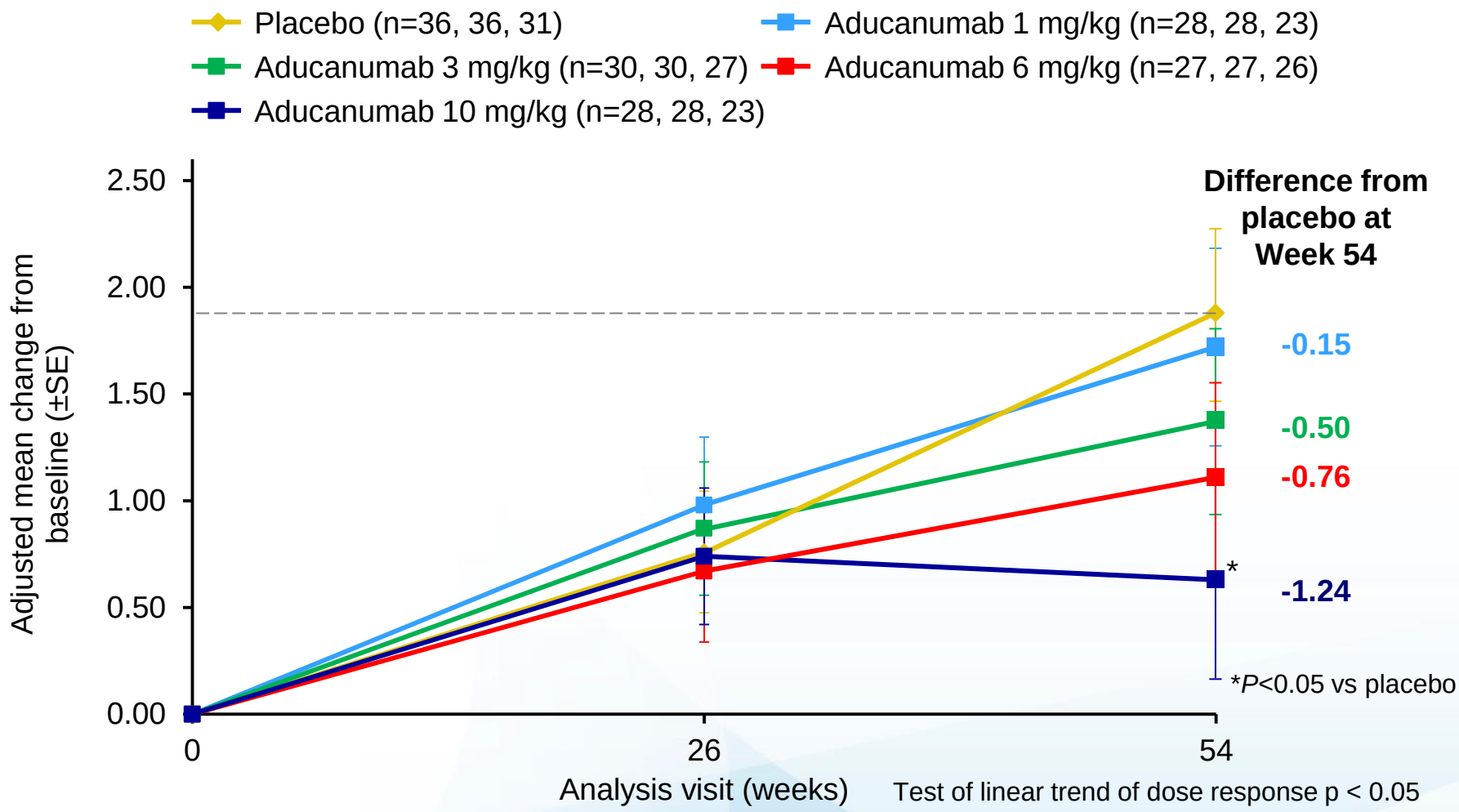
Amyloid Plaque Reduction with Aducanumab



Analyses based on observed data. ANCOVA for change from baseline with factors of treatment, laboratory ApoE ε4 status (carrier and non-carrier), and baseline composite SUVR. PD analysis population is defined as all randomized subjects who received at least 1 dose of study medication and had at least 1 post-baseline assessment of the parameter.

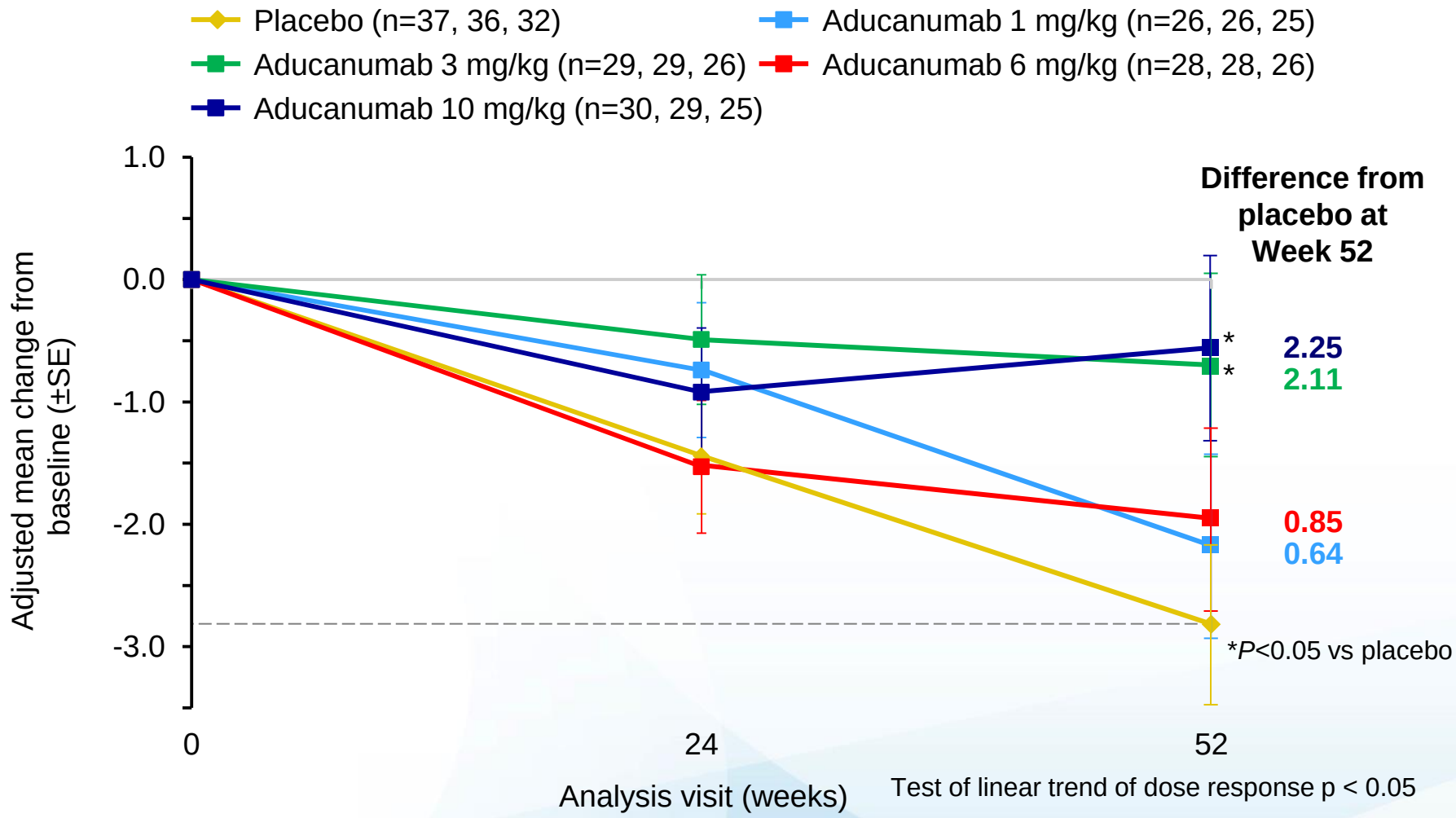
1. Ostrowitzki et al. Arch Neurol 2012; 2. Clark et al. Lancet Neurol 2012

Slowing of Decline on CDR-sb with Aducanumab



CDR-sb is an exploratory endpoint. Analyses based on observed data. ANCOVA for change from baseline with factors of treatment, laboratory ApoE ε4 status (carrier and non-carrier), and baseline CDR-sb. Efficacy analysis population is defined as all randomized subjects who received at least 1 dose of study medication and had at least 1 post-baseline questionnaire assessment.

Slowing of Decline on MMSE with Aducanumab



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MMSE is an exploratory endpoint. Analyses based on observed data. ANCOVA for change from baseline with factors of treatment, laboratory ApoE ε4 status (carrier and non-carrier), and baseline MMSE. Efficacy analysis population is defined as all randomized subjects who received at least one dose of study medication and had at least one post-baseline questionnaire assessment

ARIA: Incidence and Characteristics

		Aducanumab			
	Placebo	1 mg/kg	3 mg/kg	6 mg/kg	10 mg/kg
Subjects with at least 1 MRI	38	31	32	30	32
ARIA-E n (%)	0	1 (3)	2 (6)	10 (33)	13 (41)
ApoE ε4 carrier	0	1 (5)	1 (5)	9 (43)	11 (55)
ApoE ε4 non-carrier	0	0	1 (9)	1 (11)	2 (17)
Isolated ARIA-H, n (%)	2 (5)	2 (6)	3 (9)	0	2 (6)

Most (92%) observed within the first 5 doses

65% of events were asymptomatic

35% were symptomatic

- Mostly rated as mild to moderate (78%)
- Generally transient, typically resolving within 4 weeks
- Included headache, visual disturbances, or confusion

MRI findings typically resolved within 4-12 weeks

Summary

Statistically significant dose- and time-dependent reduction of amyloid plaque, as measured by PET imaging, evident at 6 months and 1 year of treatment

Statistically significant dose-dependent slowing of decline on MMSE and CDR-sb at 1 year

ARIA-E was the main safety and tolerability finding

- Dose- and ApoE ε4 dependent
- Monitorable and manageable

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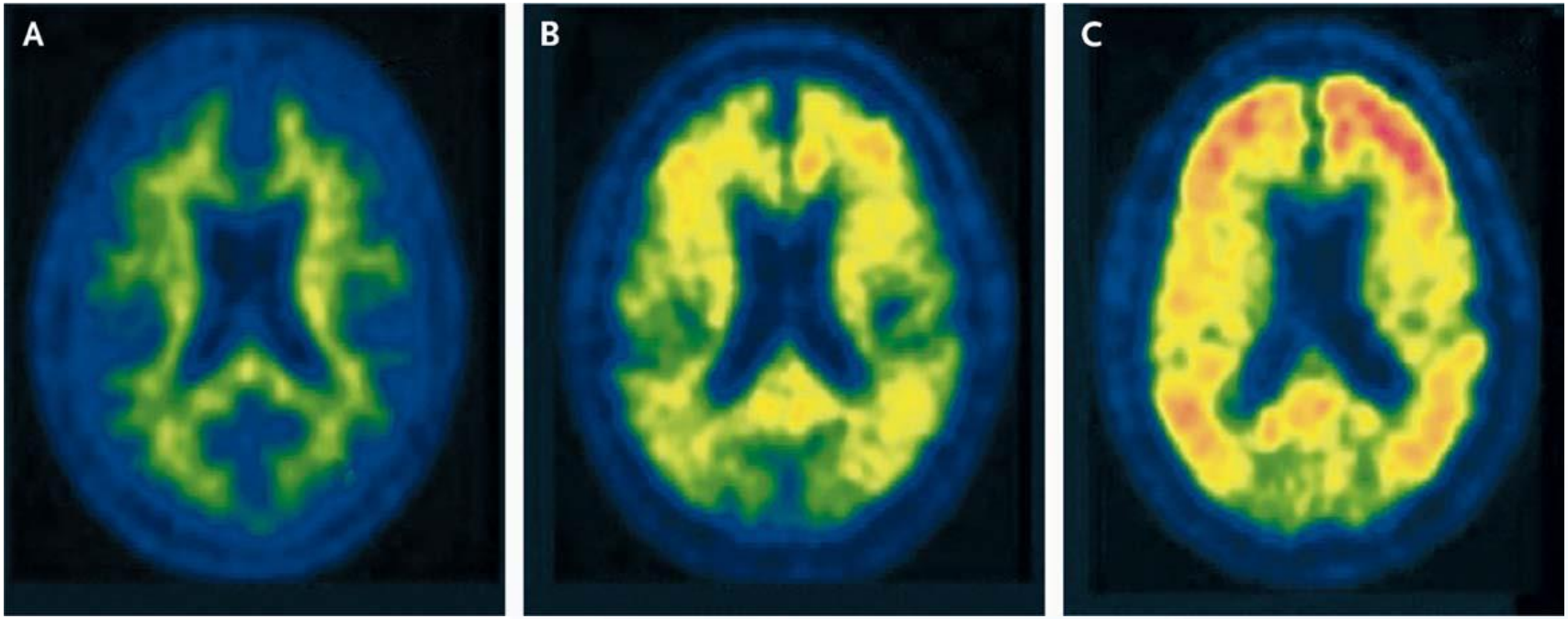
Learnings from Ph1b study allowed quicker launch of Ph3 aducanumab program:

ENGAGE and EMERGE Study

Phase 3 Design	
Population	MCI due to AD + subset of mild AD MMSE 24-30, CDR-G 0.5, RBANS ≤ 85
Enrichment	Amyloid PET positivity
Doses *Different in APOE4 carriers and non carriers*	Two dose levels (low & high) Differential dosing based on ε4 status ε4+: Titrate to low dose, high dose or placebo ε4-: Titrate to low dose, high dose or placebo
Duration	18 months + 24 month Long Term Extension
Primary endpoint	CDR sum of boxes (change from baseline at week 78)
Other endpoints	Secondary: MMSE, ADAS-Cog 13, ADCS-ADL-MCI Tertiary: vMRI, fMRI, CSF disease-related markers (subset), Amyloid PET (subset)
Sample size	~1350 per study (450/arm; 1:1:1)

Thank You!

PET Amyloid Imaging



Normal cognition

Mild cognitive impairment (MCI)

Alzheimer's disease

Biogen

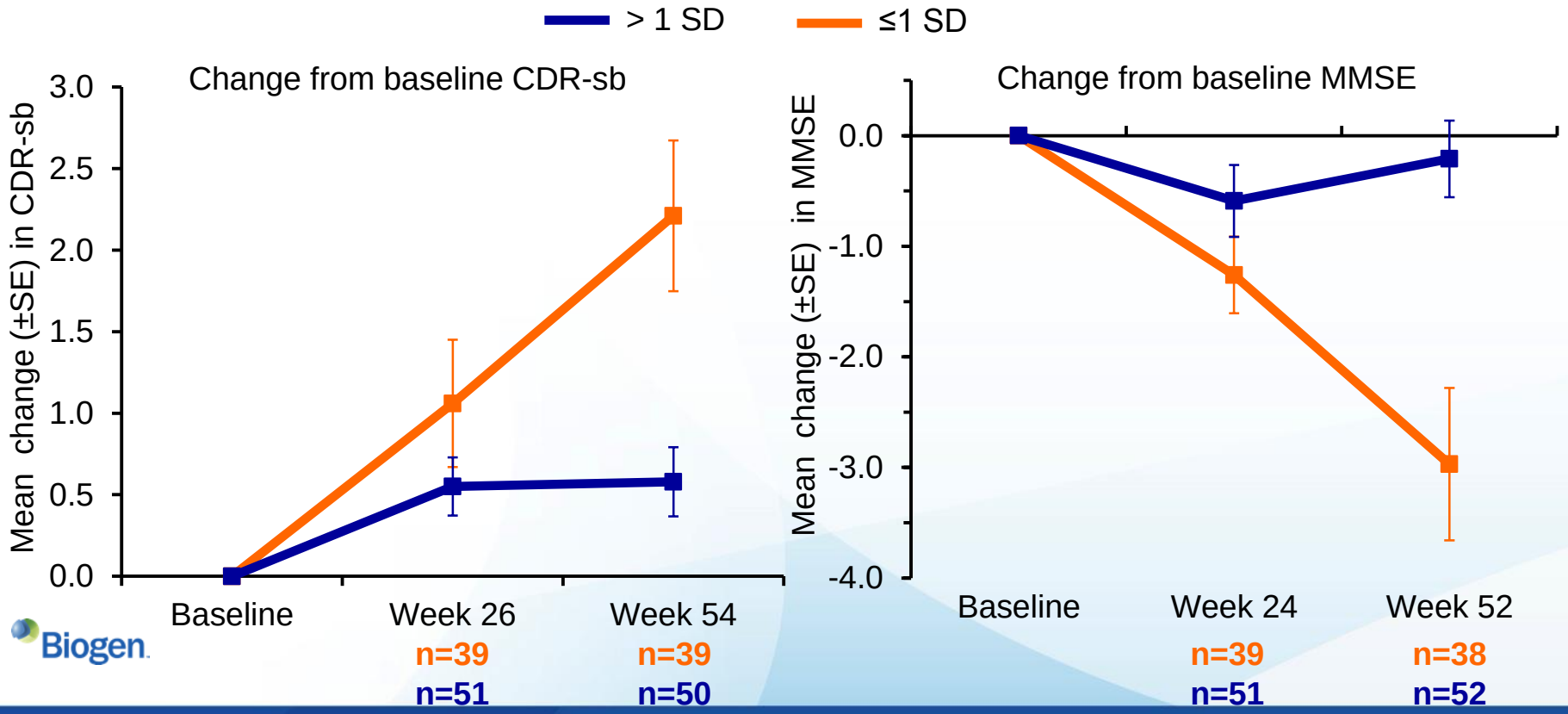
Petersen RC. N Engl J Med 2011;364:2227-2234

The NEW ENGLAND JOURNAL of MEDICINE

Correlation Between Changes in PET SUVR and CDR-sb and MMSE in Aducanumab-Treated Patients

Change in SUVR vs Change in	Spearman correlation	P-value
CDR-sb	0.27	<0.05
MMSE	-0.38	<0.001

PET Reduction Relative to SD of Week 54 Placebo Change



ARIA-E Subject Disposition

	Aducanumab			
	1 mg/kg (n=31)	3 mg/kg (n=32)	6 mg/kg (n=30)	10 mg/kg (n=32)
ARIA-E, n (% population)	1 (3)	2 (6)	10 (33)	13 (41)
Continued treatment	0	2 (6)	7 (23)	5 (16)
Same dose	0	0	1 (3)	0
Dose reduced	0	2 (6)	6 (20)	5 (16)
Discontinued treatment*	1 (3)	0	3 (10)	8 (25)
ApoE ε4 carrier	1 (5)	0	2 (10)	7 (35)
ApoE ε4 non-carrier	0	0	1 (11)	1 (8)

54% of subjects who developed ARIA-E continued treatment

None of these subjects developed recurrent ARIA-E

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* *Per protocol, subjects who develop mild, moderate, or severe ARIA-E accompanied by moderate, severe, or serious clinical symptoms at any time during the study permanently discontinued treatment.*

Center for Health Policy at BROOKINGS

Improving Productivity in Pharmaceutical Research and Development: The Role of Clinical Pharmacology and Experimental Medicine

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Precision Medicine in Cystic Fibrosis

James C. Sullivan, Ph.D.
CF Biomarkers
Vertex Pharmaceuticals Incorporated

July 28, 2015

Outline

I. Background

II. Gating Defects

III. Processing / Trafficking Defects

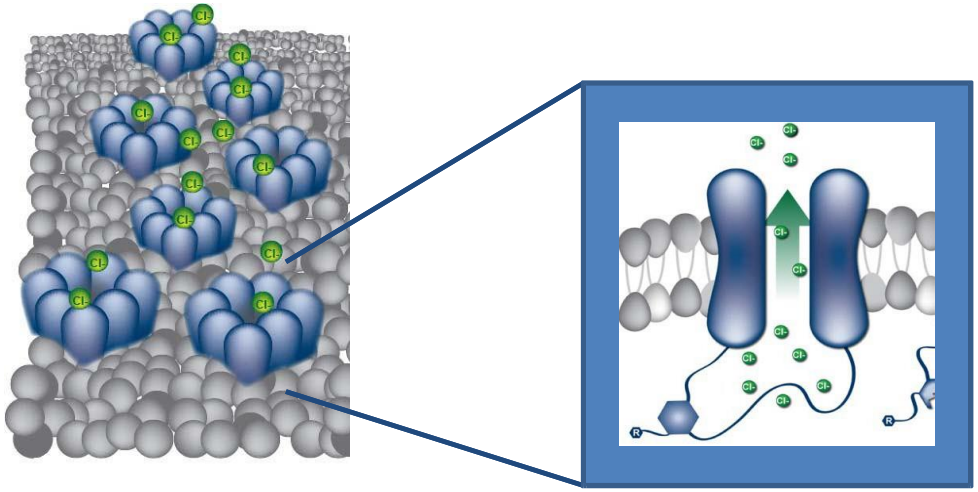
I. Overview of Cystic Fibrosis

- Cystic fibrosis (CF) is a life-limiting, rare genetic disease that affects ~70,000 people worldwide
- Although clinical manifestations occur throughout the body, progressive lung disease is the main cause of death
- CF is caused by defects in the CFTR ion channel that result from mutations in the *CFTR* gene
- Of the ~2000 *CFTR gene* mutations identified to date, 143 are known to cause CF
- *F508del* is the most common mutation

CFTR: cystic fibrosis transmembrane conductance regulator

Sosnay et al., Nature Genetics 2013; Castellani et al., JCF 2008; Riordan et al., Science 1989

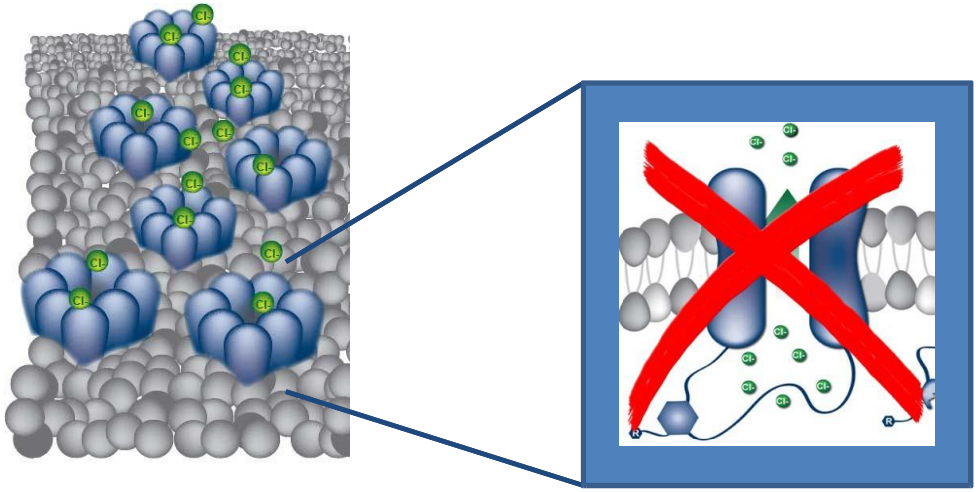
I. CFTR Is a Chloride Ion Channel that Is Normally Expressed at the Cell Surface of Epithelial Cells



- Multi-domain chloride ion channel
- Opened and closed (gated) by ATP binding and hydrolysis
- Channel opening requires phosphorylation by protein kinase A
- Regulates epithelial ion and fluid transport to facilitate airway clearance

Riordan et al., Science 1989; Anderson et al., Science 1991; Boucher Trends Mol Med 2007

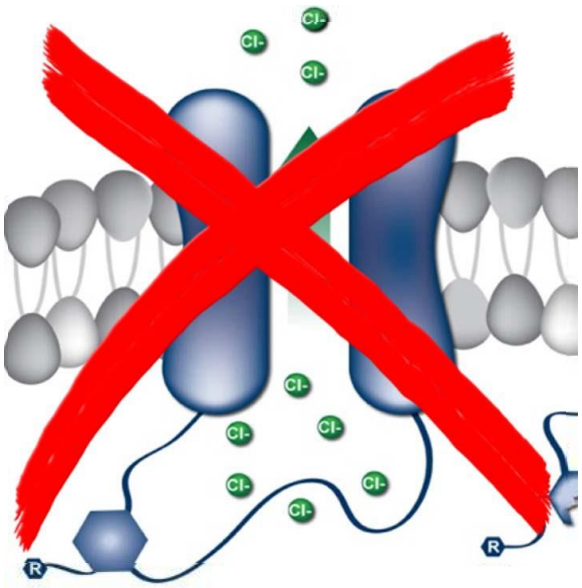
I. CF Is Caused by the Loss of Chloride Transport



- Due to defects in the quantity and/or function of the CFTR protein at the cell surface

Welsh and Smith Cell
1993

I. Loss of Chloride Transport Causes Multiple Clinical Manifestations



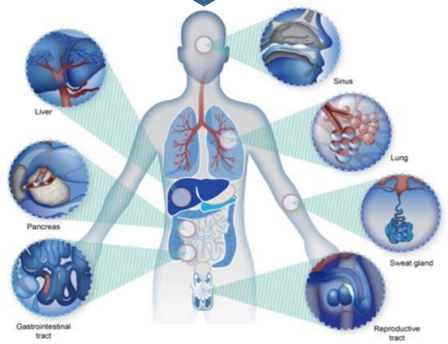
CFTR Mutations

Defect in CFTR

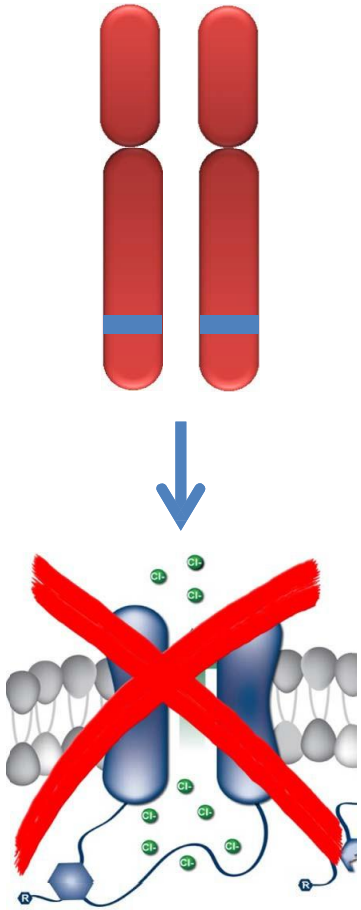
Protein Loss of

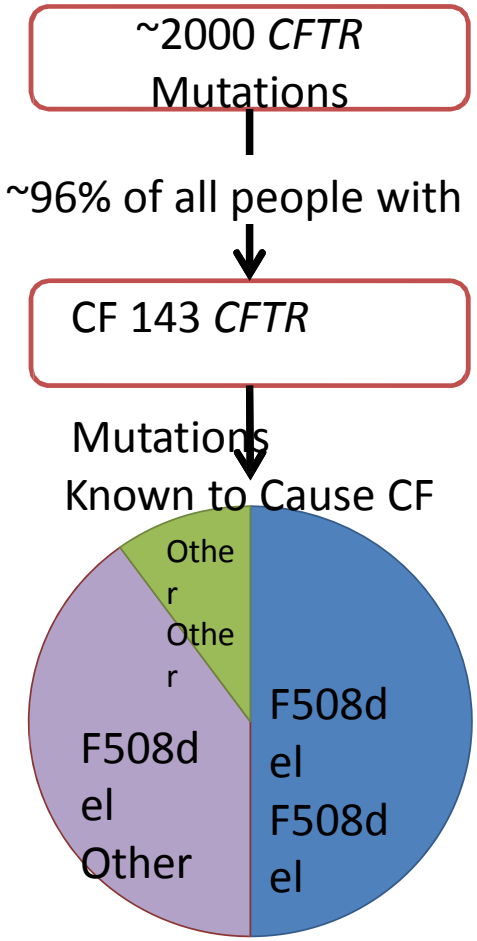
chloride and bicarbonate transport

F
ir



I. Loss of Chloride Transport Is Due to Defects in the CFTR Protein Caused by Mutations in the *CFTR* gene





Riorden et al., Science 1989; Sosnay et al., Nature Genetics 2013

I. Impact of *CFTR* Mutations on Disease Phenotype and Molecular Defect Well Understood

Natural history studies established the relationship between disease phenotype and level of CFTR dysfunction

- Suggested 10% – 20% improvement in CFTR function needed

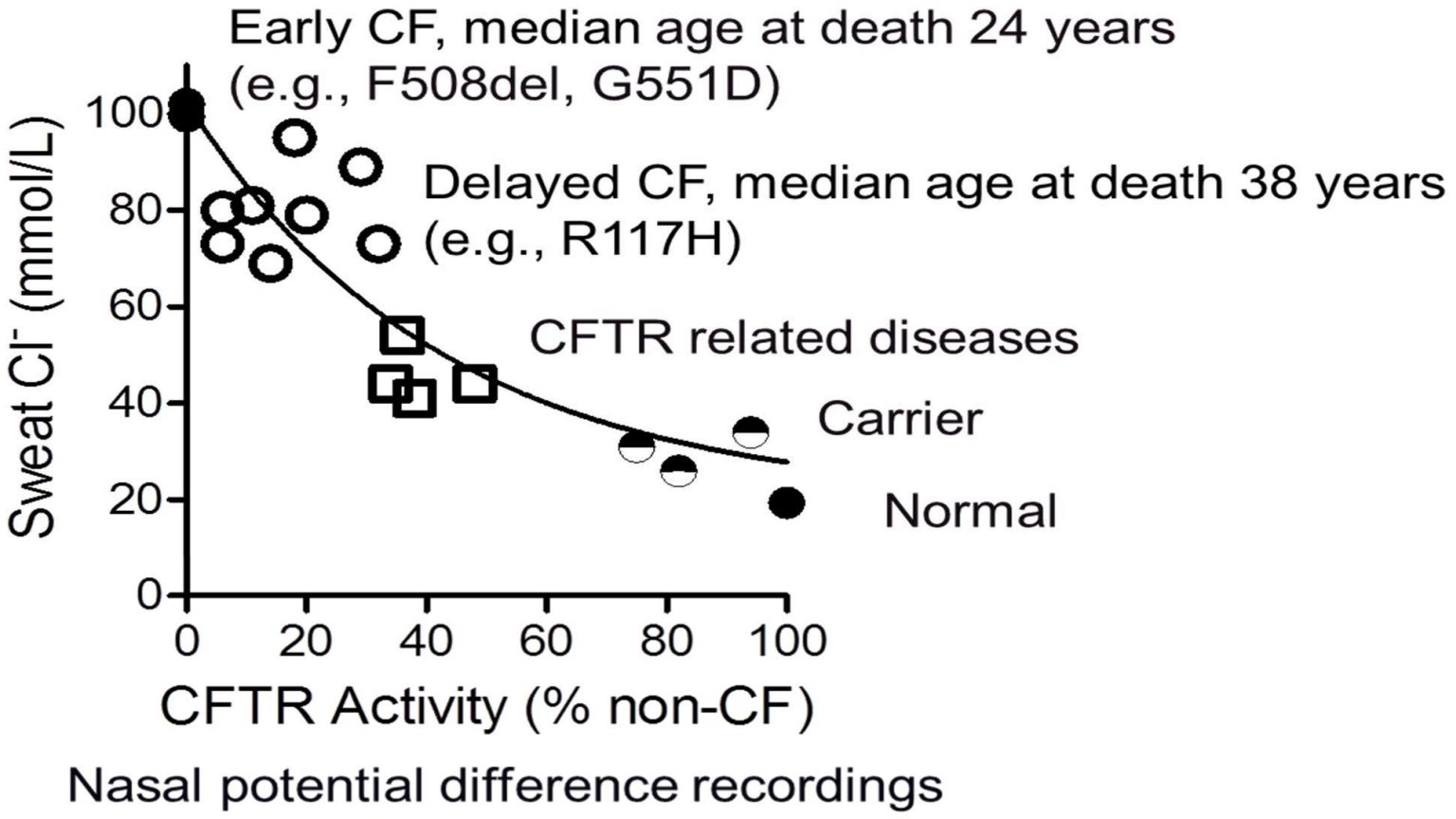
In vitro characterization of the type and severity of the molecular defects caused by different *CFTR* mutations

- Five different types of molecular defects identified that reduce the quantity and/or function of CFTR at the cell surface

Driven by academic research with private/government funding

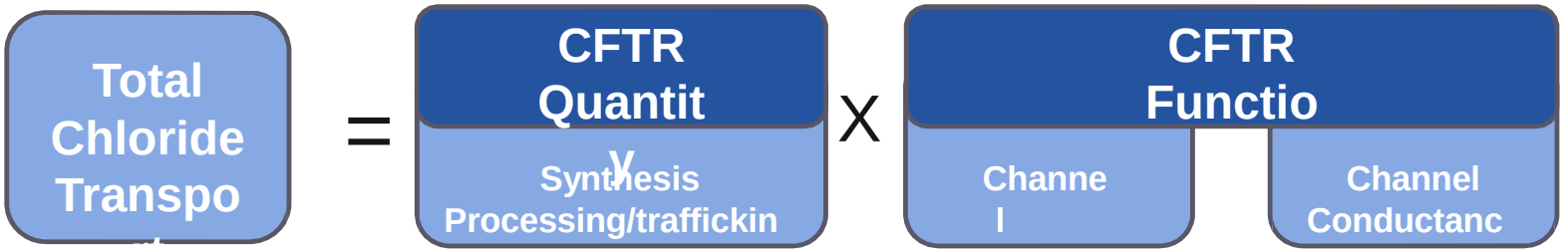
I. Level of CFTR Dysfunction Linked to Disease Phenotype

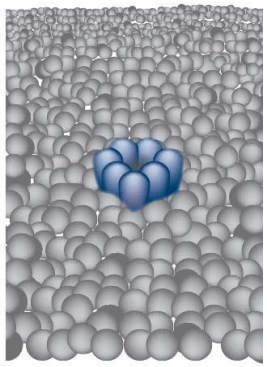
Natural history studies in people with different *CFTR* mutations



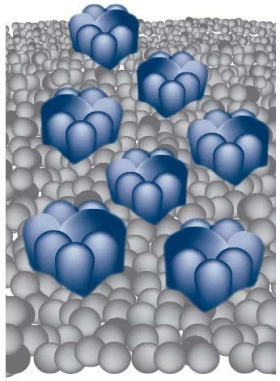
Accurso et al., J CF 2014

I. Five Different Classes of Molecular Defects Identified

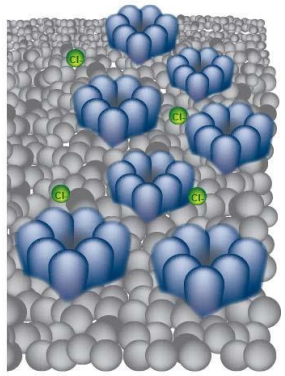




Truncated protein (Class I)
Low synthesis (Class VI)
Defective processing/trafficking (Class II)



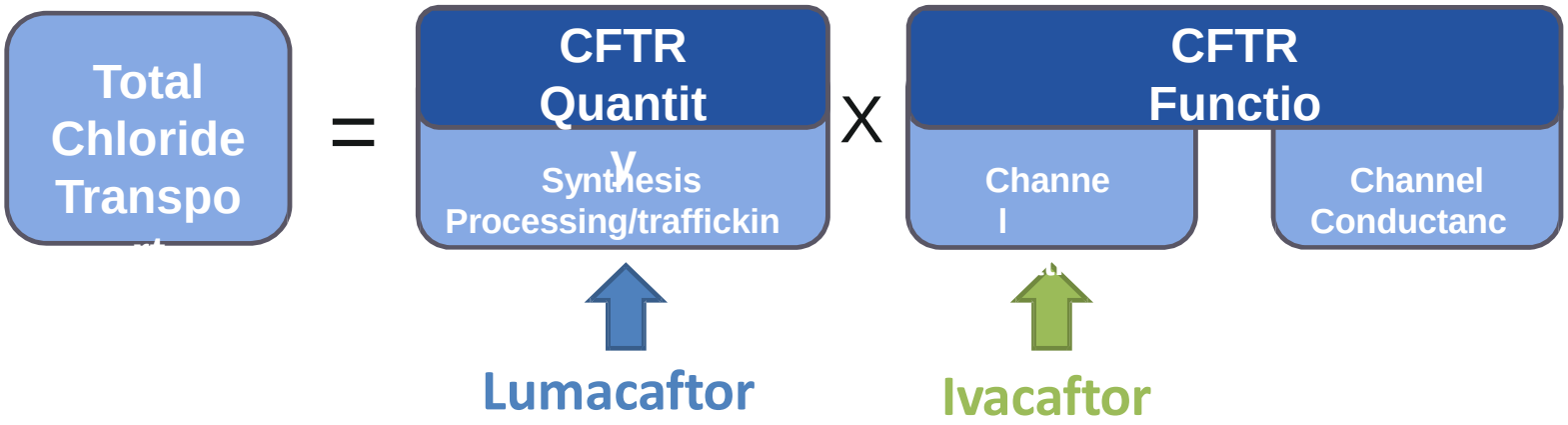
Defective Gating (Class III)



Defective Conductanc e (Class II)

Welsh and Smith Cell 1993

I. Two Approaches to Enhance Chloride Transport



Lumacaftor, VX-661

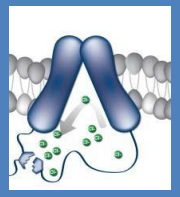
Facilitate increased chloride transport by increasing the quantity of functional CFTR delivered to the cell surface

Ivacaftor

Facilitate increased chloride transport by potentiating the channel-open probability (or gating) of the CFTR protein at the cell surface

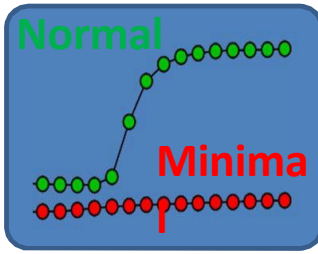
Van Goor et al., 2009; Van Goor et al., 2011

II. Ten Gating Defect Mutations



Molecular Defect

- Severe defect in the channel gating activity of



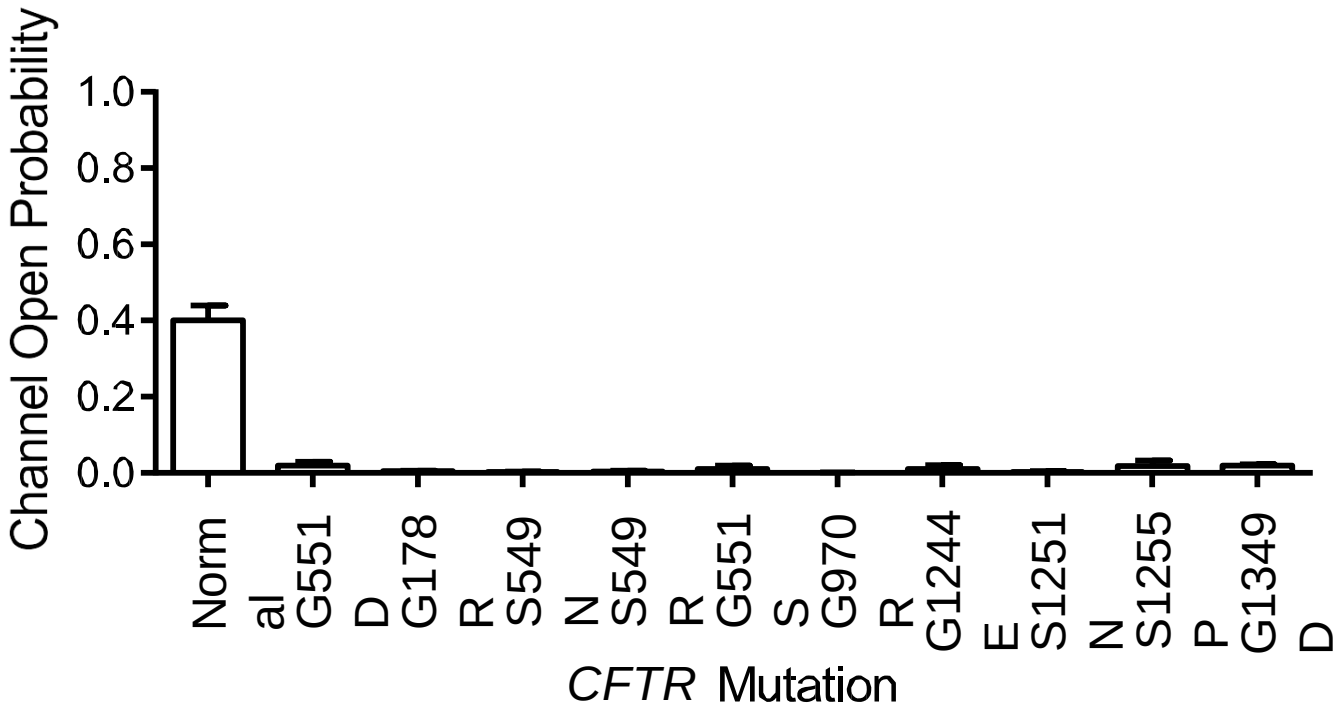
Functional Defect

- Like G551D, minimal (little-to-no) CFTR function

CF Phenotype

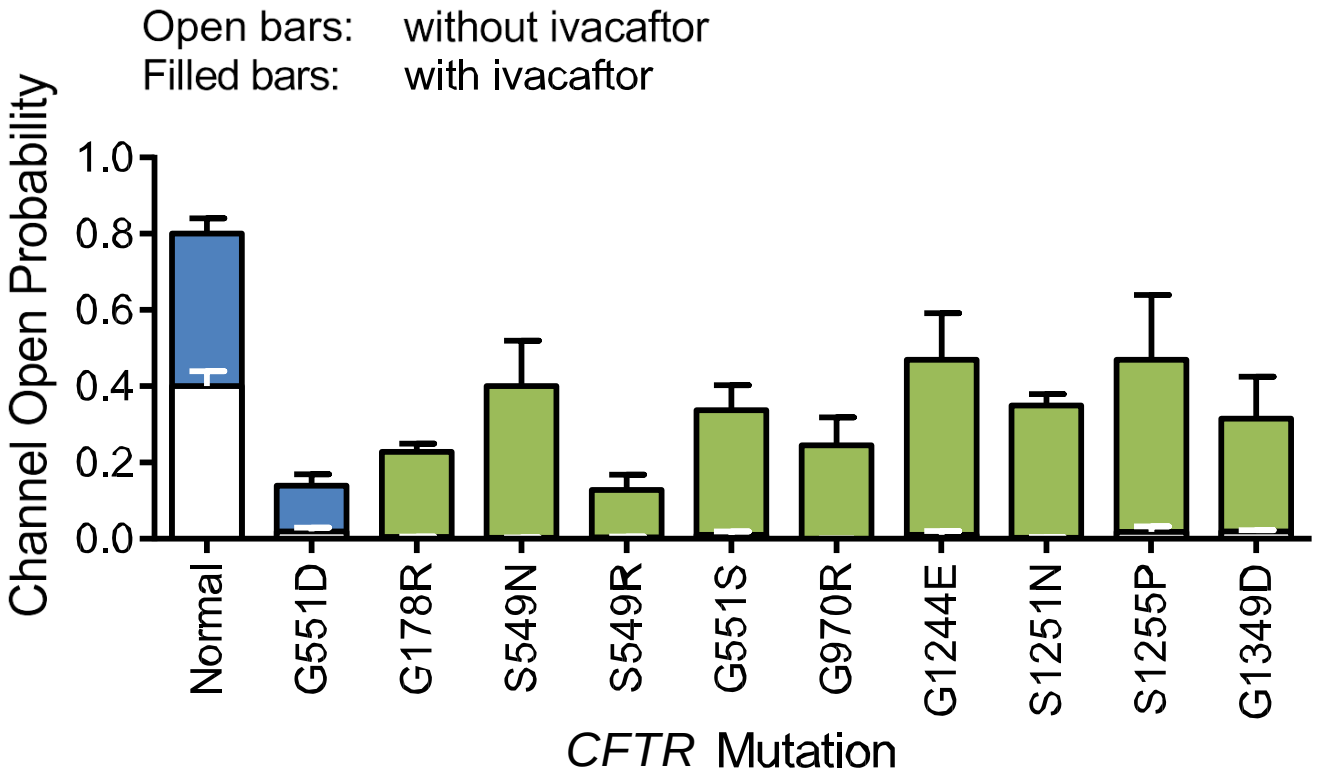
- Like G551D, typically associated with severe CF phenotype

Ten *CFTR* Mutations Associated with Severe Defects in Channel Gating Activity



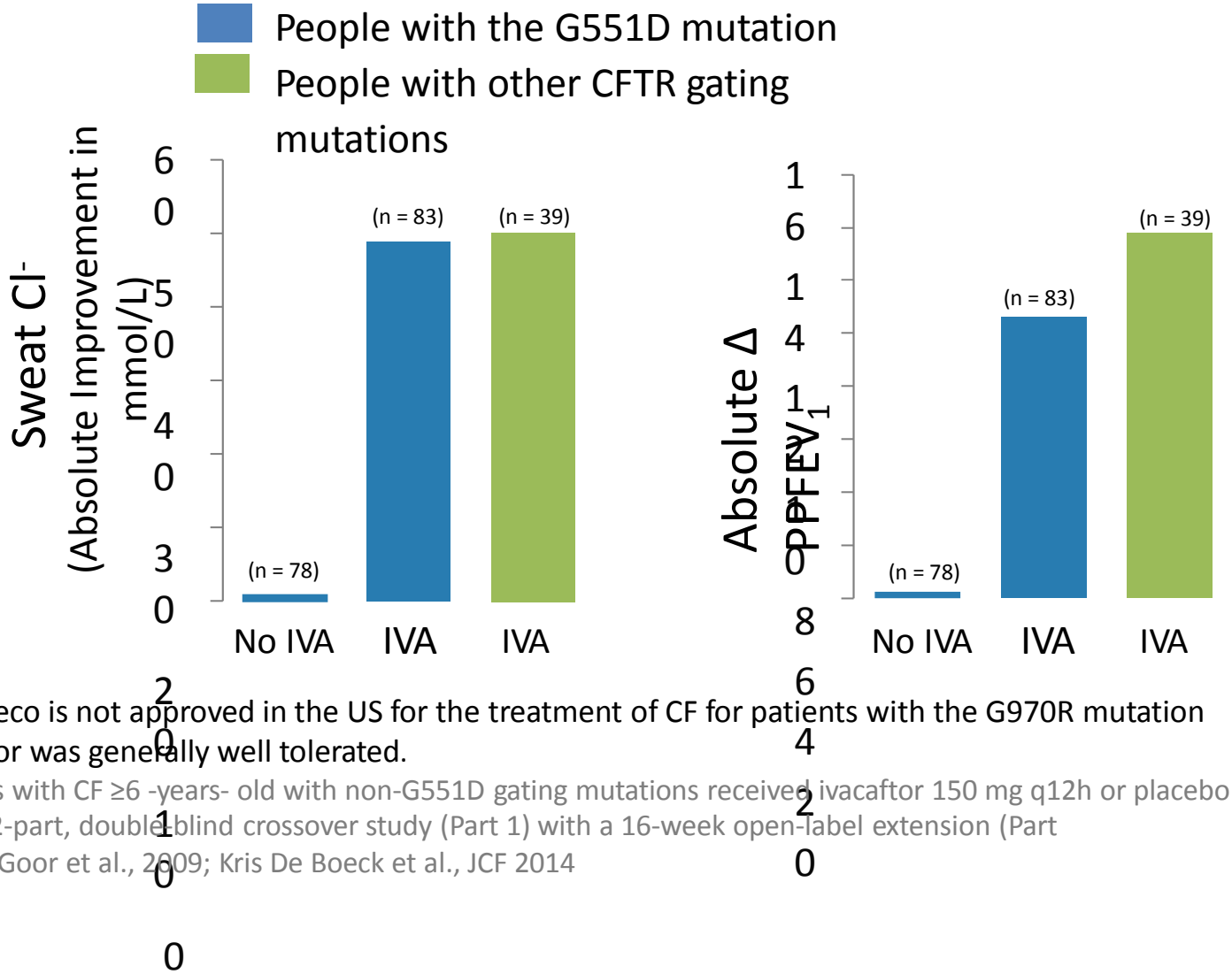
Single channel electrophysiology with Fischer rat thyroid cells Yu H, et al. *JCF* 2012

Ivacaftor Potentiated All Mutant CFTR Forms with Defects in Channel Gating



Single channel electrophysiology with Fischer rat thyroid cells Yu H, et al. *JCF* 2012

Clinical Response to Ivacaftor Was Similar Between People with *G551D* and Other *CFTR* Gating Mutations*

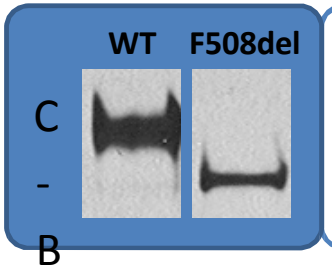


*Kalydeco is not approved in the US for the treatment of CF for patients with the G970R mutation

Ivacaftor was generally well tolerated.

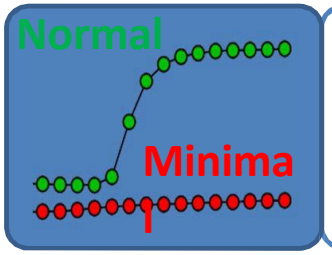
Patients with CF ≥6 -years- old with non-G551D gating mutations received ivacaftor 150 mg q12h or placebo for 8 weeks in this 2-part, double-blind crossover study (Part 1) with a 16-week open-label extension (Part 2). Van Goor et al., 2009; Kris De Boeck et al., JCF 2014

III. Approximately 50% of People with CF Are Homozygous for *F508del*



Molecular Defect

- Severe defect cellular processing and trafficking, preventing most of the CFTR protein from reaching the surface



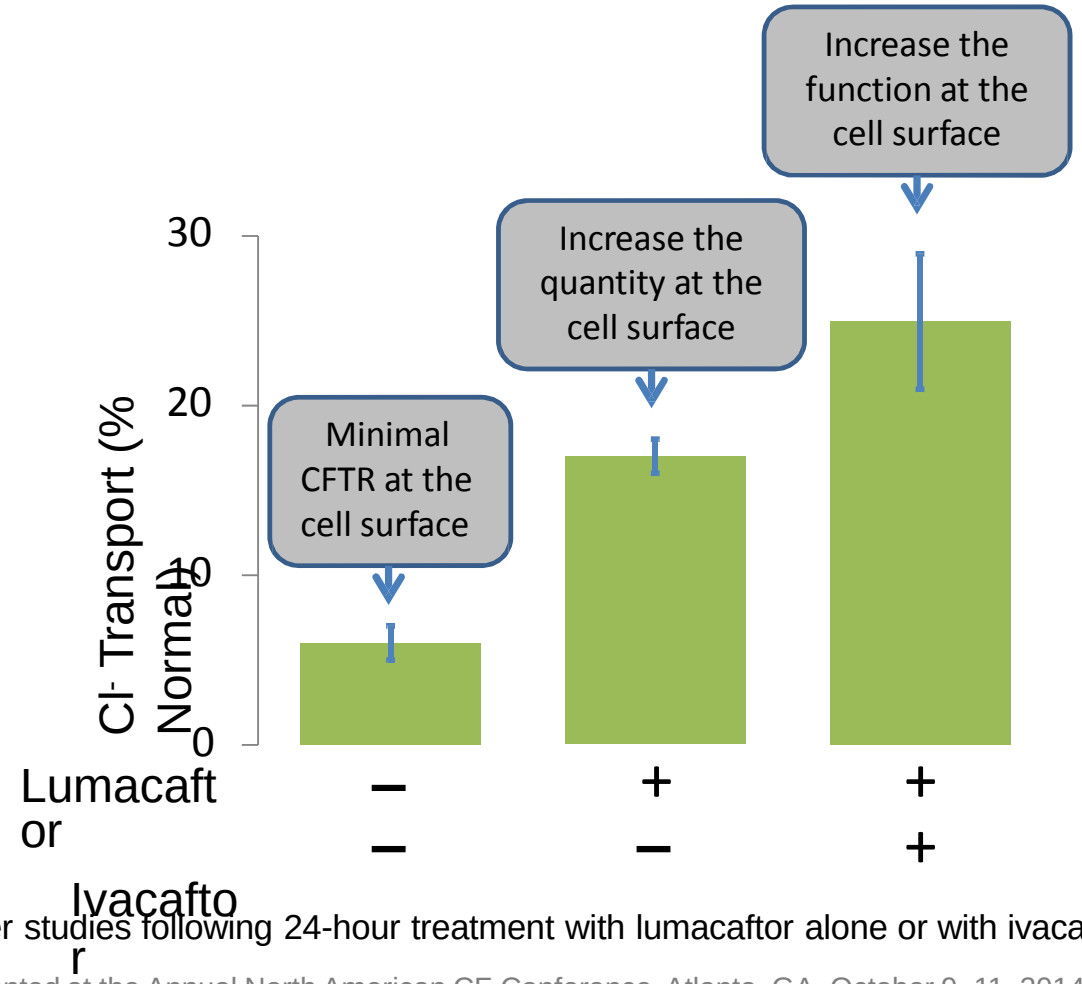
Functional Defect

- Minimal (little-to-no) chloride transport

CF phenotype

- Typically associated with severe CF phenotype

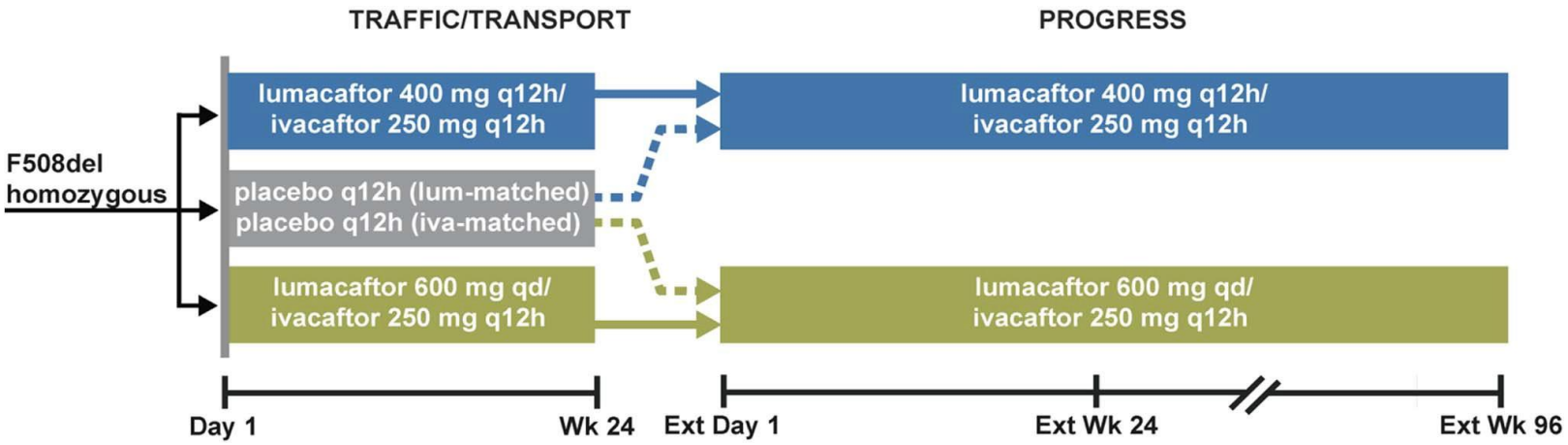
III. Combination of Lumacaftor and Ivacaftor Improved Chloride Transport in F508del/F508del-HBE



Ussing chamber studies following 24-hour treatment with lumacaftor alone or with ivacaftor (6 donor bronchi)

Van Goor F. Presented at the Annual North American CF Conference, Atlanta, GA, October 9–11, 2014.

III. Phase 3 Study of Lumacaftor/Ivacaftor Combination in People Homozygous for *F508del*



Two Phase 3, randomized, double-blind, placebo-controlled, parallel-group study. Patients who completed TRAFFIC/TRANSPORT were able to enter the PROGRESS (105) rollover study

- Conducted at 187 sites in North America, Europe, and Australia

Key eligibility criteria:

- Age ≥12 years, confirmed CF diagnosis
- Homozygous for *F508del-CFTR*
- Percent predicted FEV_1 ≥40 to ≤90 at screening

III. Safety Summary of Lumacaftor/Ivacaftor Combination in People Homozygous For *F508del*

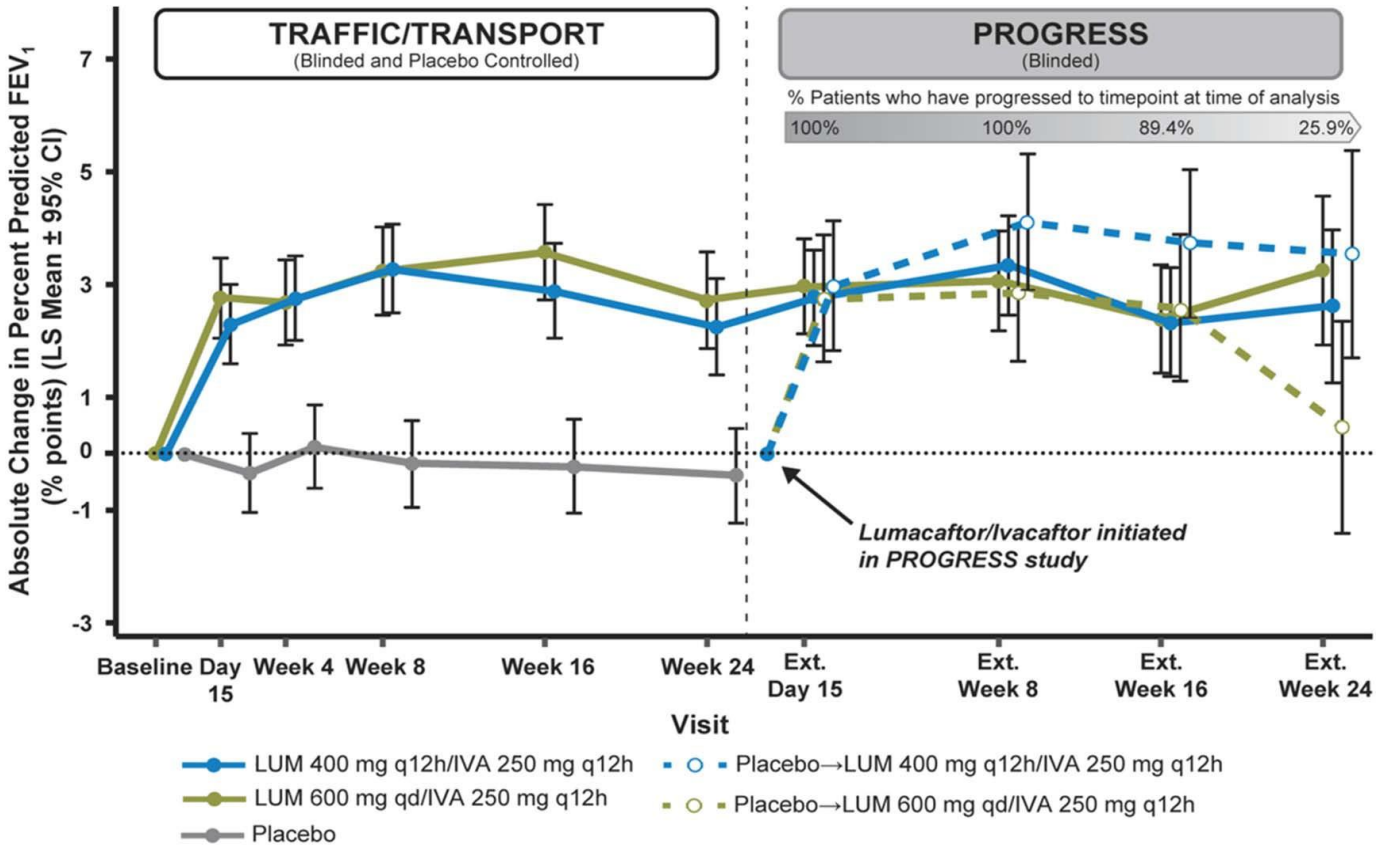
Treatment with both doses of lumacaftor/ivacaftor was generally well tolerated

- In the active group, there was a higher incidence of dyspnea, respiration abnormal, flatulence, and rash

- The frequency of LFT elevations was similar between the placebo and active groups, though there was a greater number SAEs related to abnormal liver tests in the active group (0 vs. 7)

Wainwright C, et al. Effect of lumacaftor in combination with ivacaftor in patients with cystic fibrosis who are homozygous for F508del- CFTR: pooled results from the phase 3 TRAFFIC & TRANSPORT studies [poster 250]. Presented at the Annual North American Conference of the Cystic Fibrosis Foundation, Atlanta, GA, October 9–11, 2014

III. Lumacaftor/Ivacaftor Combination Improved Lung Function (FEV_1) in People Homozygous for *F508del*



Wainwright C, et al. Effect of lumacaftor in combination with ivacaftor in patients with cystic fibrosis who are homozygous for F508del- CFTR: pooled results from the phase 3 TRAFFIC & TRANSPORT studies [poster 250]. Presented at the Annual North American Conference of the Cystic Fibrosis Foundation, Atlanta, GA, October 9–11, 2014

Acknowledgments

The patients and physicians who participated in clinical trials.

The physicians and scientists who contributed to the “science of

CFTR” Cystic Fibrosis Foundation for their support and guidance

Fred Van Goor, Paul Negulescu, Sabine Hadida, Peter Grootenhuis and the many people at Vertex who contributed to the discovery and development of ivacaftor, lumacaftor, and VX-661

Center for Health Policy at BROOKINGS

Improving Productivity in Pharmaceutical Research and Development: The Role of Clinical Pharmacology and Experimental Medicine

Center for Health Policy
The Brookings Institution

The Embassy Row Hotel • Washington, DC
July 28, 2015

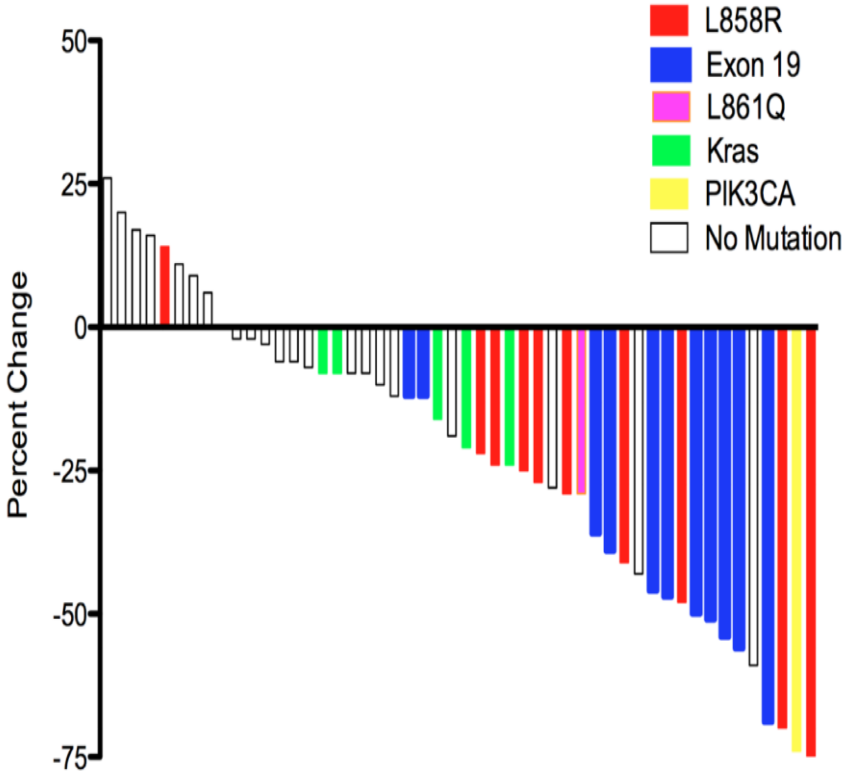
National Cancer Institute

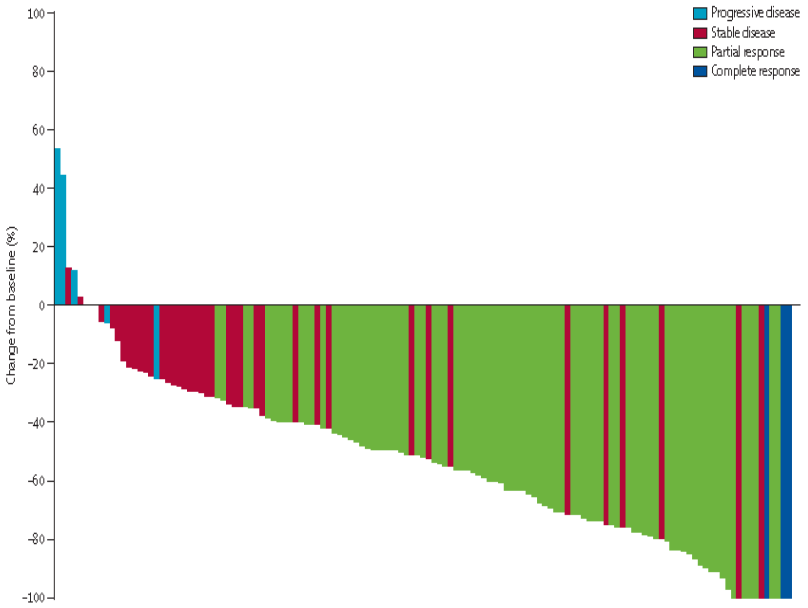
Improving Productivity in Pharmaceutical Research and Development: Precision Medicine: Trial Enrichment, Biomarker Science, and Mechanistic Reasoning to Optimize Patient Selection

Alice Chen, M.D.
Early Clinical Trials Development Program
DCTD, NCI
July 28,2015

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Matching patients to therapy on the basis of genetic features in lung cancer erlotinib in EGFR mutant NSCLC & crizotinib in ALK translocated NSCLC

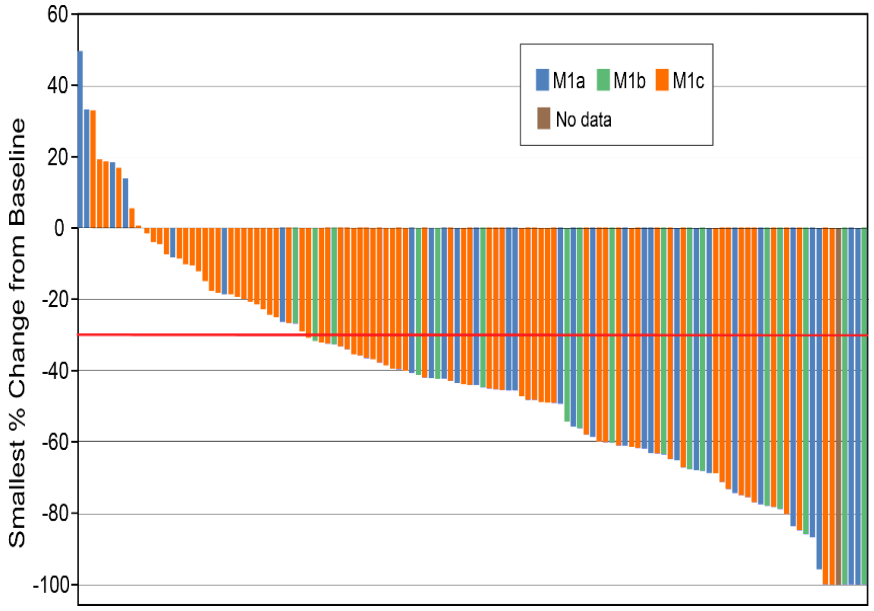


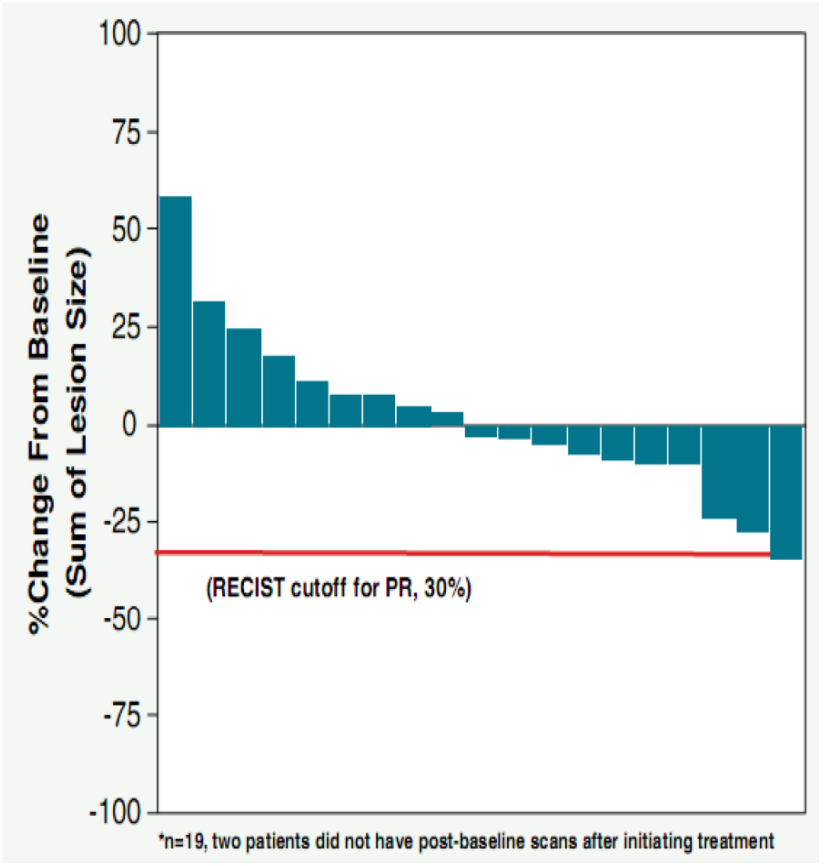


Rizvi N et al. CCR 2011

Camidge R et al. Lancet Oncol 2012

BRAF inhibitor therapy markedly more effective ^{V600E}BRAF melanoma compared to colon cancer





Sosman J et al. NEJM 2012

Kopetz, ASCO 2010

NCI-MATCH: **M**olecular **A**nalysis for **T**herapy **Ch**oice

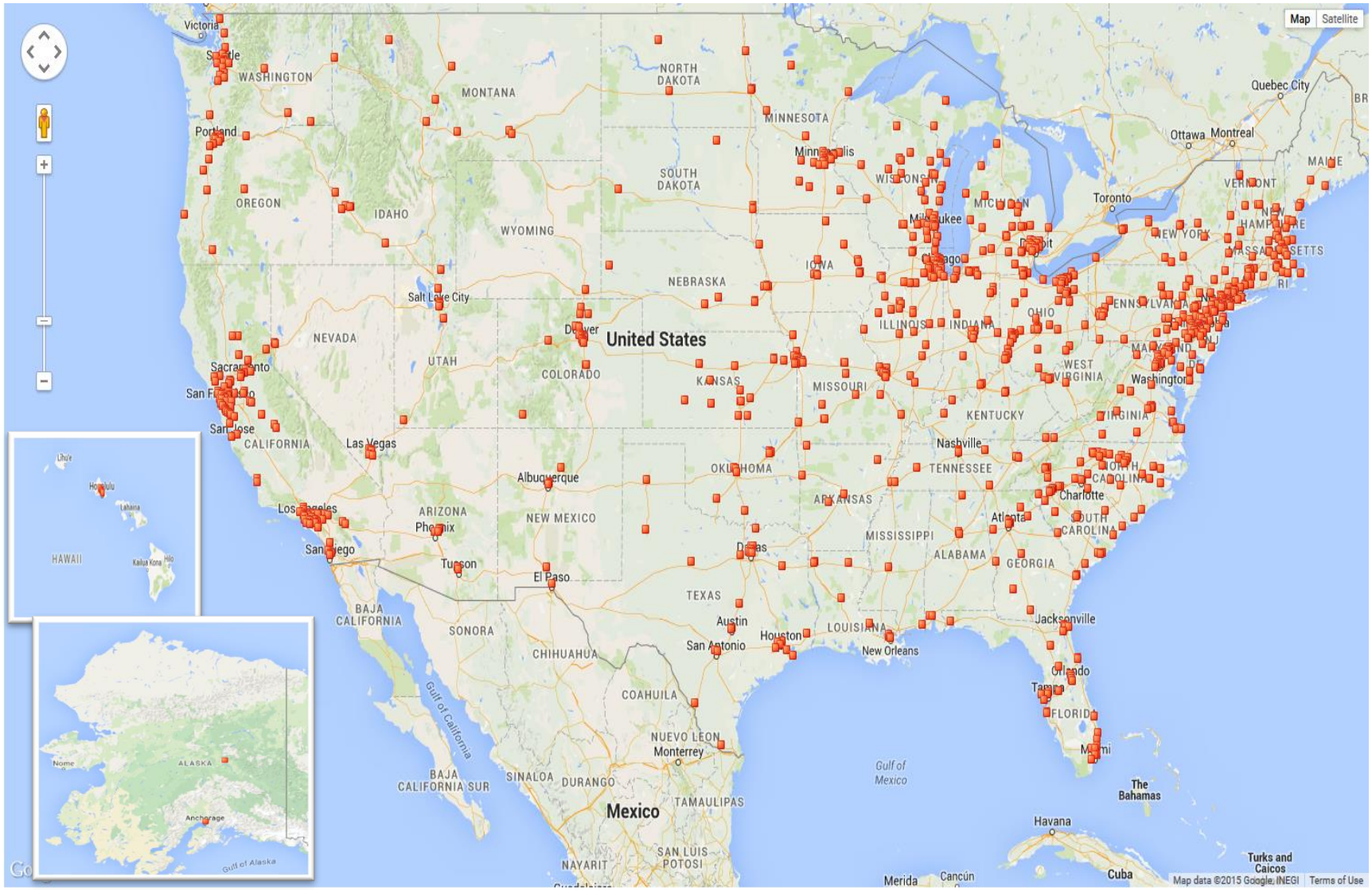
Objective

To understand the relative efficacy of the same therapy applied to oncogene-defined subsets across different tumor histologies, we propose to initiate a broad-based genomic pre-screening study to assign patients whose tumors harbor specific molecular abnormalities to relevant targeted treatments, regardless of tumor histology type

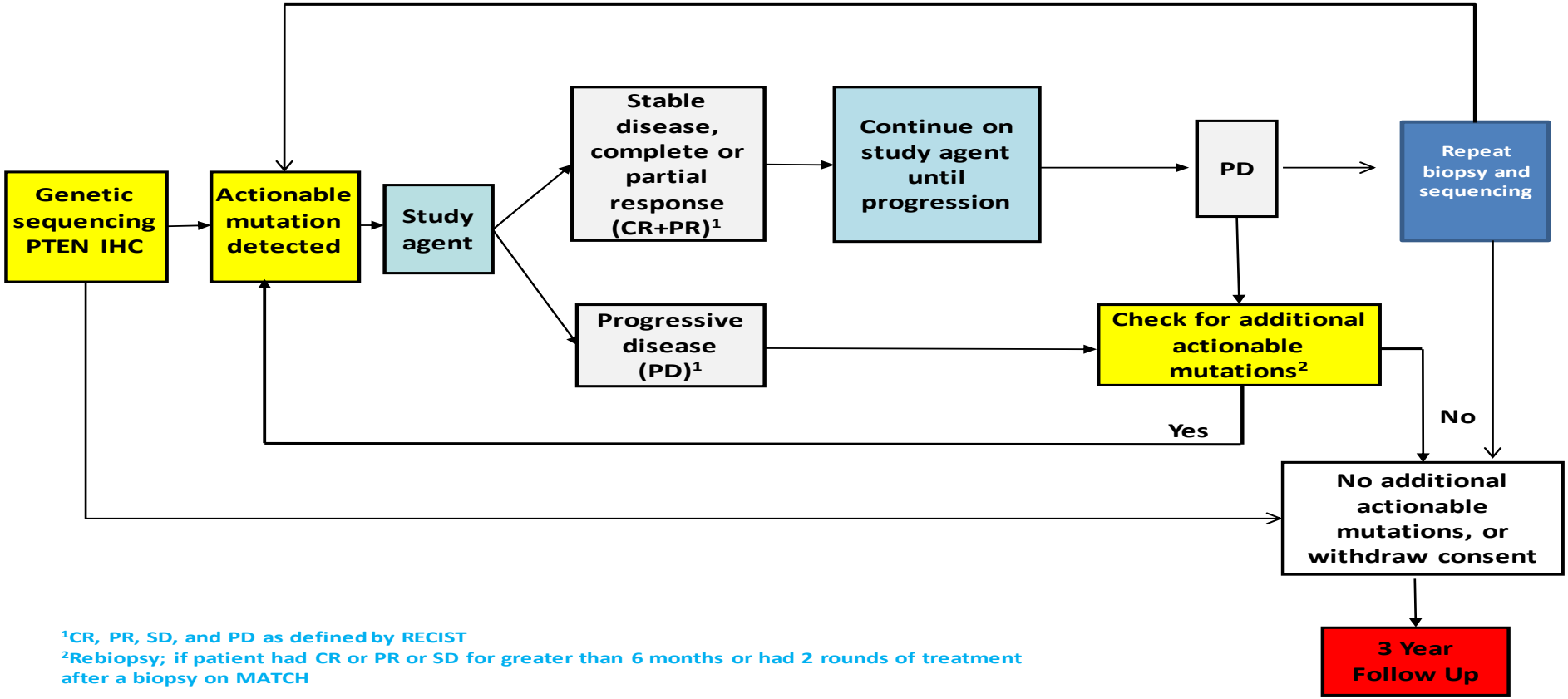
It Takes a Village

- Need to test large number of patients to find widely distributed genetic alterations
  - To be conducted throughout National Clinical Trials Network
- Need to have large number of agents so more likely to find mutations on biopsies
  - Close working relationships with pharmaceutical partners
  - Launch with 10 treatment arms, moving to more than 20 within months
- Trial Planning Expertise: More than 150 NCI & NCTN members forming subcommittees
- Work with the FDA exploring potential regulatory concerns both for trial and assay

NCTN Clinical Sites



NCI-MATCH / EAY131 SCHEMA



[1]CR, PR, SD, and PD as defined by RECIST
[2]Rebiopsy; if patient had CR or PR or SD for greater than 6 months or had 2 rounds of treatment after a biopsy on MATCH

Levels of Evidence: Drugs

- Level 1: FDA approved; evidence of target inhibition, or proof of mechanism; demonstration that patient selection with CDx are more likely to respond
- Level 2: Agent met a clinical endpoint (objective response, PFS, or OS); with evidence of target inhibition; plausible evidence of a predictive or selection assay/analyte
- Level 3: Agent demonstrated evidence of clinical activity with evidence of target inhibition; some evidence of a predictive or selection assay/analyte

Rules of Evidence for Actionable Variants Within a Gene that Will be Used for Treatment Selection

- **Level 1: Gene variant approved for selection of an approved drug (BRAF V600E and vermurafenib). The variant will be Level 1 in all tissues open to treatment with the approved drug.**
- **Level 2a: Gene variant is an eligibility criteria for an ongoing clinical trial for that treatment**
- **Level 2b: Gene variant has been identified in an N of 1 responses (TSC1 and everolimus) for that treatment**
- **Level 3: Preclinical inferential data *(in vivo* and *in vitro* models*)* that provide biological evidence sufficient to support the use of a variant for treatment selection, e.g.:**
  - Models with variants respond to treatment and models without variant do not respond to treatment
  - Gain of function mutations demonstrated in pre-clinical model, e.g. D769H variant of ERBB2 results in increased tyrosine kinase-specific activity and up regulates pathway signaling (does not require treatment evidence)
  - Loss of function genes, tumor suppressor or pathway inhibitor (e.g. NF1) any variant that produces a stop codon including frameshift or demonstrated loss of function in pre-clinical model (does not require treatment evidence)

NCI-MATCH / EAY131 Initial 10 Trial Arms at Activation

Agent(s)	Molecular Target(s)	Estimated Prevalence	Trial ID
Crizotinib	ALK Rearrangement	4%	EAY131-F
Crizotinib	ROS1 Translocations	5%	EAY131-G
Dabrafenib and Trametinib	BRAF V600E or V600K Mutations	7%	EAY131-H
Trametinib	BRAF Fusions, or Non-V600E, Non-V600K BRAF Mutations	2.8%	EAY131-R
Afatinib	EGFR Activating Mutations	1 – 4%	EAY131-A
Afatinib	HER2 Activating Mutations	2 – 5%	EAY131-B
AZD9291	EGFR T790M Mutations and Rare EGFR Activating Mutations	1 – 2%	EAY131-E
TDM1	HER2 Amplification	5%	EAY131-Q
VS6063	NF2 Loss	2%	EAY131-U
Sunitnib	cKIT Mutations	4%	EAY131-V

ECOG-ACRIN cancer research group
Reshaping the future of patient care

NATIONAL CANCER INSTITUTE

Treatment by molecular abnormality requires reliable laboratory tests

- Eligibility assays must accurately identify patients with the appropriate molecular features in their tumor
  - Screen 3000 to find 1000 with mutations allowing a treatment match
  - ECOG-ACRIN Central Biorepository and Reference Laboratory - single processing of all 3000 specimens to ensure quality control
- NCI-MATCH investigators have developed standard procedures for
  - Sample collection and shipping
  - A precise and reproducible next generation sequencing assay
  - “Locked” procedures assure reliability

CLIA Lab Network

- Genetic platform: Ion Torrent™ Personal Genome Machine (PGM™) System custom panel
  - 143 genes
  - Developed at NCI Frederick National Laboratory for Cancer Research
- Assay highly precise and reproducible across four labs
  - Massachusetts General Hospital
  - Molecular Characterization Laboratory at NCI FNLCR
  - U Texas MD Anderson Cancer Center
  - Yale University

NCI Precision Medicine Clinical Trials

- **NCI-MATCH**: Signal finding across solid tumors/lymphomas to open in mid August
- **ALCHEMIST**: Phase III randomized: Adjuvant non-squamous NSCLC: *IN PROGRESS*
- **LungMAP**: Phase II/III randomized: 2nd Line Squamous Lung Cancer: *IN PROGRESS*
- **M-PACT**: 700 patient pilot; refractory solid tumors: *IN PROGRESS*
- **Exceptional Responders Initiative**: *IN PROGRESS*

Center for Health Policy at BROOKINGS

Improving Productivity in Pharmaceutical Research and Development: The Role of Clinical Pharmacology and Experimental Medicine

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The Embassy Row Hotel • Washington, DC
July 28, 2015

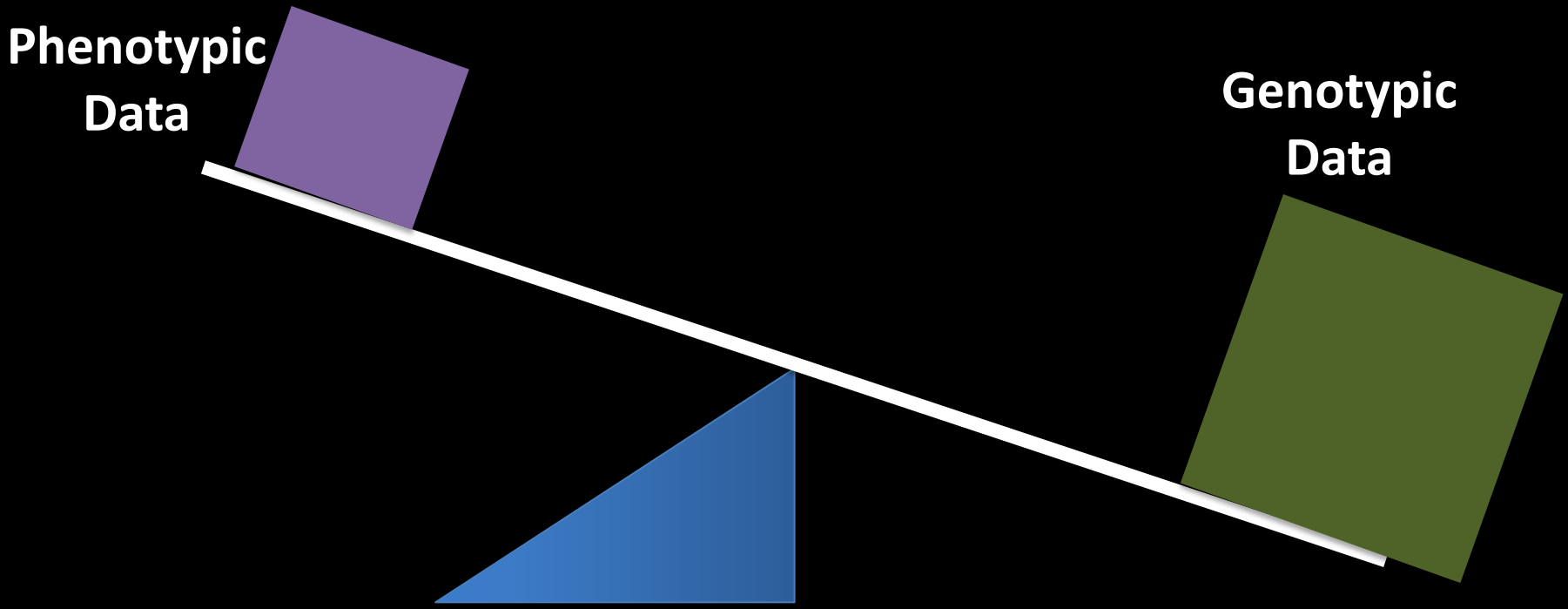
PROSTATE CANCER DREAM CHALLENGE
MARCH 16, 2015 – JULY 27, 2015

Prostate Cancer Challenge Website: https://www.synapse.org/#!Synapse:syn2813558/wiki/70844

Description of Challenge Data Overview

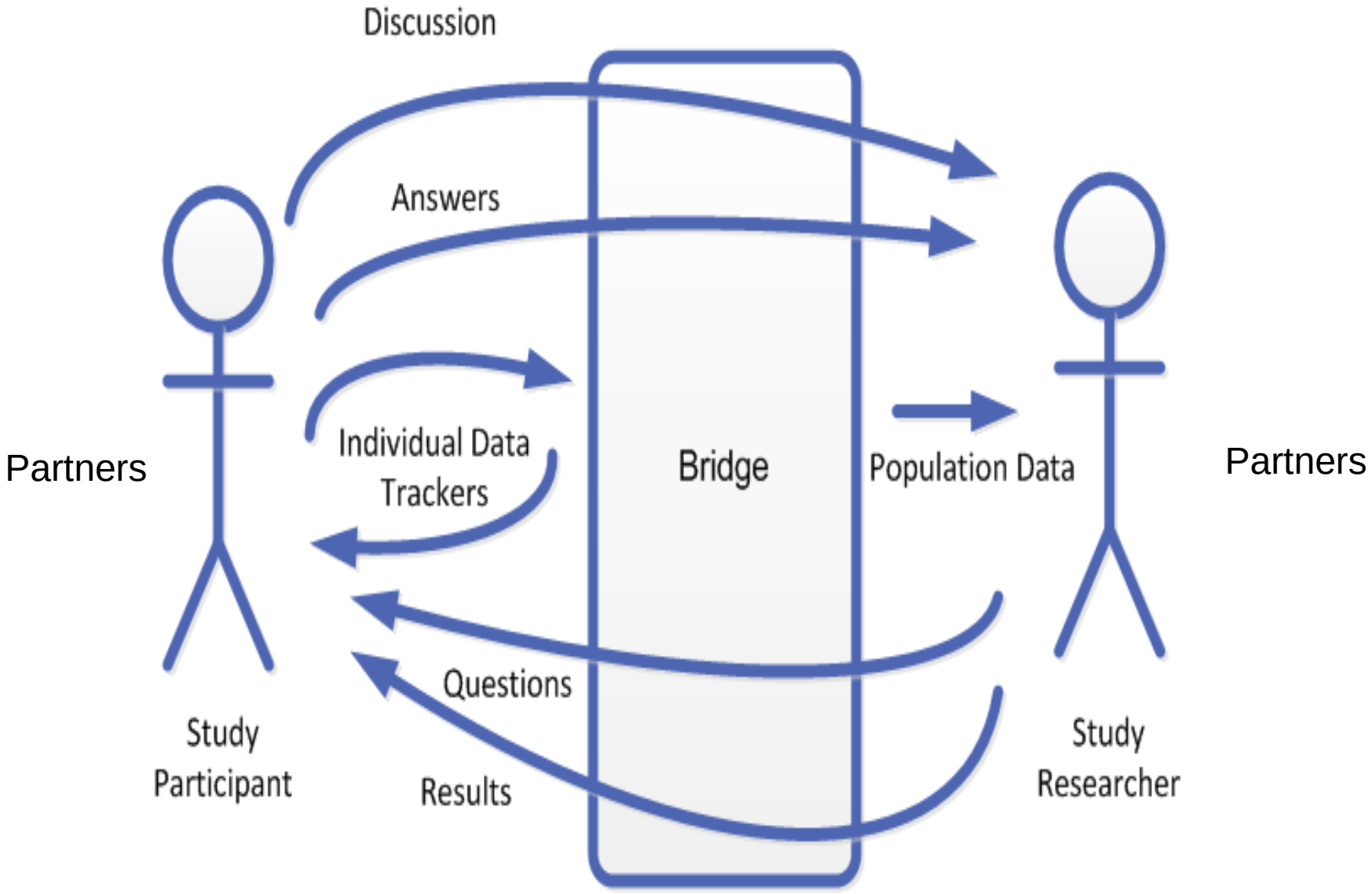
- Four prostate cancer clinical trial comparator arm data sets from Project Data Sphere (PDS) are used for the challenge.
  - 3 trials (ASCENT2, CELGENE, EFC6546) made up the training data sets
  - 1 trial (AZ) are held back for leaderboard and validation
- Homogenous patient population
  - first line metastatic Castration Resistant Prostate Cancer (mCRPC) patients undergoing Docetaxel treatment in the control arm of trials
- Raw trial data are used to generate Challenge data

Asymmetry of Data:
The public can help with this



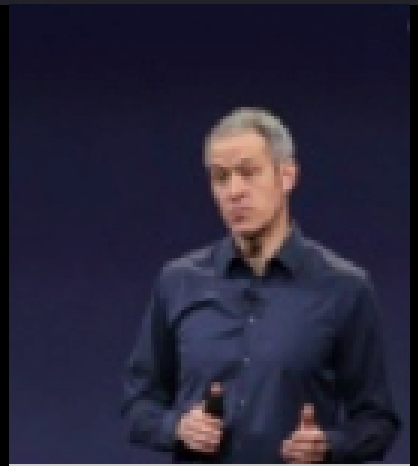
Current Measures	Smartphone Measures
Insensitive	Sensitive
Subjective	Objective
Episodic	Continuous
Provider-Centered	Individual-Centered
In Clinic	Remote
Unidimensional	Multidimensional
Limited Feedback	Real-time Feedback

Participant –Centered Research Studies with Feedback Loops



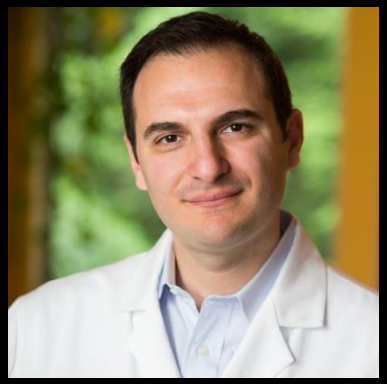
Anecdotes into Signals

mHealth Research Kit



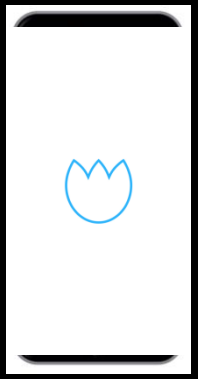
Dorsey

Trister



Klein

mPower



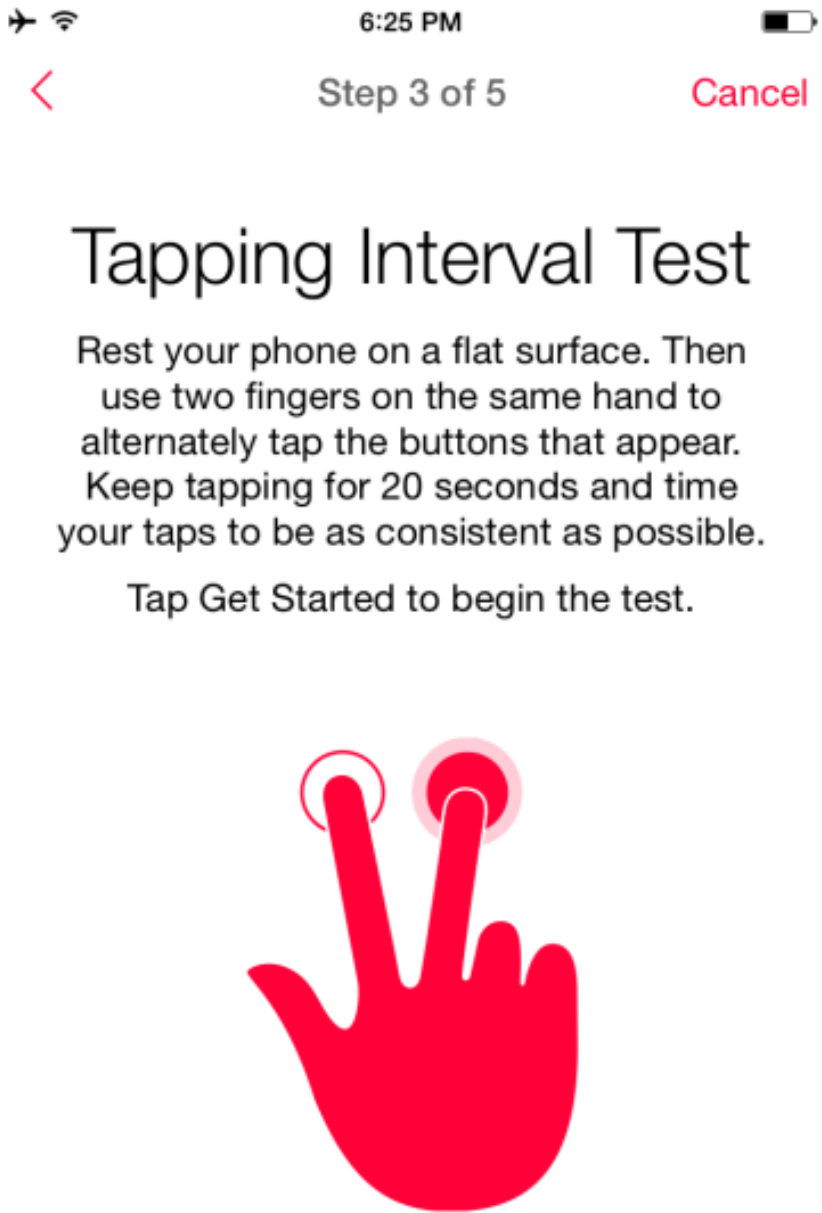
Kieburtz

Tanner

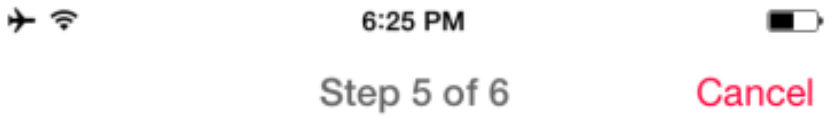
Kruger

Bloem

Parkinson mPower Study App



Parkinson mPower Study App



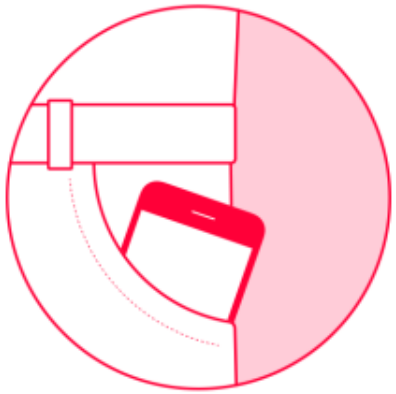
Parkinson mPower Study App

6:26 PM

Step 1 of 6 Cancel

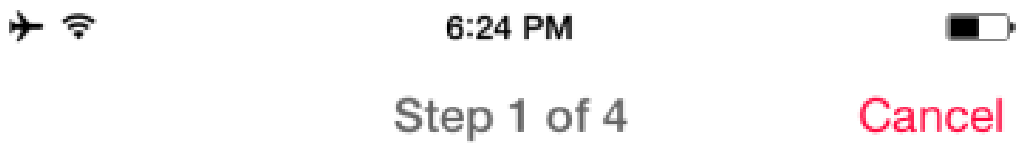
Gait and Balance Test

This test measures your gait and balance as you walk and stand still. To complete this test, you'll need to put your phone in your pocket and connect headphones to follow audio instructions.



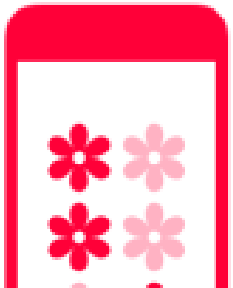
Get Started

Parkinson mPower Study App



Spatial Memory Test

This test measures your spatial memory by showing you patterns and asking you to recall and repeat them.



Tracking four key symptoms of PD using Surveys - Structured Activities - Passive Measurements

	Motor Initiation	Gait/Balance	Hypophonia	Memory
Passive	GPS - Displacement Vectors	GPS - Displacement Vectors	-	-
Structured Activity	Tapping Activity	Walking Activity	Voice Activity	Memory Game
Surveys	MDS-UPDRS PDQ8	MDS-UPDRS PDQ8	MDS-UPDRS PDQ8	MDS-UPDRS PDQ8

* All structured activities also include timing with relation to med administration

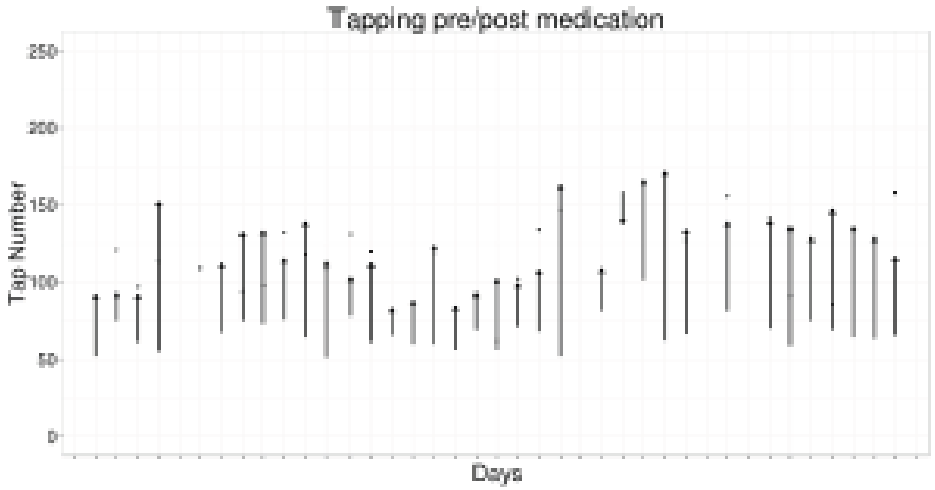
Numbers of downloads and enrolled in mPower

- 57,200 downloads from app store
- 15,439 consented (27% of total downloads)
- 11,360 enrolled (73.5% of total consented)
- Core group of participants after 10 weeks: 500+(much larger earlier)
- 78% of those still enrolled choose to share data broadly

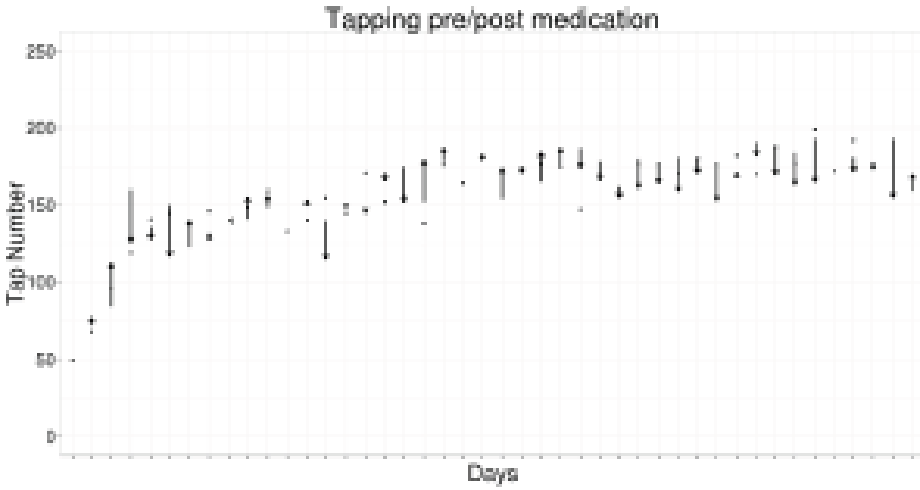
New measures of PD:
Benefits of unpacking the dimensions of tapping

Traditional Measures	First-order Features
Number of Taps	Number of taps, Mean tapping interval, Median tapping interval, Minimum tapping interval, maximum tapping interval, Standard deviation of tapping interval, Kurtosis of tapping interval, Interquartile range of tapping interval, Interquartile range of right button X, Range right button X ,Standard deviation right button X, Interquartile range of left button X, Range left button X ,Standard deviation left button X, Interquartile range of right button Y, Range right button Y ,Standard deviatiion right button Y, Interquartile range of left button Y, Range left button Y ,Standard deviation left button Y, Correlation X and Y, Skew tapping interval, No-button tapping frequency

Personalized approaches to unpacking multidimensional data from remote sensors

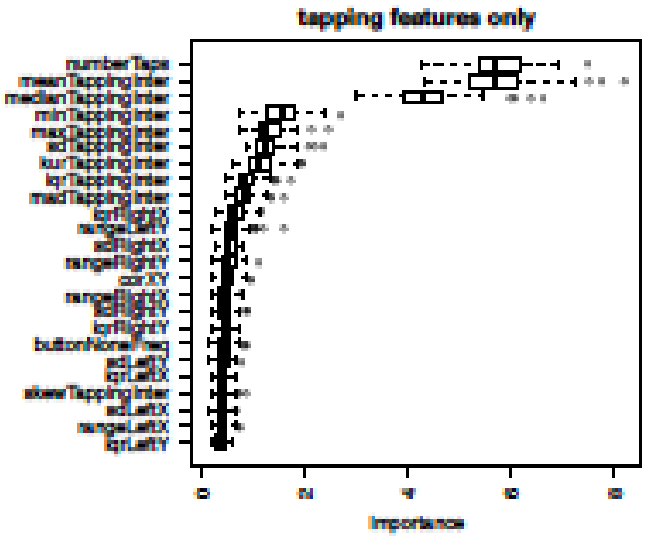


62 year old man
2009 Onset of Symptoms / Start meds
Mean change: 51 taps
Max change: 111 taps
Min change: -21 taps

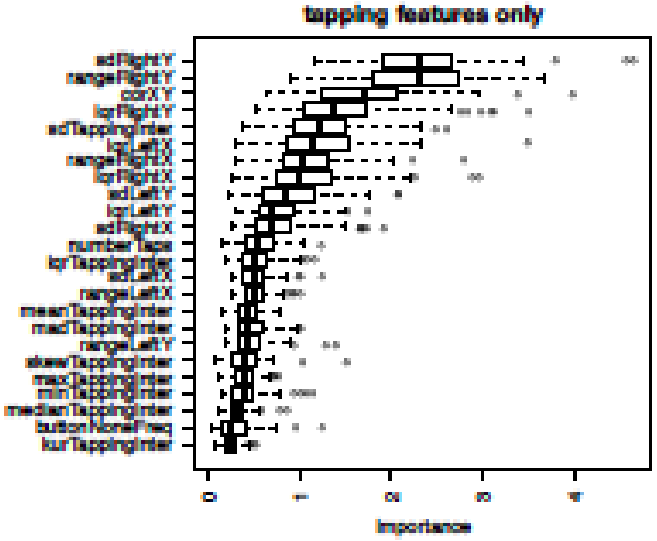


67 year old woman
2004 Onset of Symptoms / 2009 meds
Mean change: -4 taps
Max change: 28 taps
Min change: -38 taps

Different features are important to predict effect of medications for different patients



Number of Taps
Mean Tapping Interval
Median Tapping Interval



Standard Deviation R Y
Range Right Y
Correlation X Y

Is there evidence of modulators beyond medications?

- 5,192 unique participants provided 17,076 responses to questions about what made them feel better or worse on that day

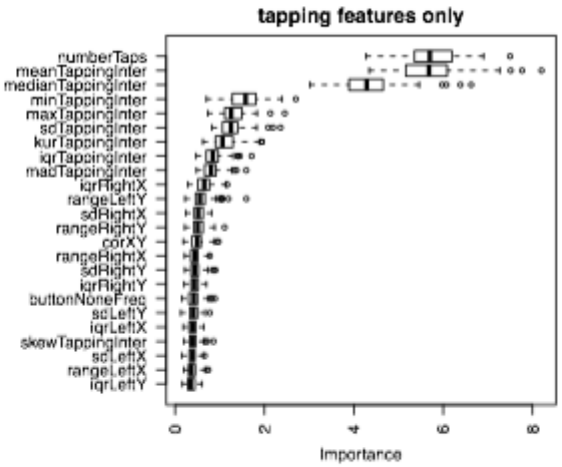
Examples of Better:
"I went to visit with family that made me feel better"
"Sinemet and lying down for an hour in the afternoon."
"Laying down"
"The sun starting to come out in the warmth of the day because were entering spring"
"I got some really good news about a stray cat of the nursing back to health."
"Meetings"
"Computer games"
"Completing a list of tasks for daily activities"
"Looking for furniture for my new house"
"Practicing Zen Meditation!"

Examples of Worse:
"Walking"
"Not getting a good nights sleep the night before"
"I don't think anyone in my family really understands what Parkinson's disease is and how it is impacting my life and my work."
"Worrying that I not getting things done around the house"
"Having a glass of wine"
"Nothing"
"Sadness regarding race relations in America!"
"Getting comfortable sleeping. Keep moving my sleeping position which leads to restless night."

How can mPower impact clinical practice?

Anticipating an inevitable transition that underlies the concept of precision medicine

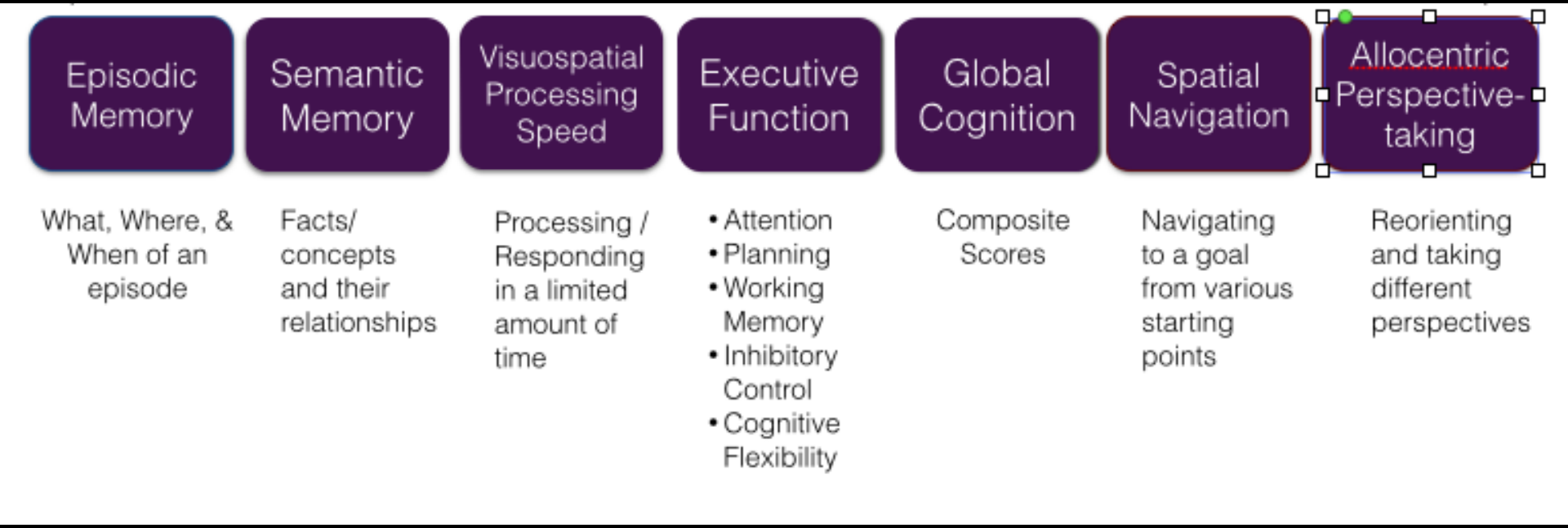
Straw man proposal for a novel scorecard that yields a sensor-based phenotype to allow for clinical tracking of features



Diseases as clusters of specific features

Number of taps		
Standard deviation right button Y		
Standard deviation left button Y		
Mean tapping interval		
Median tapping interval		
Minimum tapping interval		
Maximum tapping interval		
Standard deviation of tapping interval		
Kurtosis of tapping interval		
Interquartile range of tapping interval		
Skew tapping interval		
Correlation X and Y		
Interquartile range of right button X		
Range right button X		
Standard deviation right button X		
Interquartile range of left button X		
Range left button X		
Standard deviation left button X		
Interquartile range of right button Y		
Range right button Y		
Interquartile range of left button Y		
Range left button Y		

Need for better ways to follow Dementia



Federated Approaches for Digital Phenotyping

Open Data

Open Source Code

Direct Comparisons

Diversity of Cohorts

participant centered data from apps

benefits to understanding how to enroll from early trials through post-approval

benefits to the individual

(Movement Disorders, Rheumatoid Arthritis, Anemia, Melanoma, Cognition, Mood)

TECHNOLOGY

App-enabled trial participation: Tectonic shift or tepid rumble?

APPLE'S CHIEF OPERATING OFFICER, JEFF WILLIAMS, SURPRISED CROWDS AT THE spring launch when he revealed "ResearchKit," a collection of iPhone apps designed to allow individuals to collect their clinical data—and contribute to the precision medicine movement—outside the confines of hospitals and labs. But are these simply a smattering of souped-up health apps in a sea of thousands (that is, no big deal)? Are they support tools for uncontrolled clinical trials, which won't produce meaningful results (not to mention superfluous, given that patient-centered outcomes initiatives are well under way)? Or are they precursors heralding a tectonic shift in how people participate in their health management as well as in human disease research and clinical trials? The answer might depend more on human psychology than human health science.

CLINICAL TRIAL CONUNDRUM

Much of our understanding of the effects of modulators (such as drugs) on human diseases comes from clinical studies. Today, tens of billions of dollars are spent on clinical trials that range from large longitudinal observational studies to intensive testing of potential new drugs. Trials are typically coordinated through physicians at specific institutions and

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Applications of Clinical Pharmacology to Support Demonstration of Efficacy

Robert Temple, MD
Deputy Center Director for Clinical Science
Center for Drug Evaluation and Research
Food and Drug Administration

Brookings-FDA: Clinical Pharmacology
July 28, 2015

Two Main Tasks

1. Consider how Clinical Pharmacology (taken broadly to refer to effects on biomarkers and various endpoints as well as PK-PD findings relating clinical outcome to blood levels) can help us choose doses and patients.

2. Consider whether and how some kinds of pharmacologic evidence or exposure-response information can provide the "confirmatory evidence" that would support reliance on a single trial.

Dosing

There is a long history of inadequate dose finding, sometimes with severe consequences. In some cases at least, this represented failure to even look at D/R.

Classic case is thiazide diuretics. Probably based on effects on Na clearance, the standard chlorthalidone dose was 100 mg, but 2 studies in 1978 using a randomized fixed-dose D/R study showed that 25 mg had full effect but caused less increase in UA (1/3 of all gout was diuretic induced in those days), less hypokalemia (100 mg caused death in an NHLBI trial, MRFIT, I believe, and had to be stopped) and less glucose intolerance.

TABLE 1

DATA OF MATERSON

Fall in blood pressure (systolic/diastolic) from baseline in erect and supine position with each of four dose levels of chlorthalidone and placebo.

Dose	Fall in Blood Pressure (mmHg)	
	Supine	Standing
Placebo	0/2	0/0
12.5 mg	5/4	6/4
25 mg	11/5	15/7
50 mg	10/6	14/5
75 mg	11/6	14/6

Better Dose Response

After the chlorthalidone experience, in the advice we began to give sponsors, in ICH E-4, and in regulations at 21 CFR 314.126, we urged better dose finding using the randomized fixed-dose, dose-response study, with fair success, but there are still horrible examples, where better attention could have made a difference.

When would it?

When the D/R (or C/R curves) are steep for either effectiveness or toxicity, we should always remember that surprises turn up. Using more drug than you really need is not smart, even if there is no obvious bad effect. A good example was fluoxetine. We were prepared to approve 60-80 mg, but a good D/R showed that 20 mg was fully effective and this became top dose, avoiding a dose that would have increased side effects and persisted for weeks after D/C.

Astemizole

Astemizole was a relatively non-sedating antihistamine with a several day half-life. To get an effect on day 1, the recommended dose was 10 mg, but the dose was then maintained at 10 mg, giving concentrations at lease 3x what was needed.

A loading dose (10 mg day 1, 3 mg after) would have done as well and would NOT have cause Torsade de Pointes arrhythmias, which led to WD in 1999 (OK, nowadays with TQT study, we'd have figured it out).

Alosetron

Alosetron was the first drug for diarrhea-type irritable bowel (women only) and the MAIN side effect was CONSTIPATION. Could that have suggested some more D/R data? Or interrupting therapy? It did not, and only 1 dose (2 mg) was studied. Ischemic colitis and surgery requiring constipation led to WD, with later return for severe cases at a 1 mg dose.

Well, we've gotten better, but it is difficult and costly to study enough doses, so we tend to see studies of very close doses that, not surprisingly, do not show D/R but could easily have missed it.

Exceptions, studying a broad range, are rare, as was done for risperidone.

Risperidone Fixed Dose Studies (8 week BPRS change from baseline)

	Study	
Dose	**024**	**204**
Placebo (n=86)		+2.2
1 mg (n=226)	-6.7	
2 mg (n=87)		-2.9
4 mg (n=227)	-10.2	
6 mg (n=88)		-11.2
8 mg (n=228)	-9.9	
10 mg (n=85)		-5.7
12 mg (n=225)	-9.0	
16 mg (n=85)		-8.5
16 mg (n=223)	-9.7	

Risperidone ADR's

	Dose Group				
ADR	0	2	6	10	16
Parkinsonism Scores	1.2	0.9	1.8	2.4	2.6
EPS Rate	13%	13%	16%	20%	31%

	Dose Group				
ADR	1	4	8	12	16
Parkinsonism Score	0.6	1.7	2.4	2.9	4.1
EPS Rate	7%	12%	18%	18%	21%

PK/PD – The Answer?

ICH E-4 gives moderate support to using what has now become routine – population PK data – to shed further light on D/R and as you've heard today, where the curves are steep as they are for both stroke and bleeding with dabigatran and edoxaban,

- C/R data show striking effects of concentration
- Would SEEM to provide a basis for concentration-based dose adjustment (or perhaps coagulation-measure based adjustment).

Might blood level data have suggested a relation of concentration to ischemic colitis or bad constipation with Alosetron?

Other Clin Pharm
Clin Pharm in Dose Selection

Note, many biomarkers have no direct relation to effect size, e.g., prognostic biomarkers and many predictive markers, so they may not help choose dose. But mechanistic markers do, e.g., sweat chloride in cystic fibrosis, perhaps RAS inhibition for ACEIs, ARBs, or BBs. [Anecdote: captopril at doses of 5 mg or so had major ACEI inhibition but doses of 600 mg were studied and caused agranulocytosis, which lower doses did not. Labeling made the drug second line because of this. D/R study was a late, not early study.]

Certainly, for platelet inhibitors and anti-coagulants pharmacologic effect are being used to choose the dose ranges. But, as you've seen, we might do even better with monitoring to optimize B/R.

It seems clear that whenever there is a measurable PD effect thought to reflect an effect on the mechanism of disease, effects on this outcome should figure prominently in dose selection.

And the place to pay most attention is when there are clear dose-related major benefits and risks.

Contribution to Evidence of Effectiveness

In 1998 guidance "Providing Clinical Evidence of Effectiveness for Human Drug and Biologic Products," a guidance written in response to FDAMA's 1997 permission to rely on a single AC & W study plus "confirmatory evidence." FDA identified a number of situations in which a single controlled trial could provide substantial evidence or effectiveness. Most were examples of other controlled trials that supported the use, but section IIC2h stated:

"When the pathophysiology of a disease and the mechanism of action of a therapy are very well understood, it may be possible to link specific pharmacologic effects to a strong likelihood of clinical effectiveness. [In some cases these effects can alone support approval as valid surrogates (blood pressure, LDL cholesterol) and if the relation to clinical benefit is less certain can support accelerated approval.] When the pharmacologic effect is not considered an acceptable effectiveness endpoint, but the linkage between it and the clinical outcome is strong, not merely on theoretical grounds but based on prior therapeutic experience or well-understood pathophysiology, a single adequate and well-controlled study can sometimes be substantiated by persuasive data from a well-controlled study or studies showing the relevant pharmacologic effect."

Evidence Guidance

The guidance illustrates cases where pharmacologic pathophysiologic endpoints could support a single study with some relatively obvious cases (i.e., it is cautious)

- Replacement therapy, e.g., a measure of a coagulation factor when it is clear that the disease is caused by a deficiency of that factor.
- Correction of an inborn error of metabolism

But there are others:

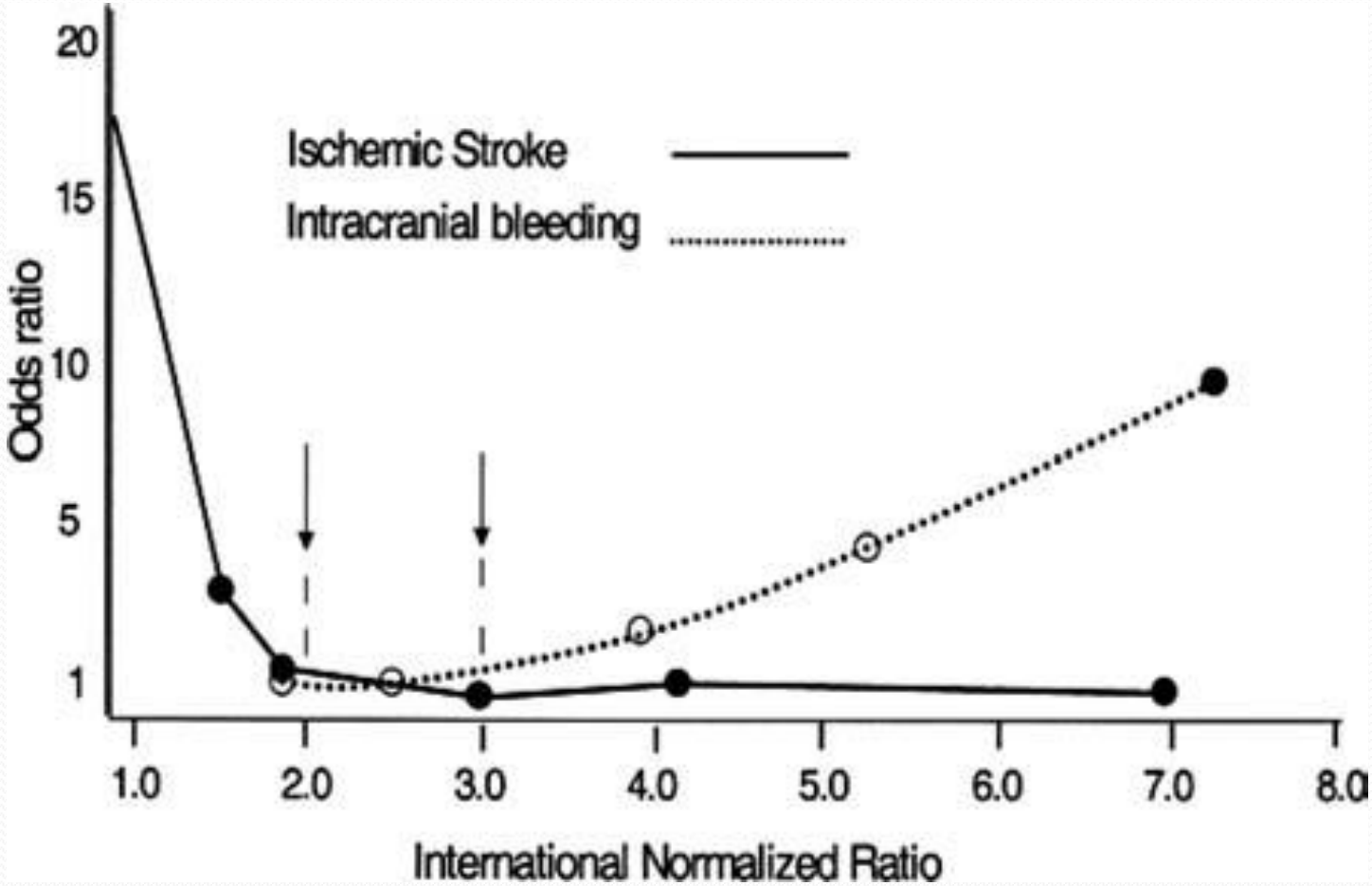
- We rely on a single clinical study in a particular condition (UTI intra-abdominal infection community acquired pnuemonia) for many anti-infectives, at least partly because we know the drug kills the organism causing the infection.
- As we gain experience with drugs for CF, effects on sweat chloride are being considered.

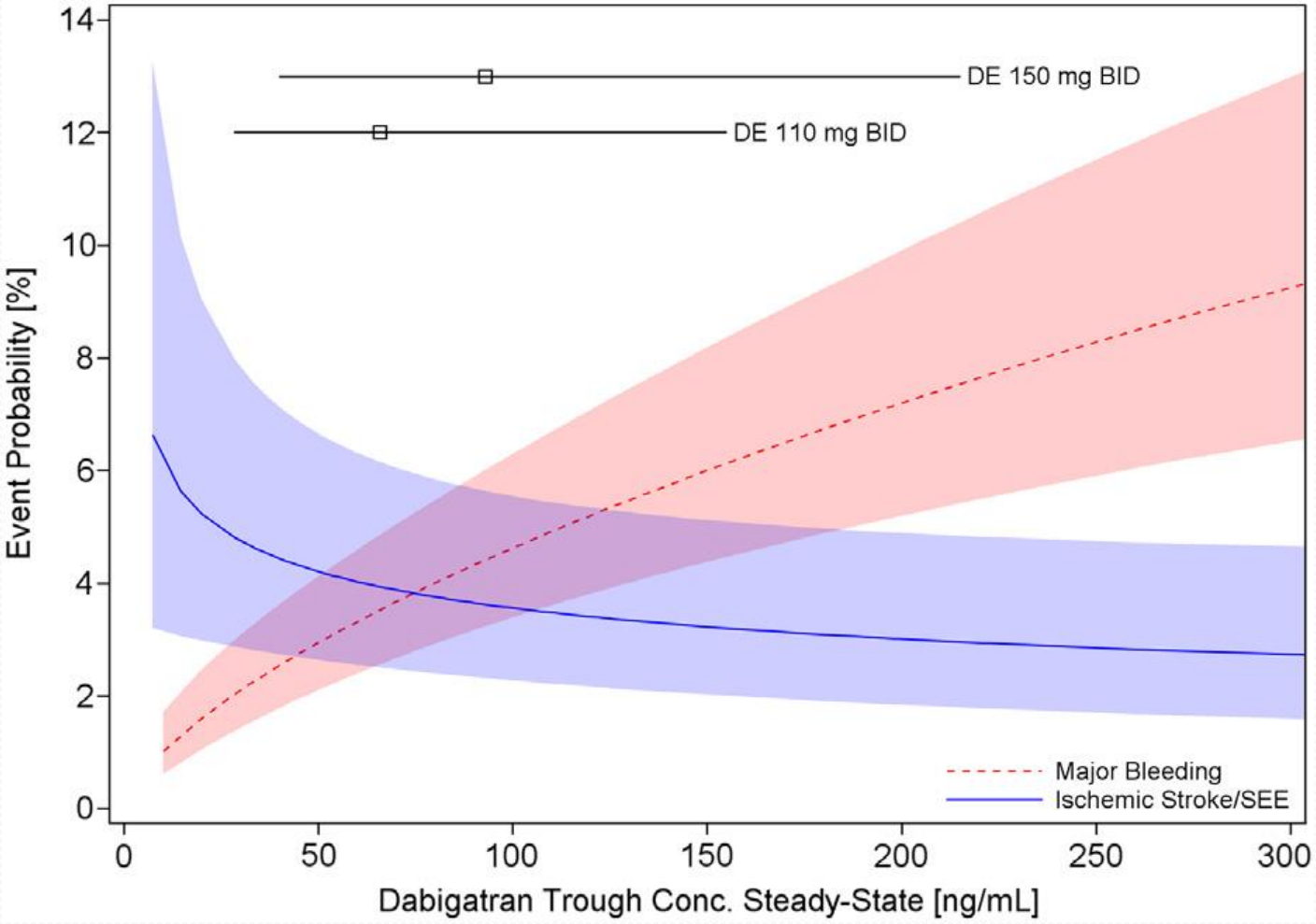
Clin Pharm Evidence

Of course, mechanistic markers CAN be the surrogate endpoints that are the basis for accelerated approval, but in this case the burden is less because there is a well-controlled study.

Apart from mechanistic confirmation, evidence of D/R either in the clinical study or for the pharmacologic effect, and especially when the C/R for both in a single trial is clearly parallel, adds to the weight of evidence.

Additional Slides


Ischemic Stroke
Intracranial bleeding
Odds ratio
20
15
10
5
1
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
International Normalized Ratio


14
12
10
8
6
4
2
0
Event Probability [%]
DE 150 mg BID
DE 110 mg BID
Major Bleeding
Ischemic Stroke/SEE
0
50
100
150
200
250
300
Dabigatran Trough Conc. Steady-State [ng/mL]

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Session IV: Applications of Clinical Pharmacology to Support Demonstration of Efficacy

Confirmatory Evidence – Leveraging Exposure-Response

Jack Cook

Pfizer, Inc.

E-R Is Fundamental to Drug Development

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

7 April 2015
EMA/117491/2015
Product Development Scientific Support Department

Report from Dose Finding Workshop

European Medicines Agency, London, 04 – 05 December 2014

- "… workshop re-emphasised the importance of rigorous, scientific dose finding … and the characterisation of D-E-R relationship for successful drug development, approval, labelling and beyond i.e. lifecycle management of the medicinal products."

E-R May Provide Greater Assurance of Efficacy than a Repeated Clinical Trial

CLINICAL PHARMACOLOGY & THERAPEUTICS
VOLUME 73 NUMBER 6 JUNE 2003

COMMENTARY

Hypothesis: A single clinical trial plus causal* evidence of effectiveness is sufficient for drug approval

Carl C. Peck, MD, Donald B. Rubin, PhD, and Lewis B. Sheiner, MD *Washington, DC, Cambridge, Mass, and San Francisco, Calif*

Clin Pharmacol Ther 2003;73:481-90

*vs emperic

Regulatory Guidances State that E-R Can Provide Confirmatory Evidence

ICH-E4 Guideline for Industry: Dose-Response Information to Support Drug Registration (1994)

- A well-controlled dose-response study is also a study that can serve as primary evidence of effectiveness.

US FDA Guidance for Industry: Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications (2003):

- Represent a well-controlled clinical study, in some cases a particularly persuasive one, contributing to substantial evidence of effectiveness (where clinical endpoints or accepted surrogates are studied)
- Add to the weight of evidence supporting efficacy where mechanism of action is well understood (e.g., when an effect on a reasonably well-established biomarker/surrogate is used as an endpoint)
- Support, or in some cases provide primary evidence for, approval of different doses, dosing regimens, or dosage forms, or use of a drug in different populations, when effectiveness is already well-established in other settings and the study demonstrates a PK-PD relationship that is similar to, or different in an interpretable way from the established setting

E-R Has Been Used as Confirmatory Evidence

Neurotin (Gabapentin) Package Insert

14 CLINICAL STUDIES

14.1 Postherpetic Neuralgia

> "Pharmacokinetic/pharmacodynamic modeling provided confirmatory evidence of efficacy across all doses."

2 trials were submitted, ... used different doses and titration regimens (2002)

2015!: Why Isn't E-R the "Norm" for Confirmatory Evidence in Applicable Cases?

Scientific and Regulatory Reasons for Delay and Denial of FDA Approved Initial Applications for New Drugs, 2000-2012 - Sacks et al, JAMA. 2014;311:378-384

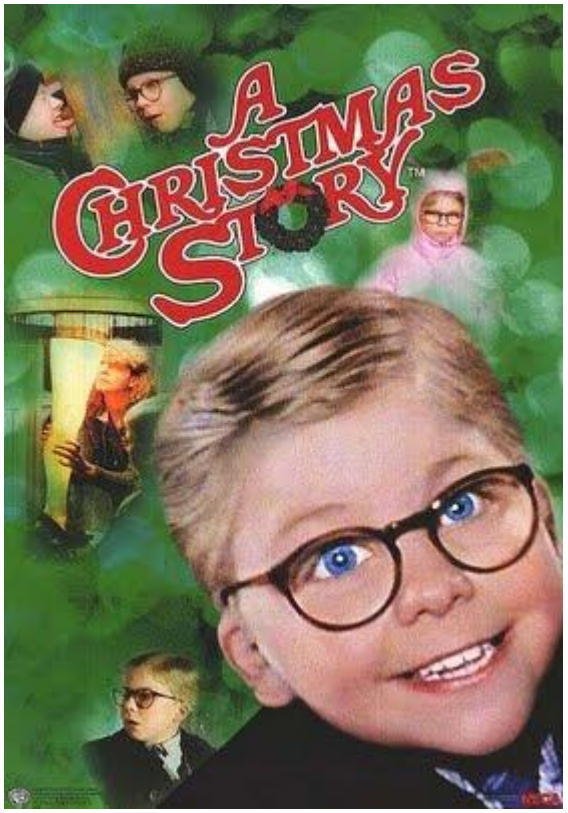
RESULTS Of the 302 identified NME applications, 151 (50%) were approved when first submitted and 222 (73.5%) were ultimately approved. Seventy-one applications required 1 or more resubmissions before approval, with a median delay to approval of 435 days following the first unsuccessful submission. Of the unsuccessful first-time applications, 24 (15.9%) included uncertainties related to dose selection, 20 (13.2%) choice of study end points that failed to adequately reflect a clinically meaningful effect, 20 (13.2%) inconsistent results when different end points were tested, 17 (11.3%) inconsistent results when different trials or study sites were compared, and 20 (13.2%) poor efficacy when compared with the standard of care. The frequency of safety deficiencies was similar among never-approved drugs compared with those with delayed approval (43 of 80 never approved [53.8%] vs 37 of 71 eventually approved [52.1%]; difference, 1.7% [95% CI, −14.86% to 18.05%]; $P = .87$). However, efficacy deficiencies were significantly more frequent among the never-approved drugs than among those with delayed approvals (61 of 80 never approved [76.3%] vs 28 of 71 eventually approved [39.4%]; difference, 36.9% [95% CI, 20.25% to 50.86%]; $P < .001$).

CONCLUSIONS AND RELEVANCE Several potentially preventable deficiencies, including failure to select optimal drug doses and suitable study end points, accounted for significant delays in the approval of new drugs. Understanding the reasons for previous failures is helpful to improve the efficiency of clinical development for new drugs.

Challenge 1: Industry's Attidudes

- We too often focus on maximizing efficacy and thus we evaluate doses near the maximum tolerated dose
- We limit the number of doses because we try to power for pairwise comparisons
- We think we know more than we actually do about dose-response
- We believe that there is regulatory uncertainty with use dose response vs certainty of replicated Phase 3 trials with pairwise comparisons

Challenge 2: Regulatory and the Ralphie Experiment



Experiment

- Ralphie was to receive a couple of presents:
  - Provided a very specific example for the gift from his parents
    - I want a Red Ryder carbine-action, two hundred shot Range Model air rifle with a compass in the stock and this thing which tells time
  - Did not provide any examples for what he wanted from his aunt
    - It is suggested that regulatory guidances are currently a little closer to this …

Results - Which Approach Achieved the Desired Outcome?

Parent's Gift

Aunt's Gift

A Potential Solution

- Need clear regulatory guidance/statement from EMA, FDA for Phase 2b dose-ranging studies
  - Specifically support regression approach for design and analysis
  - Examples/what's needed to be considered adequate confirmatory evidence
  - Support estimation approach to supplement traditional confirmatory analyses from Phase 3 trial for regulatory decisions (approval, dose recommendations)
- A concerted regulatory effort/guidance can broadly and rapidly influence whole industry
  - "Industry" can also use this to help change "industry"
- Need to generate further discussion and recommendations for next steps
  - What was done in 1994-2003 has not had the desired impact

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Session IV: Applications of Clinical Pharmacology to Support Demonstration of Efficacy

Dominant Challenges in the Rare/Ultra-rare Bio-innovation Space: Implications and Actions for Clinical Pharmacology

Steve Ryder
SVP, Chief Development Officer
Alexion Pharmaceuticals

Contributors
Alexion Clinical Pharmacology Working Group, including Yang Dai, Xiang Gao, Chetan Lathia, Megan Melch, Jonathan Monteleone, Wei-Jian Pan, Rajandra Pradha, Jian-Ping Tang, and Nancy Silliman

Disclosure

I and all contributors are full-time employees of Alexion Pharmaceuticals and may hold equity interest in Alexion Pharmaceuticals

Understanding the disease

- ***Challenges:***
  - Rare/ultra-rare diseases are almost always poorly understood and poorly researched.
  - This extends to both the preclinical and clinical areas
- ***Actions:***
  - Develop preclinical disease models that mimic disease progression to better inform physiology (including pathophysiology) and experimental pharmacology
    - Develop systems pharmacology models to understand the role of target, exposure at the target and target binding resulting in downstream activity
    - Extend to models of preclinical efficacy and toxicity
    - Translate preclinical pharmaco-kinetic/pharmaco-dynamic (Pk/Pd) data using physiologically based Pk modeling to project starting dose for First-in-Human (FIH) trials
  - Deepen understanding of the clinical disease, its course, associated pathophysiology, and morbidities
    - Initiate robust and informative Natural History studies using ascertained diagnostic criteria (genomic, biochemical, clinical)
      - Requires close partnerships with caregivers, patients, patient advocacy groups, regulatory scientists and leading professionals
      - Longitudinally assess potentially relevant Pd, physiological and clinical parameters
      - These Natural History data provide the foundational basis for developing systematic models of disease progression, including the development of Bayesian Objective Performance Criteria (OPC)

➢ Both preclinical and clinical actions transcend any single treatment and jump-start future research.

Study Design and Assessment

- ***Challenges:***
  - Almost always there is no precedent for designing studies in the treatment of rare/ultra-rare disease. Irreversible disease morbidity/mortality may constrain design and analytical approaches
  - Assessment tools are imported and logically applied – but almost never validated in the disease under study. Assigning primary and secondary status is based on understanding the continuum of the disease and logical extrapolation of assessment tools
- ***Actions:***
  - Use applied Clinical Pharmacology to enhance study design and analytical strength
    - Based on preclinical Pk/Pd assessments from relevant animal models, pharmacokinetic (Pk) models from FIH trials, and disease progression models from Natural History studies, in-silico trial simulation may be used to develop and optimize alternative and innovative study designs for therapeutic trials
    - Determine optimal sampling times based on Pk/Pd models to increase likelihood of successfully collecting the most relevant data
    - Using dose/exposure-ranging response to understand onset , maintenance, offset of efficacy/safety (including immunogenicity)
    - Use data from all patients and healthy volunteers to inform dosing in various patient subsets (eg, effect of renal and hepatic function, age, gender) using the totality of information
    - Embed evaluating the effect of immunogenicity on Pk/Pd, efficacy/safety/toleration
  - Thoroughly review assessment tools in alternative disease areas with relevant morbidity/functional disability and pre-apply to selected Natural History cohorts

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Clinical Pharmacology, Bayesian Statistics and Substantial Evidence of Effectiveness:

Carl Peck

Adjunct Professor, UCSF

NDA Partners LLC

University of California
San Francisco
UCSF
School of Pharmacy

Thesis

- Randomized, clinical pharmacology dose-response & exposure-response trials can yield causal evidence of effectiveness
- These data can inform the probabilities and conditions that a drug will be effective for its intended purposes and populations
- These probabilities can be employed in a combined Bayesian & Frequentist statistical framework to greatly improve efficiency and informativeness of demonstrating substantial evidence of effectiveness

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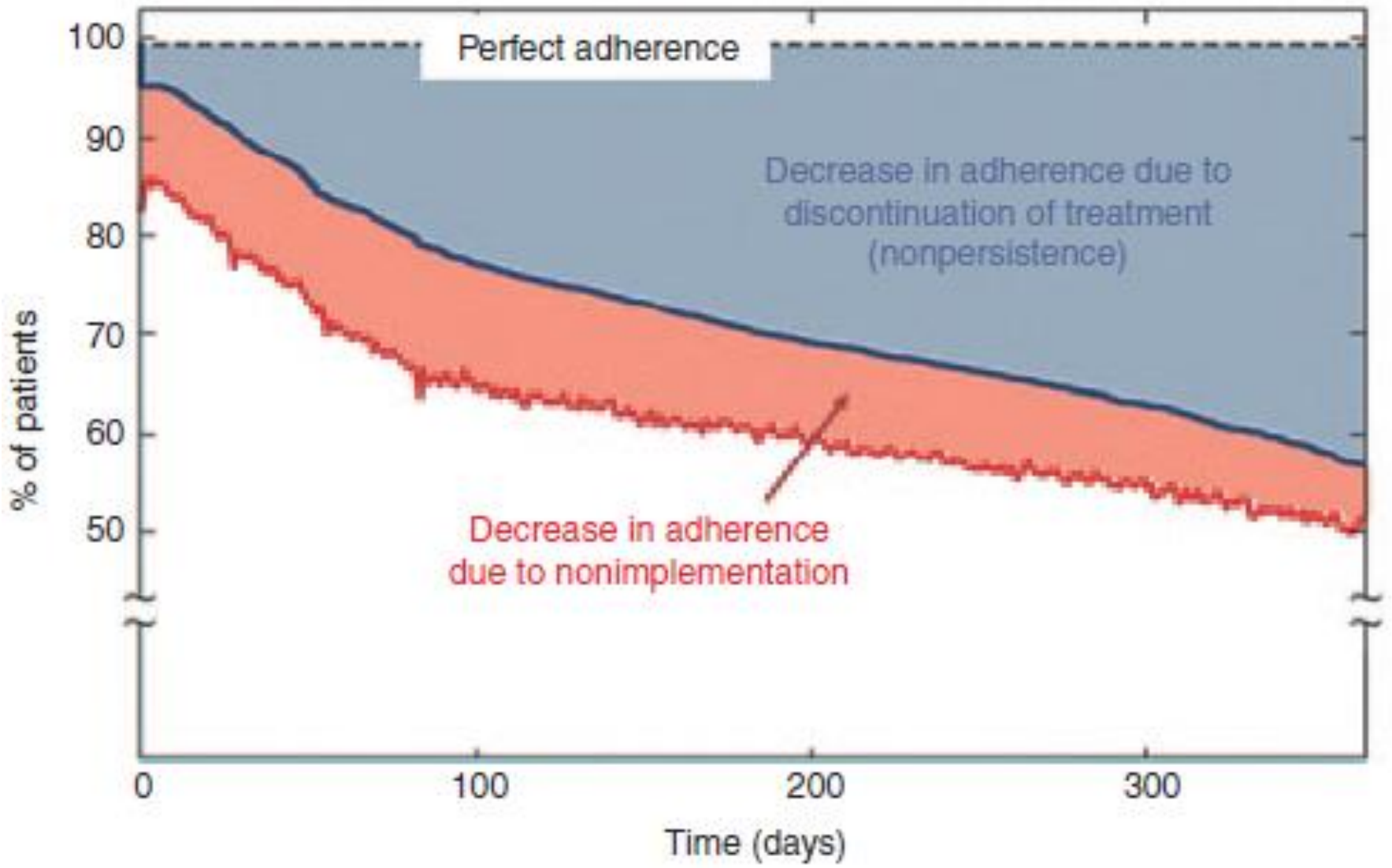
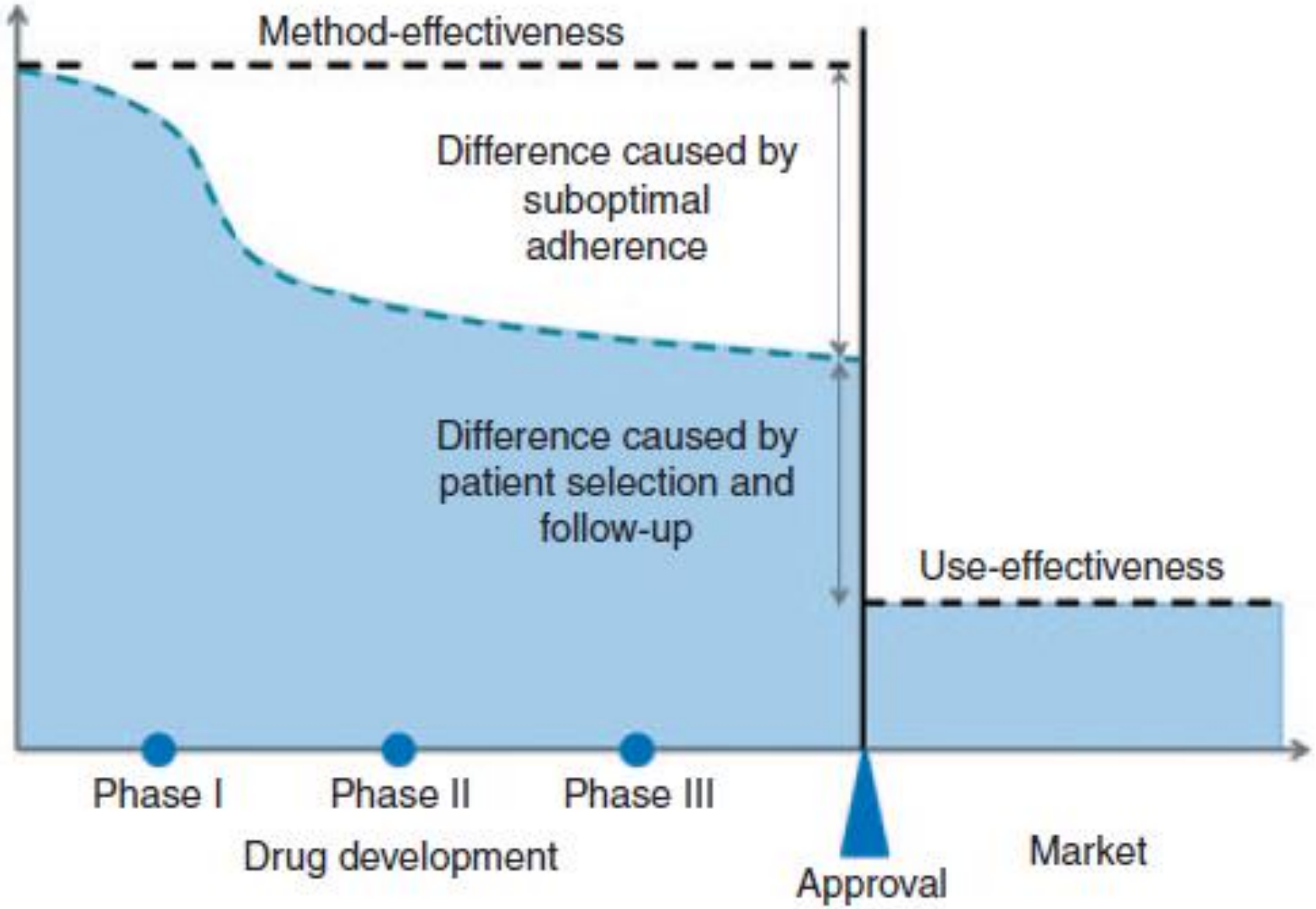
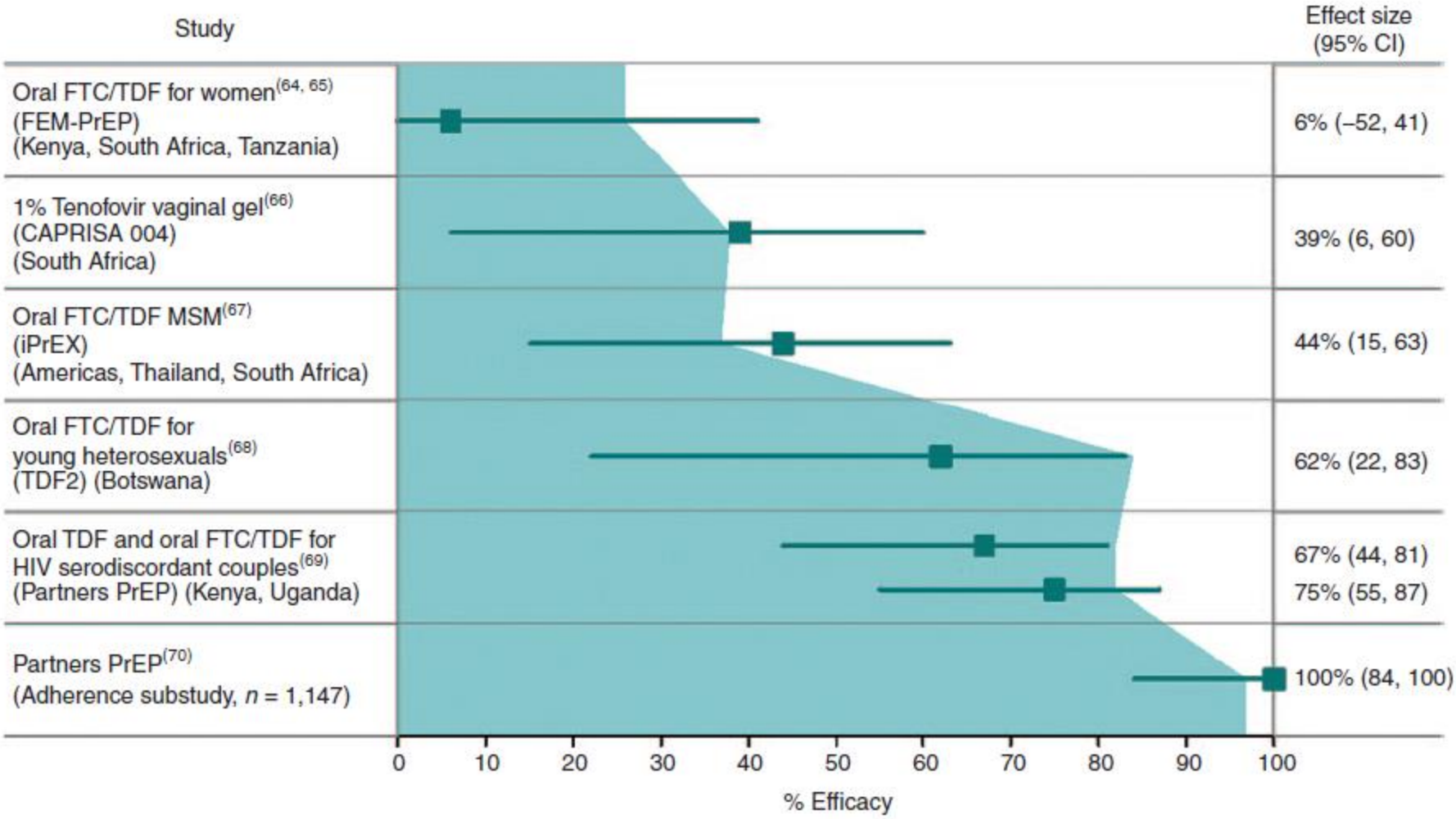
Adherence is the extent to which patients take their medicines as prescribed


100
90
80
70
60
50
% of patients
Perfect adherence
Decrease in adherence due to discontinuation of treatment (nonpersistence)
Decrease in adherence due to nonimplementation
0
100
200
300
Time (days)


Method-effectiveness
Difference caused by suboptimal adherence
Difference caused by patient selection and follow-up
Use-effectiveness
Phase I
Phase II
Phase III
Drug development
Approval
Market

Consequences of poor adherence in clinical trials

- Failure of a treatment
- Inappropriate dose escalation
- Overestimated dose requirements
- Emergence of drug resistant organisms
- Underestimation of dose related adverse effects
- Distorted pharmaco-economic analyses


Study
Effect size (95% CI)
Oral FTC/TDF for women[64, 65] (FEM-PrEP) (Kenya, South Africa, Tanzania)
6% (–52, 41)
1% Tenofovir vaginal gel[66] (CAPRISA 004) (South Africa)
39% (6, 60)
Oral FTC/TDF MSM[67] (iPrEX) (Americas, Thailand, South Africa)
44% (15, 63)
Oral FTC/TDF for young heterosexuals[68] (TDF2) (Botswana)
62% (22, 83)
Oral TDF and oral FTC/TDF for HIV serodiscordant couples[69] (Partners PrEP) (Kenya, Uganda)
67% (44, 81)
75% (55, 87)
Partners PrEP[70] (Adherence substudy, n = 1,147)
100% (84, 100)
0
10
20
30
40
50
60
70
80
90
100
% Efficacy

Methods of measuring adherence

FLAWED

- Returned tablet counts
- Face to face interviews
- Patient diaries

RELIABLE

- Professional drug administration
- Electronic detection of package entry
- Ingestible smart sensors
- Plasma drug levels

Tenofovir pre-exposure HIV prophylaxis

	Oral	Gel
• Tablet count	88%	83%
• Interview	90%	90%
• Plasma drug level	29%	25%
• Vaginal swab level	-	49%

Marrazzzo J.M.et al (2015)

Diseases where strict adherence necessary

- ALL treated with 6MP
- CML treated with imatinib
- HIV disease treated with protease inhibitors

Good adherence –cui bono?

- Drug developers
  - stronger claims for efficacy
  - fewer trial participants
  - increased statistical power

- Regulators
  - better dosing recommendations
  - Combine ITT with adherence assessment

- Patients
  -More effective and safe medicines

Drugs don’t work in patients who don’t take them.

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Center for Health Policy at BROOKINGS

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The Embassy Row Hotel • Washington, DC
July 28, 2015