Why drugs fail in clinical trials

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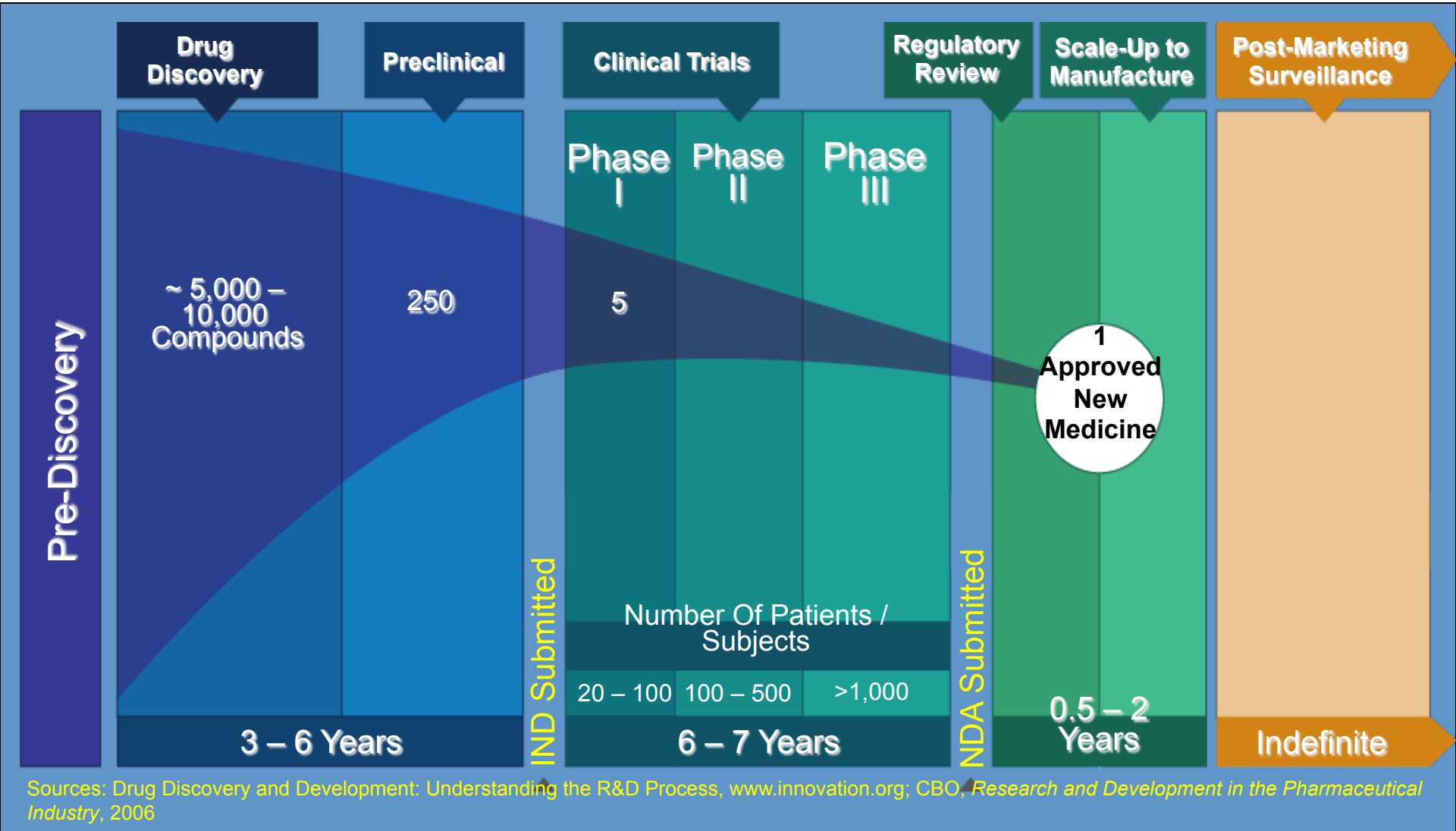
Imperial College London

Drug development is a tough business



Sources: Drug Discovery and Development: Understanding the R&D Process, www.innovation.org; CBO, *Research and Development in the Pharmaceutical Industry*, 2006

Lack of efficacy is a major reason for failure in early clinical development

Success rates have fallen from 28%(06/07) to 18% (08/09)

Reasons and areas of failure

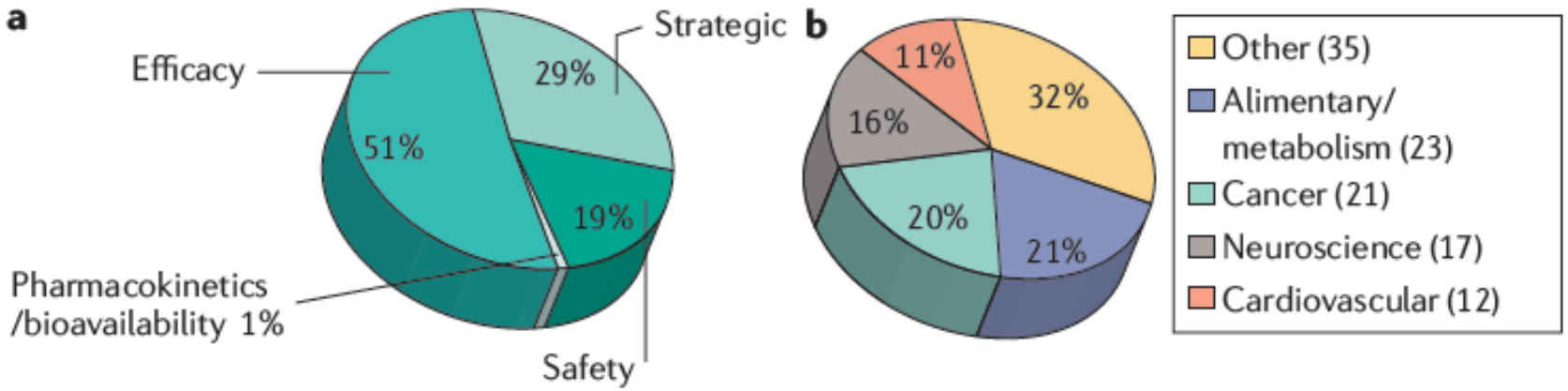


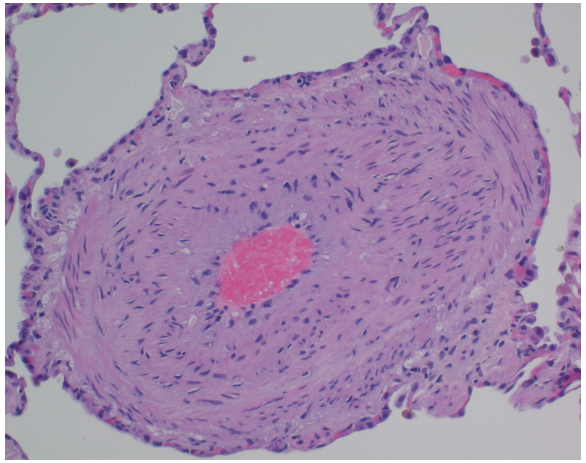
Figure 1 | **Phase II failures: 2008–2010.** The 108 failures are divided according to reason for failure when reported (87 drugs) (**a**) and therapeutic area (**b**).

The chances of a drug in Phase III proceeding to launch is 50%

Arrowsmith Nat Rev Drug Discovery 2011

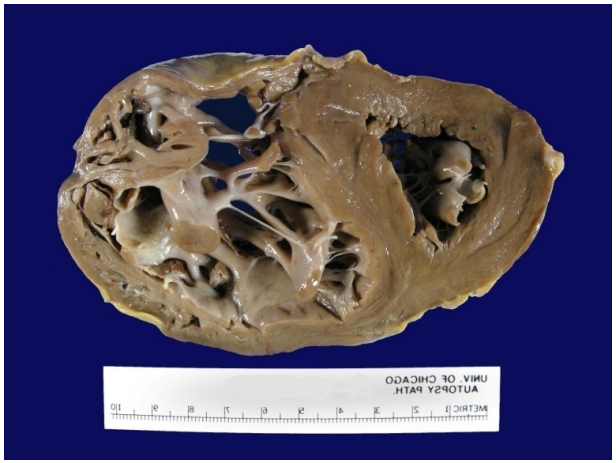
Pulmonary Arterial Hypertension as case study

Pulmonary vascular remodelling



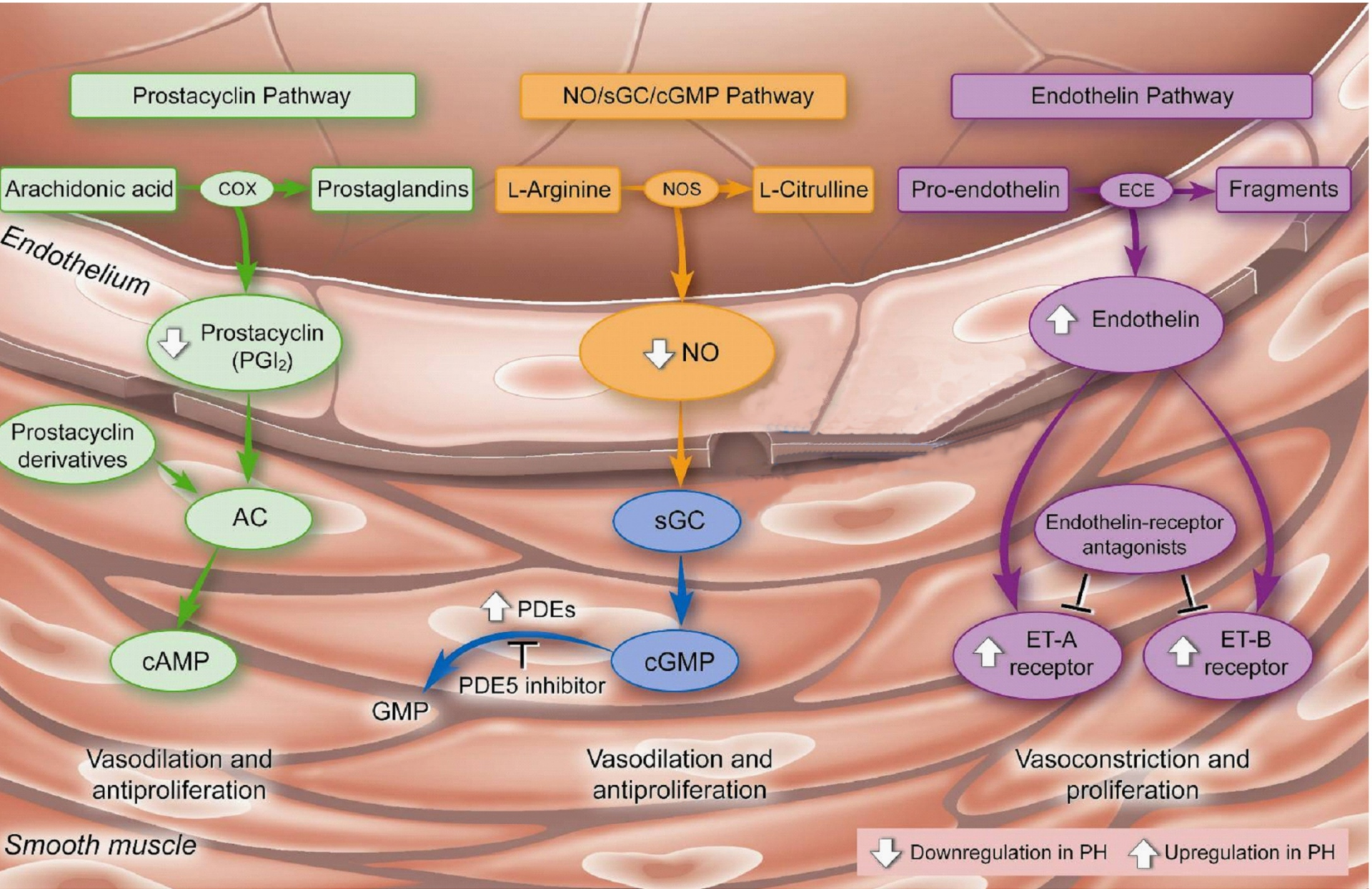
Increased pulmonary vascular resistance

Mean pulmonary artery pressure above 25mmHg (normal around 12)



Heart failure

Molecular Pathology: Imbalance of vasoactive mediators



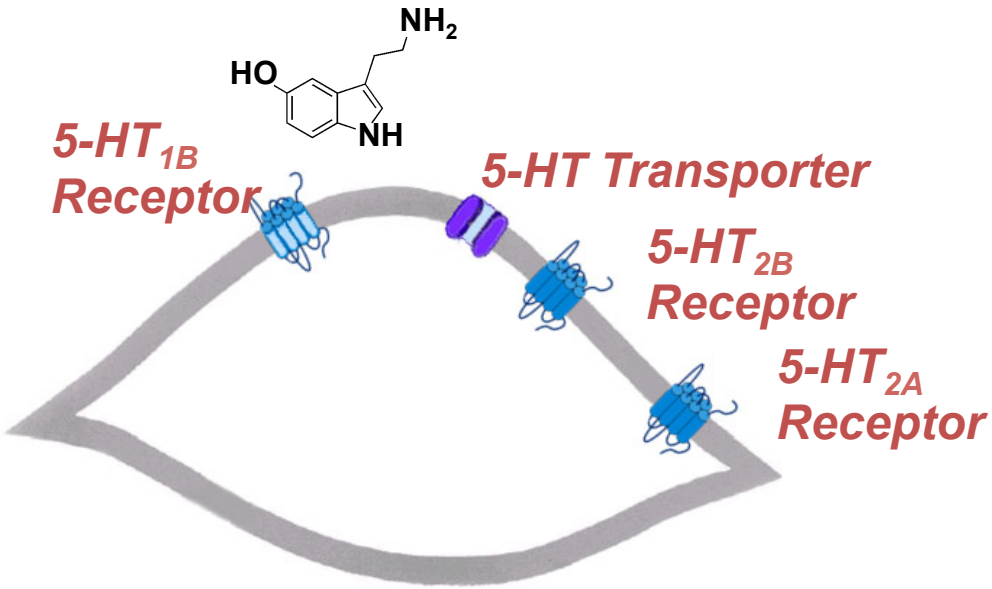
Some disappointments due to poor efficacy

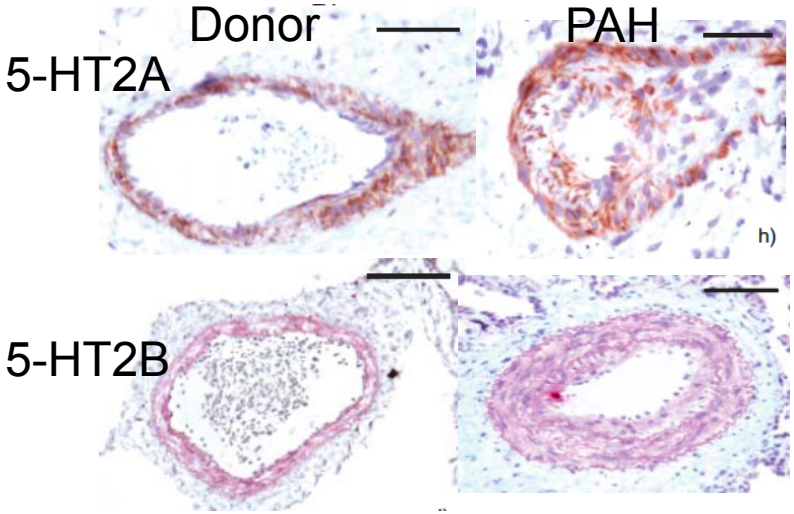
- Terguride – a serotonin receptor antagonist
- Aviptadil – vasoactive intestinal polypeptide
- Statins
- Imatinib – a tyrosine kinase inhibitor

Case study 1: Terguride

Chasing a valid drug target?

Serotonin receptors in pulmonary hypertension



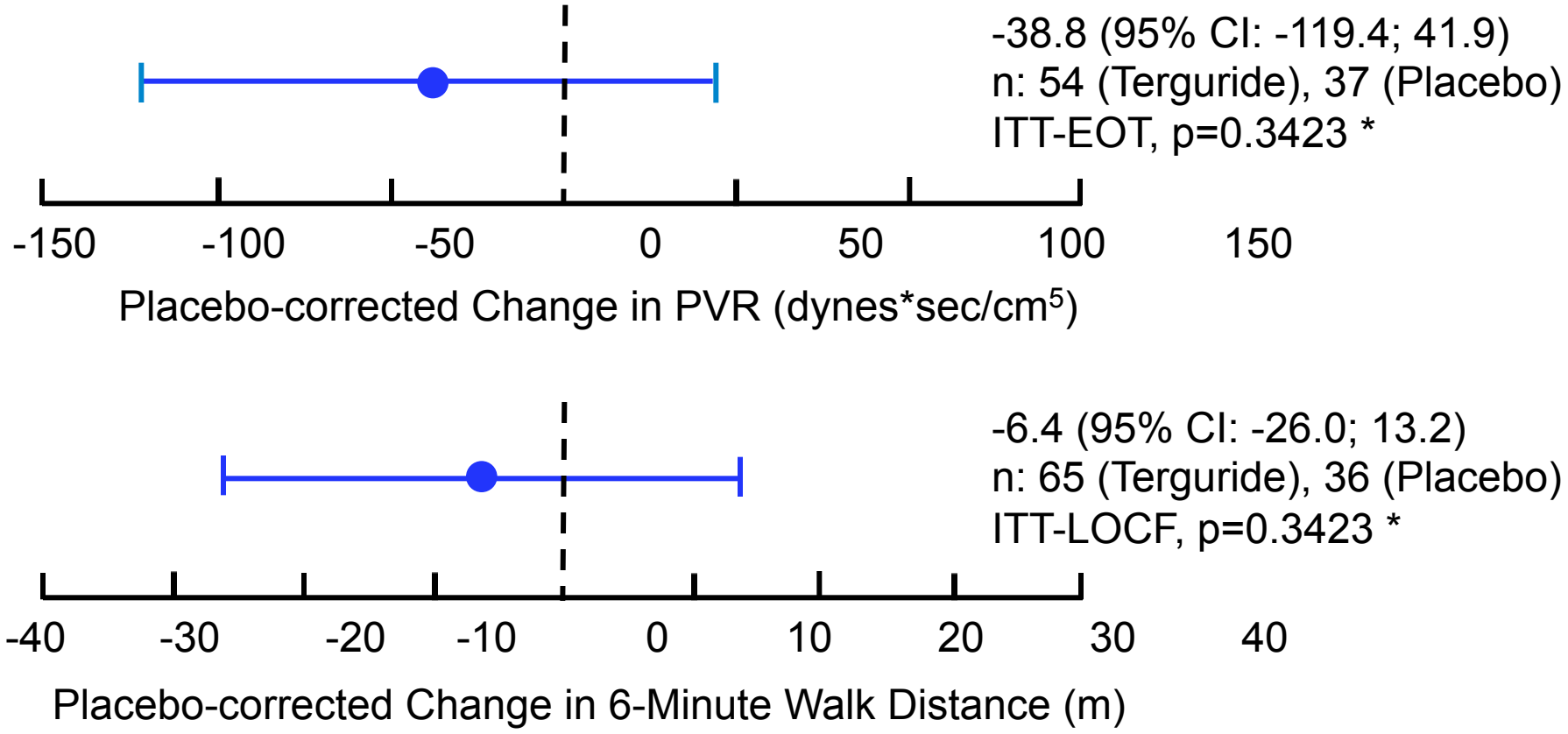


5-HT transporter:
Smooth muscle cell hyperplasia
Lee SL et al (1991)
Eddahibi S et al (1999)

5-HT1B, 5-HT2A receptors:
Pulmonary vasoconstriction
Mac Lean et al (1996)
Keegan A et al (2001)

5-HT2B receptor:
Cell proliferation, elastase synthesis, TGF-β synthesis
Launay JM et al (2002)
Mitani Y et al (2002)

No significant treatment effect of Terguride on PVR and 6 MW distance



* two-tailed fixed effect ANCOVA analysis with treatment, baseline PVR and 6MWD as covariates

http://conference.thoracic.org/2012/Search/abstractDetails.php?id=358

Learning point 1: Choose the right target

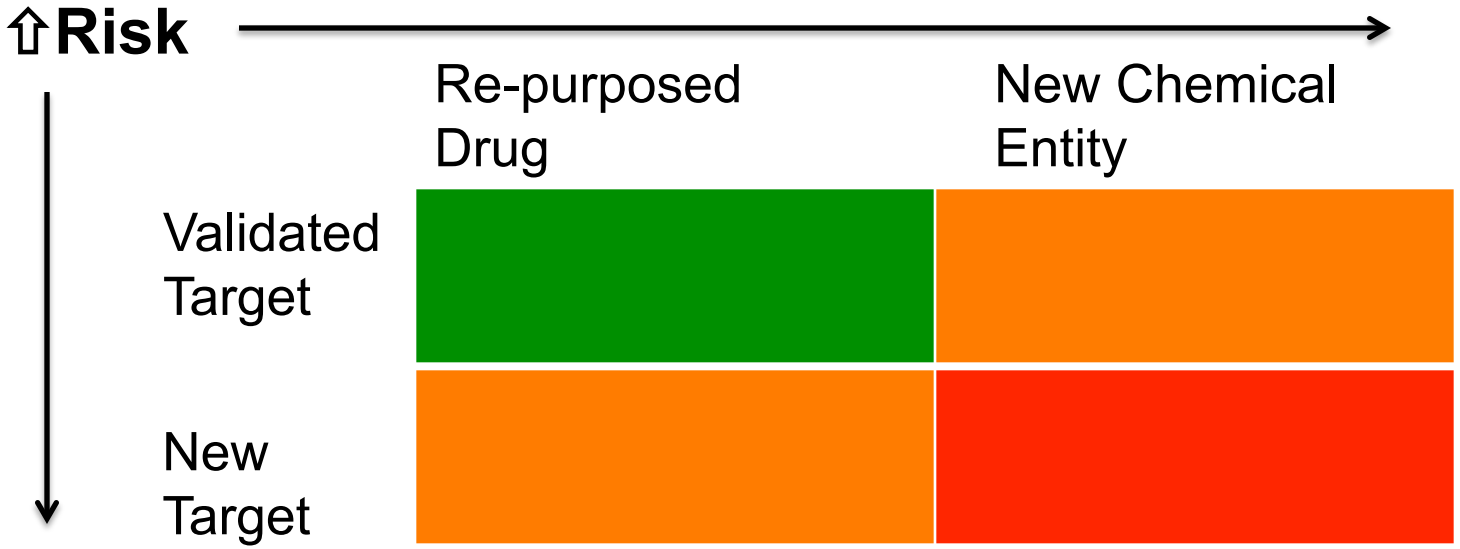
Is the drug target valid for the disease?

Where do targets come from?

– Knowledge of disease pathology
– Efficacy of existing treatments
– Genomics

Reducing risk in drug development

- Exploring established pathways
  - Oral prostanoids
  - “Tissue-targeted” endothelin receptor antagonist
  - sGC stimulators
- Re-purposed from other diseases
  - Tyrosine kinase inhibitors



Learning point 2:
Animal studies are no guarantee of success

Animal studies provide useful data on

- Toxicity
- Pharmacokinetics

Less reliable for efficacy studies

The best model of human disease is the patient

Table 4. *Agents shown to prevent and/or reverse monocrotaline-induced PH in rats*

Agent	Reference
ACE inhibitors	11, 80, 113
Angiotensin receptor antagonists	82
Dexfenfluramine	111
Dichloroacetate	103
Difluoromethylornithine (DFMO)	203
Elastase	81
Elastase inhibitors	28
Epidermal growth factor inhibitor	104
Endothelin receptor antagonists	27, 30, 132, 198
Gene therapy (prostacyclin synthase, antisurvivin)	71, 102, 118, 141
Guanylate cyclase activators	39
HMG-CoA reductase inhibitors	66
Isosorbide dinitrate	81
K^+ channel openers	168
PDGF inhibitors	143
Phosphodiesterase (4 and 5) inhibitors	74, 78, 94
Propylthiouracil	156
Prostanoids	72, 122
Prostacyclin receptor agonists	87
Rapamycin	119, 202
Rho kinase inhibitors	1, 165
Resveratrol	29
Serine/threonine kinase inhibitor	86
Serotonin transport inhibitors	55
Stem cells ("EPCs" and mesenchymal)	8, 79, 191, 201
Steroids	
• Methylprednisolone	90
• Prednisolone	81
• Estradiol	167
• Dehydroepiandrosterone	63
Trimetazidine	54

PH, pulmonary hypertension.

Many drugs work in animal models

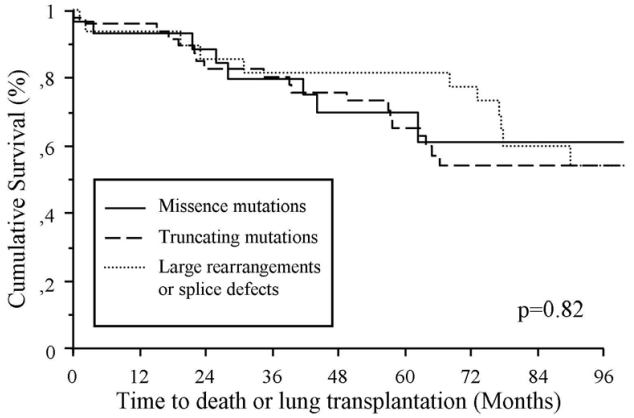
Stenmark et al 2009

Learning point 3: Genetics is a powerful indicator of valid drugs targets

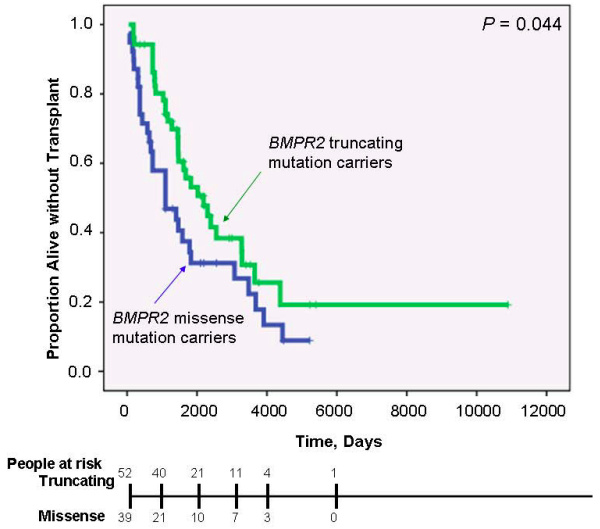
Many pharma companies are now focusing on rare diseases

7000 rare disease (<5/100,000) and genetic factors identified in some 80%

BMPR2 mutations

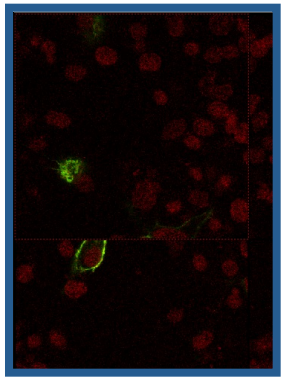


Girerd et al Respiratory Res 2010

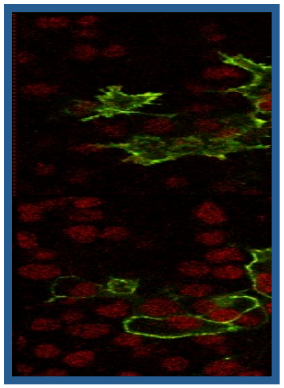


Austin et al Respiratory Res 2010

wtBMPR-II-5'myc

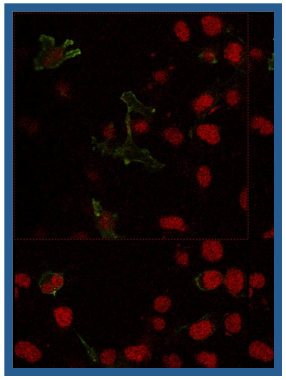


Control

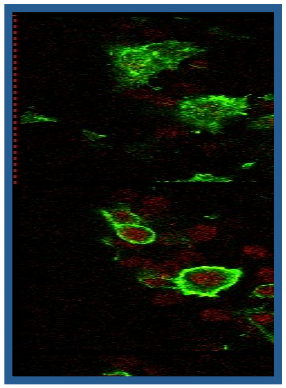


4-phenylbutyrate

C118W- 5'myc



Control



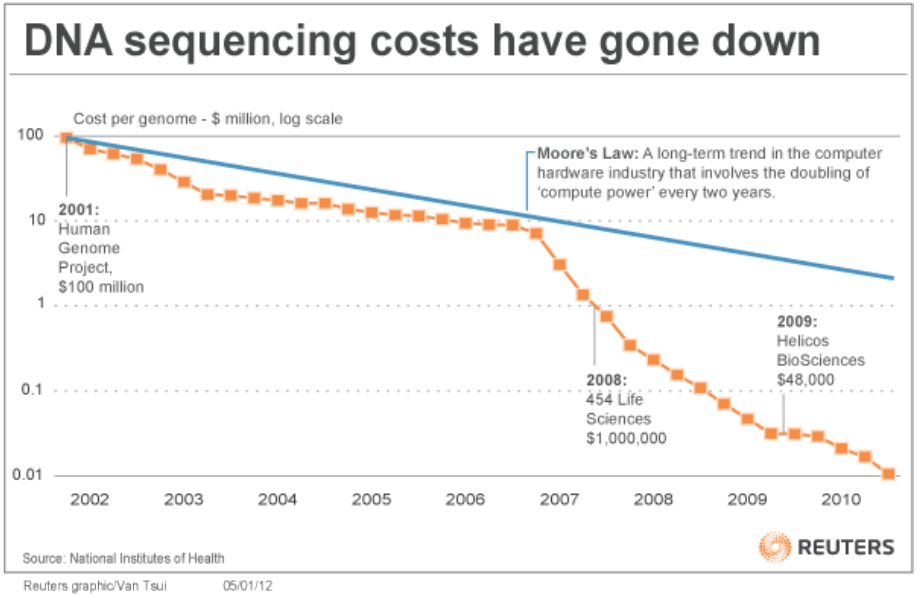
4-phenylbutyrate

Sobolewski et al. Hum Mol Genet. 2008 15;17:3180-90

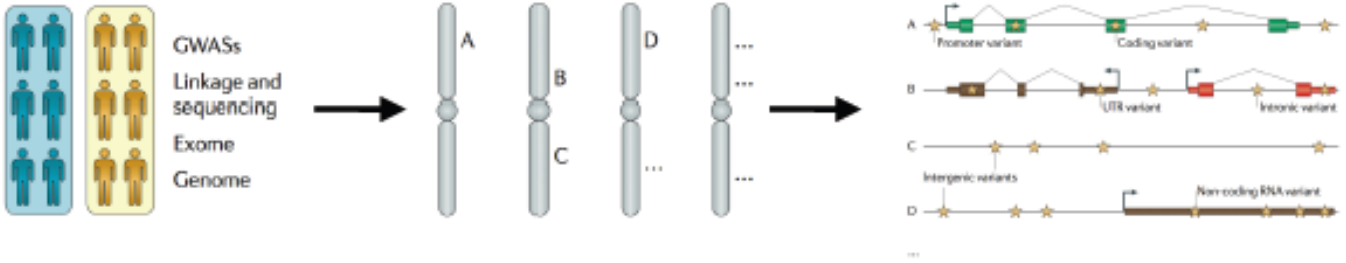
“Soon $1,000 Will Map Your Genes”

Wall Street Journal, Financial Times and Reuters Jan 9th 2012

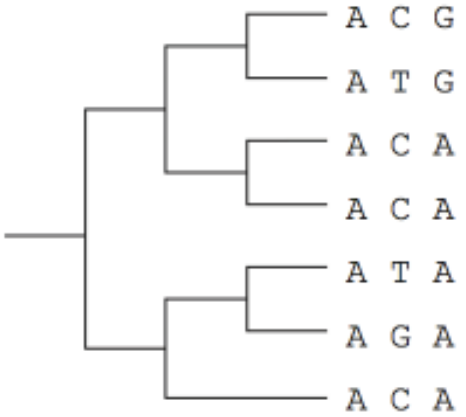
Life Technologies says its new Ion Proton sequencer – a $149K instrument about the size of a laser printer – can read a whole human genome in less than a day for $1000, including all chemicals, running costs and preliminary data analysis.

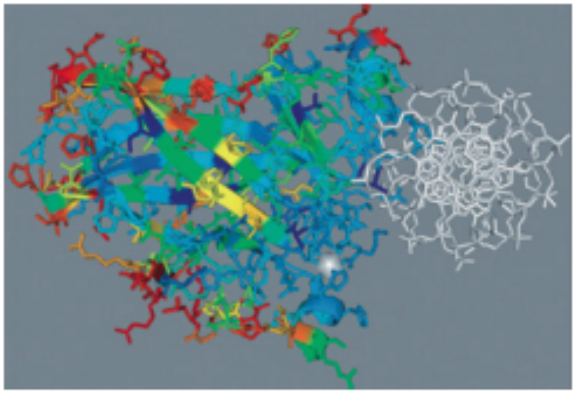


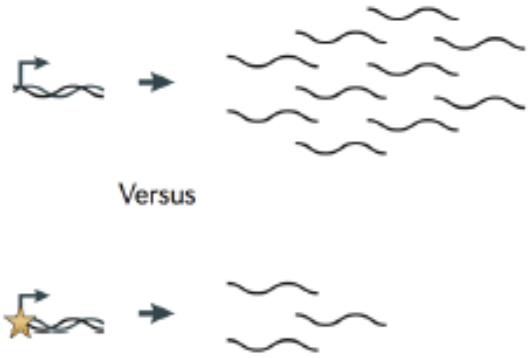
Scientists say that breaking the $1,000 barrier—roughly the price of an MRI test—will accelerate an already fast-moving transformation in genetic discovery and drug development.



Long list of candidate variants







Comparative Genomics

Protein Structure / Biochemistry

Experimental Assay

Cooper *et al.*, 2011

Success of Mendelian randomisation in systemic vascular disease

The interleukin-6 receptor as a target for prevention of coronary heart disease: a mendelian randomisation analysis

*The Interleukin-6 Receptor Mendelian Randomisation Analysis (IL6R MR) Consortium**

Lancet 2012; 379: 1214-24

Association between C reactive protein and coronary heart disease: mendelian randomisation analysis based on individual participant data

C Reactive Protein Coronary Heart Disease Genetics Collaboration (CCGC)

BMJ 2011

Separating the Mechanism-Based and Off-Target Actions of Cholesteryl Ester Transfer Protein Inhibitors With *CETP* Gene Polymorphisms

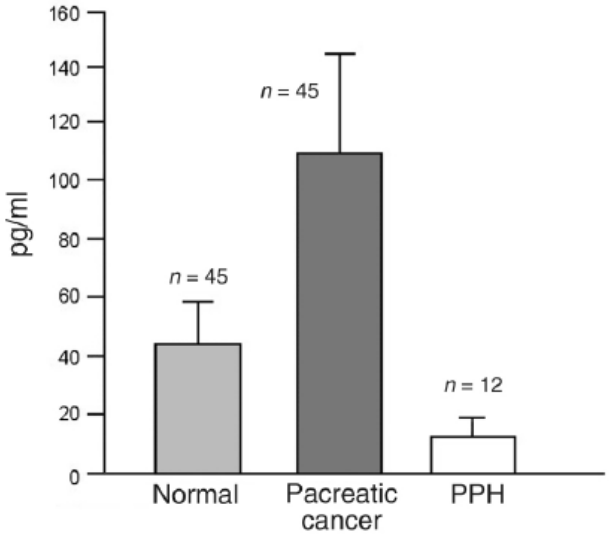
Circulation 2010

Case study 2: Aviptadil

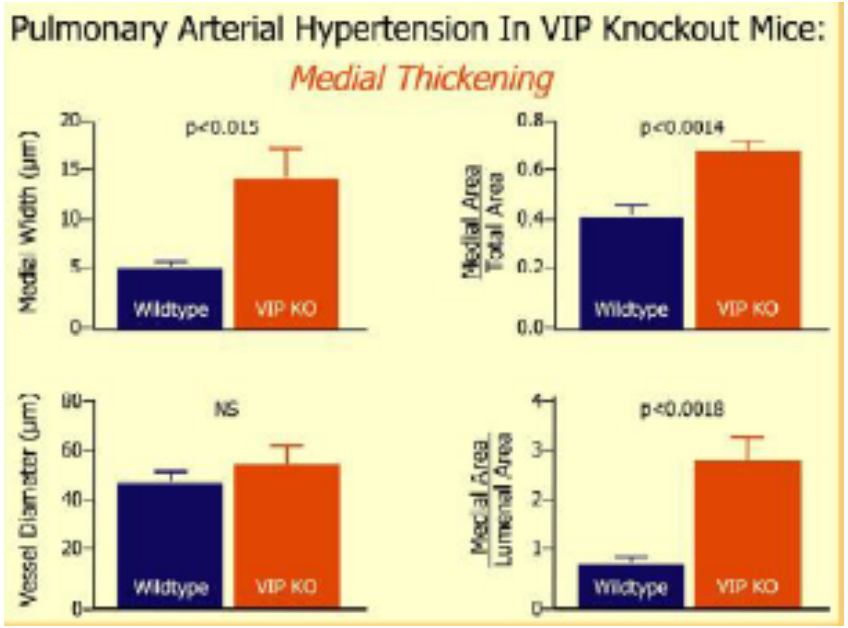
Choosing the right formulation

VIP deficiency and PAH

VIP levels are reduced in PAH

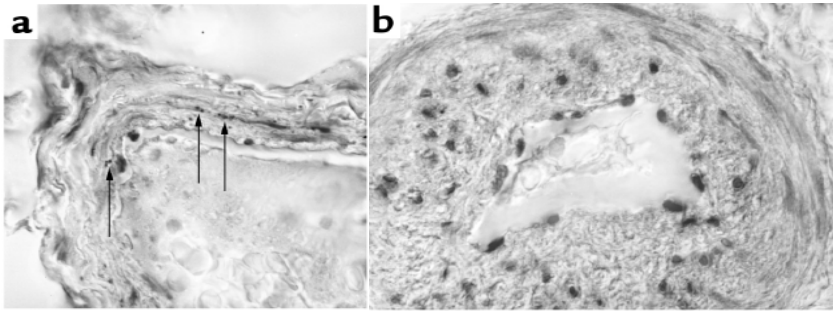


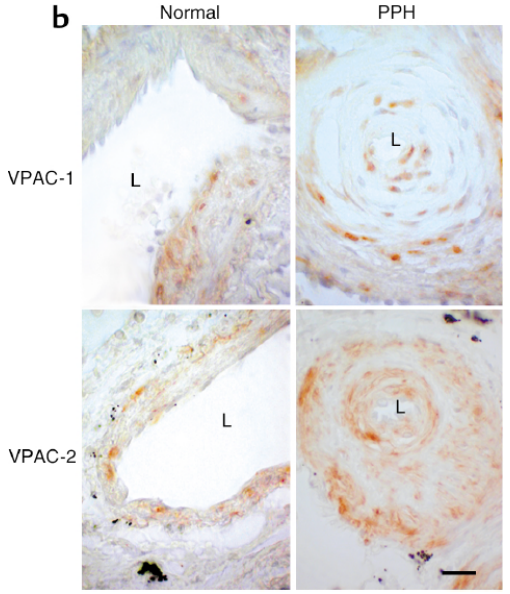
Knocking out VIP leads to PH in the mouse

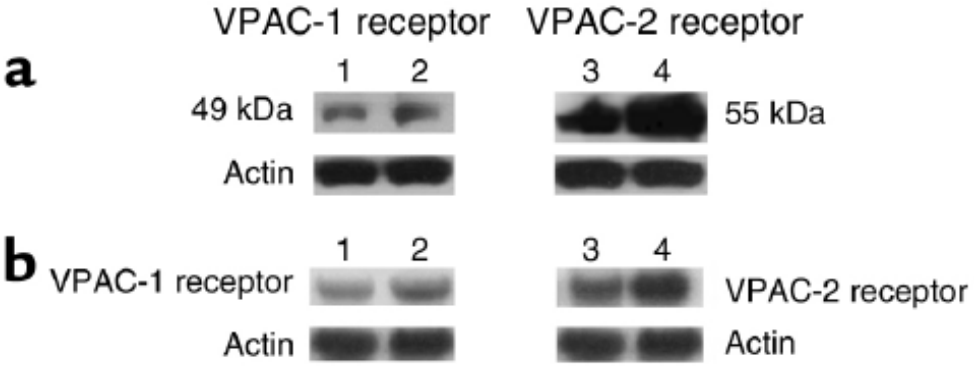


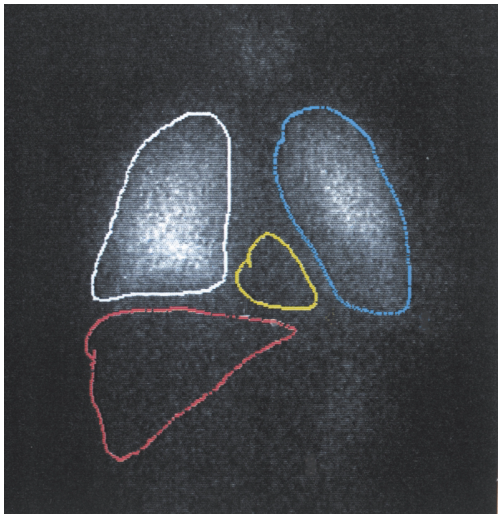
Petkov et al 2003

VIP receptors are present in diseased lung



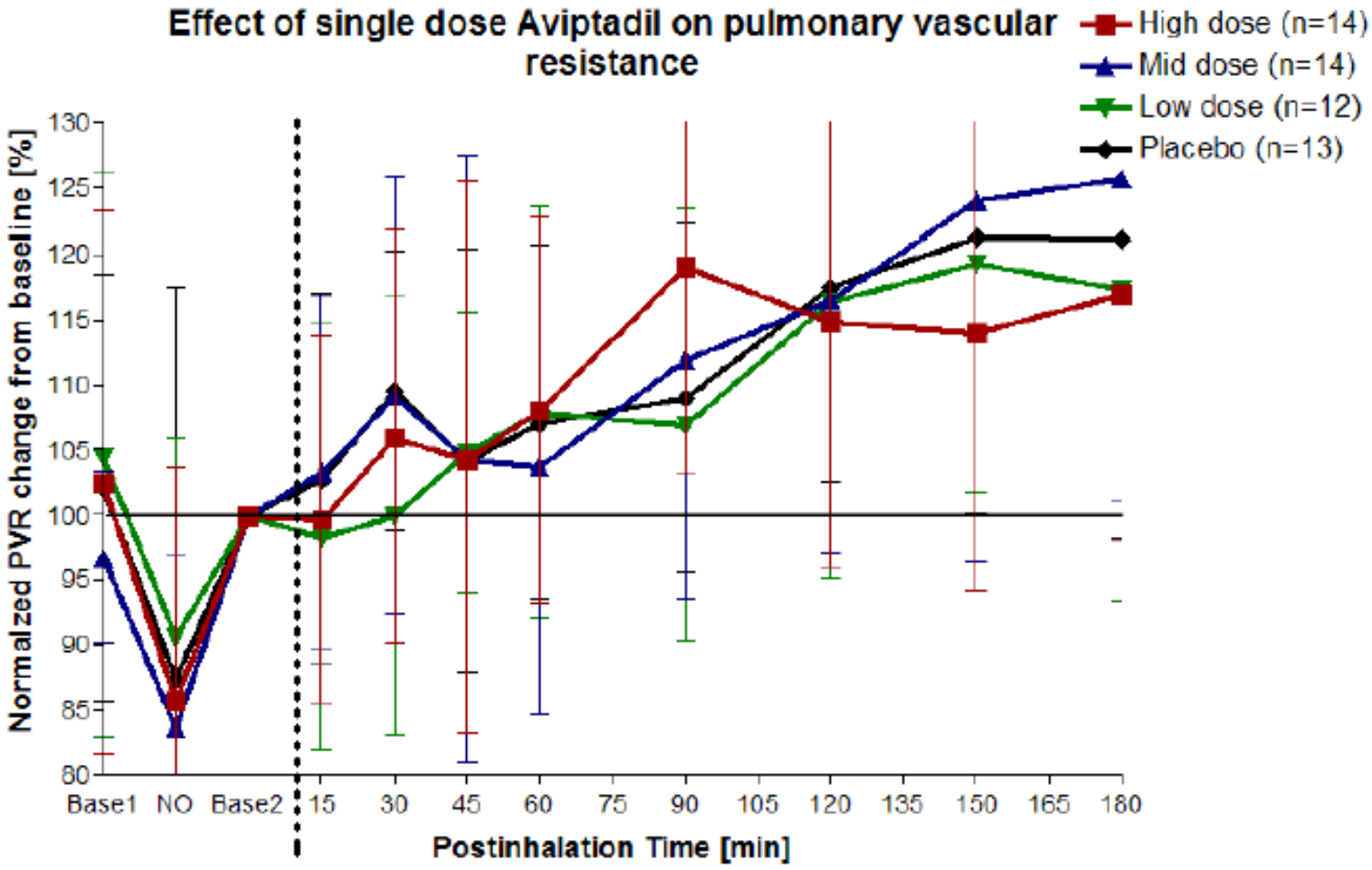






Petkov et al 2003

Inhaled VIP ineffective as a treatment



http://www.escardio.org/congresses/esc-2010/congress-topic/Pages/pulmonary-circulation.aspx

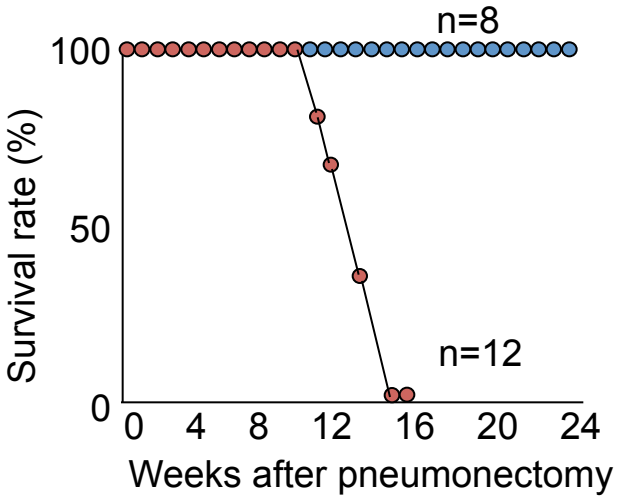
Learning point 4: Ensure the drug gets to the target

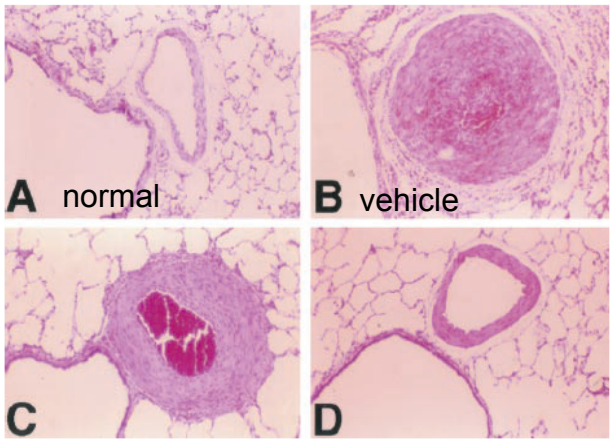
- Is the formulation right?
- What drug concentration is achieved?
- In the case of a peptide, is it neutralised by antibodies?

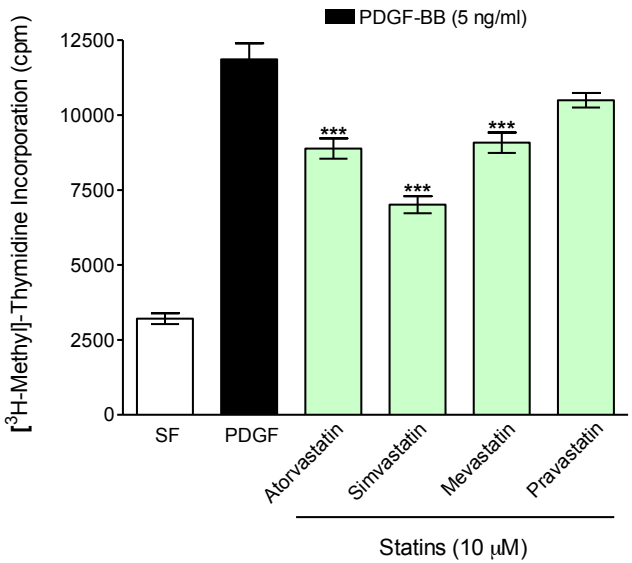
Case study 3: Statins

Choosing the right dose

Statins as a treatment for PAH

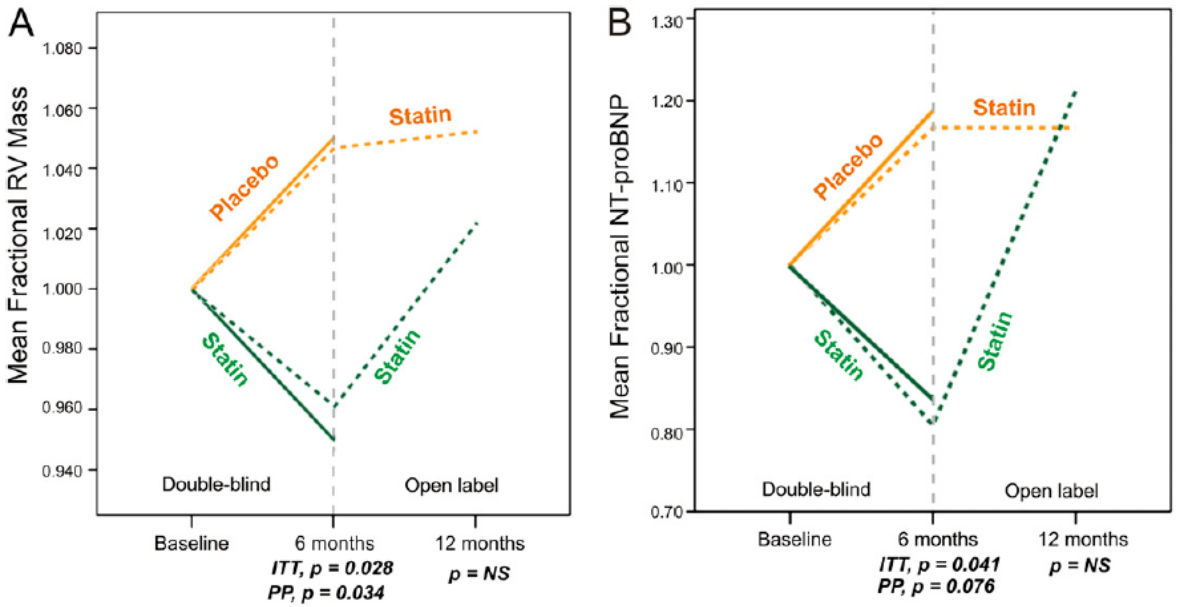




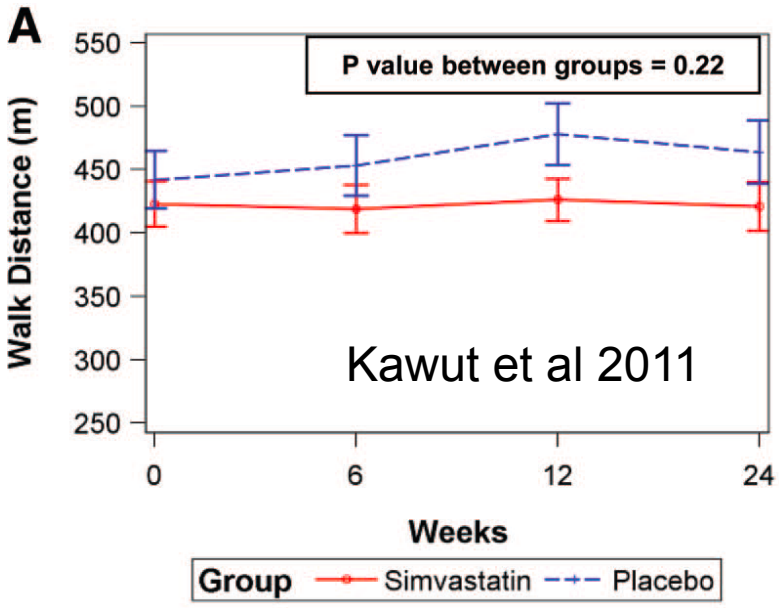


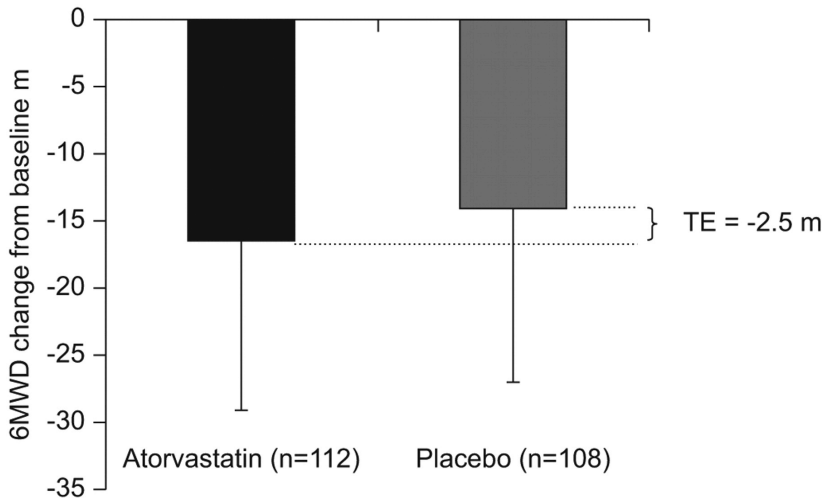
Nishimura et al 2003

Clinical trials of statins in PAH



Wilkins et al 2010





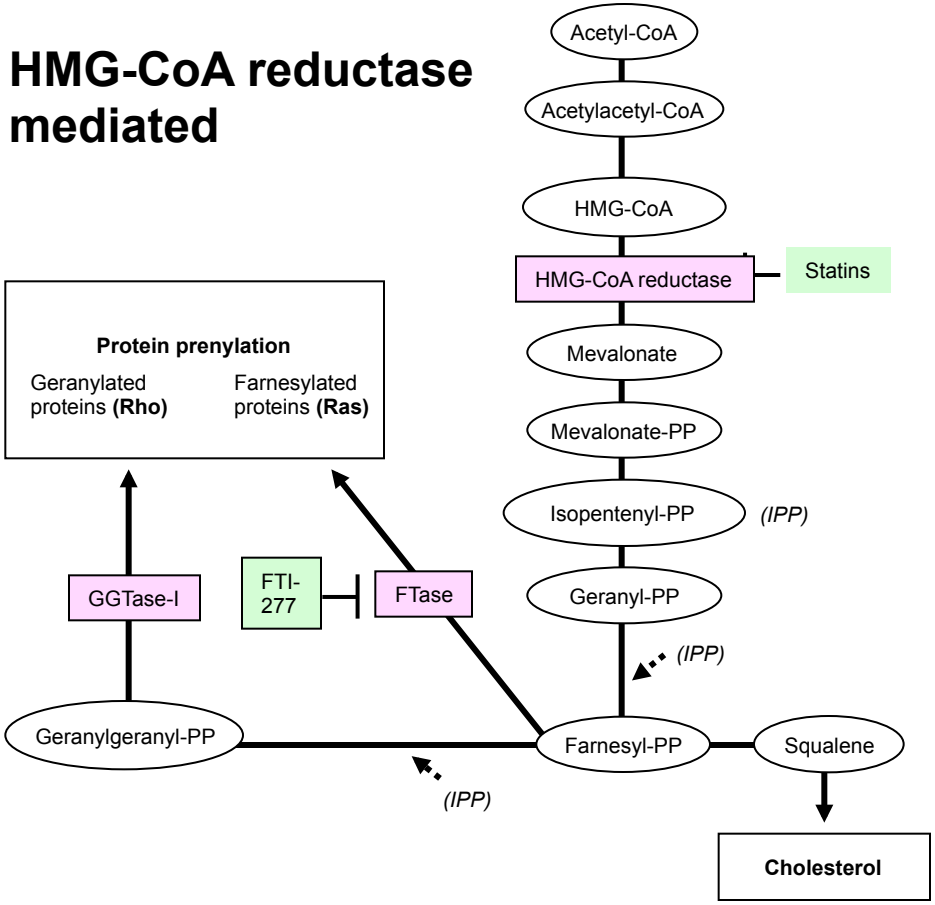
Zeng et al 2012

Dose - related

Higher doses used in animal studies compared to humans

Target - related

HMG-CoA reductase mediated



Non- HMG-CoA reductase mediated

Statins selectively inhibit leukocyte function antigen-1 by binding to a novel regulatory integrin site

Weitz-schmidt et al *Nat Med 2001*

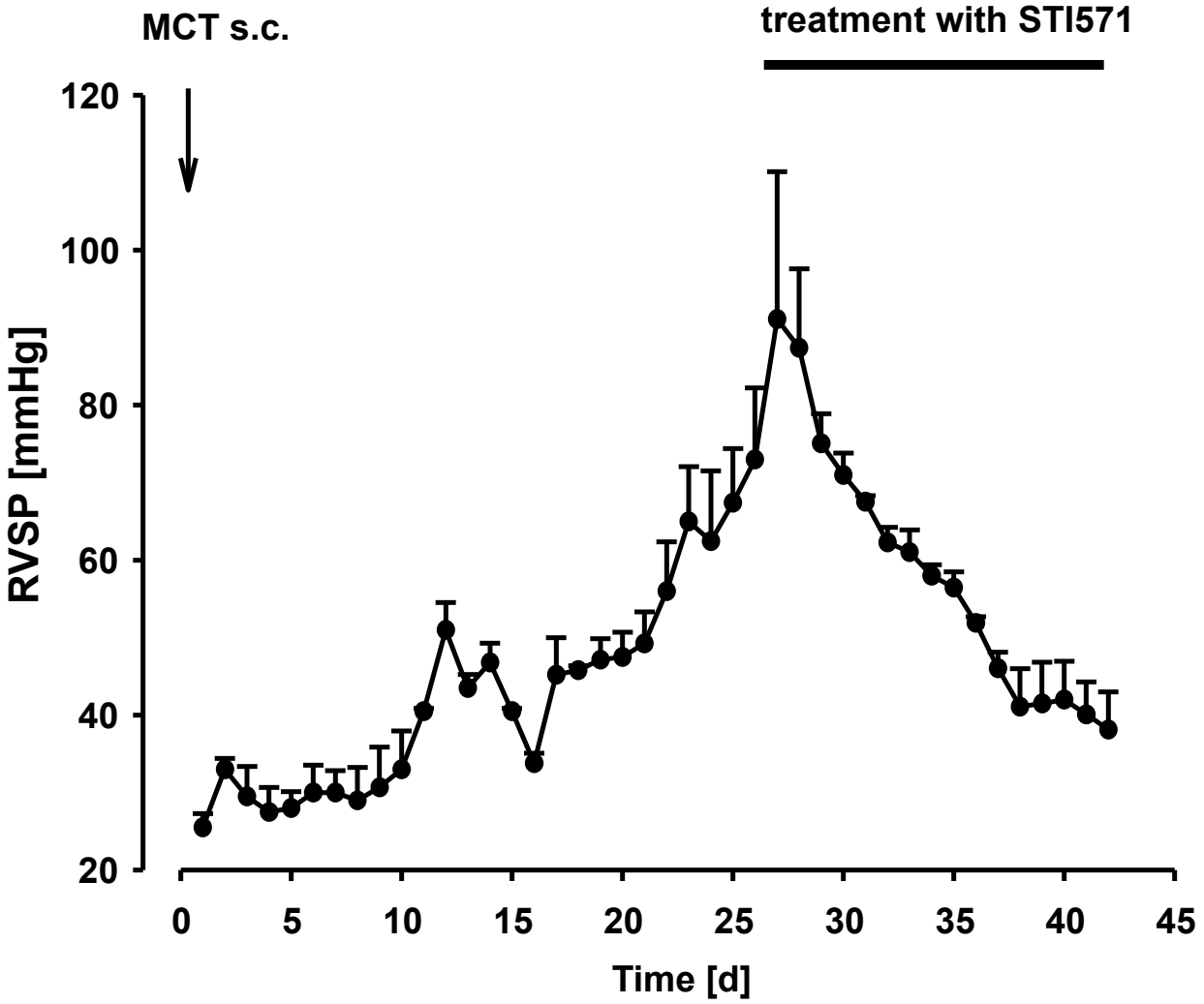
Learning point 5: Understand the dose-response relationship

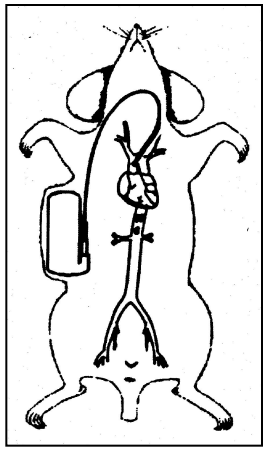
– Specifically, the relationship between efficacy and toxicity

Case study 4: Imatinib

Choosing the right patient population

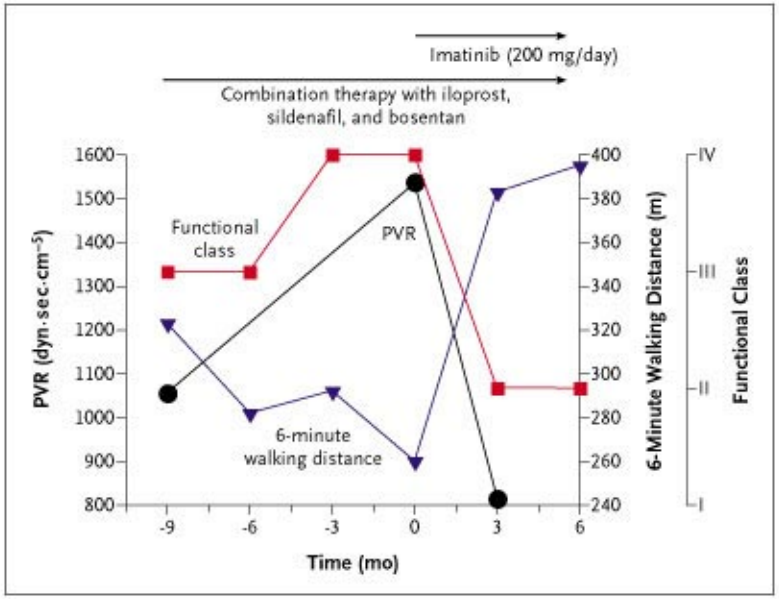
Imatinib reverses MCT-induced PAH



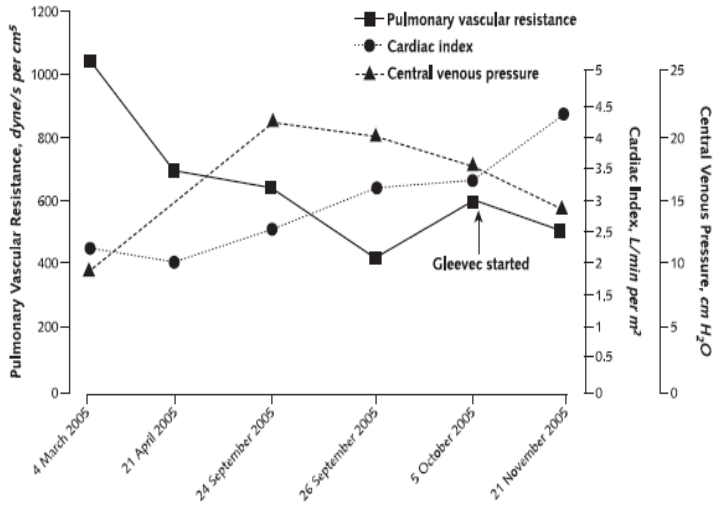


Schermuly et al., J Clin Invest, 2005

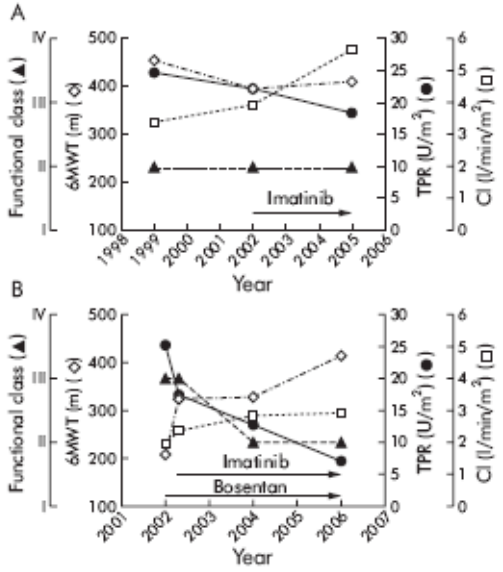
Case reports of Imatinib in IPAH



Ghofrani et. al., NEJM 2005



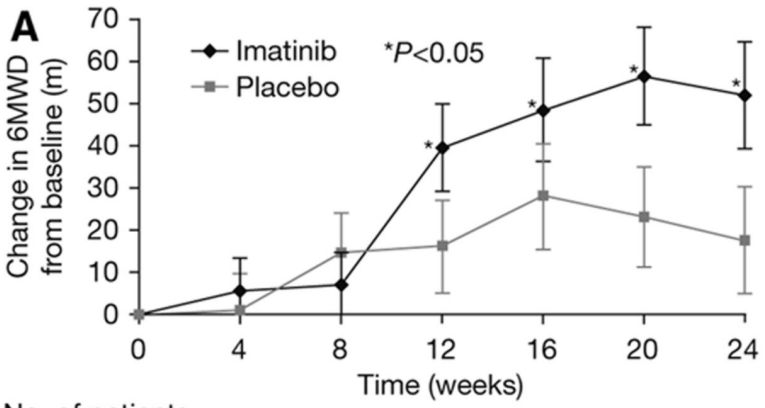
Patterson et. al., Ann Int Med 2006



Souza et. al., Thorax 2006

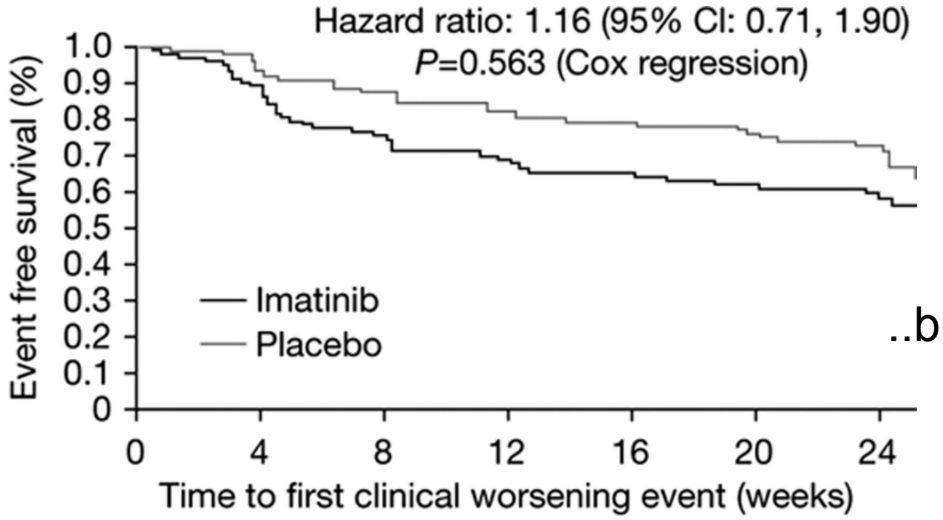
Imatinib in PAH

Improvement in 6MWD …….. and haemodynamics



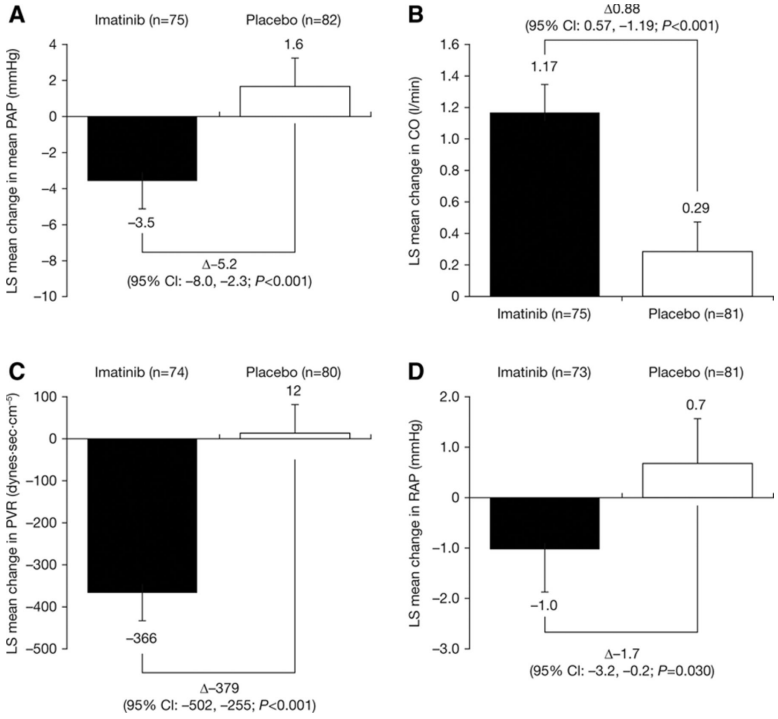
No. of patients

Imatinib	103	89	84	76	71	72	66
Placebo	98	93	91	88	82	84	80



No. of patients

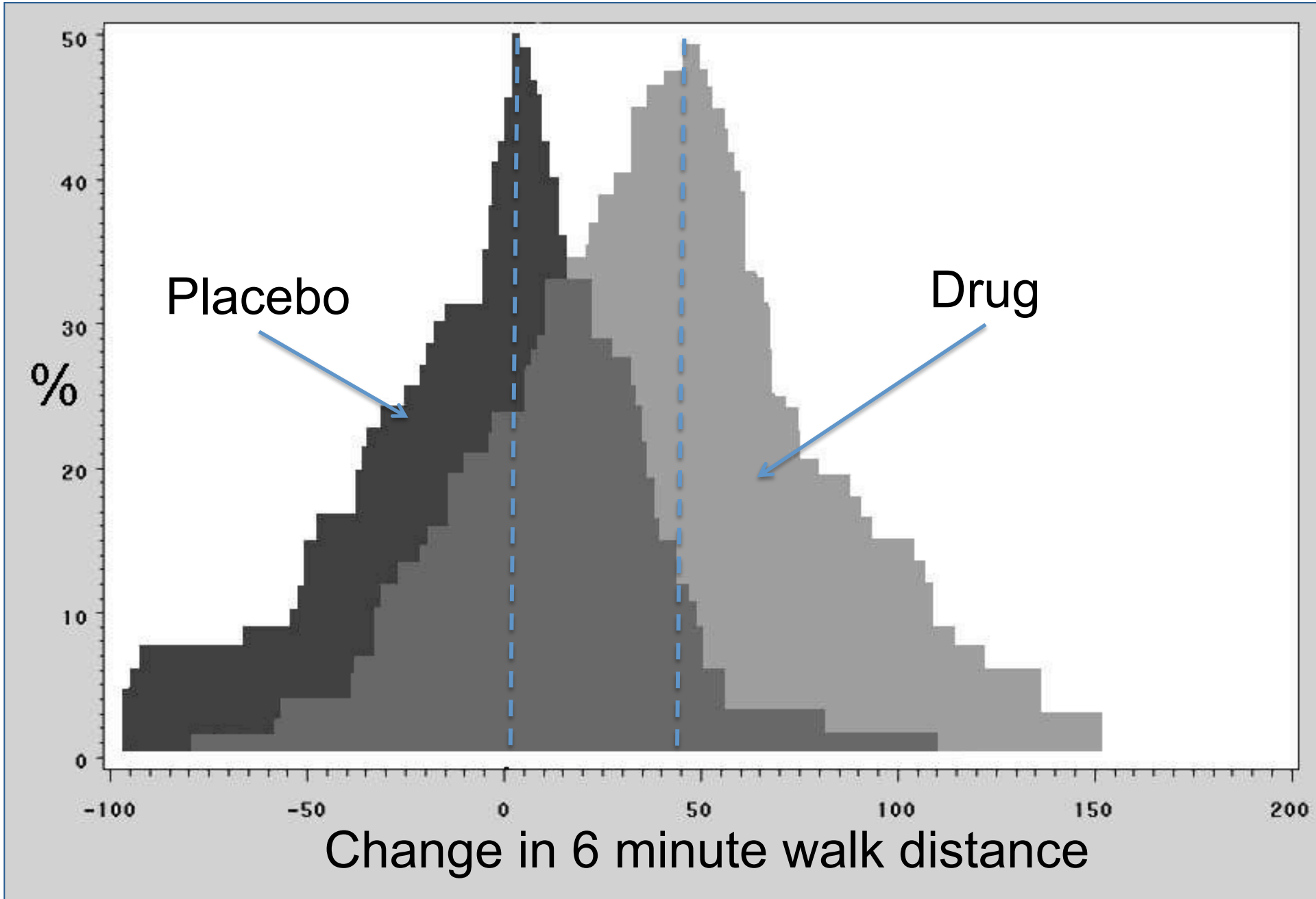
Imatinib	103	93	70	66	60	58	45
Placebo	98	91	85	80	75	72	54



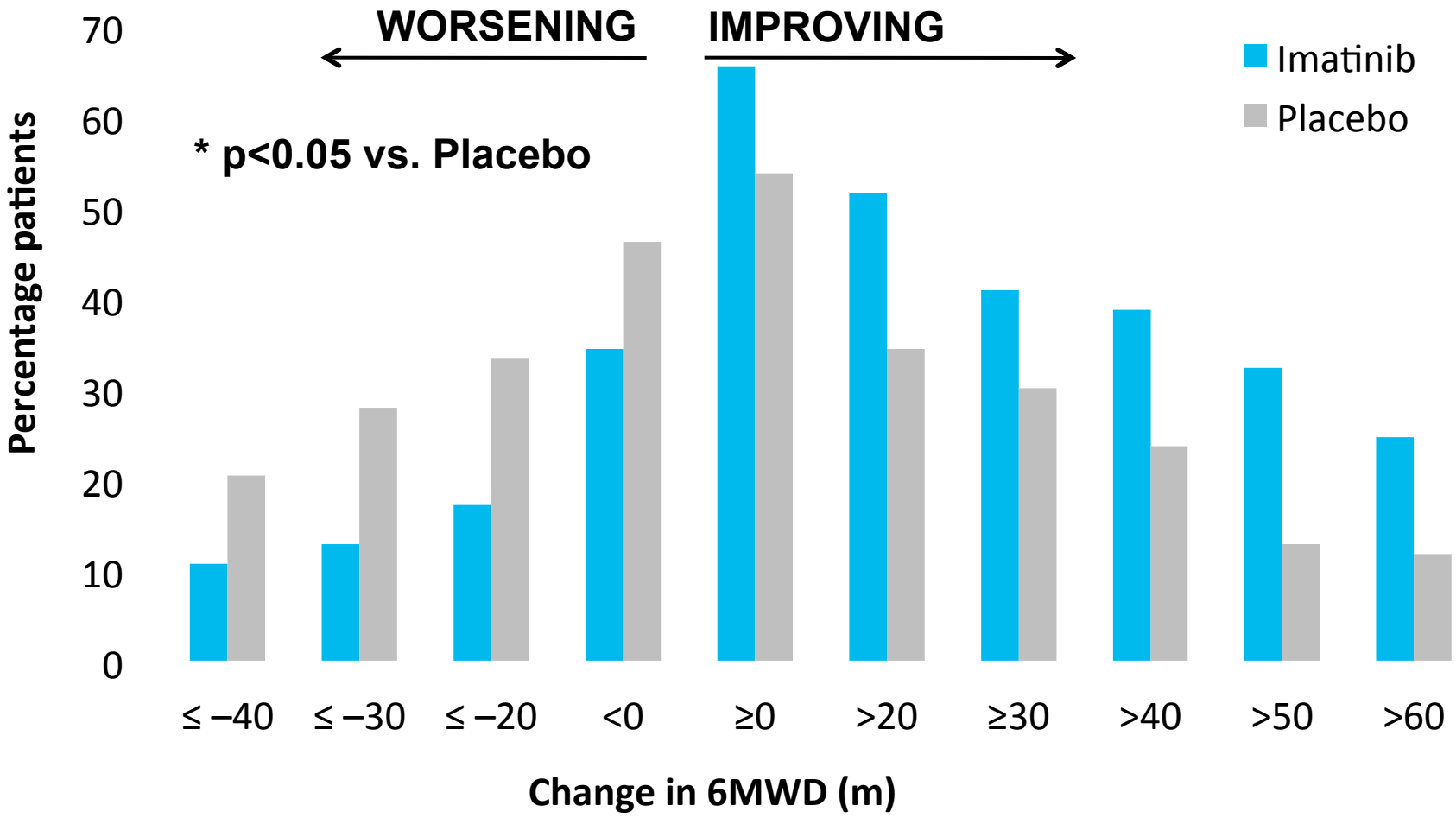
..but no improvement in clinical outcome

Hoeper M M et al. Circulation 2013;127:1128-1138

Variability in drug response



Phenotypically Augmented Clinical Trials

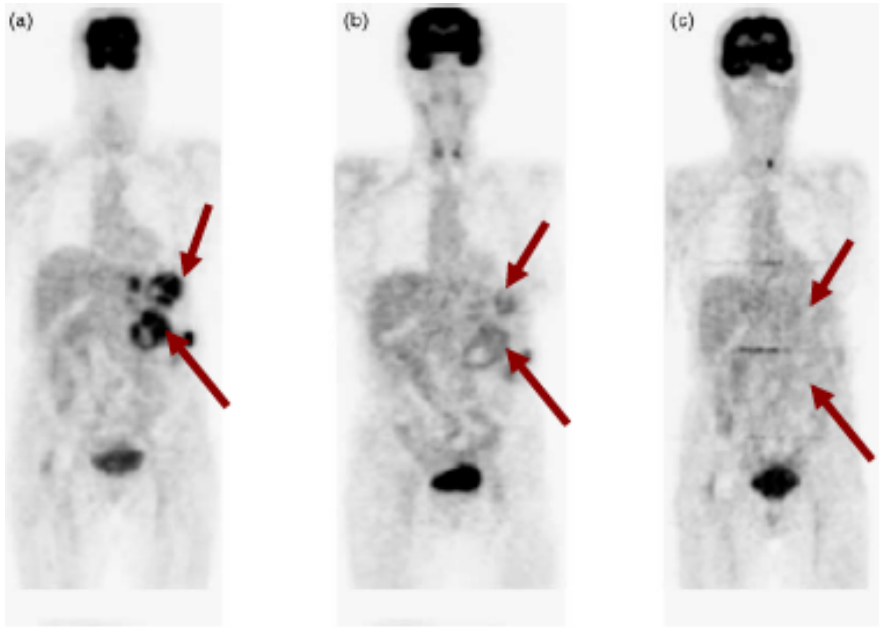


Responder analysis of absolute change in 6MWD from baseline to Week 24

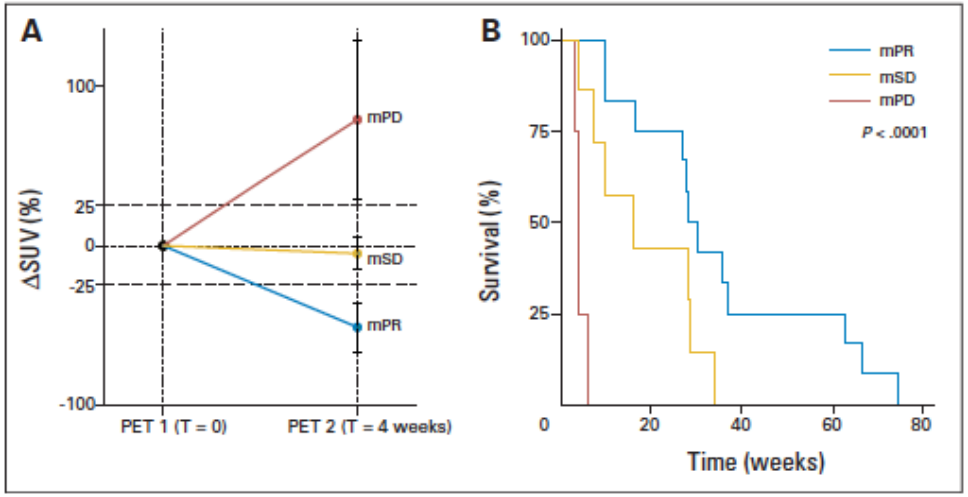
Learning point 6: Target the right patient population

- Is there a biomarker that predicts response?

GIST and FDG PET
Prediction of response to TKIs



Stroobants et al 2003

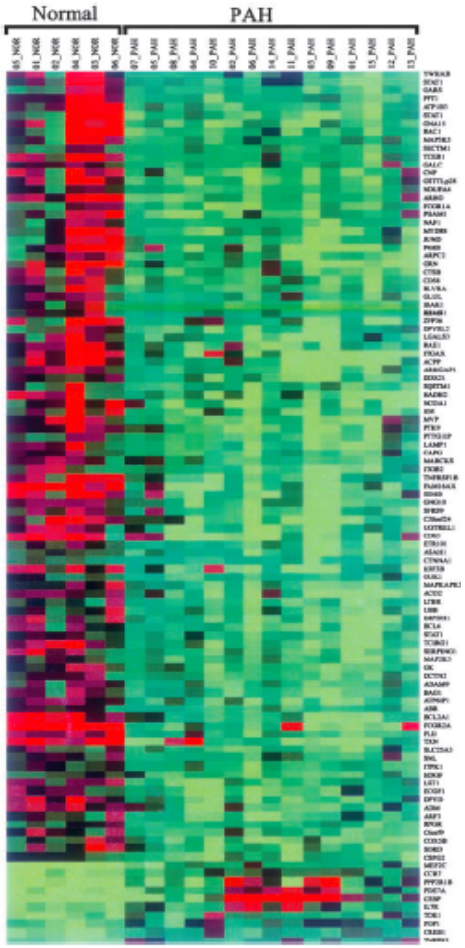


Prior et al – J Clin Oncol 2009

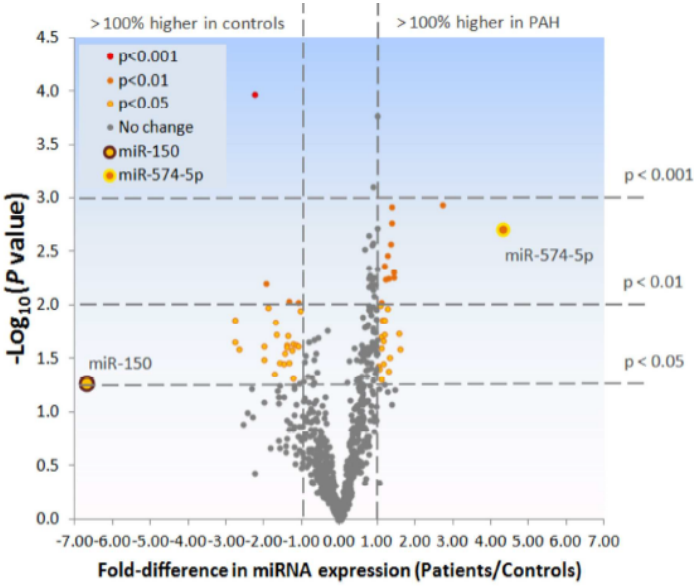
Biochemical biomarkers explored in pulmonary hypertension

- BNP
- Troponin
- Uric acid
- Creatinine
- RDW
- GDF-15
- IL-6
- Angiopoeitin
- Cytokines

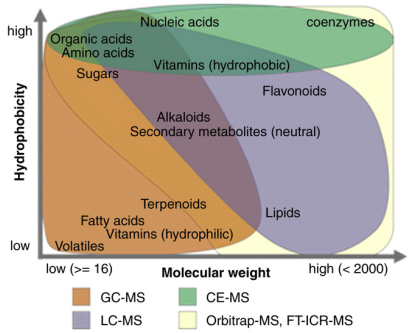
Monocyte mRNAs



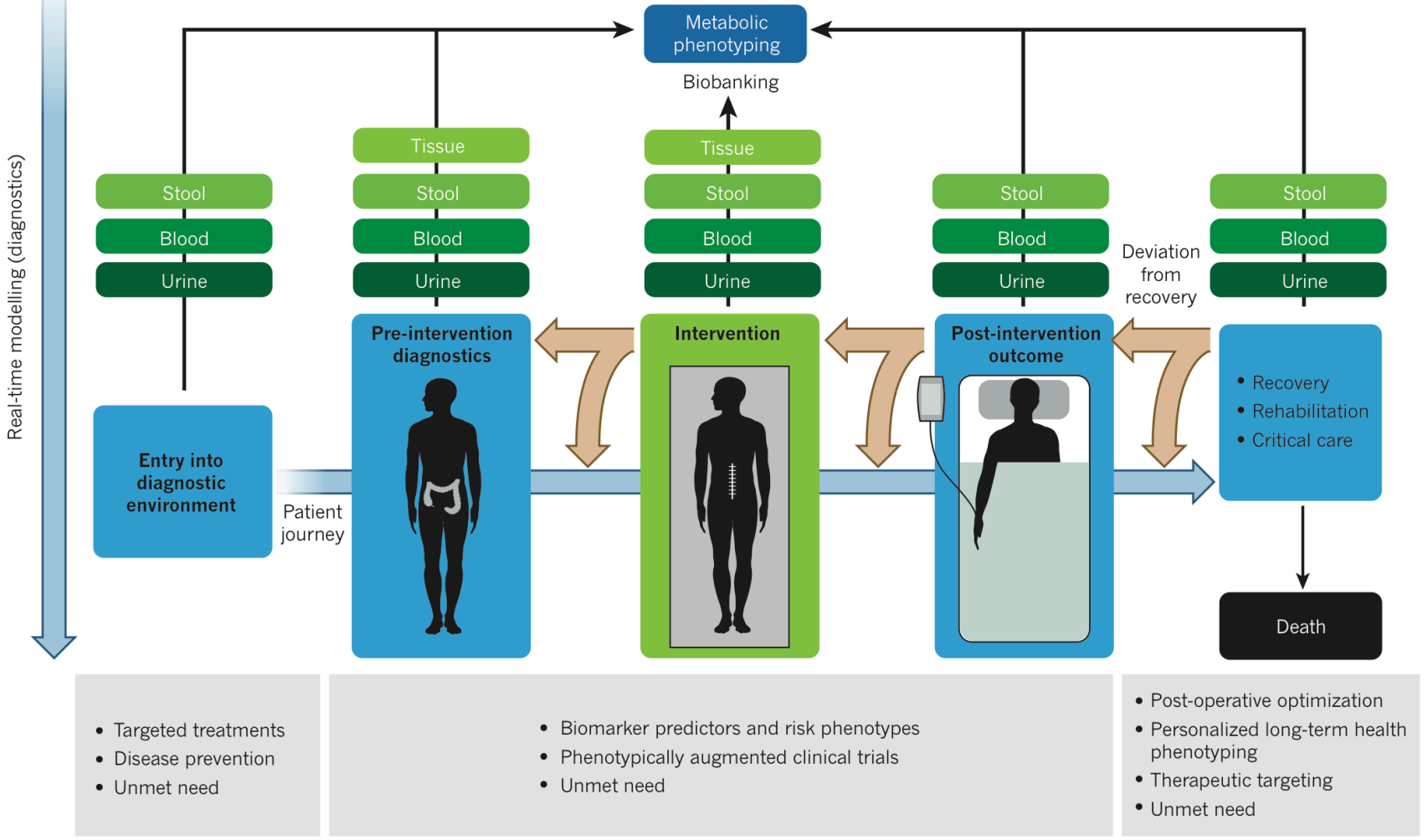
microRNAs



Metabolomics



Phenotyping Patient Journeys:
The importance of biobanks



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38 | NATURE | VOL 491 | 15 NOVEMBER 2012

Checklist for novel drugs and targets

The drug target

- Is the target druggable
- Is the target expressed in human tissue
- What is the tissue distribution of the target
- Is it altered in the disease (levels, phosphorylation etc)
- Is there an accessible biomarker that reports on the target
- Is the biomarker linked to clinical outcome
- Does the biomarker describe a subset of patients

The drug

- How selective is the drug for its target
- Does the drug reach the target in vivo
- How can the drug-target interaction be monitored to guide dose selection