# Science issues in drug repositioning

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Expert Panel at the Drug Repurposing Conference

# Major flaws in our biology knowledge

- 92% of drugs fail in clinical study
  - *"DRUG DROPOUT IN CLINICAL TRIALS IS AT UNSUSTAINABLE LEVELS, ACCORDING TO THOMSON REUTERS, CMR INTERNATIONAL" June 27, 2011 Press Release*
- *Very poor clinical efficacy prediction for target - mechanism approach*
- *Drug repositioning based on target - mechanism approach has the same efficacy problem*

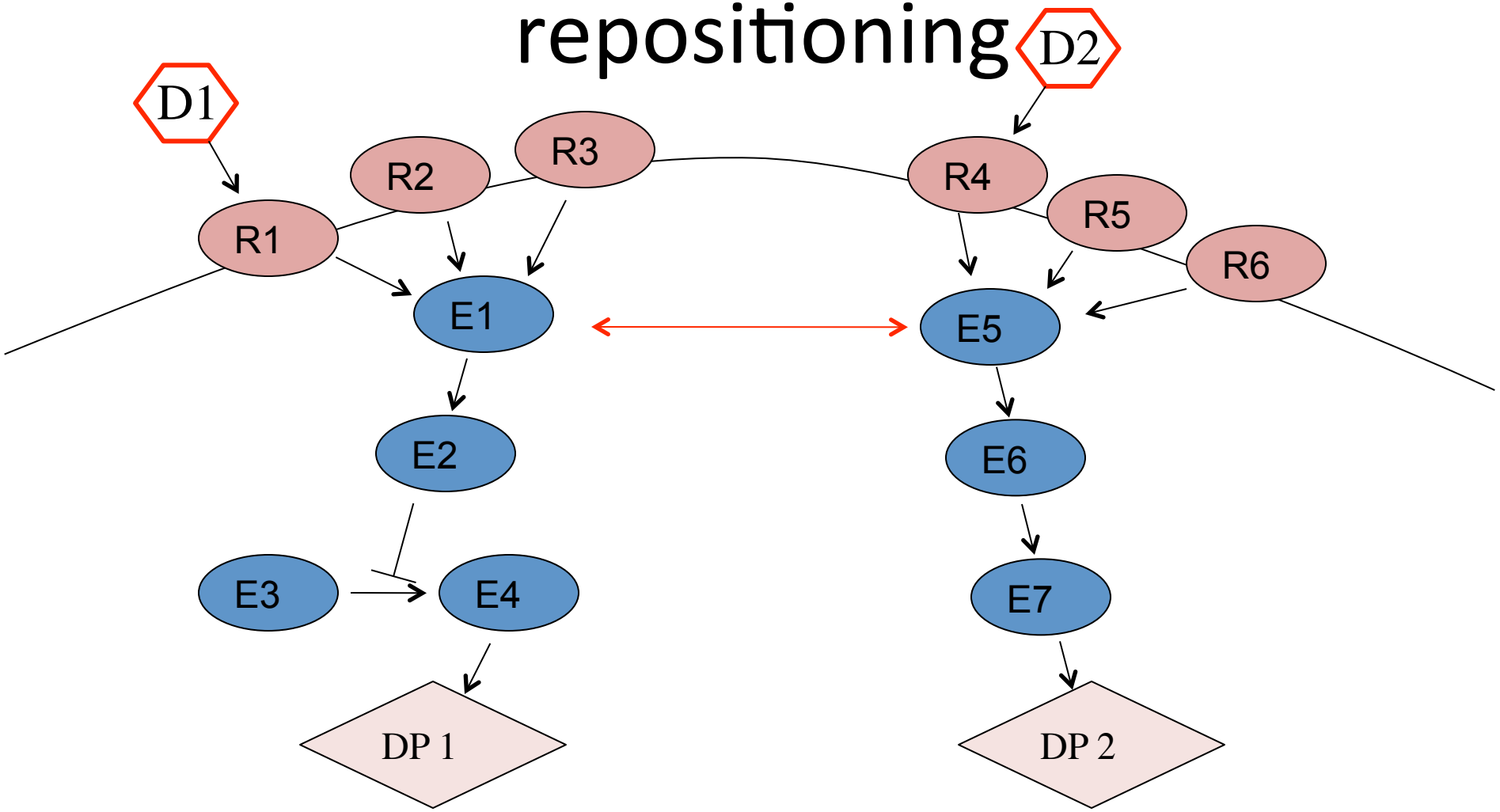
# On target or off target

- Few if any approved drugs have a single target
  - rise of poly-pharmacology
- Probing for a new medical use
  - using mechanism unbiased rodent screens
  - 30% of clinical phase drugs have a new use
  - 90% of the new uses are “on target”
  - over 200 drugs studied by Melior Discovery
- Major flaws in our biology knowledge

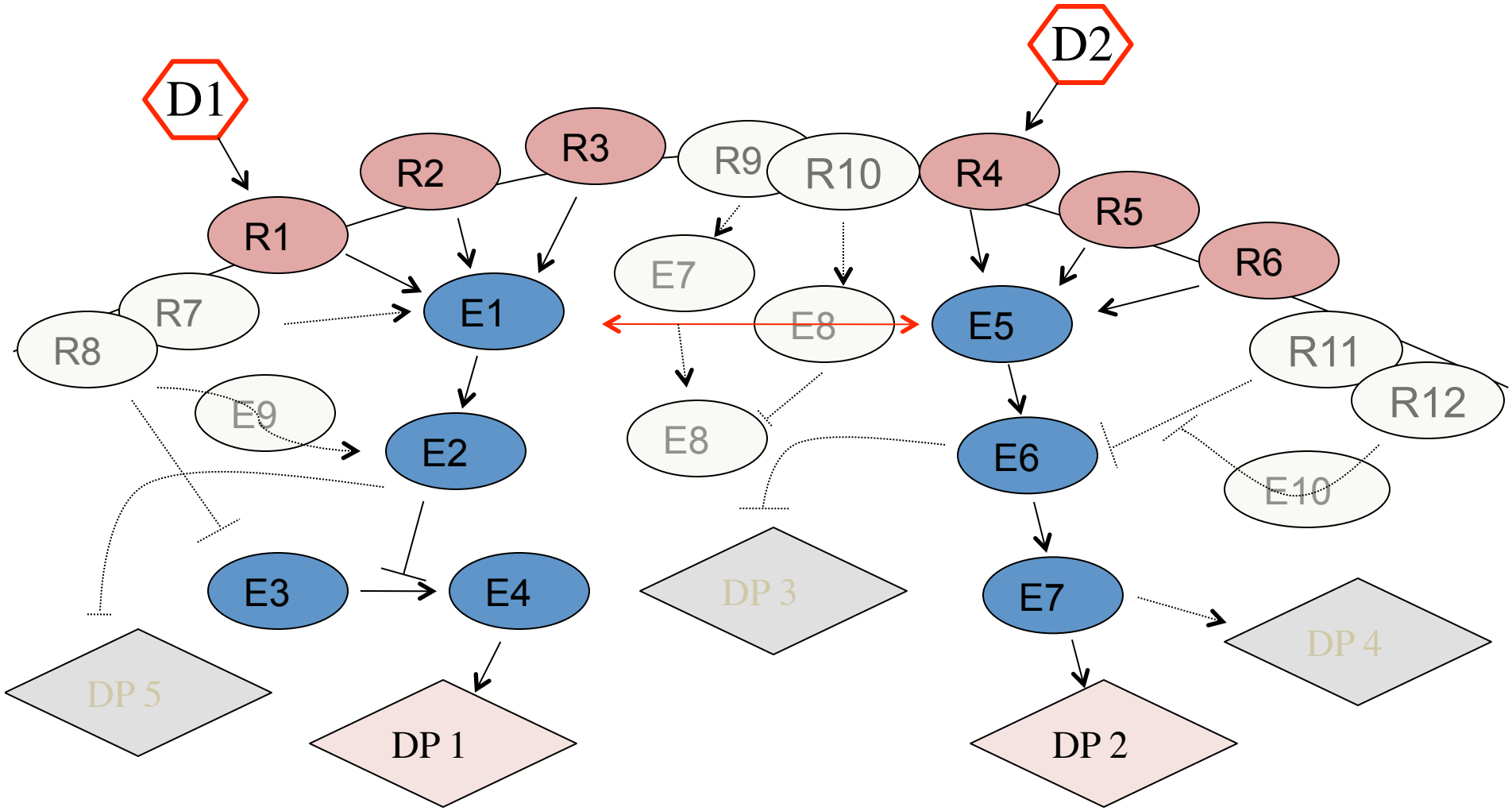
# Network biology challenges

- 85% of mechanistic blocks do nothing
  - rise of poly-pharmacology
  - network robustness
  - block downstream or upstream?
  - eg. P-38 alpha blockers and no clinical efficacy
- Network biology is in its infancy
  - efficacy most likely in a rich biology scenario
  - rise of academic collaborations

# Target-based drug discovery: An approach to drug repositioning



# ….the real picture



# Drug repositioning advantage

- Develop a known drug for a new use
  - bypass the 80% pre-clinical failure rate
  - bypass much of the clinical toxicity failure rate
  - bypass some of the efficacy failure rate??
- A drug that does something means a perturbable signalling pathway
- Avoid the signalling extremes
  - isolated nodes and the very dense nodes

# Rise of portals and collaborations

- Portals to drug company compounds and data
  - eg. CTSA portal, Pfizer, GSK, Novartis
- Portals to literature structures and data
  - eg. EMBL databases, NCGC NPC-browser
- Collaborations between academia, pharma and government
  - eg. NCATS, CDD

# Phenotypic screening advantage

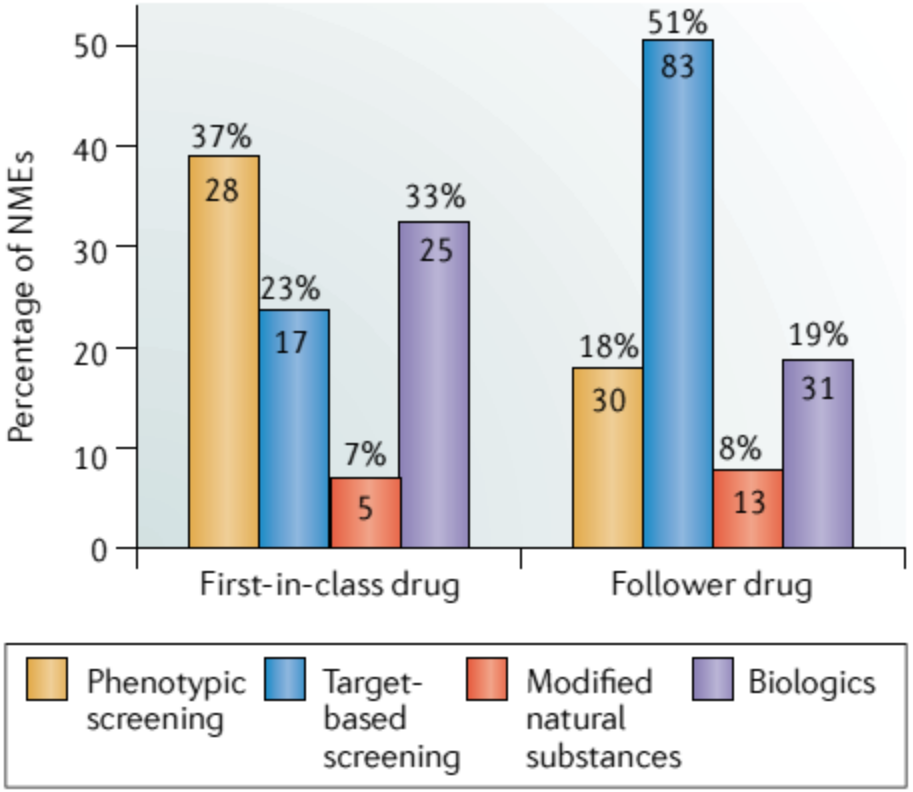



Figure 2 | **The distribution of new drugs discovered between 1999 and 2008, according to the discovery strategy.** The graph illustrates the number of new molecular

The majority of small-molecule first-in-class NMEs that were discovered between 1999 and 2008 were first discovered using phenotypic assays (FIG. 2): 28 of the first-in-class NMEs came from phenotypic screening approaches, compared with 17 from target-based approaches.

How were new medicines discovered? *David C. Swinney and Jason Anthony Nature Reviews Drug Discovery 2011 (10) 507-519.*

# Database repositioning limitations

- Repositioning a drug for TB treatment as an example
- Bacteria have evolved to be impermeable
- Gram+ more permeable than gram- and:
- Mycobacteria are the least permeant
- Antibacterial target screening is a disaster
  - eg. GSK, Pfizer experience
- Efflux pump inhibitors a clinical disaster
  - eg. MDR-1 inhibitor clinical failures
- No predictors for mycobacterial penetration
- Suggests limited impact of database approaches on real TB drug discovery
  - Need to know the scope and limitations of predictive methods
  - And relative applicability of domains

# Summary

- Drug repositioning is a very fast growing area with a lot of potential
- Be realistic and a bit optimistic
- But don't expect miracles