Connectivity Map

An introduction

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May 14, 2012

References

The Connectivity Map: Using Gene-Expression Signatures to Connect Small Molecules, Genes, and Disease

Justin Lamb,[1*] Emily D. Crawford,[1†] David Peck,[1] Joshua W. Modell,[1] Irene C. Blat,[1] Matthew J. Wrobel,[1] Jim Lerner,[1] Jean-Philippe Brunet,[1] Aravind Subramanian,[1] Kenneth N. Ross,[1] Michael Reich,[1] Haley Hieronymus,[1,2] Guo Wei,[1,2] Scott A. Armstrong,[2,3] Stephen J. Haggarty,[1,4] Paul A. Clemons,[1] Ru Wei,[1] Steven A. Carr,[1] Eric S. Lander,[1,5,6] Todd R. Golub[1,2,3,5,7*]

***Science* 313(5795): 1929-1935.**

Cited in Scopus: 489 (as Oct 10, 2011)

INNOVATION

The Connectivity Map: a new tool for biomedical research

Justin Lamb

***Nature Reviews Cancer* 7(1): 54-60.**

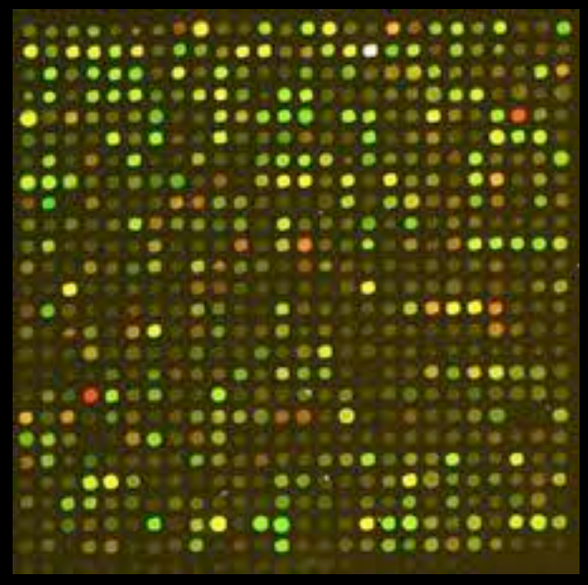
Cited in Scopus: 73 (as Oct 10, 2011)

Goals

- Create a large drug-response profile database.
- Use microarray profiles to query best matching or mismatching drugs
- Drug repurposing

Goals

Control	Treatment
Cell	Cell + Drug

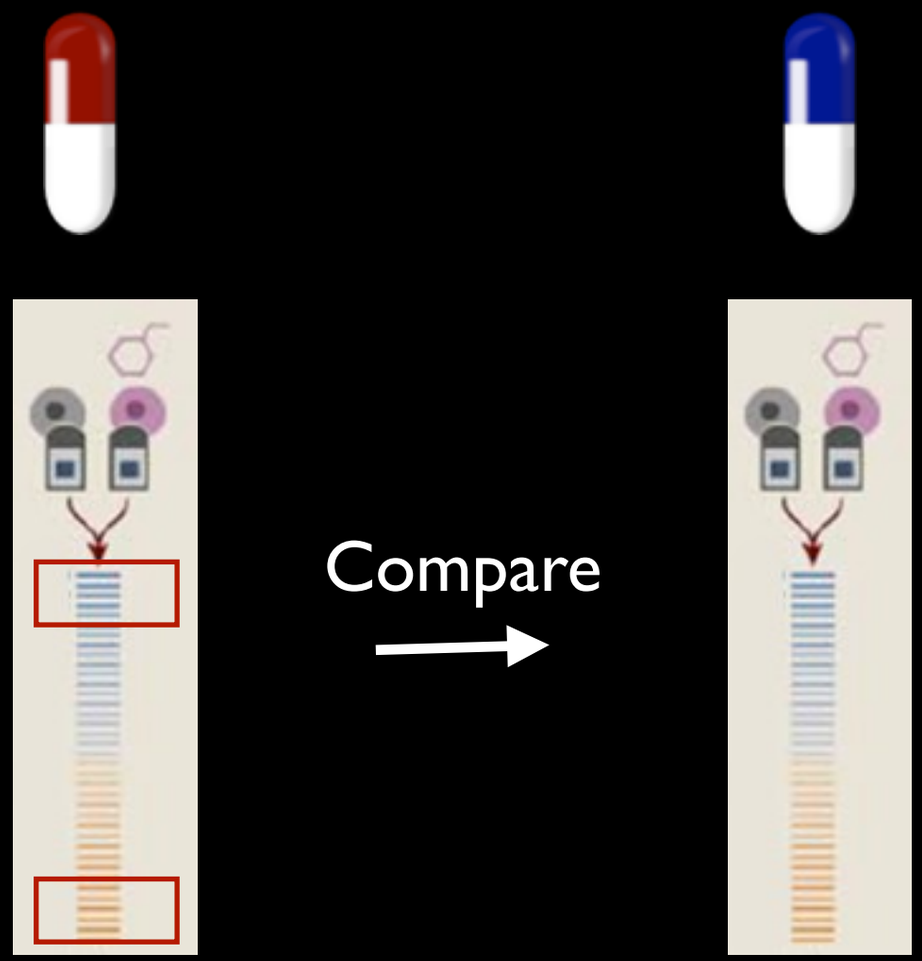


Gene	Control	Treatment	Fold Change
A	1	5	5/1
B	1	1	1/1
C	5	1	1/5
...			

measurement of mRNA

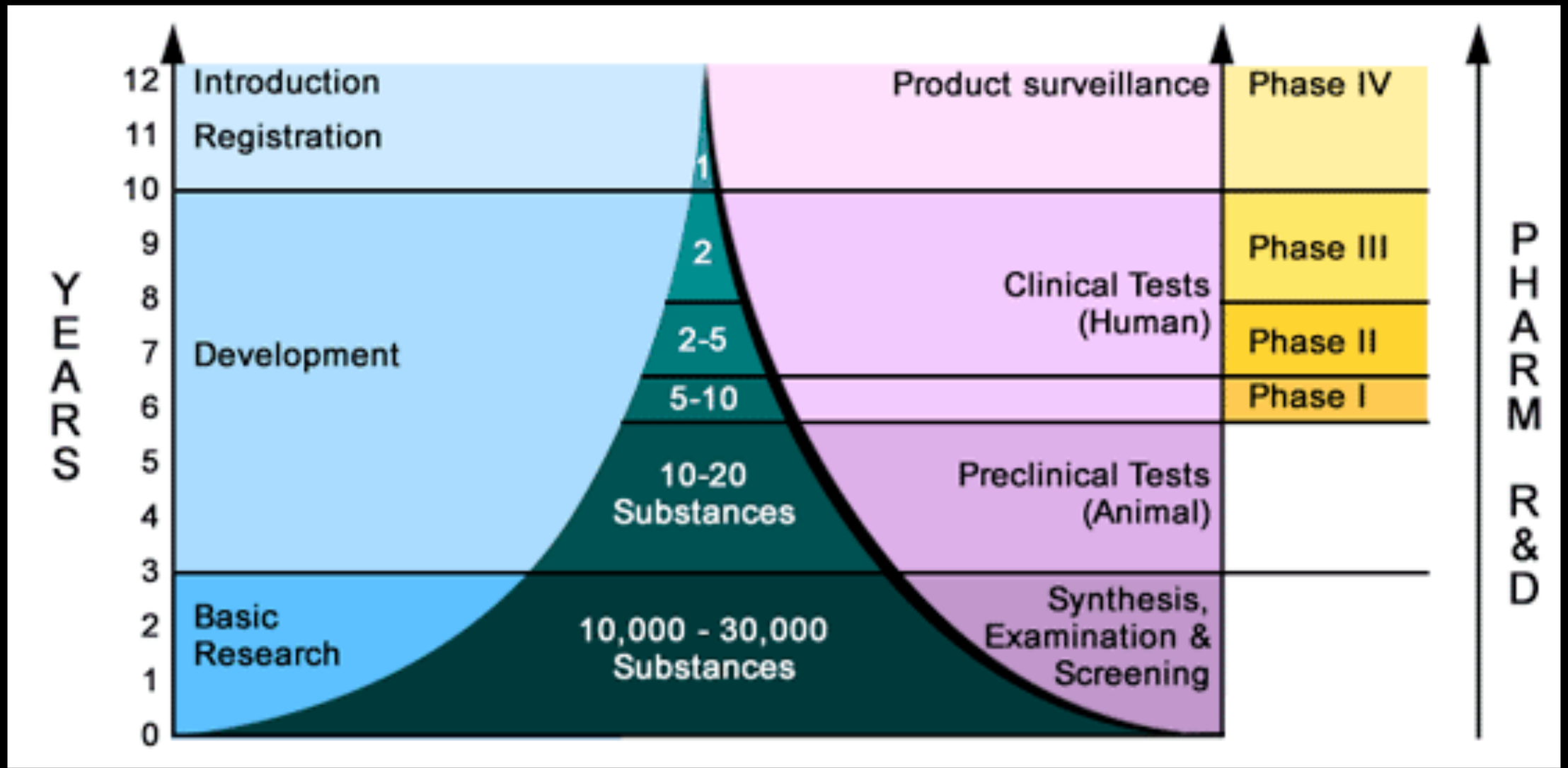
	Drug 1	Drug 2	Drug 3	Drug ...	Drug N
Gene 1					
Gene 2					
Gene 3					
Gene 4					
Gene 5					
Gene 6					
Gene ...					
Gene M					

Drug Similarity

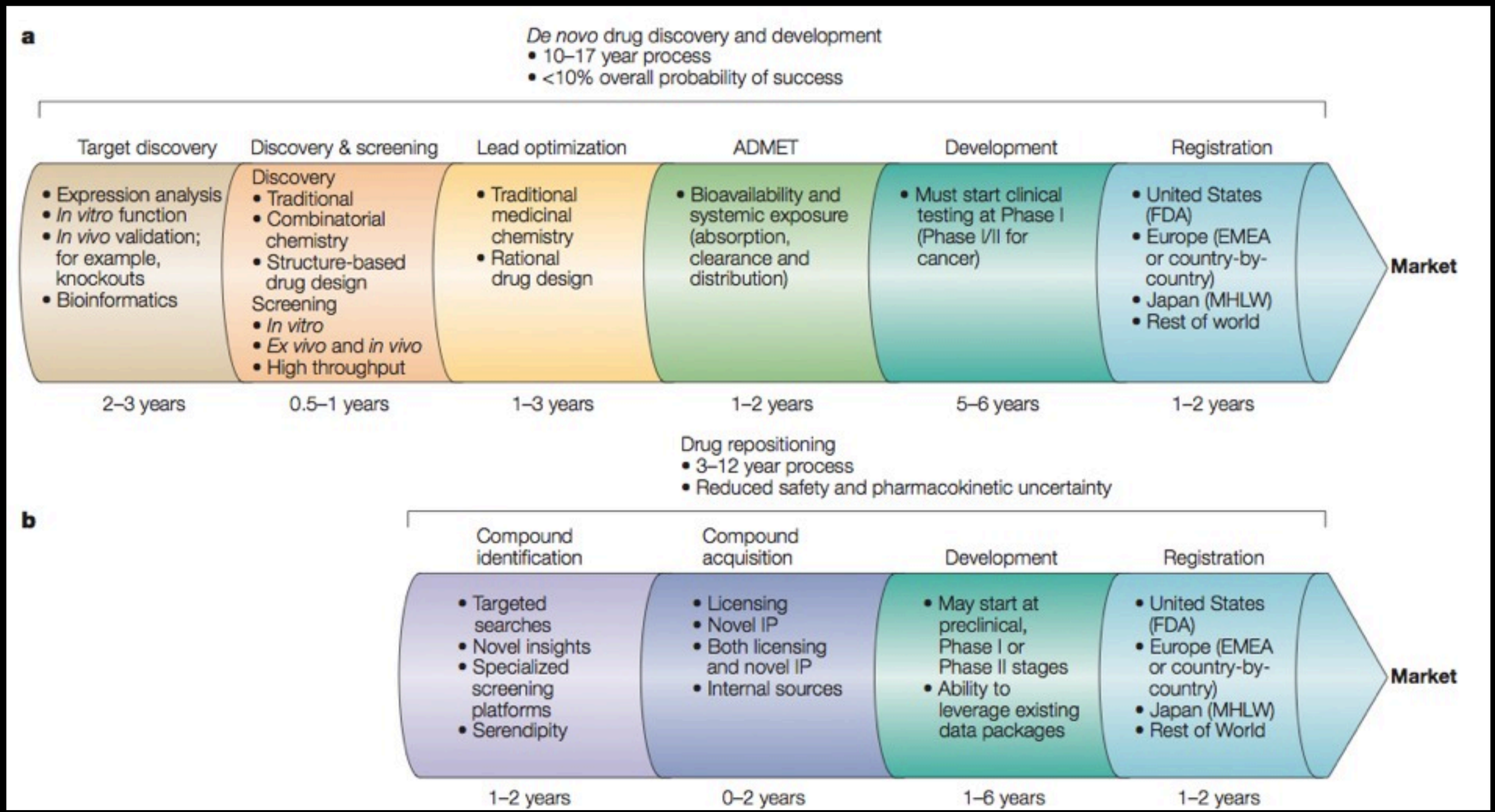


Drug Repurposing

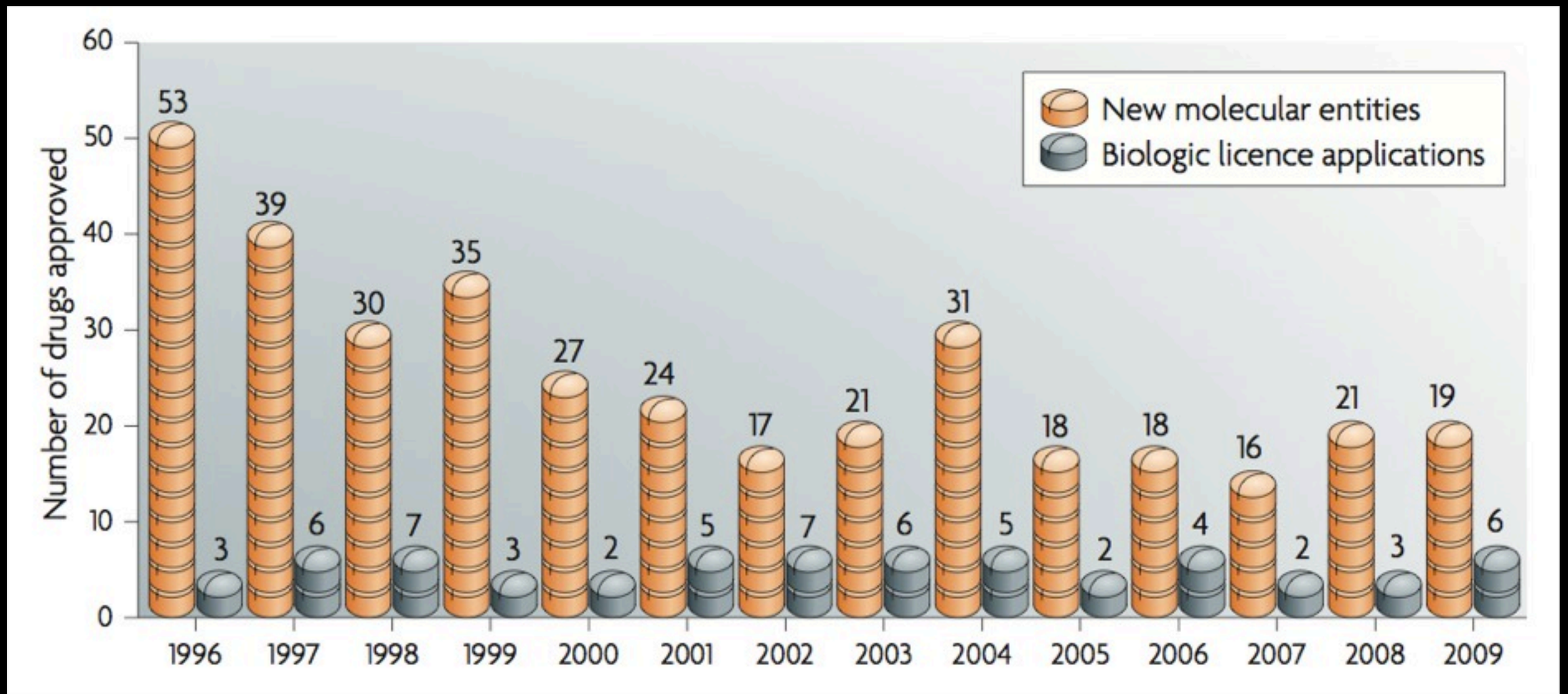
Drug Development Process



http://www.msd.com.hk/health_info/drug_education/e_ddp_introduction.html



Ashburn, Ted T, and Karl B Thor. 2004. “Drug repositioning: identifying and developing new uses for existing drugs.” *Nature Reviews Drug Discovery* 3(8): 673–683.



Hughes, Bethan. 2010. "2009 FDA drug approvals." *Nature Reviews Drug Discovery* 9(2): 89–92.

- 2007: 69 drugs, but 16 are new drugs
- average 15 years and US$800 million for a new drug to market
- New drugs approved by FDA each year remain at 20~30 compounds.

New uses for old drugs

New uses for old drugs

It takes too long and costs too much to bring new drugs to market. So let's beef up efforts to screen existing drugs for new uses, argue **Curtis R. Chong** and **David J. Sullivan Jr.**

Chong, Curtis R, and David J Sullivan. 2007. "New uses for old drugs." *Nature* 448(7154): 645–646.

"The most fruitful basis for the discovery of a new drug is to start with an old drug"
-- Nobel laureate James Black

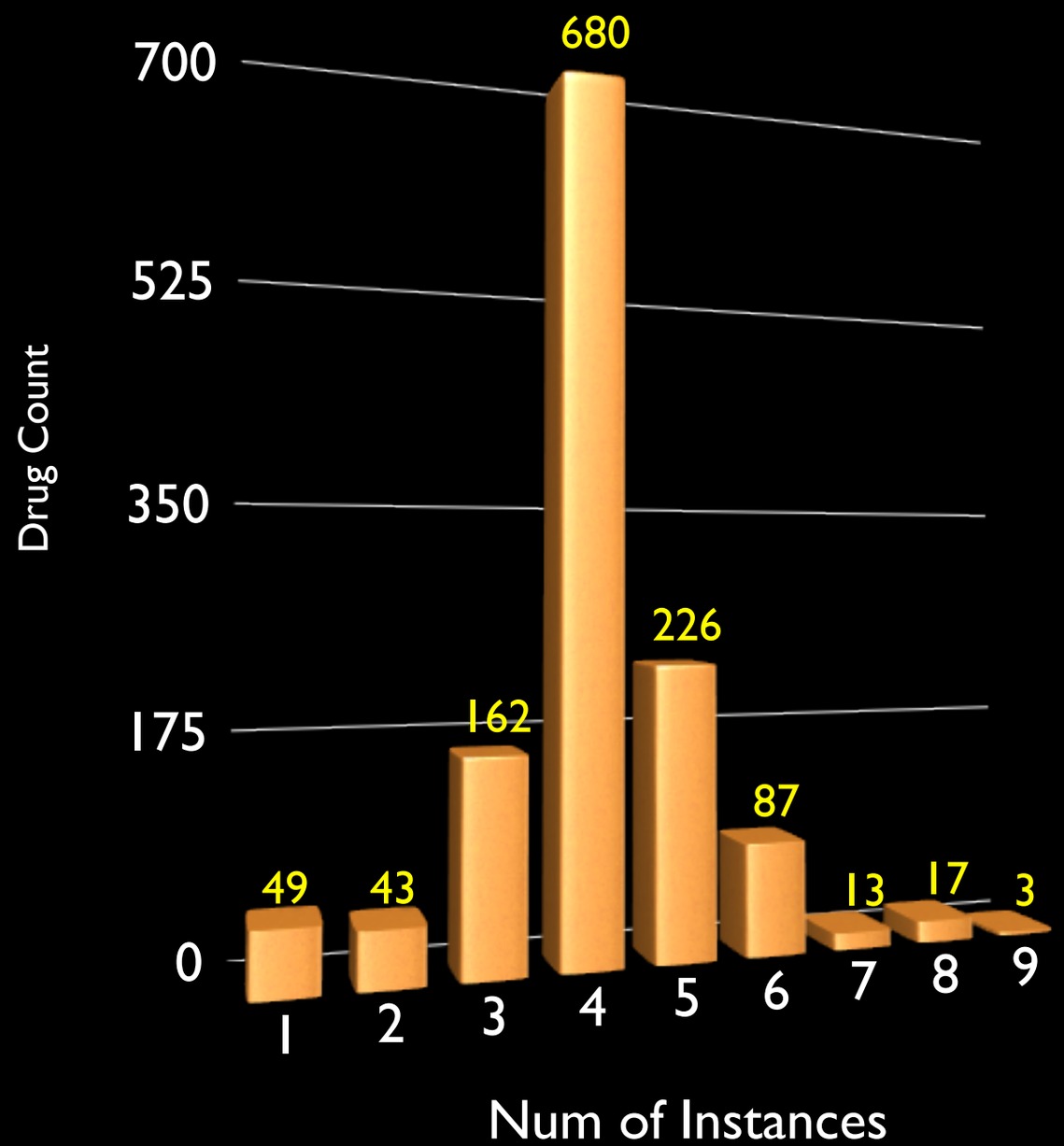
Drug repurposing examples

- Nelfinavir for cancer
- Tamoxifen for bipolar disorder
- Gleevec for rheumatoid arthiritis
- Pentylenetetrazole for Down Syndrome
- Astemizole for malaria
- Lipitor for alzhemimers
- Lipitor for influenza mortality
- Metformin for cancer

CDD Community Group Meeting, SFO, Oct 1, 2009

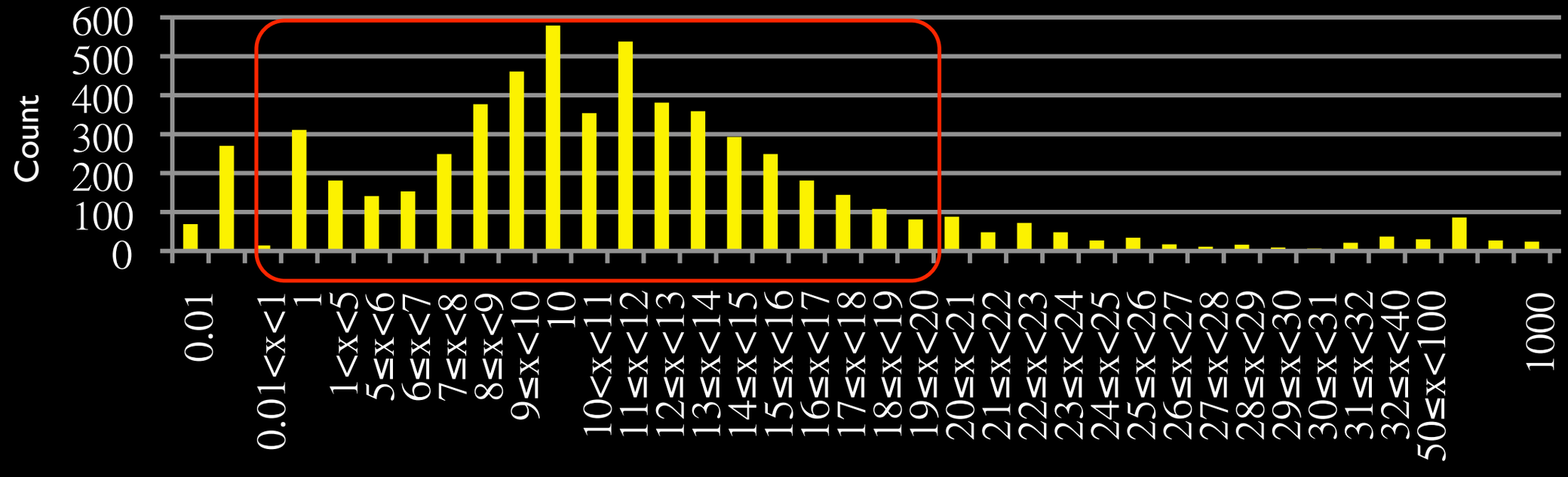
Database

Drugs



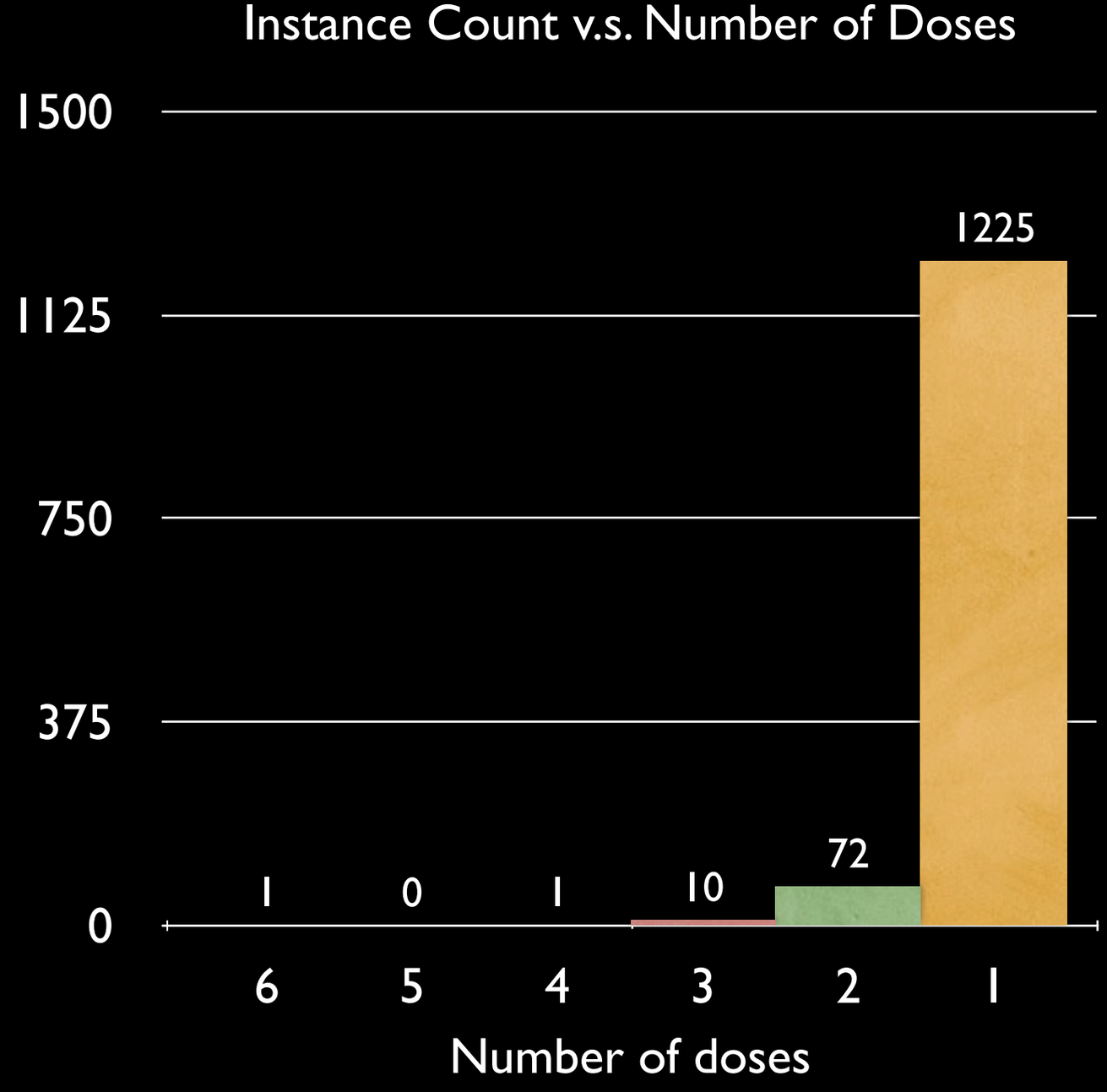
- 1309 small molecules
- 680 drugs have been conducted 4 times each.
- 6100 instances
- 7056 microarrays

Drug dosage

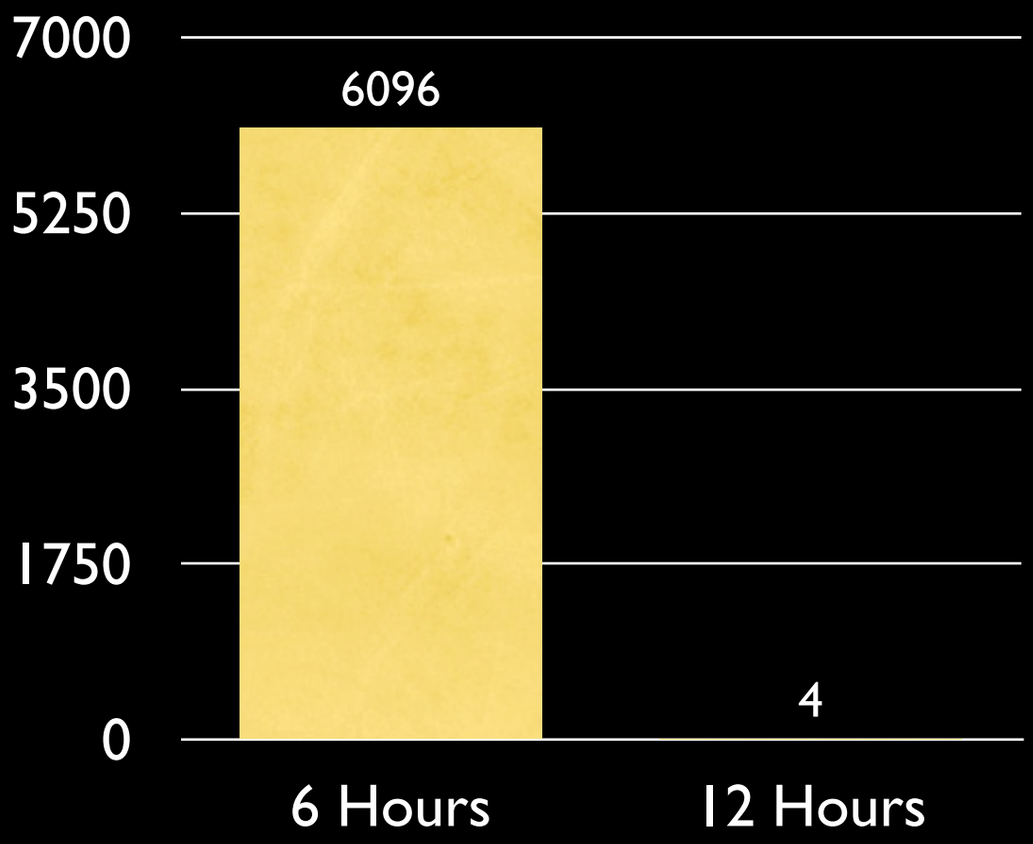


- Most drugs are tested between 1μM and 20μM

Dose count

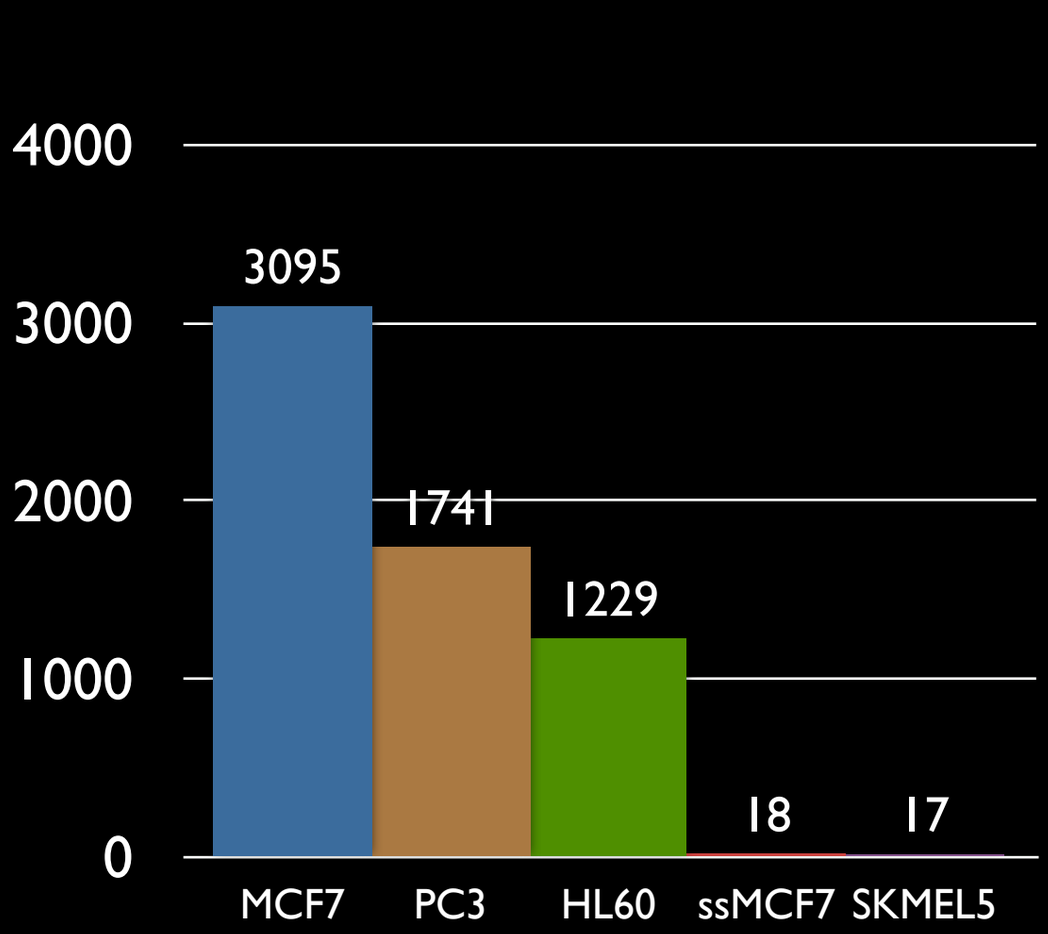

Instance Count v.s. Number of Doses
1500
1125
750
375
0
1225
72
10
1
0
1
6
5
4
3
2
1
Number of doses

Duration



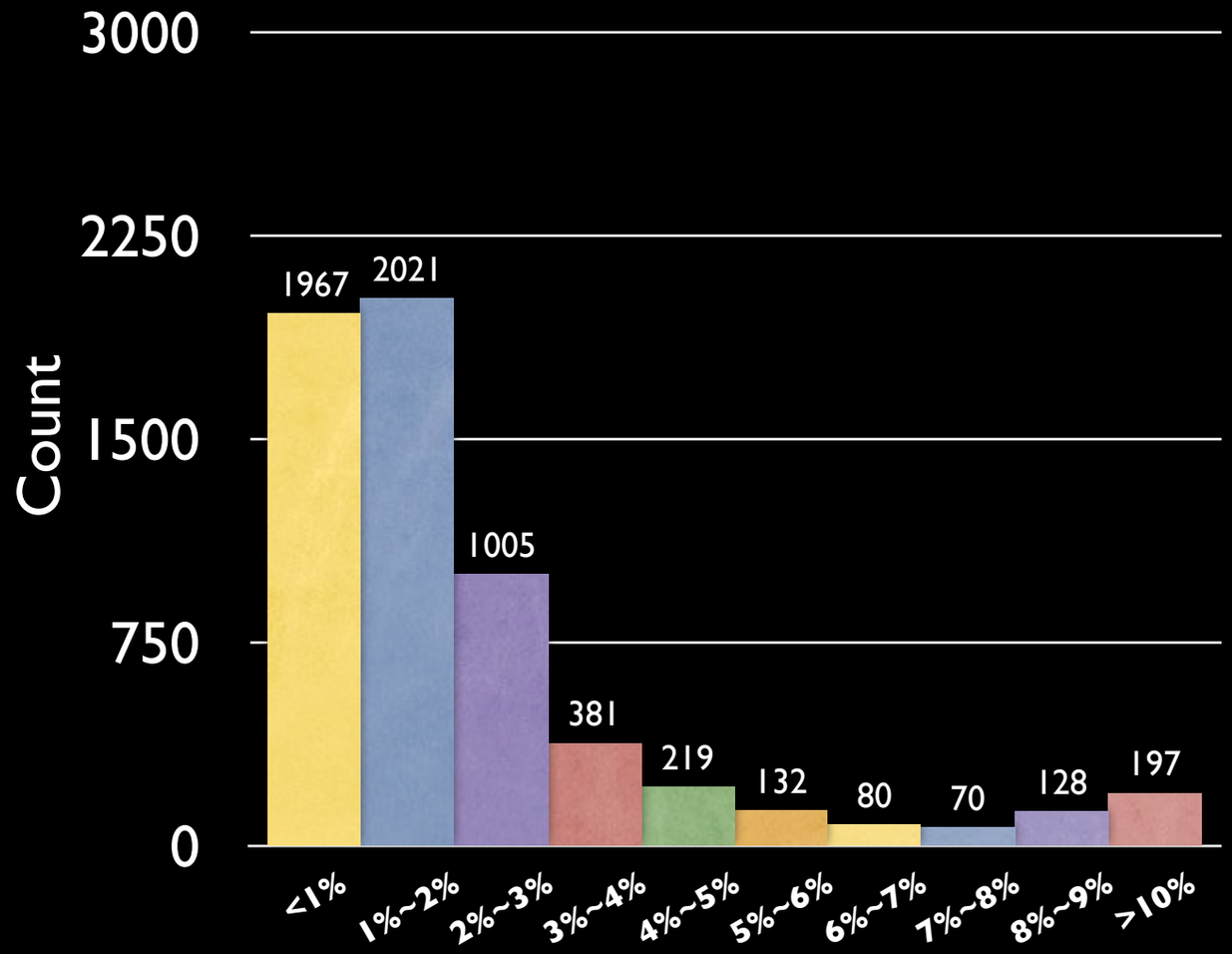
- Most drugs are conducted for 6 hours.
- Primary effects, not second effects

Cell Type



MCF7	Breast cancer
PC3	Prostate Cancer
HL60	Leukemia
ssMCF7	Breast cancer charcoal-stripped serum
SKMEL5	Skin Cancer

Fold Change

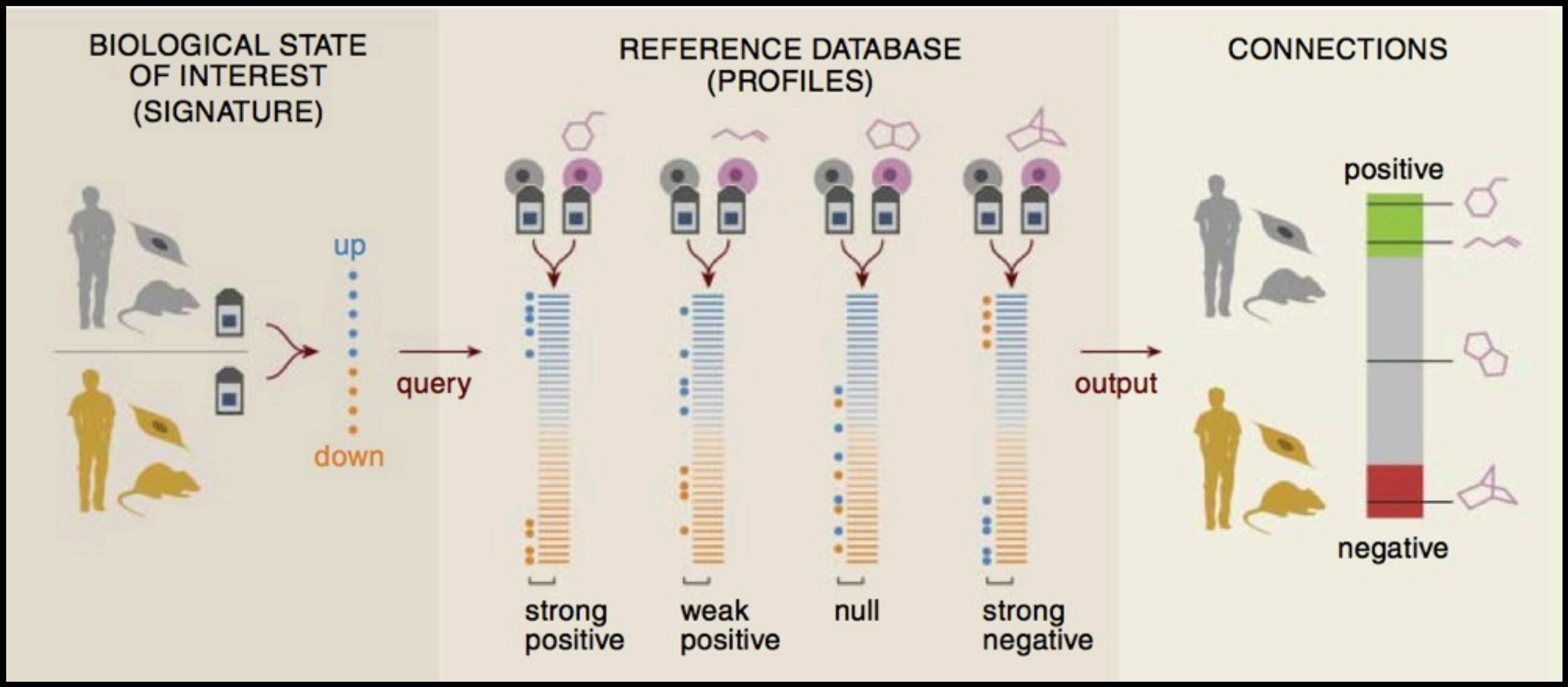


- 64% of 6100 instances have less than 2% of probes having 2-Fold change.

Instances

- Each instance is defined as one drug treatment over a sample of controls.
  - e.g. cells treated with vorinostat versus untreated ones.
- Instance = Drug type x Cell type x Duration x Dose
  - e.g. 10μM vorinostat on MCF7 for 6 hours
- 6100 instances over 1309 drugs


Cell Type
Drug
Dosage



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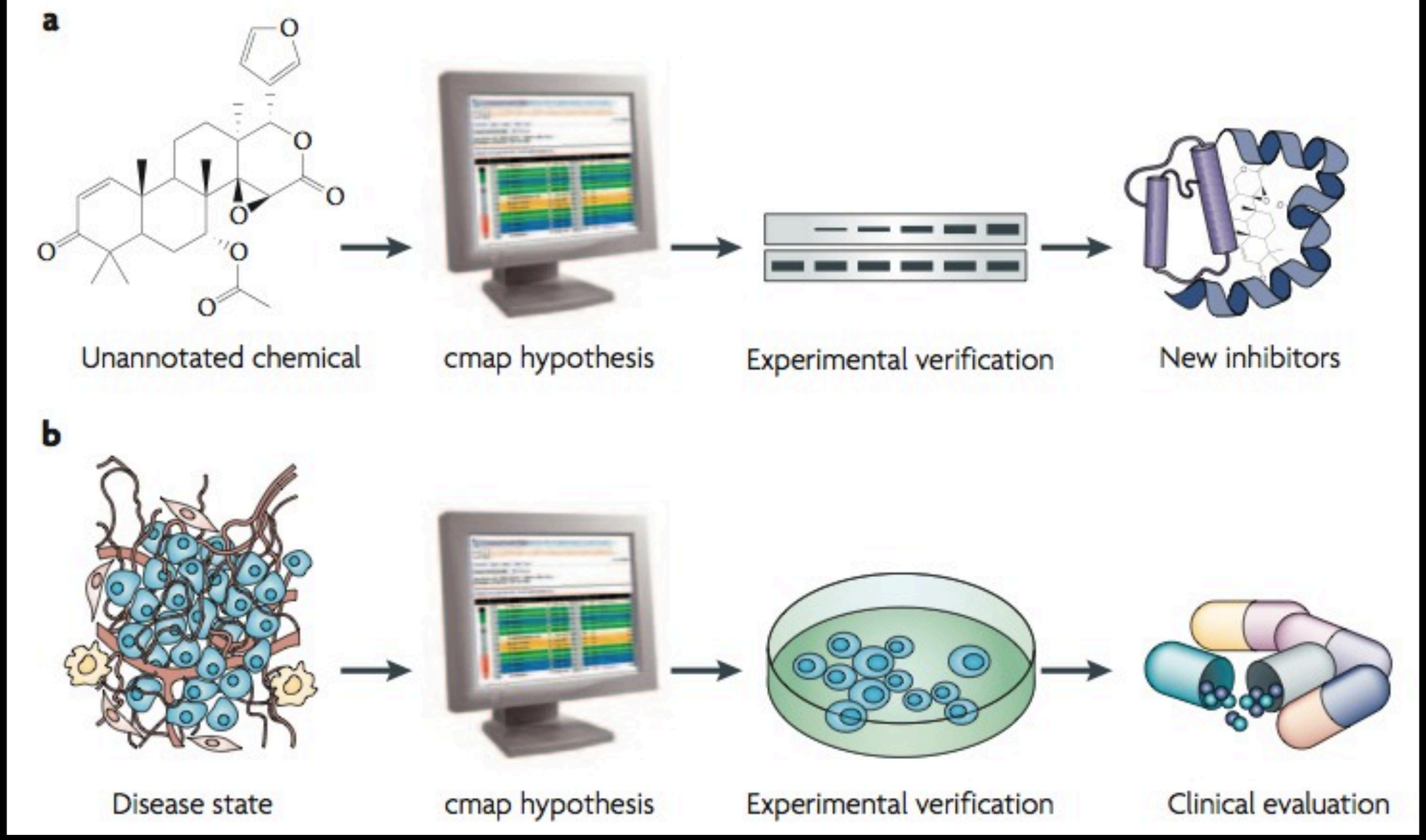


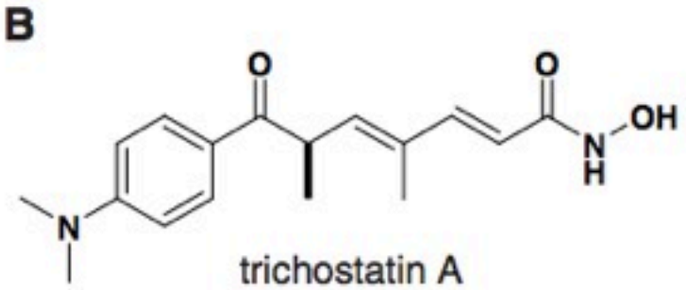
Lamb, Justin. 2007. "The Connectivity Map: a new tool for biomedical research." *Nature Reviews Cancer* 7(1): 54–60.

Drug-Drug similarity

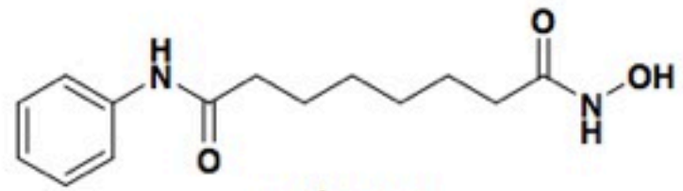
A

rank	perturbagen	dose	cell	score
1	vorinostat [1000]	10 µM	MCF7	1
2	trichostatin A [873]	1 µM	MCF7	0.969
3	trichostatin A [992]	100 nM	MCF7	0.931
4	trichostatin A [1050]	100 nM	MCF7	0.929
5	vorinostat [1058]	10 µM	MCF7	0.917
6	trichostatin A [981]	1 µM	MCF7	0.915
7	HC toxin [909]	100 nM	MCF7	0.914
8	trichostatin A [1112]	100 nM	MCF7	0.908
9	trichostatin A [1072]	1 µM	MCF7	0.906
10	trichostatin A [1014]	1 µM	MCF7	0.893
11	trichostatin A [332]	100 nM	MCF7	0.882
12	trichostatin A [331]	100 nM	MCF7	0.846
13	trichostatin A [448]	100 nM	PC3	0.788
14	valproic acid [345]	10 mM	MCF7	0.743
15	valproic acid [23]	1 mM	MCF7	0.735
16	valproic acid [1047]	1 mM	MCF7	0.733
17	trichostatin A [413]	100 nM	ssMCF7	0.725
18	valproic acid [410]	10 mM	HL60	0.725
19	valproic acid [458]	1 mM	PC3	0.680
33	valproic acid [409]	1 mM	HL60	0.634
39	valproic acid [1020]	500 µM	MCF7	0.619
52	valproic acid [346]	2 mM	MCF7	0.582
61	valproic acid [1078]	500 µM	MCF7	0.563
71	valproic acid [629]	1 mM	SKMEL5	0.539
72	valproic acid [347]	500 µM	MCF7	0.539
73	valproic acid [989]	1 mM	MCF7	0.538
76	valproic acid [433]	1 mM	PC3	0.528
89	trichostatin A [364]	100 nM	HL60	0.507
92	valproic acid [497]	1 mM	ssMCF7	0.501
297	valproic acid [348]	50 µM	MCF7	0
388	valproic acid [994]	200 µM	MCF7	0
403	valproic acid [1002]	50 µM	MCF7	0
419	valproic acid [1060]	50 µM	MCF7	-0.537

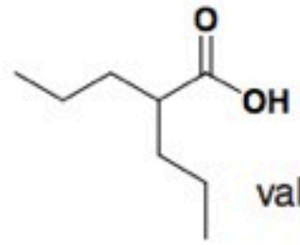
B



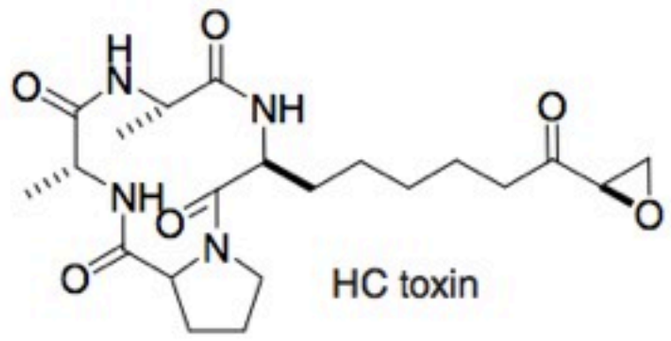
trichostatin A



vorinostat



valproic acid



HC toxin

Input: 13 HDAC gene signature

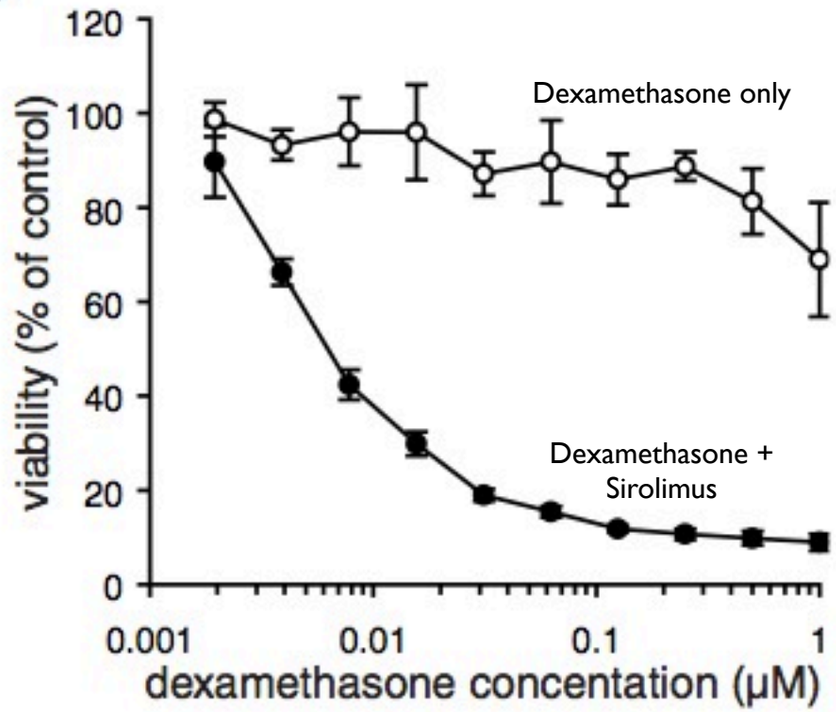
Lamb, J et al. 2006. "The Connectivity Map: using gene-expression signatures to connect small molecules, genes, and disease." *Science* 313(5795): 1929–1935.

Drug-disease

A

rank	perturbagen	dose	cell	score
1	sirolimus [1059]	100 nM	MCF7	1
2	sirolimus [987]	100 nM	MCF7	0.979
7	sirolimus [1045]	100 nM	MCF7	0.930
11	sirolimus [1022]	100 nM	MCF7	0.897
16	sirolimus [1080]	100 nM	MCF7	0.880
30	sirolimus [1001]	100 nM	MCF7	0.810
35	sirolimus [402]	100 nM	ssMCF7	0.793
39	sirolimus [362]	100 nM	HL60	0.778
64	sirolimus [921]	100 nM	MCF7	0.687
104	sirolimus [326]	100 nM	MCF7	0.530

B



Lamb, J et al. 2006. “The Connectivity Map: using gene-expression signatures to connect small molecules, genes, and disease.” *Science* 313(5795): 1929–1935.

Sirolimus reverses gluco-corticoid resistance in acute lymphoblastic leukemia.

Databases

STRING	http://string-db.org/
KEGG	http://www.genome.jp/kegg/
PubChem	http://pubchem.ncbi.nlm.nih.gov/
DrugBank	http://www.drugbank.ca/
PubMed	http://www.ncbi.nlm.nih.gov/pubmed