Drug Discovery, Development and Commercialization, Winter 2013

Drug Discovery: Proteomics, Genomics

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It Was the Best of Times, It Was the Worst of Times

It was the best of times, it was the worst of times, it was the age of wisdom, it was the age of foolishness, it was the epoch of belief, it was the epoch of incredulity, it was the season of Light, it was the season of Darkness, it was the spring of hope, it was the winter of despair, we had everything before us, we had nothing before us, we were all going direct to heaven, we were all going direct the other way - in short, the period was so far like the present period, that some of its noisiest authorities insisted on its being received, for good or for evil, in the superlative degree of comparison only.

Charles Dickens, *A Tale of Two Cities*
English novelist (1812 - 1870)

OMICS - The Best of Times

Omics

From Wikipedia, the free encyclopedia

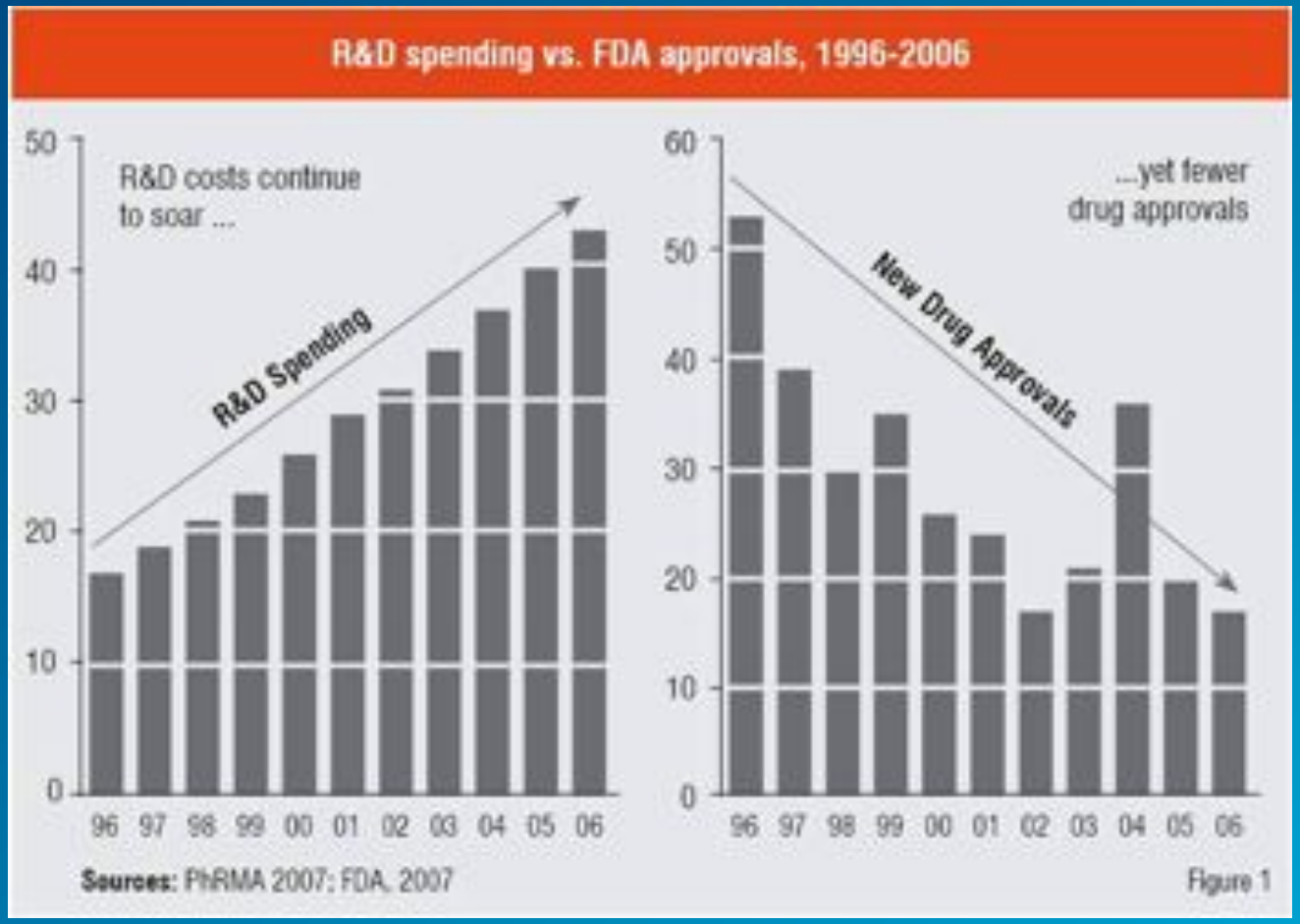
For the suffix indicating nomenclature, see -nomics.

The English-language neologism **omics** informally refers to a field of study in biology ending in -omics, such as genomics or proteomics. The related suffix **-ome** is used to address the objects of study of such fields, such as the genome or proteome, respectively.

Functional genomics aims at identifying the functions of as many genes as possible of a given organism. It combines different -omics techniques such as transcriptomics and proteomics with saturated mutant collections.[1]

The suffix -ome as used in molecular biology refers to a *totality* of some sort; it is an example of a "neo-suffix" formed by abstraction from various Greek terms in -ωμα, a sequence that does not form an identifiable suffix in Greek.

The Worst of Times



Source: http://www.pharmafocusasia.com/strategy/drug_discovery_india_force_to_reckon.htm

Stated Another Way

- *Glass ½ Empty*: drug discovery in the traditional sense is in a woeful state
- *Glass ½ Full*:
  - We have an explosion of data and hence a new emerging understanding of complex biological systems
  - Information technology is advancing rapidly

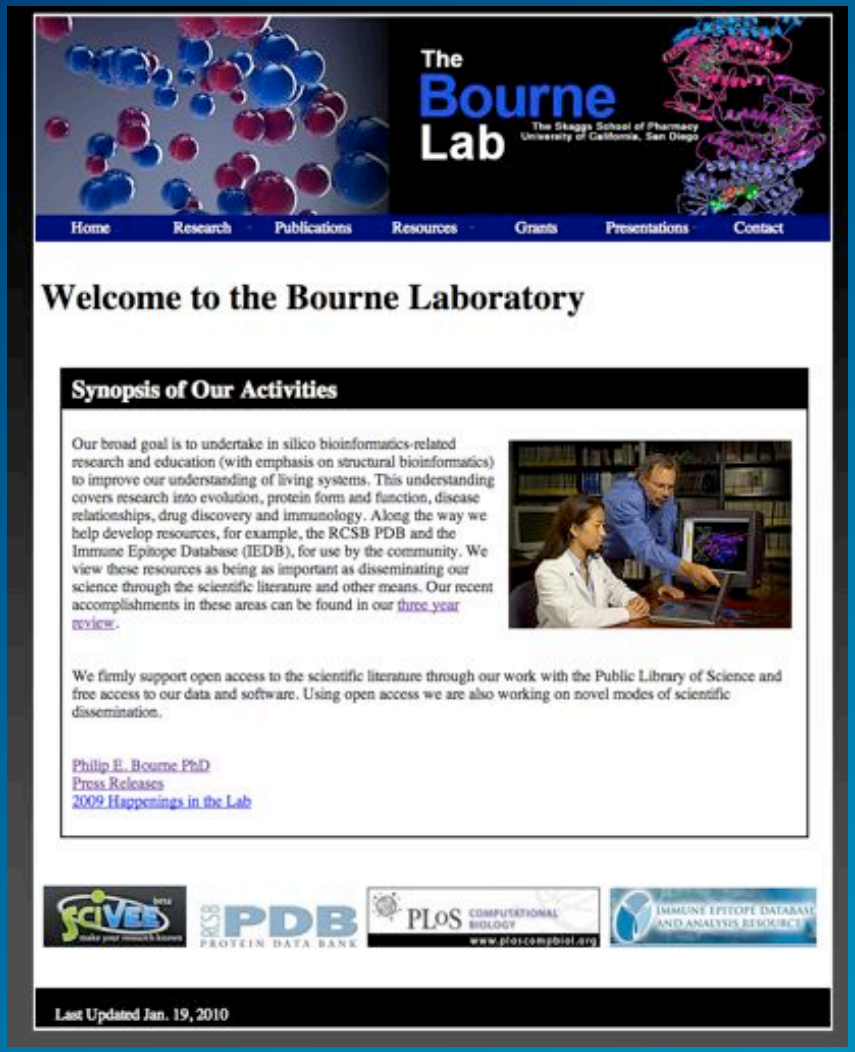
Let Optimism Rule

- Let optimism rule – let IT, traditional computational chemistry and cheminfomatics meet bioinformatics, systems biology and information science to discover drugs in new ways – *Systems Pharmacology*

Agenda

- Where my perspective comes from
- The omics revolution
- The open science & IT revolutions
- The impact on drug discovery
- Applying the new biology to drug discovery
  - Example 1 – Drug repositioning
  - Example 2 - Determining side-effects
- Words of caution

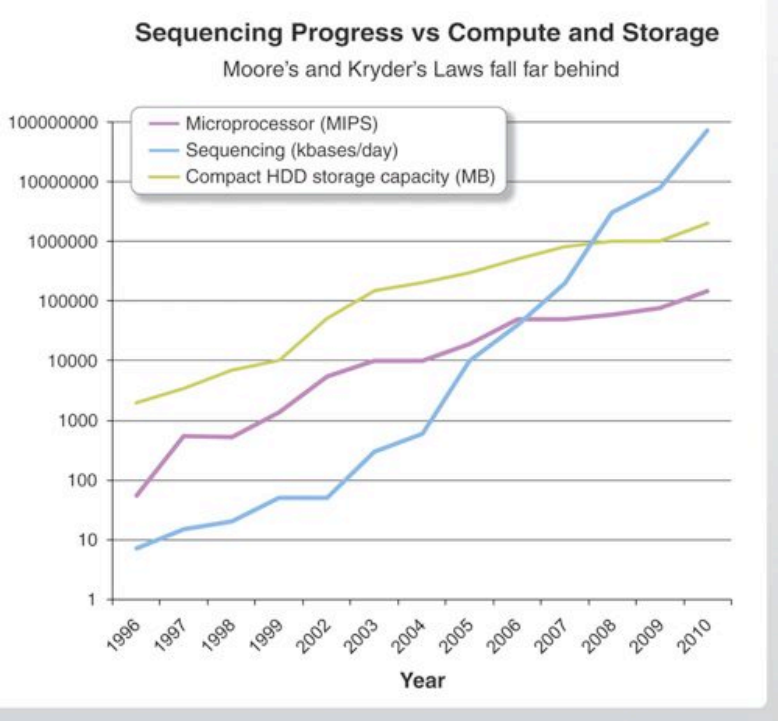
My Perspective/Bias



- We work in the area of structural bioinformatics & more broadly computational biology
- We distribute the equivalent to ¼ the Library of Congress to approx. 300,000 scientists each month
- We are interested in improving the drug discovery process through computationally driven hypotheses on the complete biological system – *systems pharmacology*

- Personally:
  - Open science advocate
  - Started 4 companies
  - Spent whole life in the ivory tower
  - AVC of Innovation & Industrial Alliances

The Omics Driver



- DNA sequence data are doubling every 5 months
- Funders are demanding data sharing plans
- The long tail is neglected

On the Future of Genomic Data
Science 11 February 2011:
vol. 331 no. 6018 728-729

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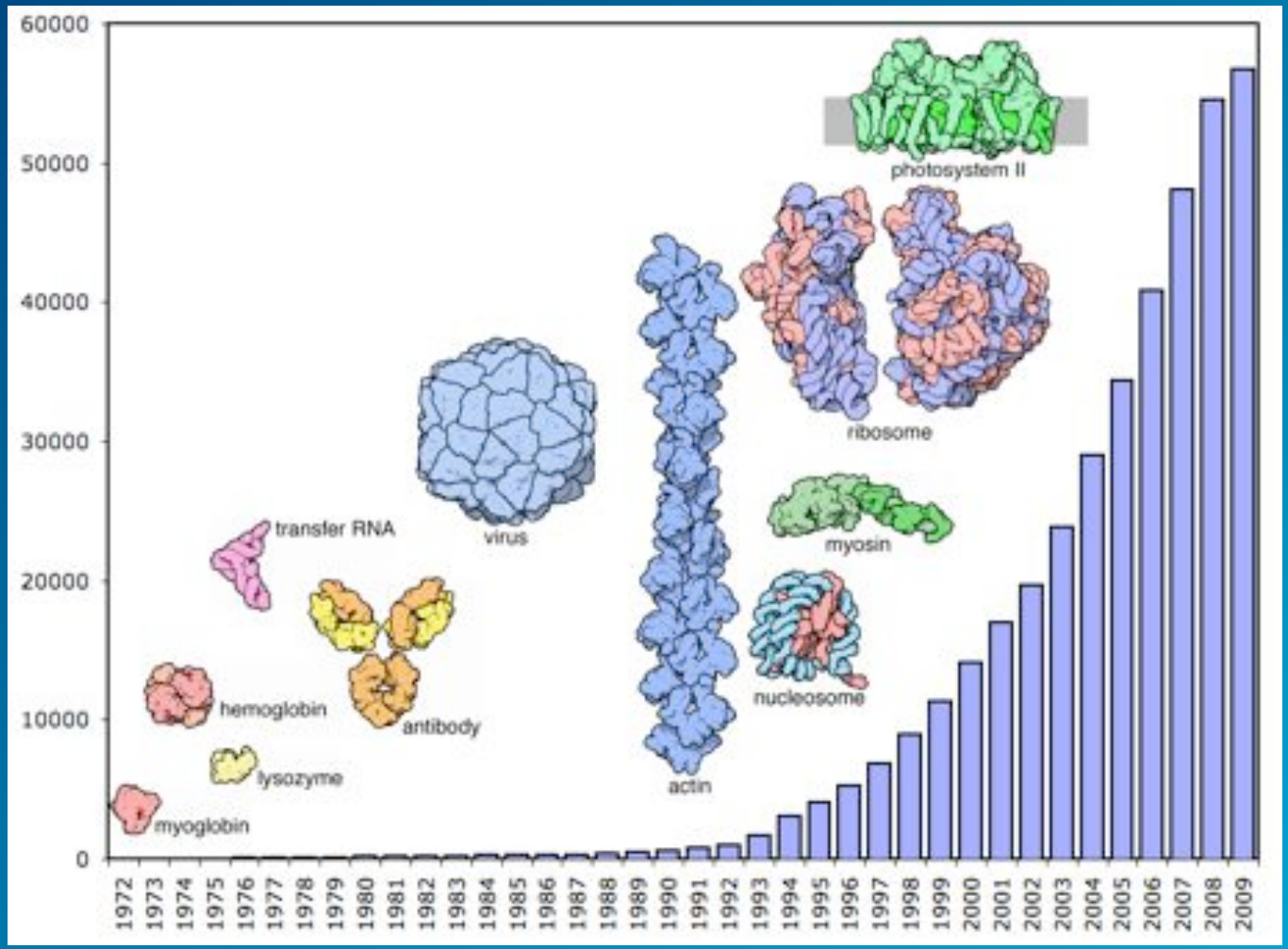
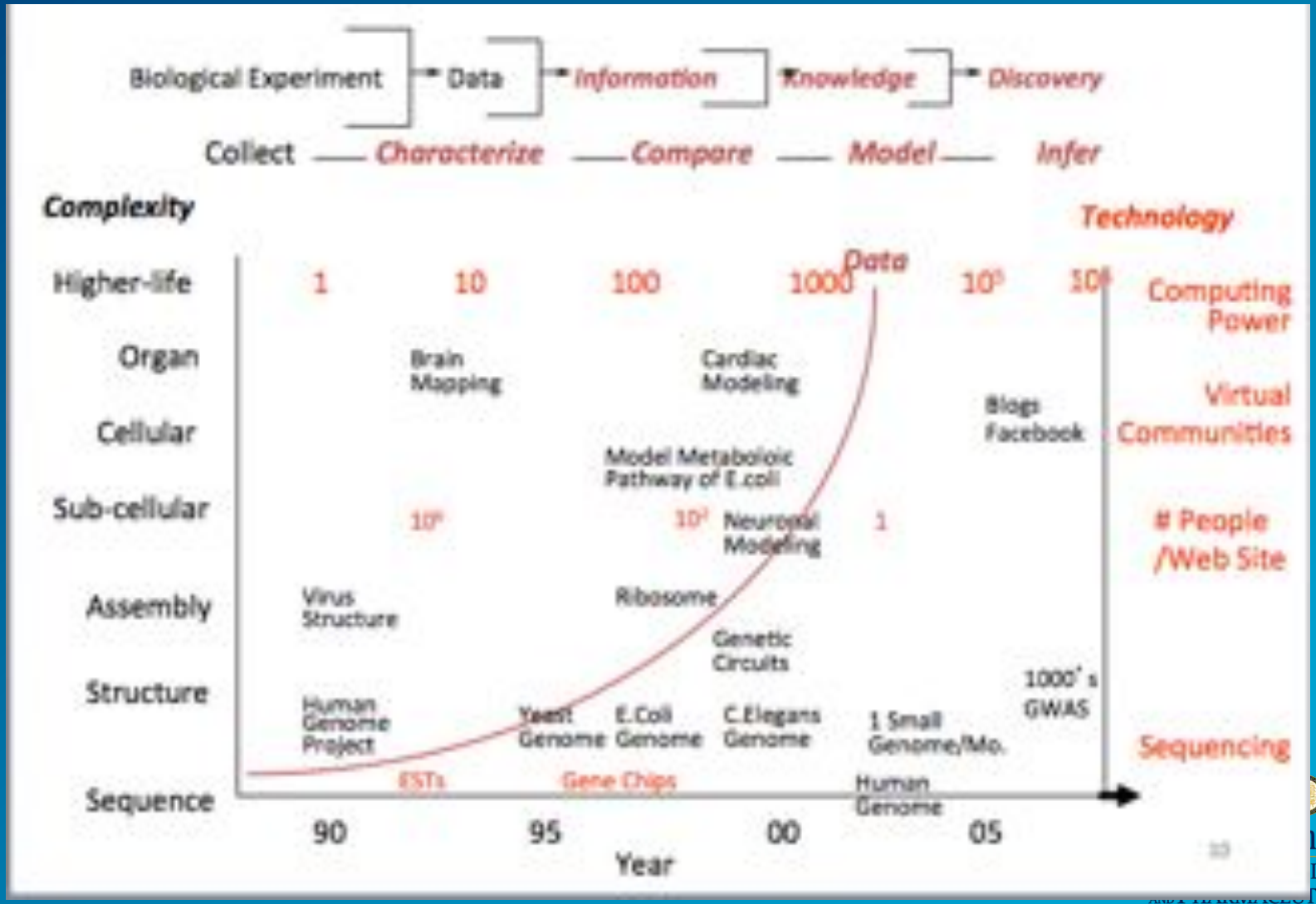
Its Not Just About Numbers its About Complexity



Courtesy of the RCSB Protein Data Bank

The OMICS Revolution in One Slide



Metagenomics

- New type of genomics

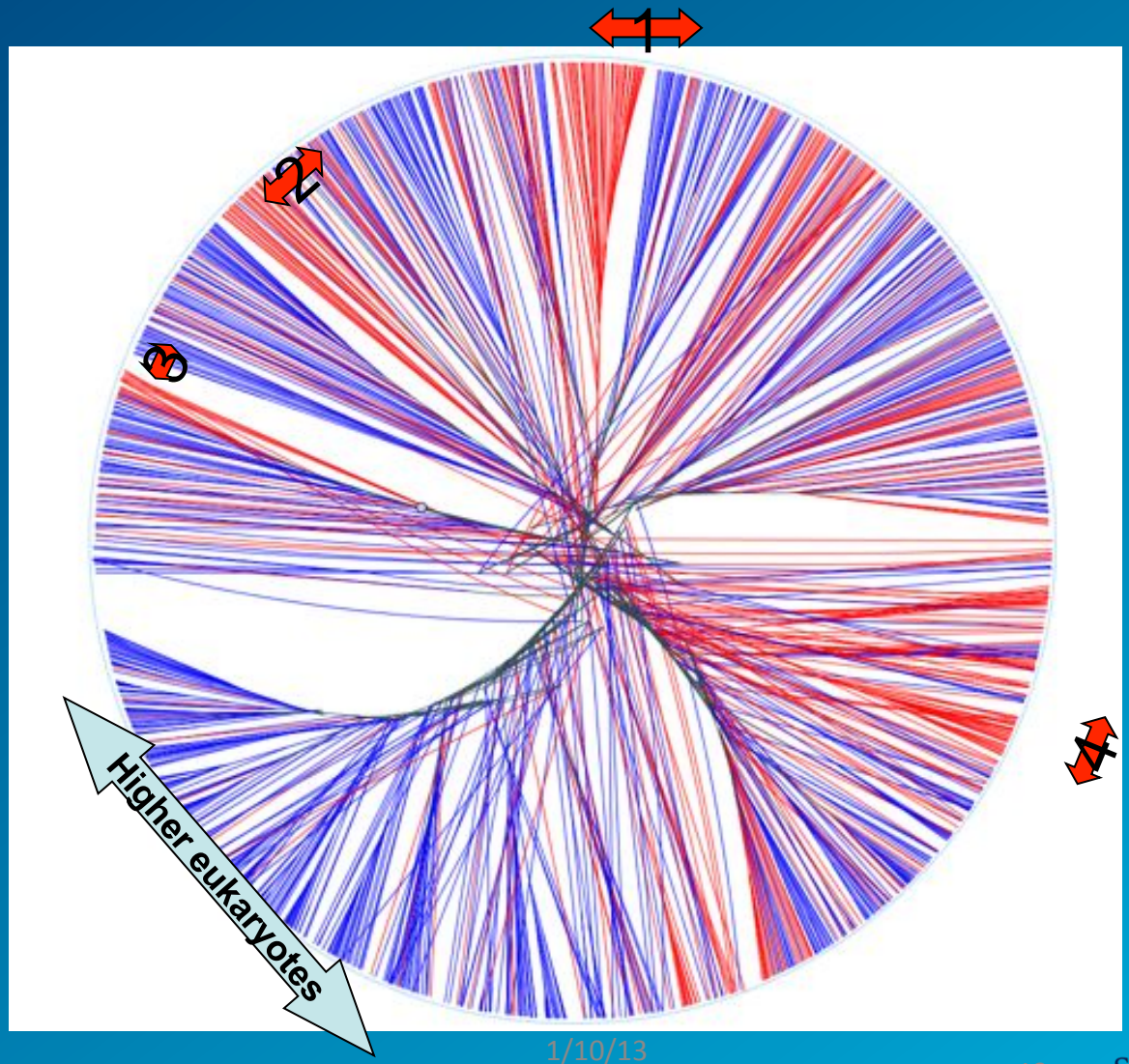
- New data (and lots of it) and new types of data – Initial ocean survey
  - 17M new (predicted proteins!) 4-5 x growth in just few months and much more coming
  - New challenges and exacerbation of old challenges

Metagenomics: Early Results

- More then 99.5% of DNA in very environment studied represent unknown organisms
  - Culturable organisms are exceptions, not the rule
- Most genes represent distant homologs of known genes, but there are thousands of new families
- Everything we touch turns out to be a gold mine
- Environments studied:
  - Water (ocean, lakes)
  - Soil
  - Human body (gut, oral cavity, human microbiome)

Metagenomics New Discoveries

Environmental (red) vs. Currently Known PTPases (blue)



Warning:
With Explosive Growth Comes Problems:

Currently 30% of Functional Annotations in Databases May be Wrong

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Towards Open Science

- Open access publishing
- Open source software
- Generation of scientists weaned on social networks
- Blogs, wikis, social bookmarking etc. are becoming a valid form of scientific discourse

http://www.osdd.net/

An Exemplar of Open Science
www.sagebase.org

The Open Access Battle is Not Won, but its Looking Good

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Why Don't we Do Better? A Couple of Observations

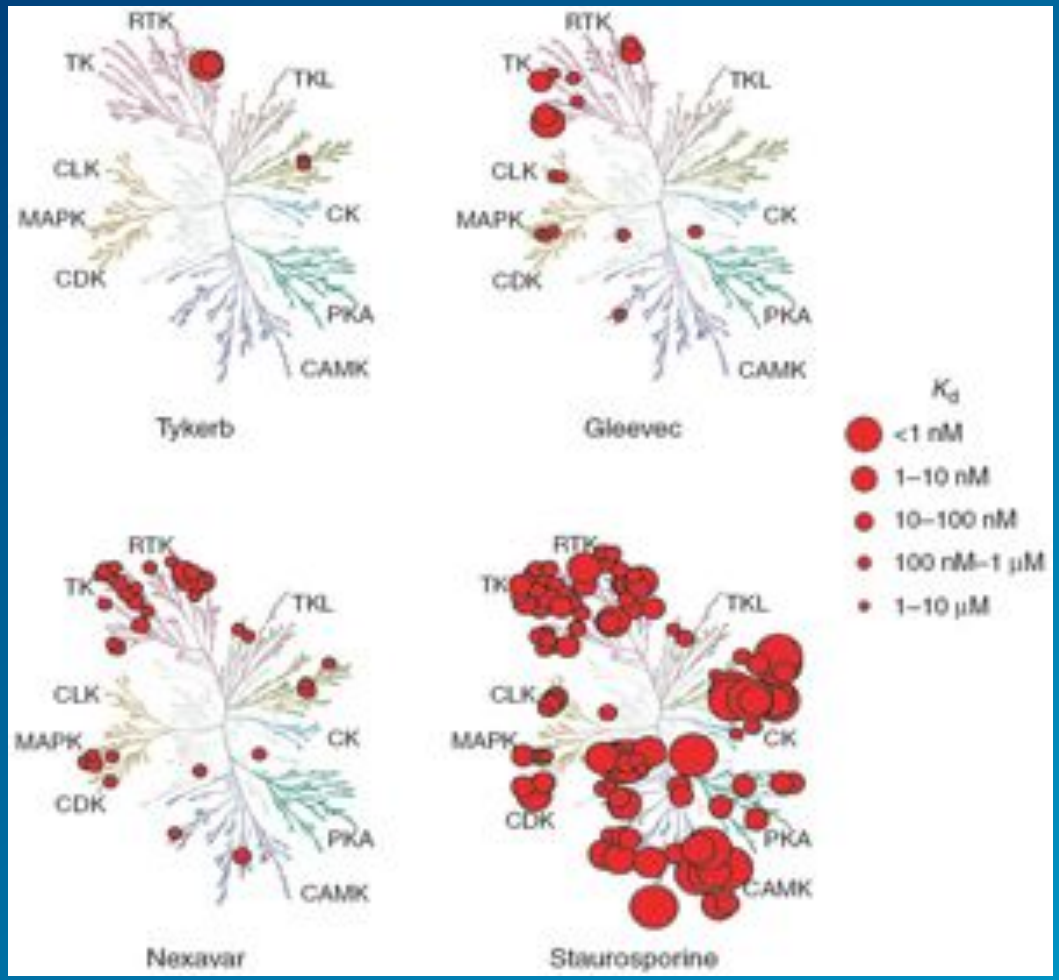
- Gene knockouts only effect phenotype in 10-20% of cases , why?
  - redundant functions
  - alternative network routes
  - robustness of interaction networks

A.L. Hopkins Nat. Chem. Biol. 2008 4:682-690

- 35% of biologically active compounds bind to more than one target

Paolini et al. Nat. Biotechnol. 2006 24:805–815

Why Don't we Do Better? A Couple of Observations



Collins and Workman 2006 *Nature Chemical Biology* 2 689-700

- Tykerb – Breast cancer
- Gleevac – Leukemia, GI cancers
- Nexavar – Kidney and liver cancer
- Staurosporine – natural product – alkaloid – uses many e.g., antifungal antihypertensive

Implications

- Ehrlich's philosophy of magic bullets targeting individual chemoreceptors has not been realized

- Stated another way – The notion of one drug, one target, one disease is a little naïve in a complex system

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What if…

- We can characterize a protein-ligand binding site from a 3D structure (primary site) and search for that site on a proteome wide scale?

- We could perhaps find alternative binding sites (off-targets) for existing pharmaceuticals and NCEs?

What Do These Off-targets Tell Us?

- Potentially many things:
  1. Nothing
  2. How to optimize a NCE
  3. A possible explanation for a side-effect of a drug already on the market
  4. A possible repositioning of a drug to treat a completely different condition
  5. The reason a drug failed
  6. A multi-target strategy to attack a pathogen

Need to Start with a 3D Drug-Receptor Complex - The PDB Contains Many Examples

Generic Name	Other Name	Treatment	PDBid
Lipitor		High cholesterol	1HWK, 1HW8…
Testosterone		Osteoporosis	1AFS, 1I9J ..
Taxol	Paclitaxel	Cancer	1JFF, 2HXF, 2HXH
Viagra	Sildenafil citrate	ED, pulmonary arterial hypertension	1TBF, 1UDT, 1XOS..
Digoxin	Lanoxin	Congestive heart failure	1IGJ

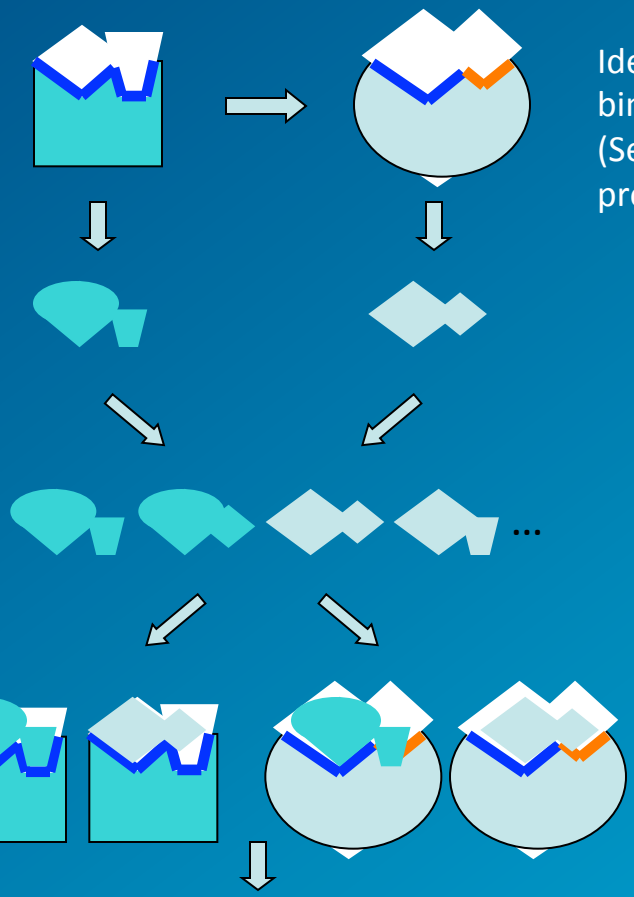
A Reverse Engineering Approach to Drug Discovery Across Gene Families

Characterize ligand binding site of primary target (Geometric Potential)

Identify off-targets by ligand binding site similarity (Sequence order independent profile-profile alignment)

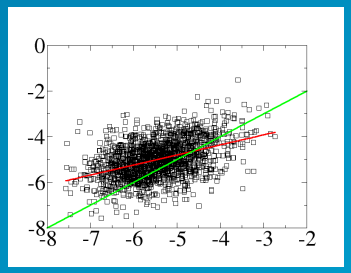
Extract known drugs or inhibitors of the primary and/or off-targets

Search for similar small molecules



Dock molecules to both primary and off-targets

Statistics analysis of docking score correlations



Xie and Bourne 2009
Bioinformatics 25(12) 305-312

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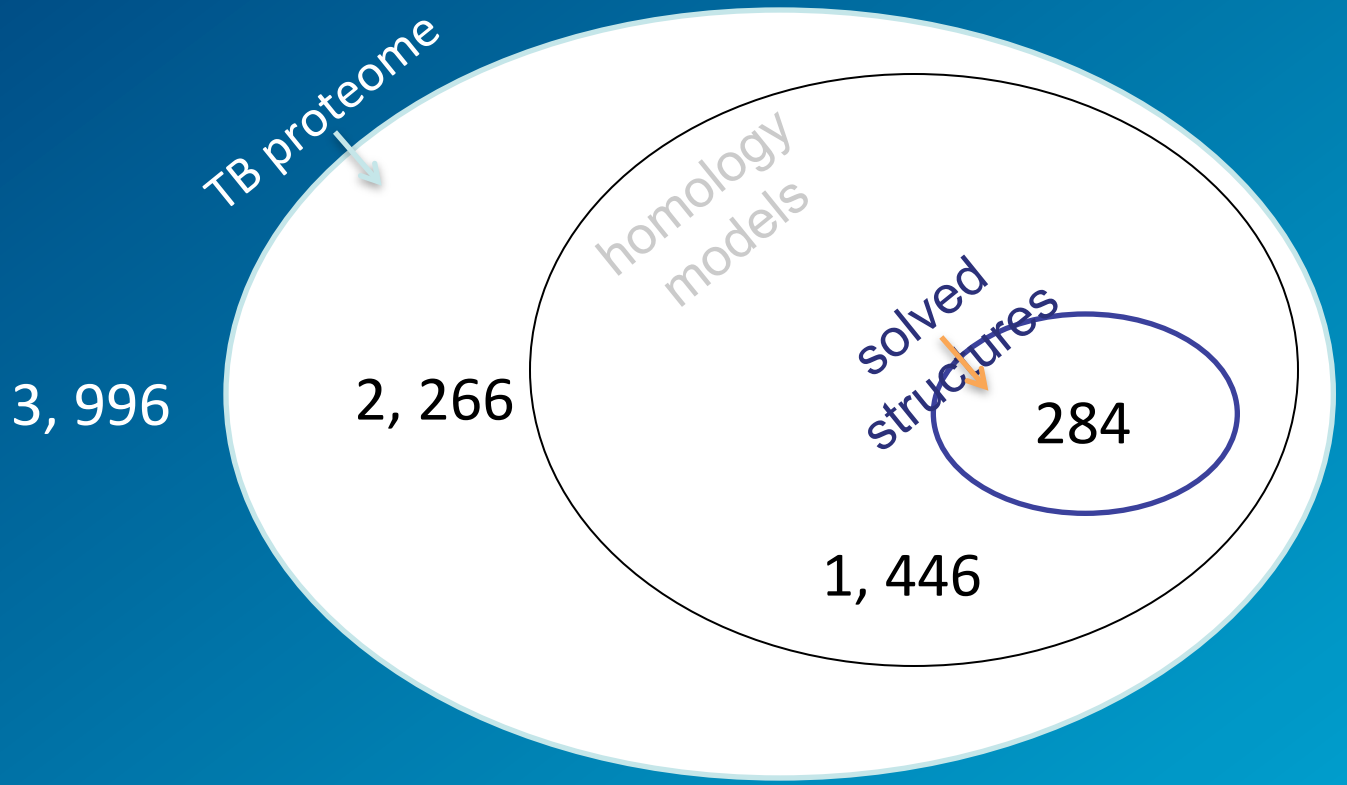
The Problem with Tuberculosis

- One third of global population infected
- 1.7 million deaths per year
- 95% of deaths in developing countries
- Anti-TB drugs hardly changed in 40 years
- MDR-TB and XDR-TB pose a threat to human health worldwide
- Development of novel, effective, and inexpensive drugs is an urgent priority

Looking at the Problem on a Large Scale

1. Determine the TB Structural Proteome

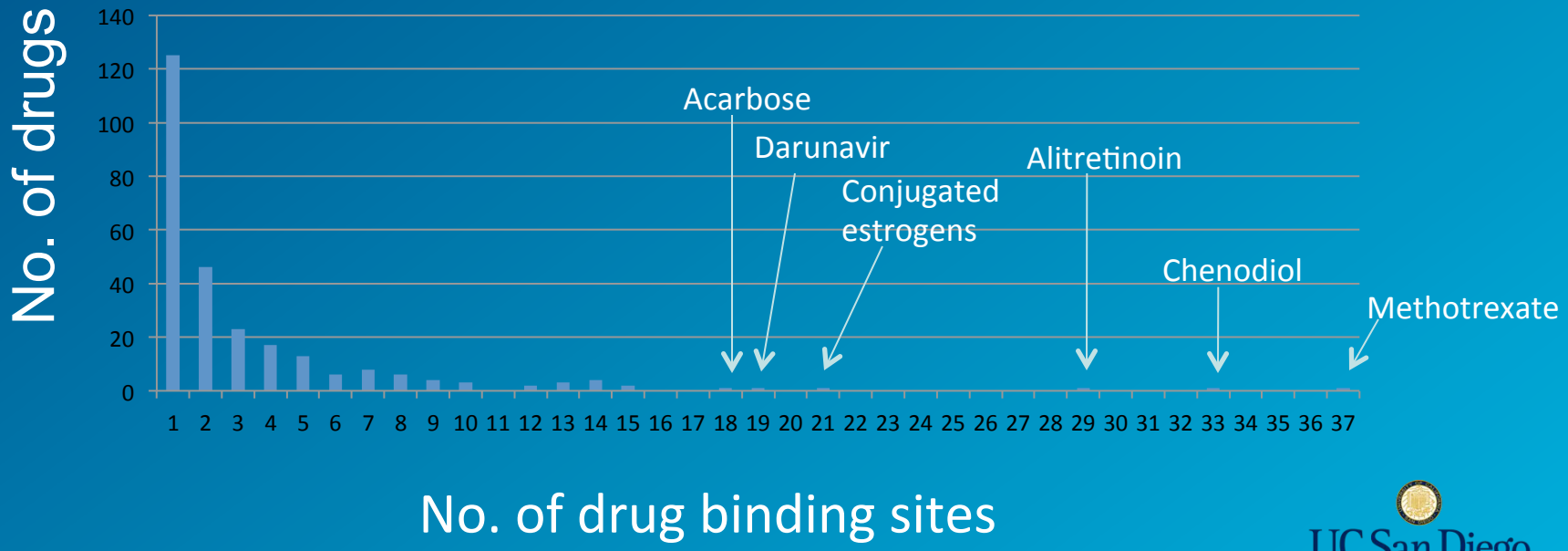
Kinnings et al 2010 PLoS Comp Biol 6(11): e1000976



- High quality homology models from ModBase (http://modbase.compbio.ucsf.edu) increase structural coverage from 7.1% to 43.3%

2. Determine all Known Drug Binding Sites in the PDB

- Searched the PDB for protein crystal structures bound with FDA-approved drugs
- **268** drugs bound in a total of **931** binding sites



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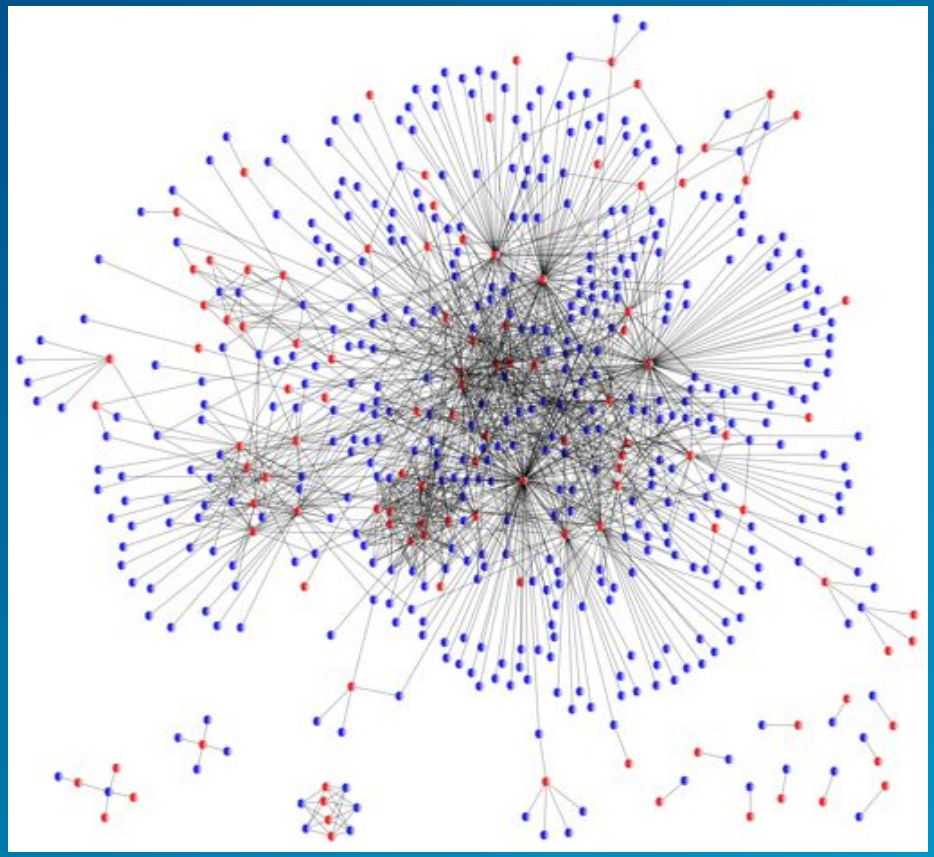
Map 2 onto 1 – The TB-Drugome

http://funsite.sdsc.edu/drugome/TB/



Similarities between the binding sites of *M.tb* proteins (blue), and binding sites containing approved drugs (red)

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Summary of the TB Story

- Entacapone and tolcapone shown to have potential for repositioning
- Direct mechanism of action avoids *M. tuberculosis* resistance mechanisms
- Possess excellent safety profiles with few side effects – already on the market
- *In vivo* support
- Assay of direct binding of entacapone and tolcapone to InhA reveals a possible lead with no chemical relationship to existing drugs

Kinnings et al. 2009 *PLoS Comp Biol* 5(7) e1000423

Summary from the TB Alliance – Medicinal Chemistry

- The minimal inhibitory concentration (MIC) of 260 uM is higher than usually considered
- MIC is 65x the estimated plasma concentration
- Have other InhA inhibitors in the pipeline

Kinnings et al. 2009 *PLoS Comp Biol* 5(7) e1000423

New Ways of Thinking

- *Polypharmacology* – One or multiple drugs binding to multiple targets for a collective effect aka *Dirty Drugs*

- *Network Pharmacology* – Measuring that effect on the whole biological network

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ABOUT THIS AUTHOR

Derek Lowe, an Arkansan by birth, got his BA from Hendrix College and his PhD in organic chemistry from Duke before spending time in Germany on a Humboldt Fellowship on his post-doc. He's worked for several major pharmaceutical

Just Released the 2008 Tribalization of Business study - an in-depth look at how 140+ organizations are managing and measuring online communities

In the Pipeline

« Pfizer's Sizing | Main | Too Near the Sun? »

December 3, 2006

The Torcetrapib Catastrophe

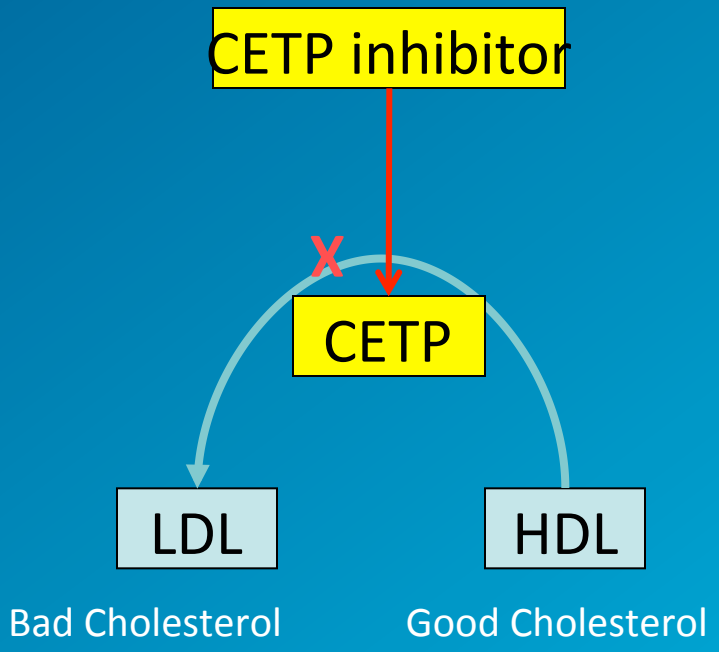
Posted by **Derek**

This is a complete clinical disaster: the world's largest drug company just ditched their potential biggest drug. And this comes two days after a press conference where they talked about how they were planning to submit it for approval within months. Development of torcetrapib, the cholesteryl-ester transfer protein inhibitor designed to raise HDL levels, has been halted. Last week, that sentence would have been the subject of nightmares at Pfizer, but now it's the top of the news. No alarm clock buzz will make it go away. If you're looking for an example of just how difficult drug development is, look no more.

Example 2 - The Torcetrapib Story

PLoS Comp Biol 2009 5(5) e1000387

Cholesteryl Ester Transfer Protein (CETP)

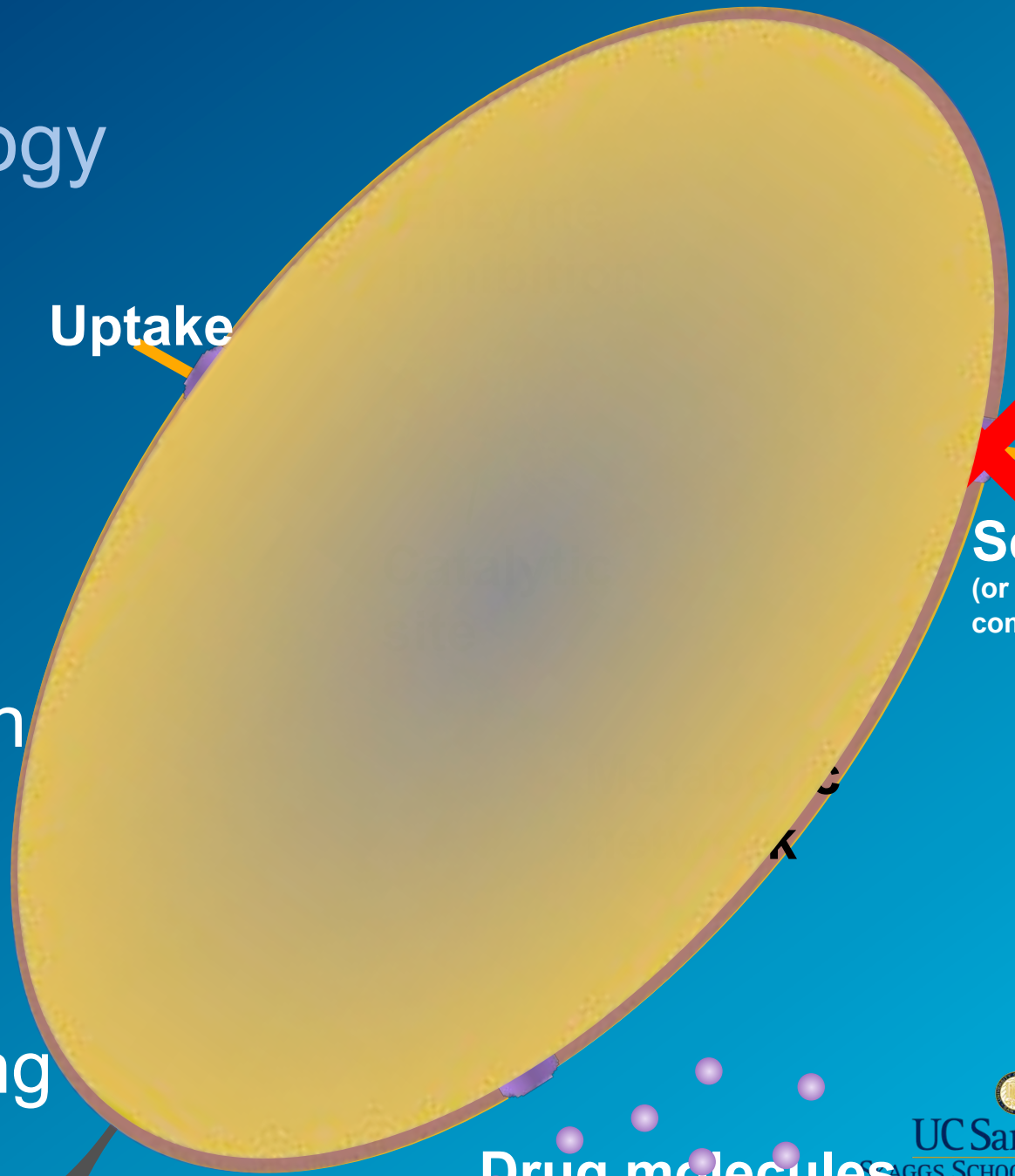


Systems Pharmacology

Systemic response

Affect protein function

Target binding



Slide from Roger Chang

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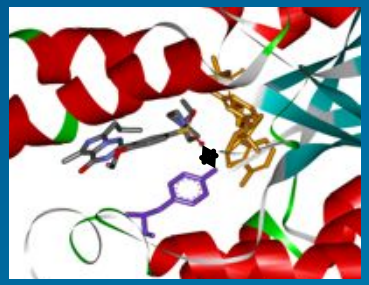
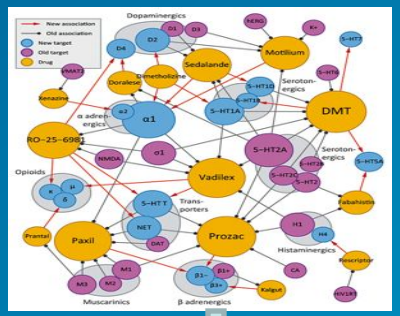
Multiscale Modeling of Drug Actions

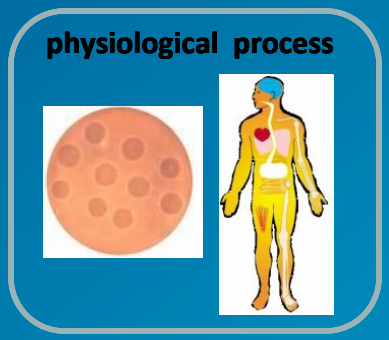
Understanding of dynamics and kinetics of protein-ligand interactions

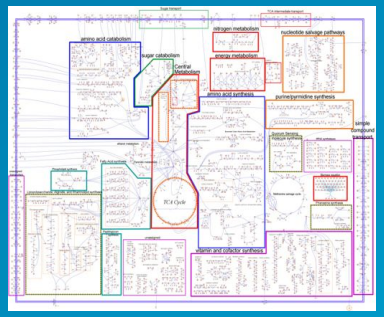


Prediction of molecular interaction network on a genome scale



Traditional Approach





Knowledge representation and discovery & model integration

Reconstruction, analysis and simulation of biological networks

Systems-based Approach

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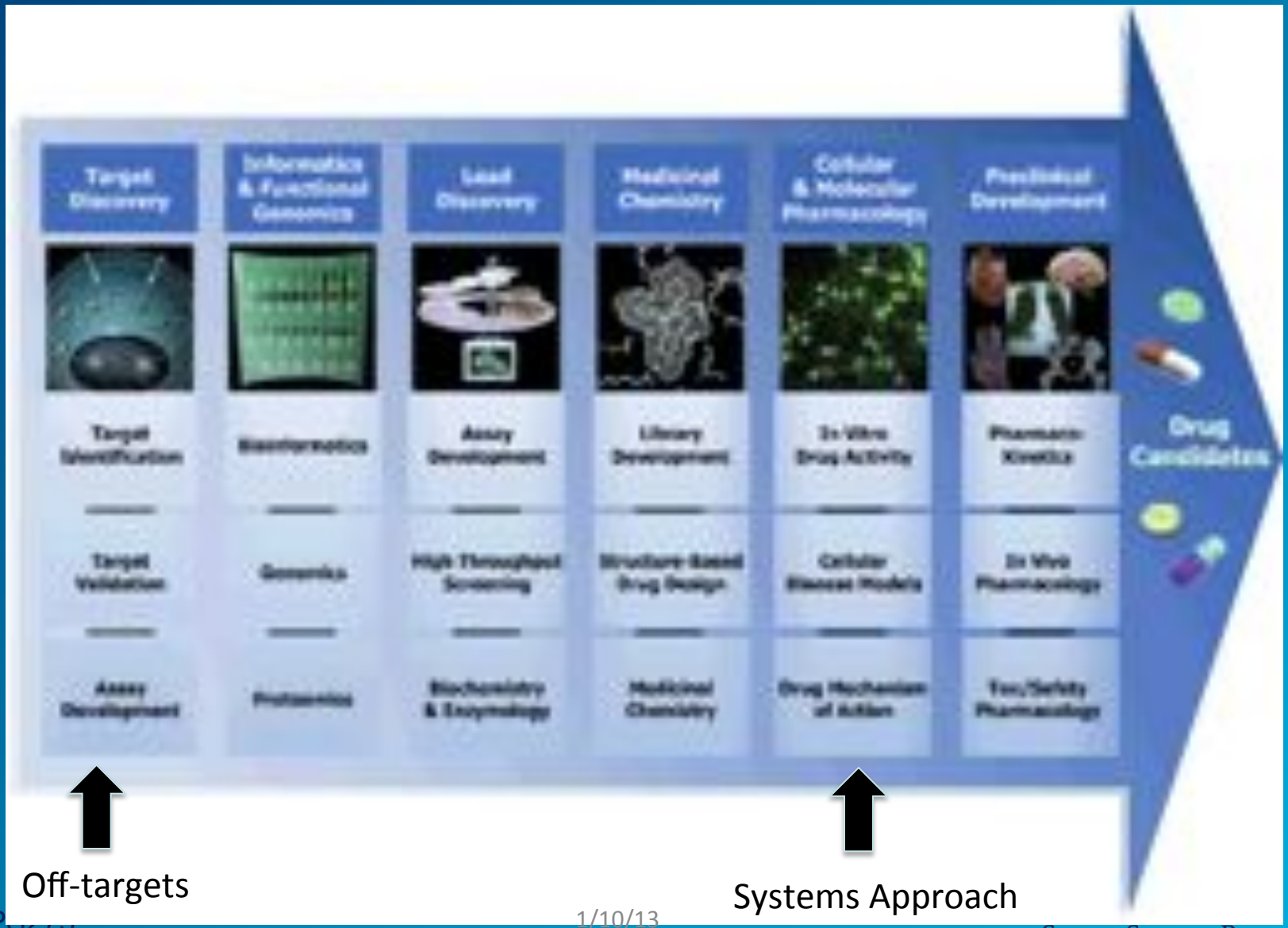
Modifications to Early Stage Drug Discovery



http://www.celgene.com/images/celgene_drug_arrow.gif

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Words of Caution

- Mistrust of computational approaches
- Bioinformatics was previously oversold
- Omics was previously oversold
- Openness is an alien culture to drug discovery

Further Reading

- L. Xie, L. Xie, S.L. Kinnings and P.E. Bourne 2012 Novel Computational Approaches to Polypharmacology as a Means to Define Responses to Individual Drugs, *Annual Review of Pharmacology and Toxicology* 52*:* 361-379 [PDF].
- And references therein

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Questions?