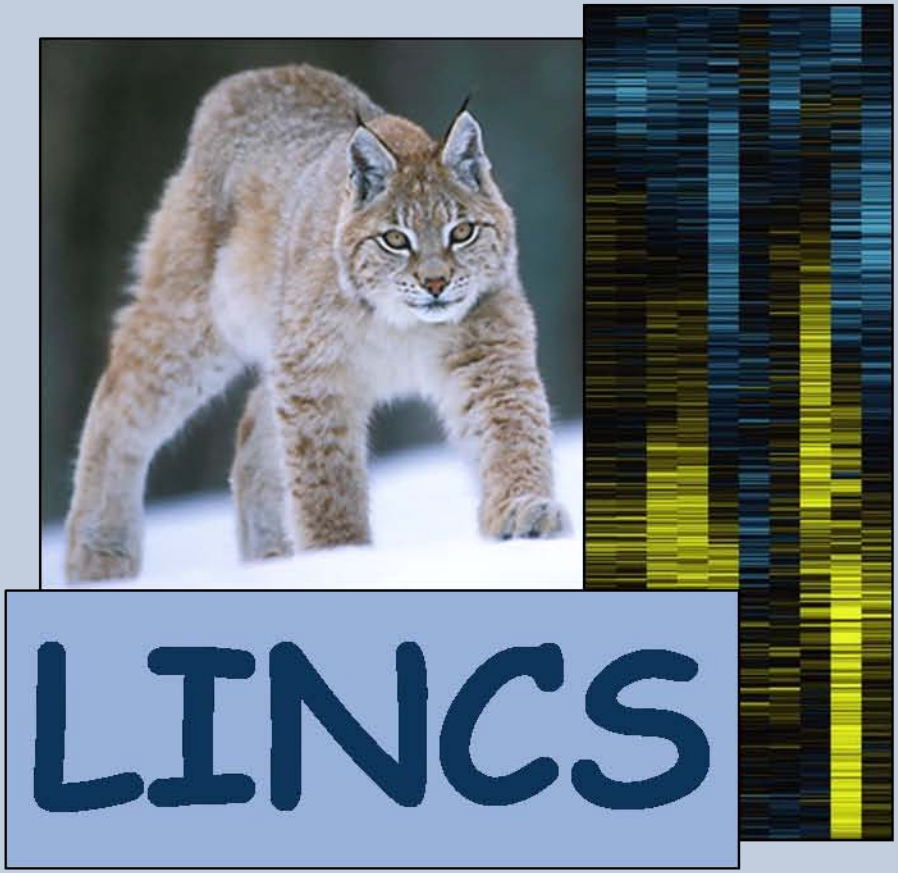
Library of Integrated Network-based Cellular Signatures

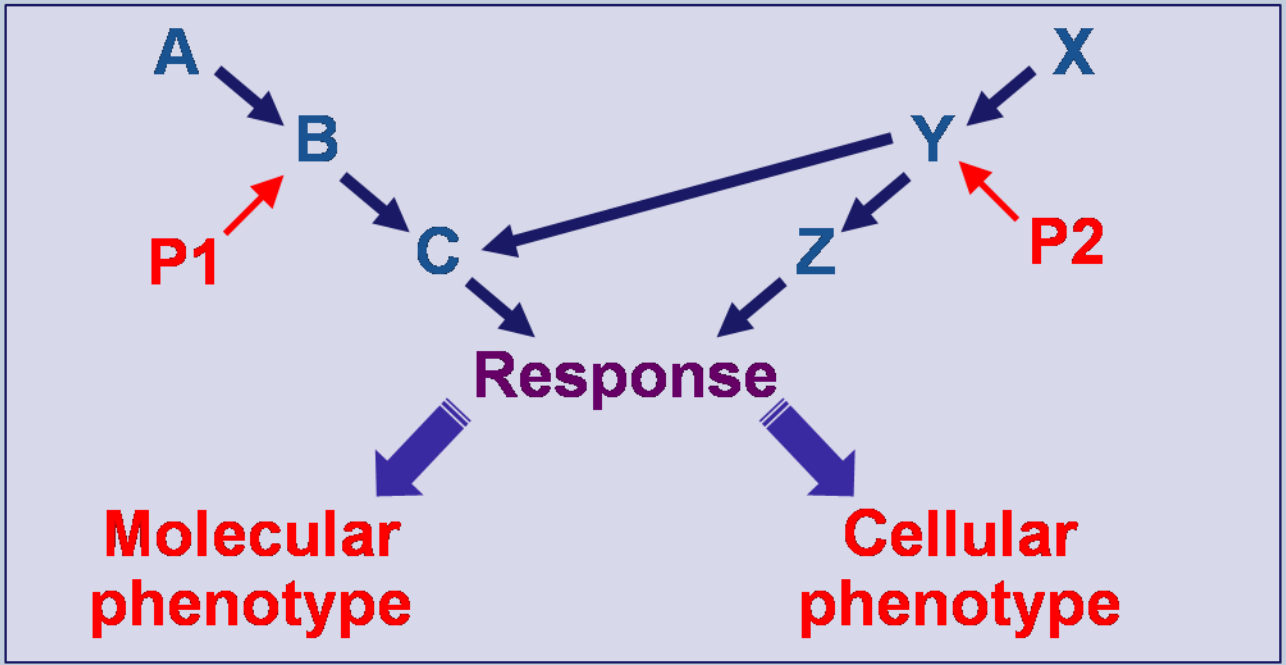


NIH Council of Councils Meeting

November 21, 2008

What is LINCS?

- LINCS will generate a set of perturbation-induced molecular activity and cellular feature signatures that can be used to infer:
  - mechanism-based relationships among perturbing conditions
  - functional associations among responding cellular components

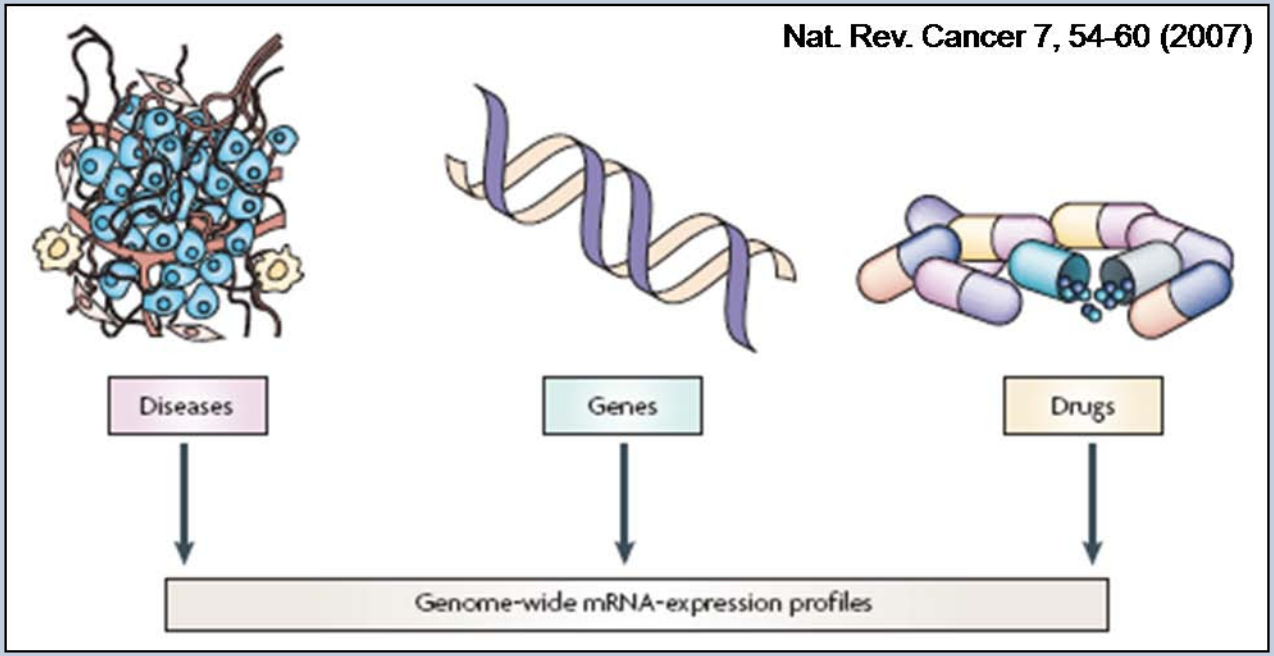


Inspiration for and feasibility of LINCS

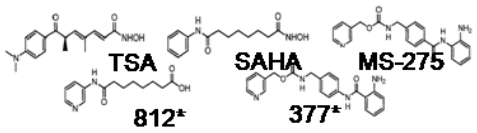
The Connectivity Map: Using Gene-Expression Signatures to Connect Small Molecules, Genes, and Disease

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*]

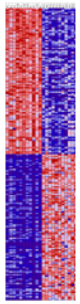
Science 313, 1929-1935 (2006)



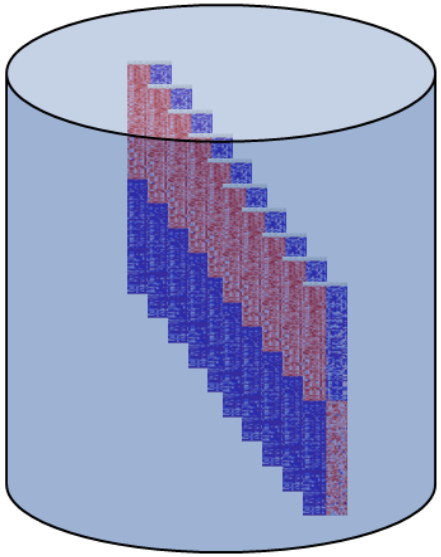
Molecular signatures for the functional classification of drugs



Science 313, 1929-1935 (2006)

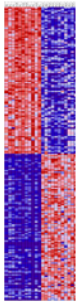


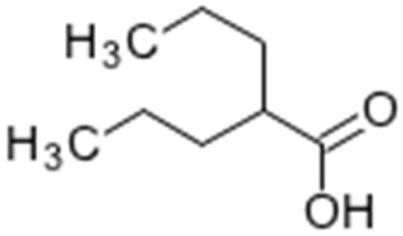
HDAC inhibitor signature



Signature Database

pattern matching





Valproic Acid

Slide courtesy of Todd Golub

Extension of the Connectivity Map concept by LINCS

LINCS will extend the utility of the Connectivity Map concept by increasing the dimensionality of:

- perturbation conditions
  - small molecules
  - siRNAs
  - environmental factors
- cell types
  - immortalized cell lines
  - primary cells
  - cells representative of different disease states
- phenotypic assays
  - molecular profiles
  - cellular features and behavior

Outcome: rich datasets from which functional associations can be derived among perturbations and responding cellular components.

Transformative potential of LINCS

The transformative potential of LINCS lies in its application to a wide range of basic, clinical and translational problems in biomedical research:

- reconstruction of predictive biological networks
- elucidation of how human genetic variants cause disease

- classification of diseases by molecular criteria: ***MAPGen***
- classification of drugs by functional effects rather than by chemical structure
- target-based design of new drugs and combination chemo-therapies
- development of novel molecular diagnostics

Network modeling of complex diseases

Challenge: *understanding complex diseases requires knowledge of how networks of pleiotropic genes interact to determine and modify quantitative phenotypes in specific cellular, organ & environmental contexts.*

Network modeling links breast cancer susceptibility and centrosome dysfunction

Nature Genet. 39, 1338-1349 (2007)

A network biology approach to prostate cancer

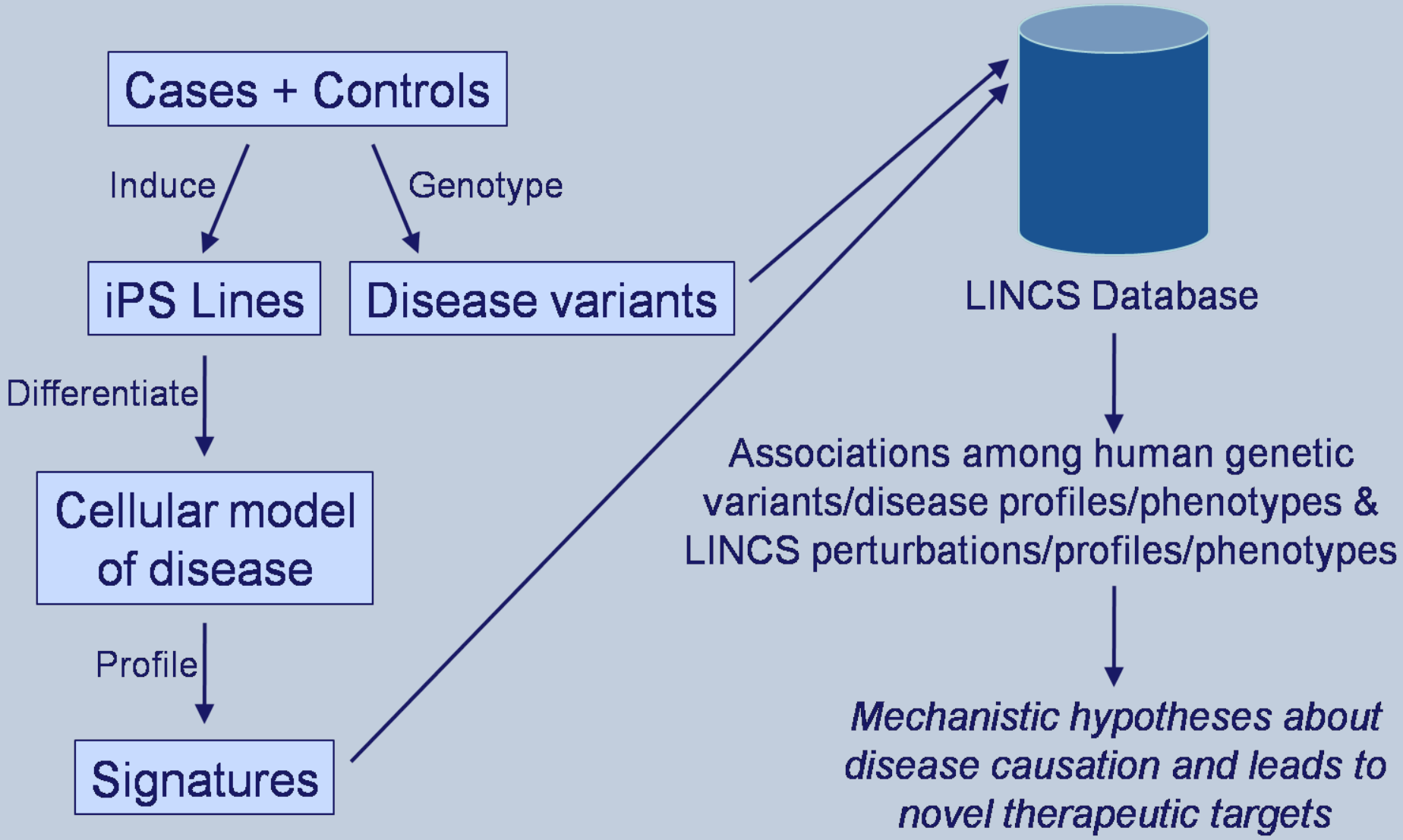
Mol. Syst. Biol. 3:82 (2007)

Variations in DNA elucidate molecular networks that cause disease

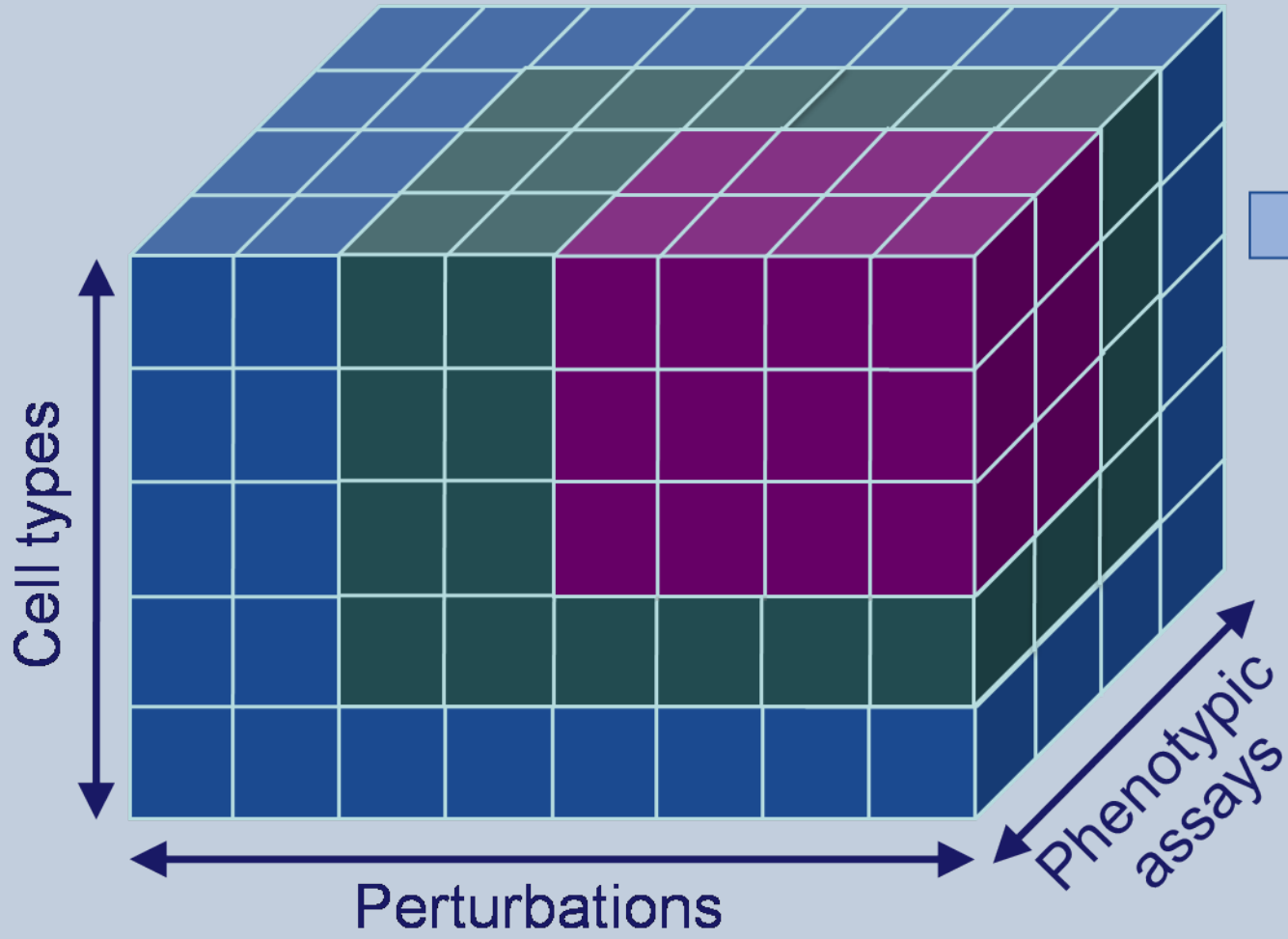
Nature 452, 429-435 (2008)

Problem: Existing reference databases are too sparse!

Next-gen disease association studies



LINCS Program Implementation



Data Generation, Analysis, Integration, Presentation Application

Functional annotation with existing knowledge

Additional dimensions to consider:

- biological replicas
- concentration of perturbation agents
- timing of exposure to perturbation agents
- informative combinations of perturbation agents

LINCS Program Implementation

Phase 1:

- Award of a data coordinating center and creation of the LINCS database
- Exploratory studies:
  - optimize the selection of cells, perturbations and assays
  - focus on driving biological problems
- Development of new cost-effective, enabling wet lab and computational technologies
- Standardization of nomenclature and experimental protocols

Outcome: set of best practices that can be expanded in Phase 2

LINCS Program Implementation

Phase 2:

- Select experimental systems from Phase 1 for more in-depth study. *Goal: generate richer datasets*
- Apply new technologies developed in Phase 1
- Provide support for new computational investigators
- Validate novel hypotheses generated by LINCS
- Apply LINCS resource to biomedical problems
- Transition to IC support for wider application of LINCS

Summary

- LINCS will generate high-content data that will provide mechanistic insights into disease etiology and the identification of novel drug targets
- LINCS will develop a strategic template for how to optimally generate and apply network-based cellular signatures in biomedical research
- LINCS will provide coordination, standardization and integration across related research projects
- LINCS will be scalable to more biological systems than are included in the initial program

LINCS Working Group

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