

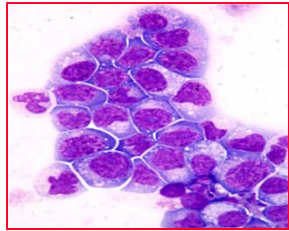
## *Cancer as Information*

Todd R. Golub, M.D.  
Dana-Farber Cancer Institute  
Integrative Cancer Biology Program  
Broad Institute of Harvard and MIT

NCAB Meeting  
June 14, 2006

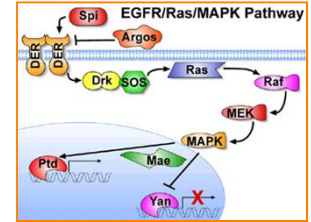


# Cancer as Information



Clinical States  
(e.g. drug-resistant)

Biological Pathways  
(e.g. kinase activation)

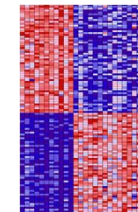


Genomic Data  
(e.g. DNA microarray)

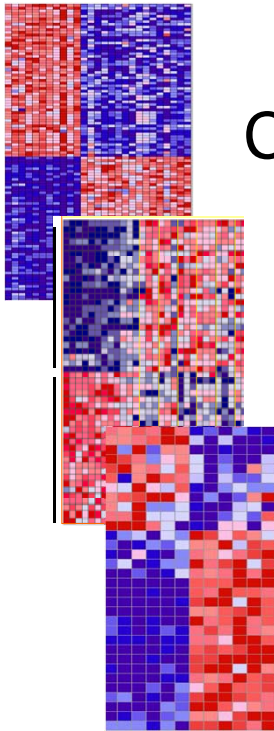


*machine learning*

'Signature'  
(e.g. gene expression profile)



# Global Views of Cancer: Gene Expression Signatures

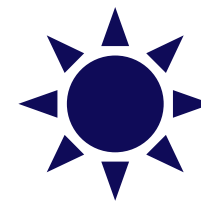
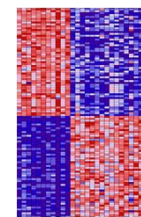


Cancer subtypes -----> Diagnostic Tests

Experimental systems -----> individual gene follow-up

Network modeling -----> cellular 'wiring diagram'

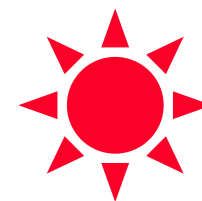
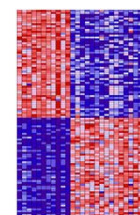
How to *modulate* signatures of biological state?



Biological State A



chemical  
library



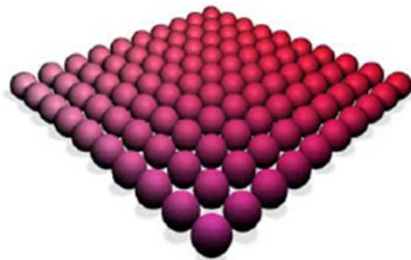
Biological State B

# Signature Amplification and Detection

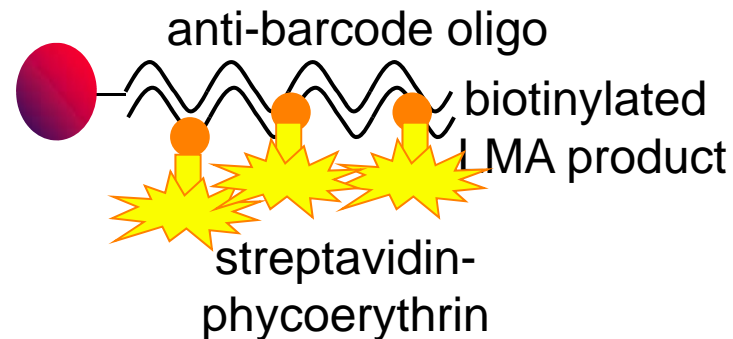
## Amplification: *Ligation-Mediated Amplification (LMA)*

- Multiplexed (< 100) annealing with barcodes
- PCR with single set of biotinylated primers

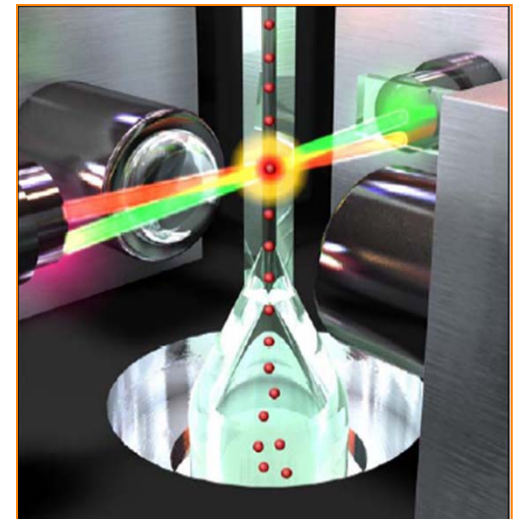
## Detection: *Luminex Beads*



100 colors  
5 micron

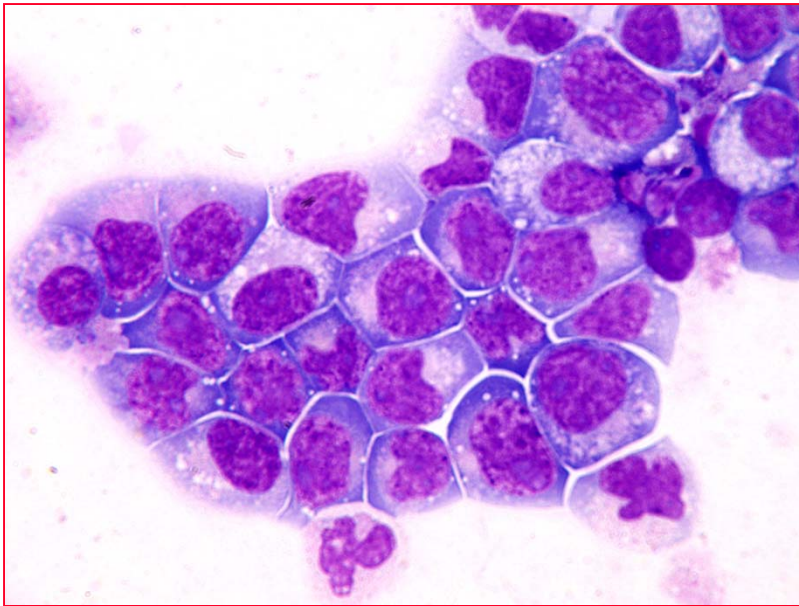
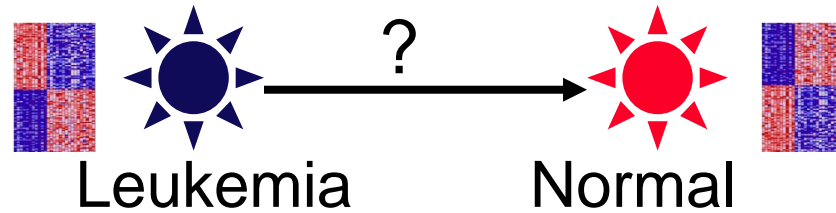


~ \$ 0.50/sample

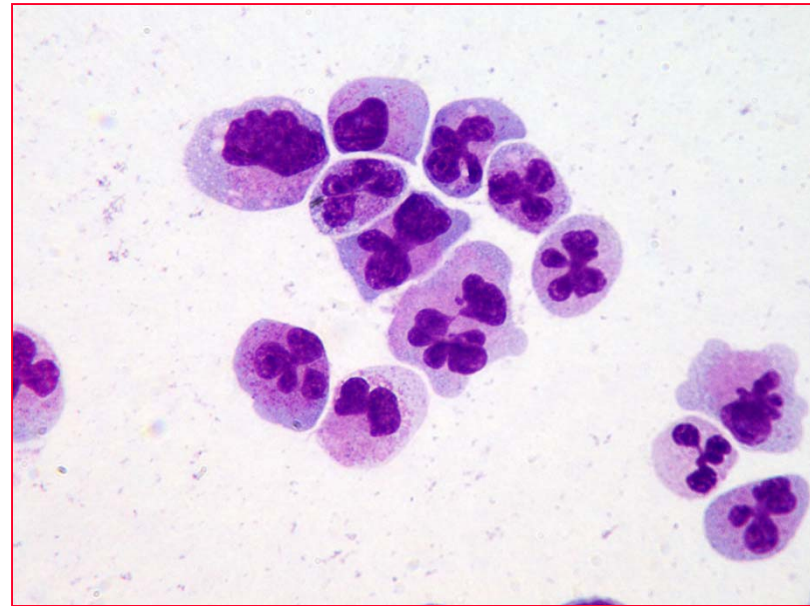


Luminex 2-laser  
Flow cytometer

# Leukemia Maturation Signature



*Vehicle*



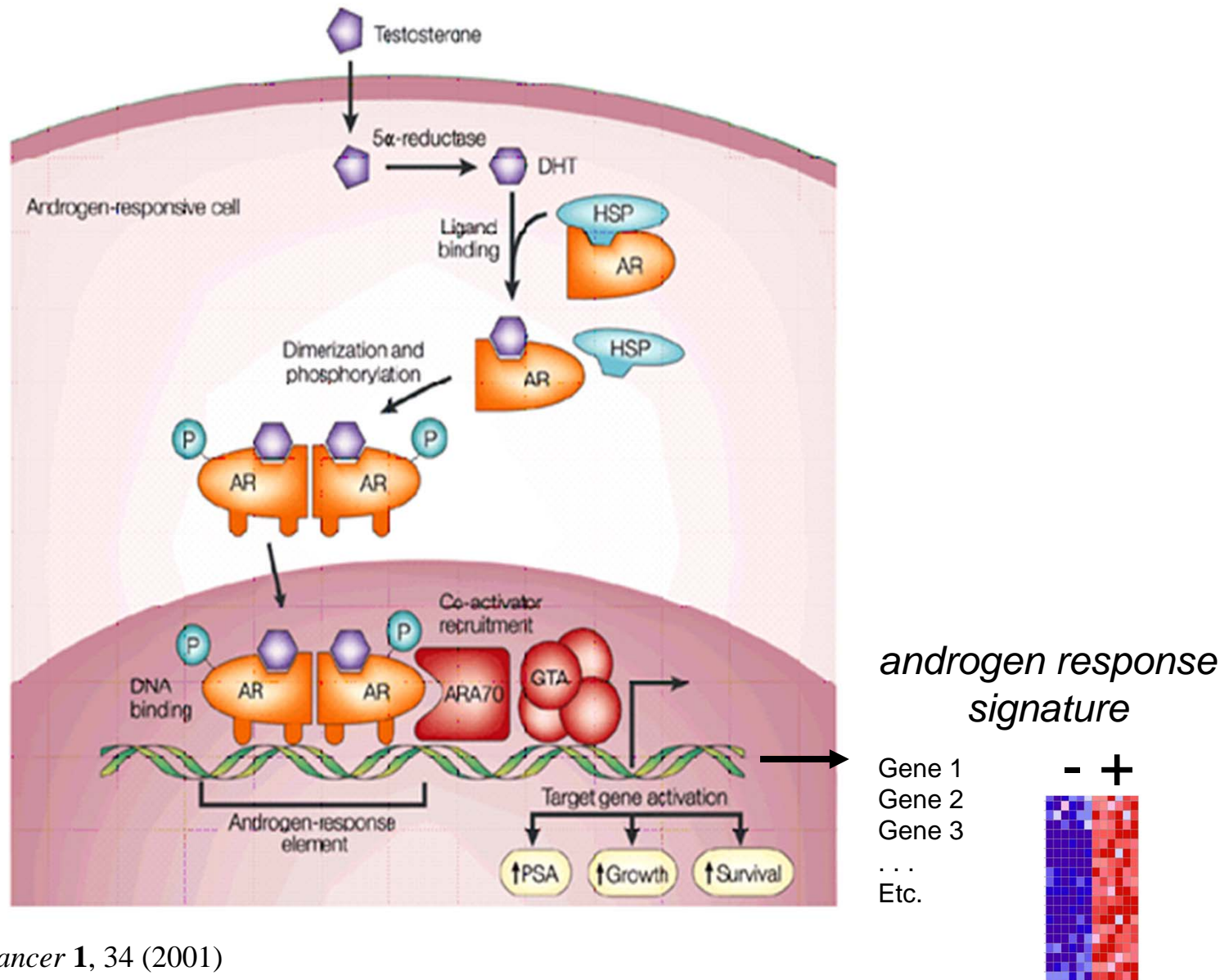
*EGFR kinase inhibitors*

Gefitinib (Iressa)

Erlotinib (Tarceva)

**Clinical trial now open**

# Androgen Receptor (AR) Pathway in Prostate Cancer



# Androgen Receptor Chemical Screen

Prostate Cancer Cells

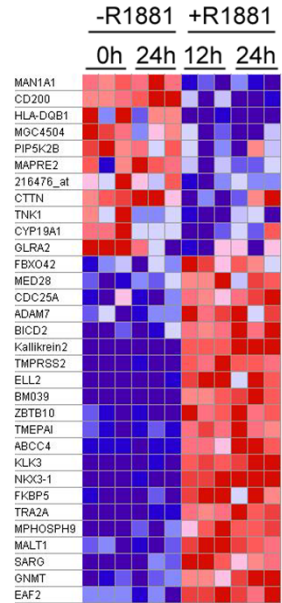


- androgen

vs.



+ androgen

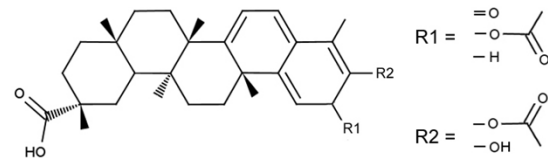
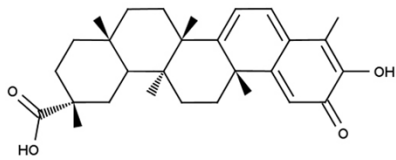


Chemical screen

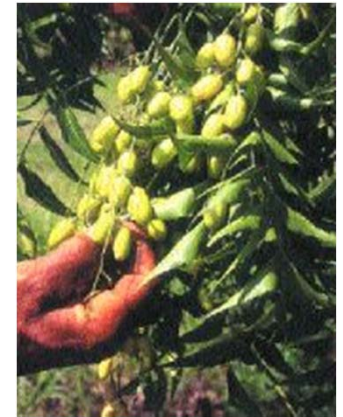
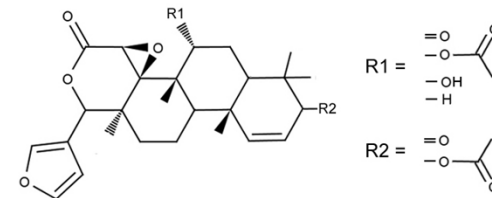
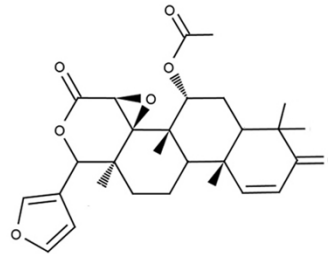


*T. wilfordii*  
(Thunder God)

*Celastrol*



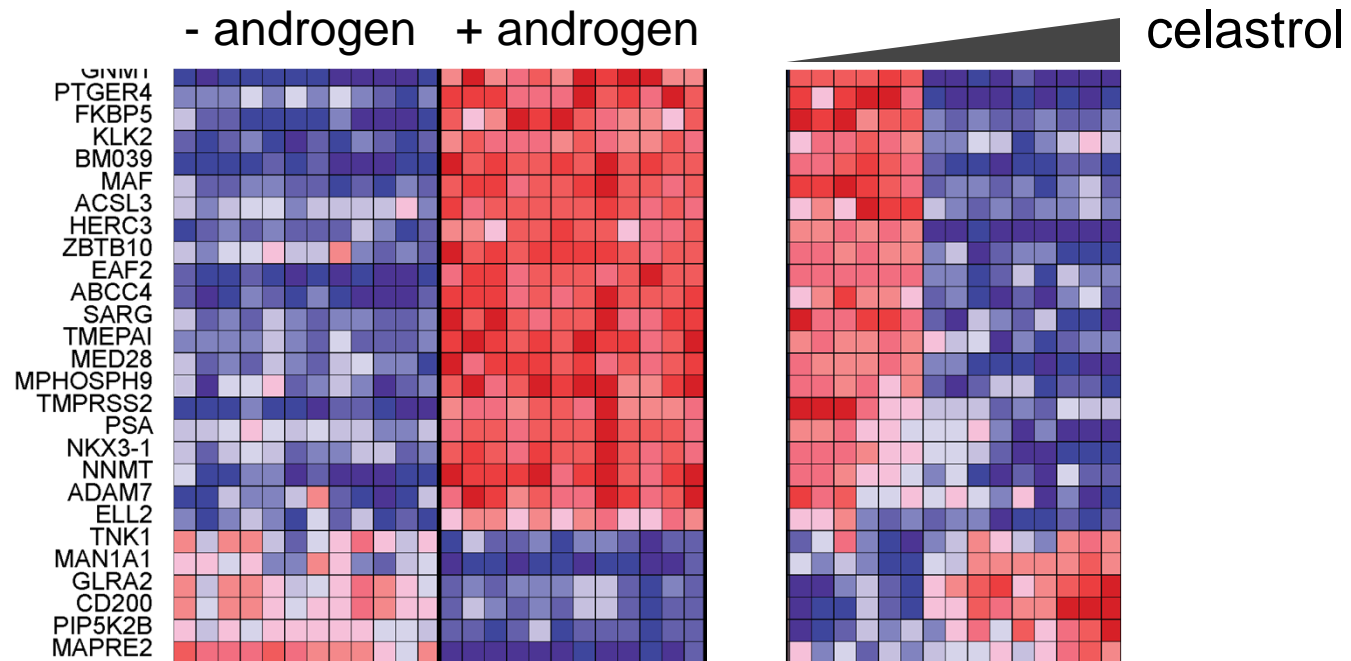
*Gedunin*



*Azadirachta indica*  
(Neem)

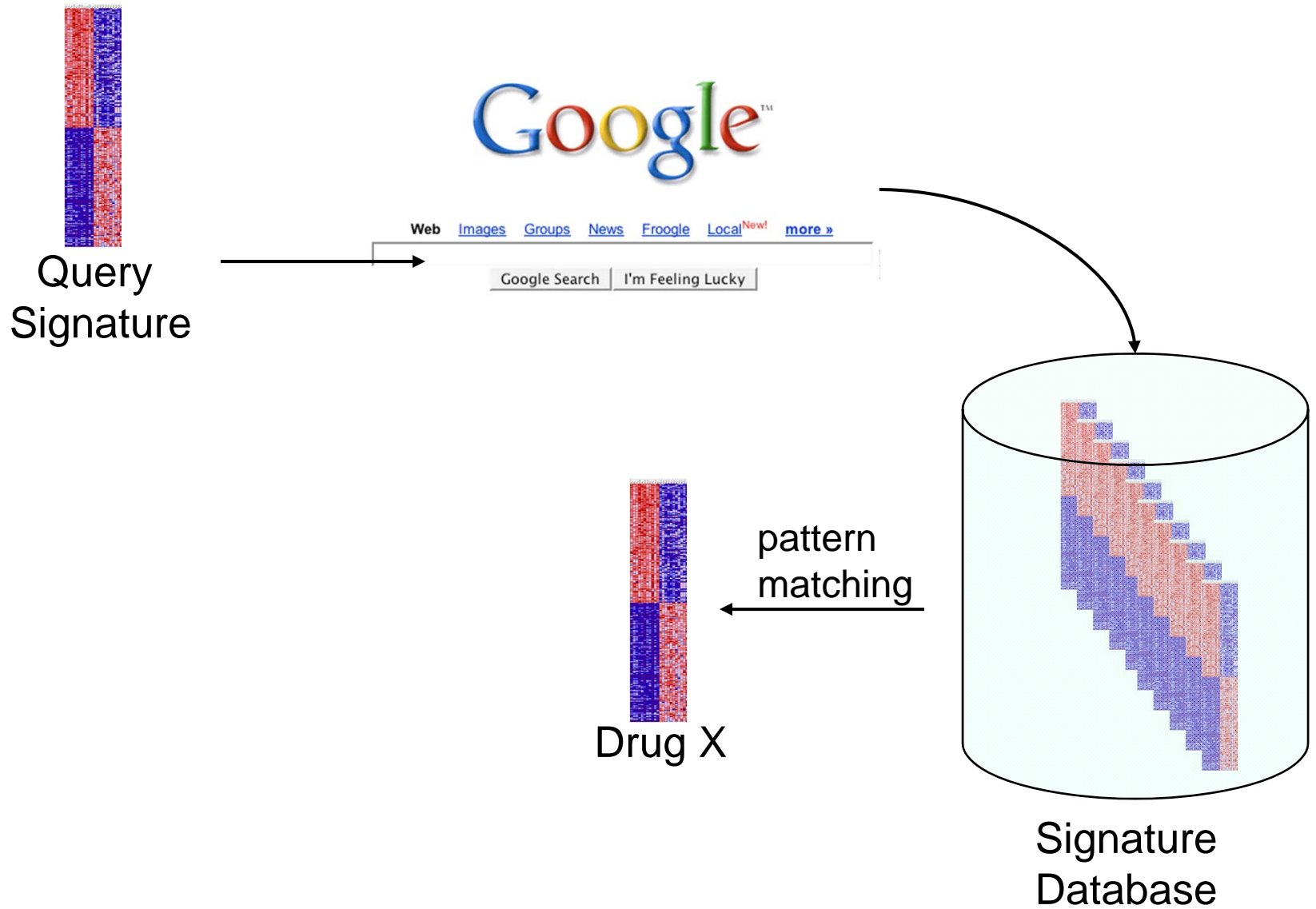


# Celastrol/Gedunin Inhibit Androgen Signature

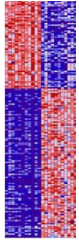
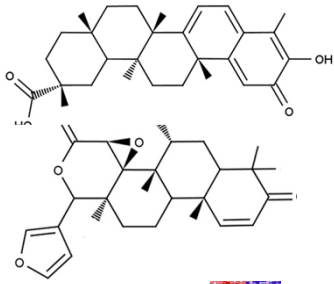


How do these compounds work?

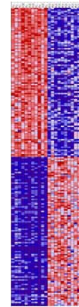
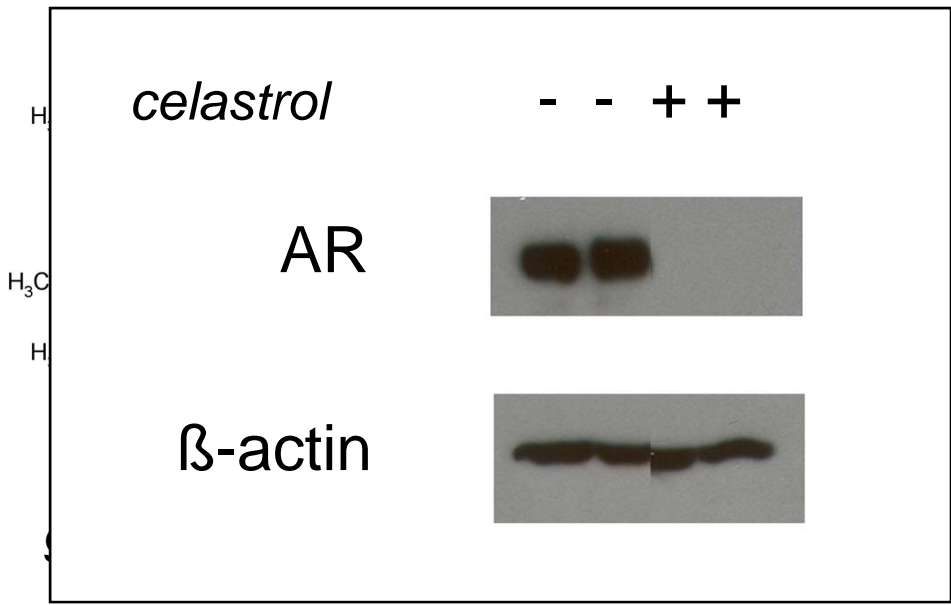
# Connectivity Map



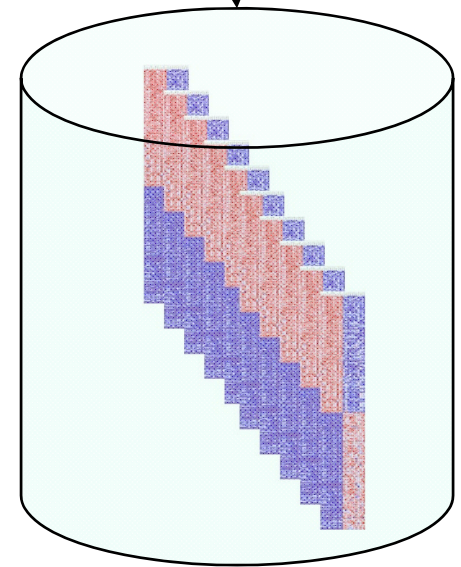
# Connectivity Map



Celastrol / Gedunin  
Signature



pattern  
matching



Signature  
Database

# Conclusions

1. Cancer states can be described in terms of genomic information.
2. High throughput chemical screens can be based on such signatures.
3. Large-scale, public domain signature database is warranted.
4. Navigating cancer biology will mean navigating genomic information.