

Microarray applications for the study of cancer

By Jake Youngberg

Overview

- Brief overview of cancer biology
- Review of how microarrays work
- Theoretical basis of microarrays
- Diagnostics applications
- Pharmacology applications
- The Future

What is cancer?

- Cancer is the disease caused the abnormal proliferation of cells in the body.
- Cancer is a heterogeneous class of diseases.
- On a cellular level cancer results from a combination of genetic abnormality and extra-cellular stimulus.

Cancer Biology Progression

1.) Normal cells

----(genetic damage)---->

Mutated cells

2.) Mutated cells

----(promotion)---->

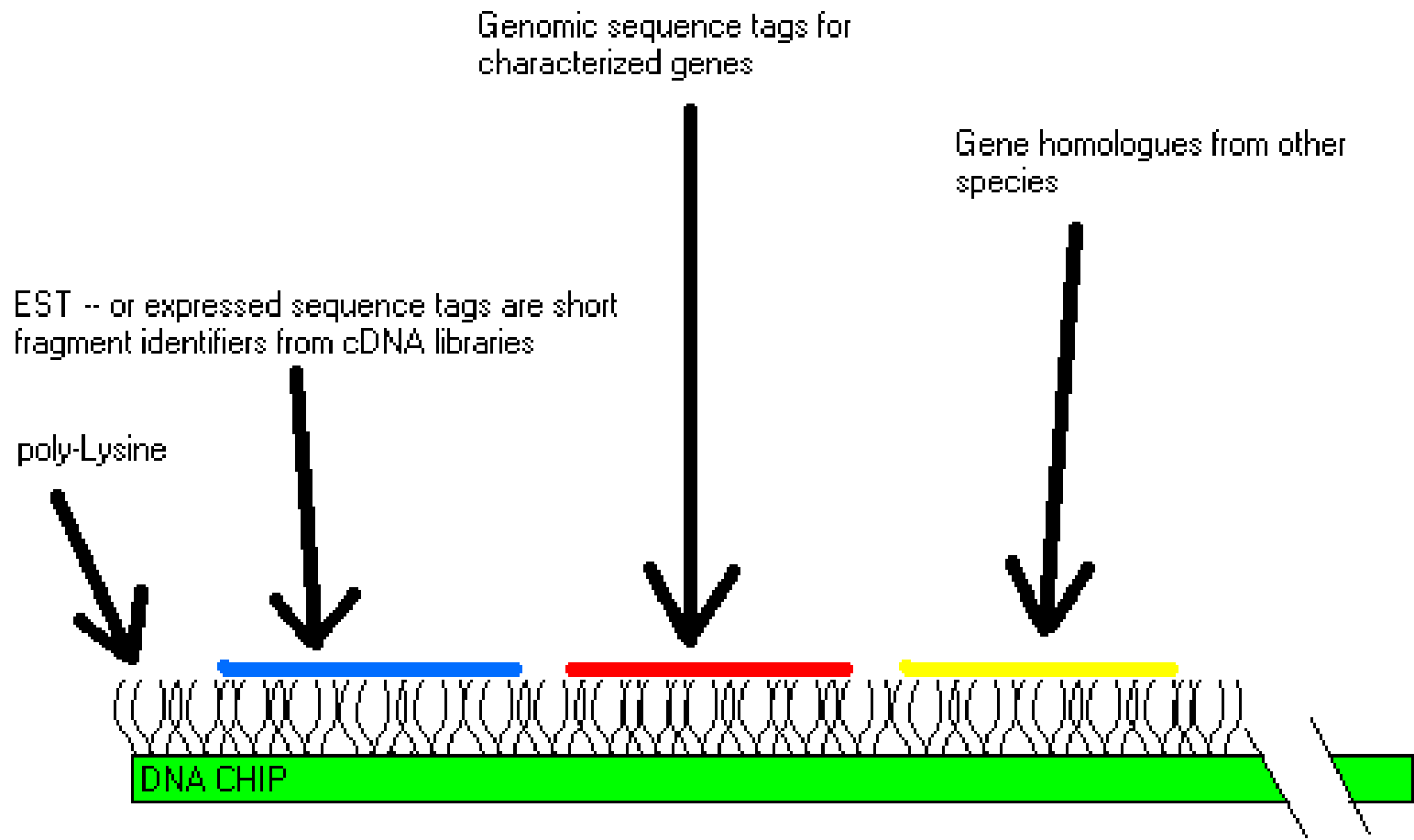
Cancerous Polyp or Adenoma

3.) Adenoma

----(subsequent mutations)----> **Malignant Cancer**

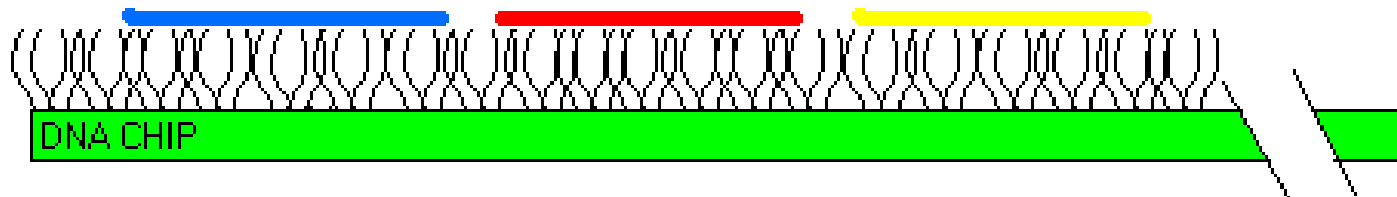
What do microarrays do?

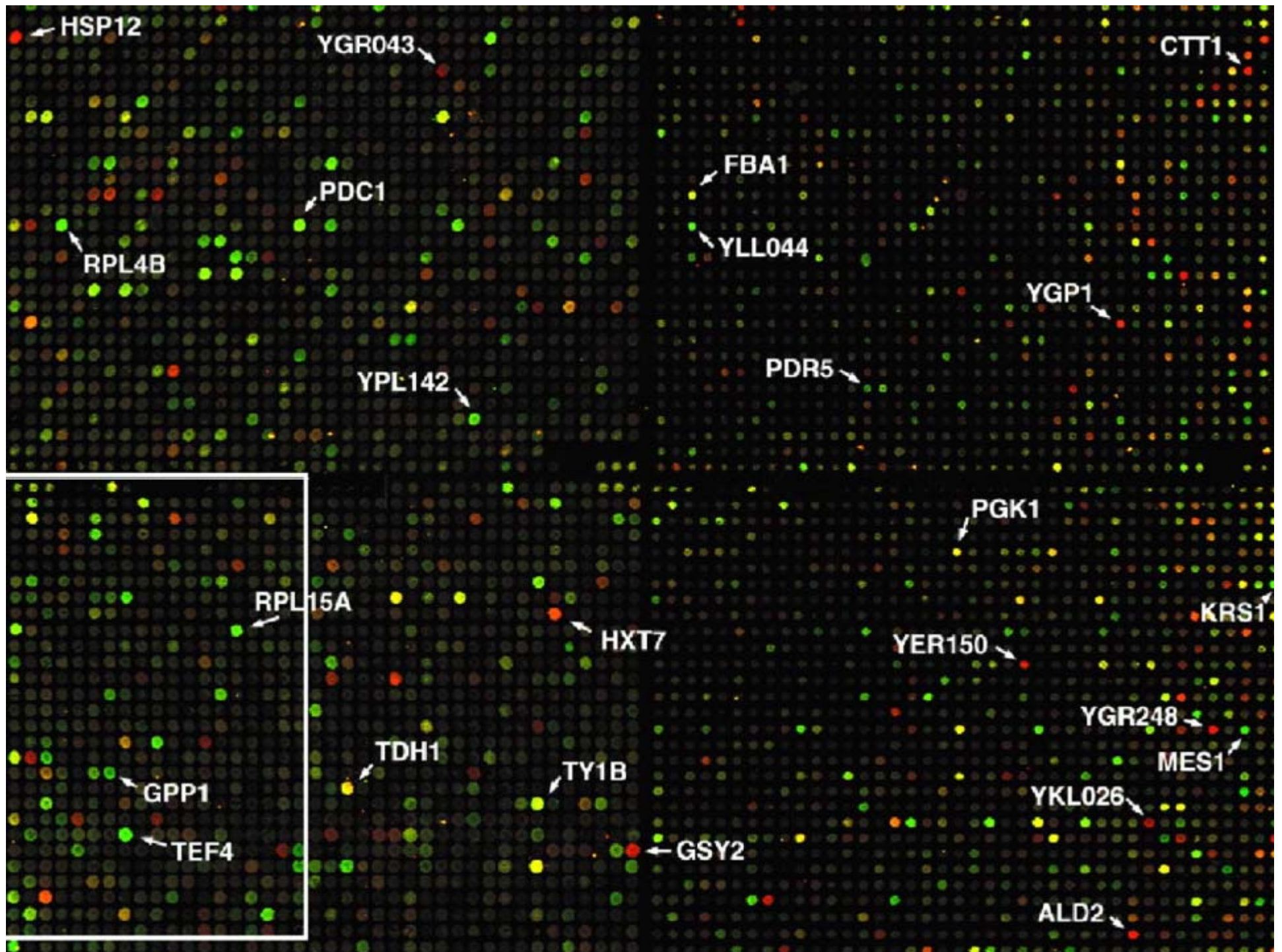
- They allow for measurements of mRNA levels in a sample on a massive scale.
- They allow for multiple sample measurements simultaneously.



mRNA sample from a cell line or
a solid tumor sample

Hybridization





Why should we care about microarrays?

- Microarrays allow the measurement of mRNA levels on a massive scale (9,703 per chip)
- Opens the possibility for transcriptional fingerprinting

Transcriptional fingerprinting

- The collection of transcriptional activated genes and the levels of mRNA are a more accurate definition of the state of the cell than the simple genetics or the histology

Two papers

- **“Systematic variation in gene expression patterns in human cancer cell lines.” Ross DT, et al. *Nat Genet* 2000 Mar;24(3): 227-235.**
- **“An information-intensive approach to the molecular pharmacology of cancer.” Weinstein JN, et al. *Science* 1997 Jan 17;275(5298): 343-9.**

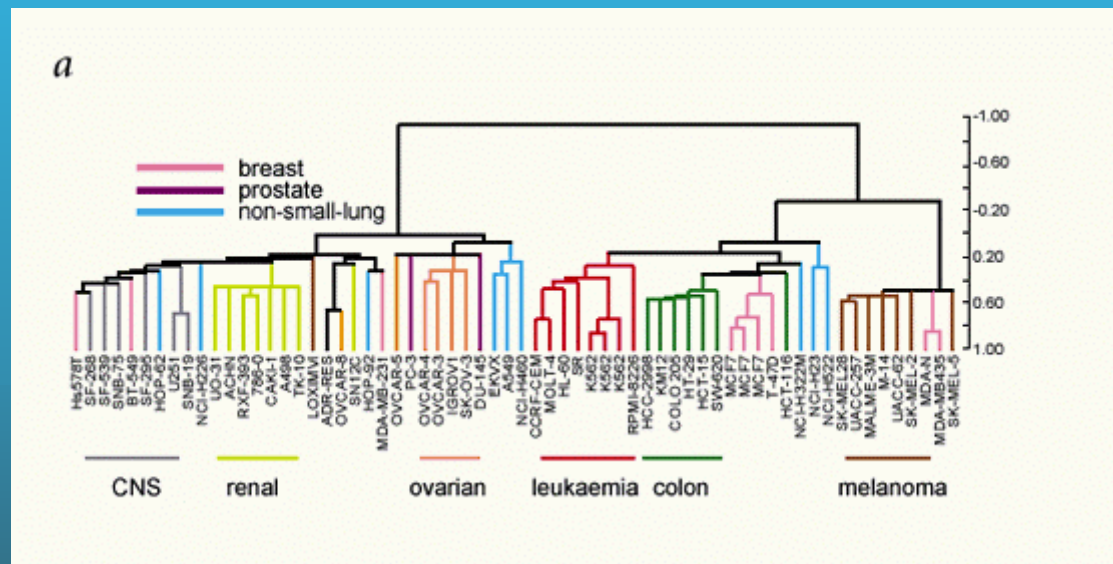
NCI60 cell lines

- 60 cell lines used in the National Cancer Institute's screen for anti-cancer drugs
- standard cell lines from different pathological origins

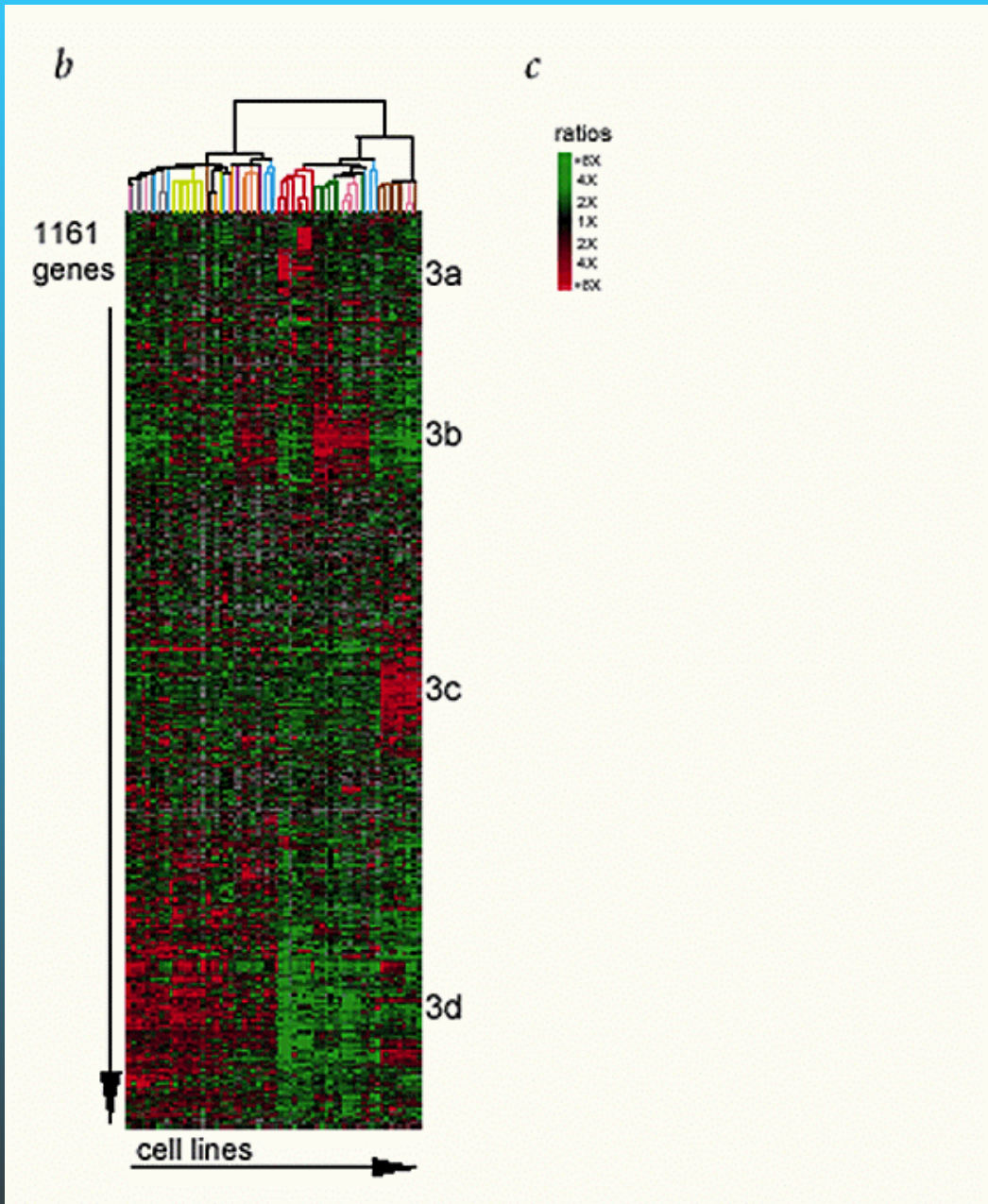
First Paper -- Diagnostics

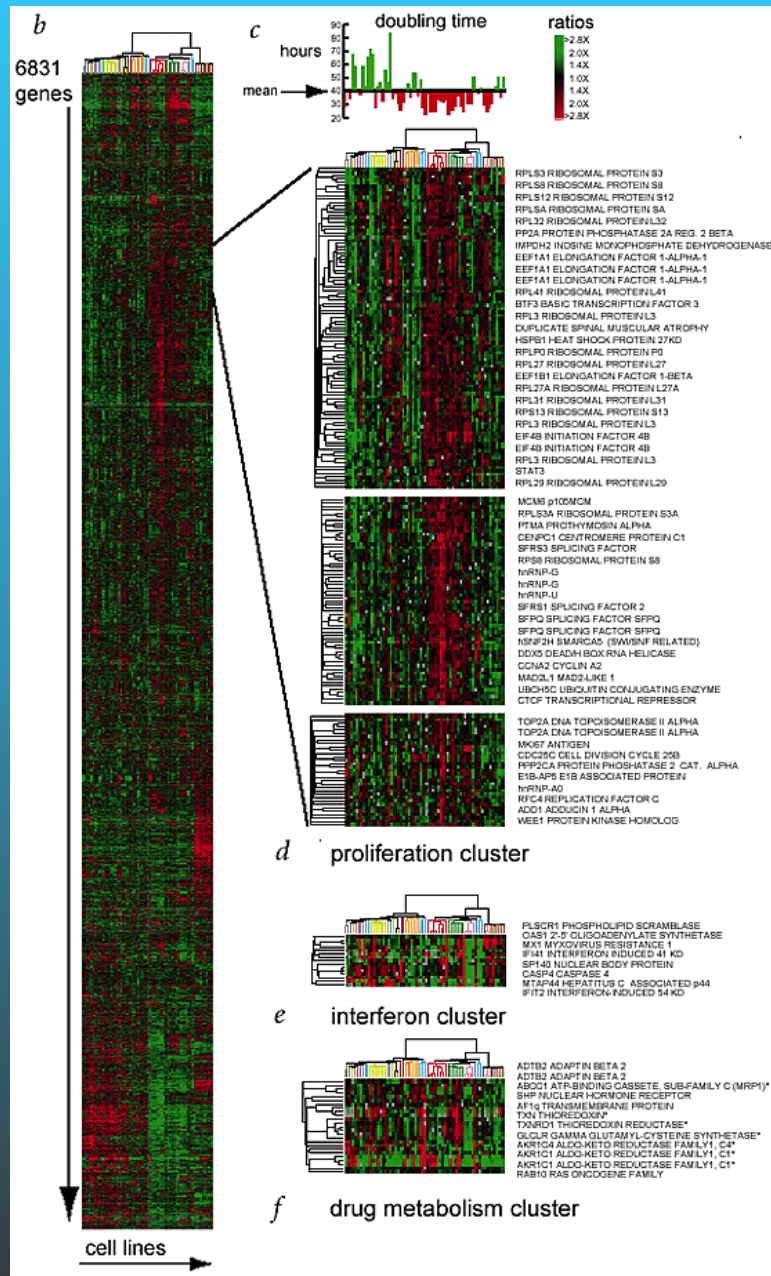
- Ross et al. took the NCI60 cell lines and surveyed their expression for over 8000 ESTs, genes, and gene homologues
- Cluster analyzed these expression patterns for similarities between histological classifications and expression groupings

Grouping from cluster analysis of genes which varied highly



This cluster diagram was created a cluster analysis of only those genes which had greater than a sevenfold difference from the standard.

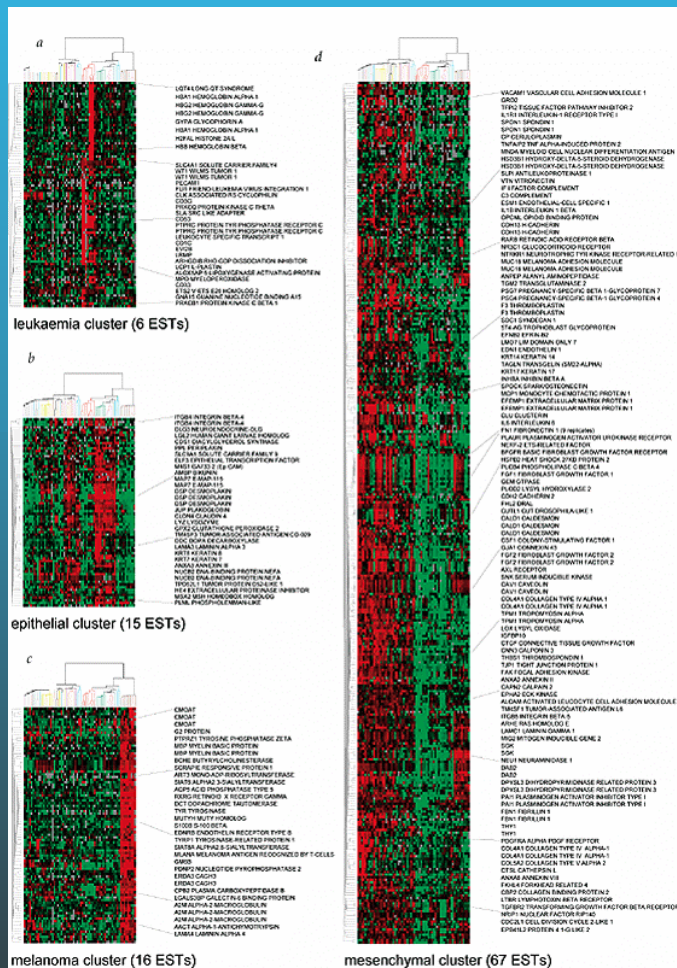




What we can learn from these diagrams?

- Expression patterns can be correlated with histological origin...
- ...but we can learn a great deal more from expression patterns.

ESTs common for given tumor types

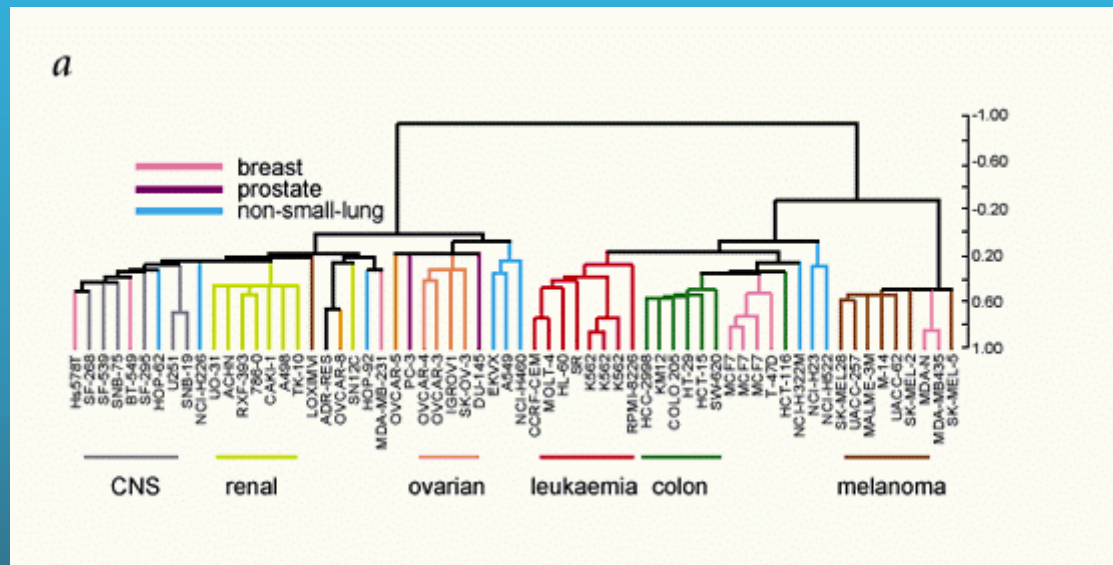


We can learn how to selectively target one type on tumor as from what pathways it has the greatest changes in.

Anomalies are the most telling...

- Two related cell lines (MDA-MB435 and MDA-N) were derived from a single patient with breast cancer
- Before considered as breast cancer, these cell lines shared expression of the genes associated with melanoma.

Higher organization of cancer categories



This kind of analysis gives us the ability to group cancers into broader categories of similarity than was previously offered by histology.

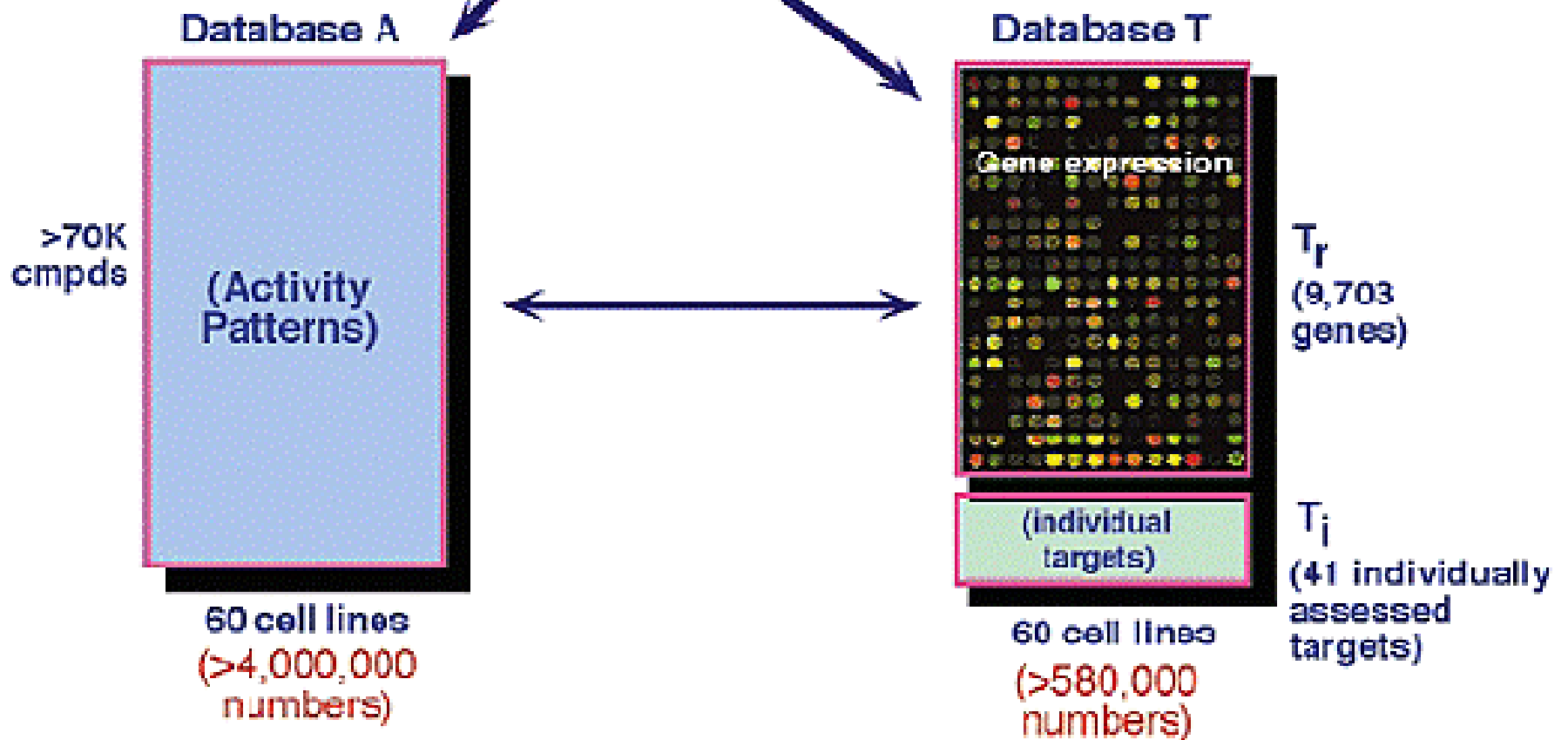
Why is all of this is good?

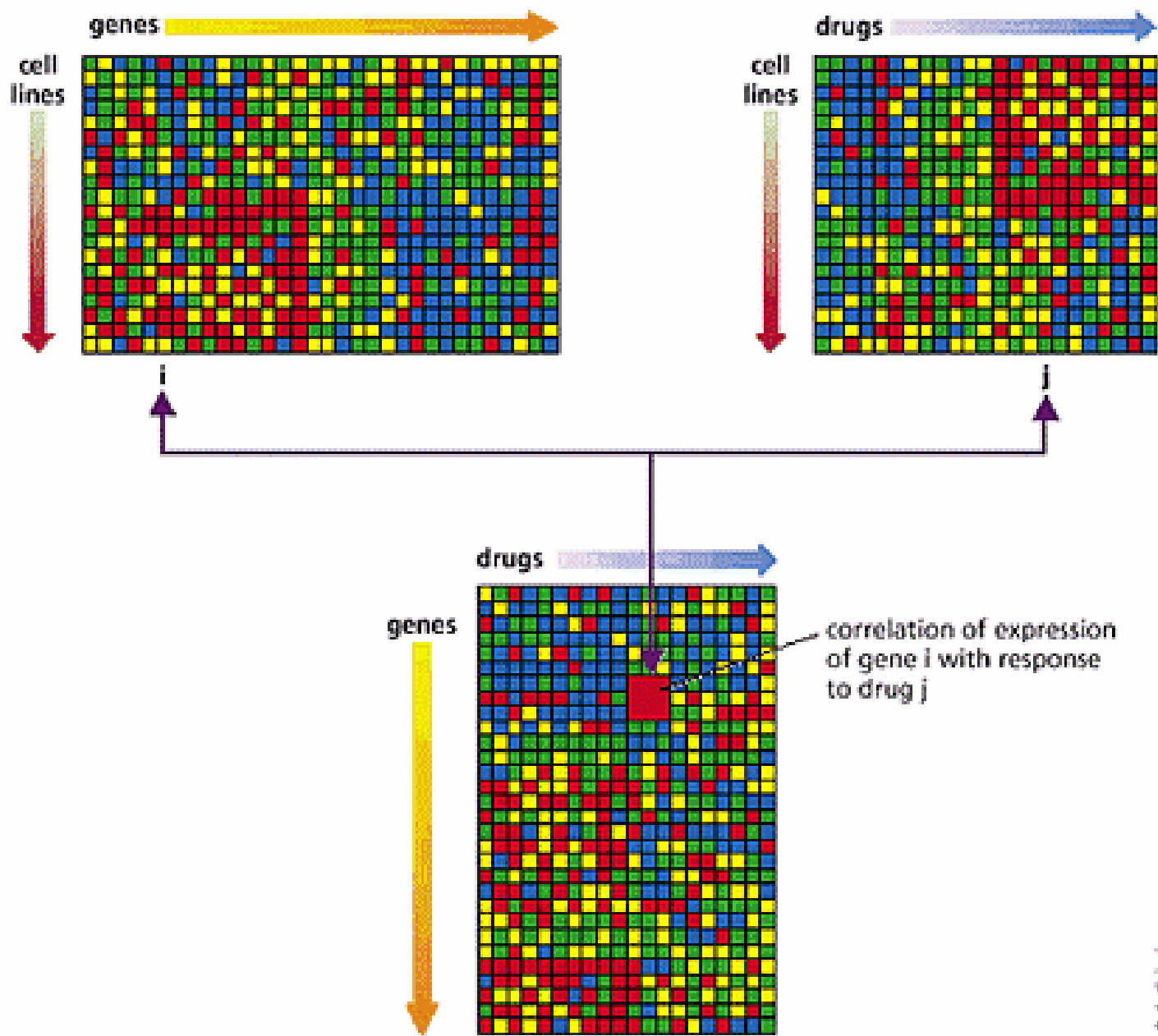
- Independent diagnosis and prognosis
 - ex. Undeterminable pathology in tumors, or heterogeneous tumors
- Rational treatment
 - don't waste your time if the drug you are using isn't going to work
- Complex modeling of cancer dynamics
- Accurate categories of tumor pathology

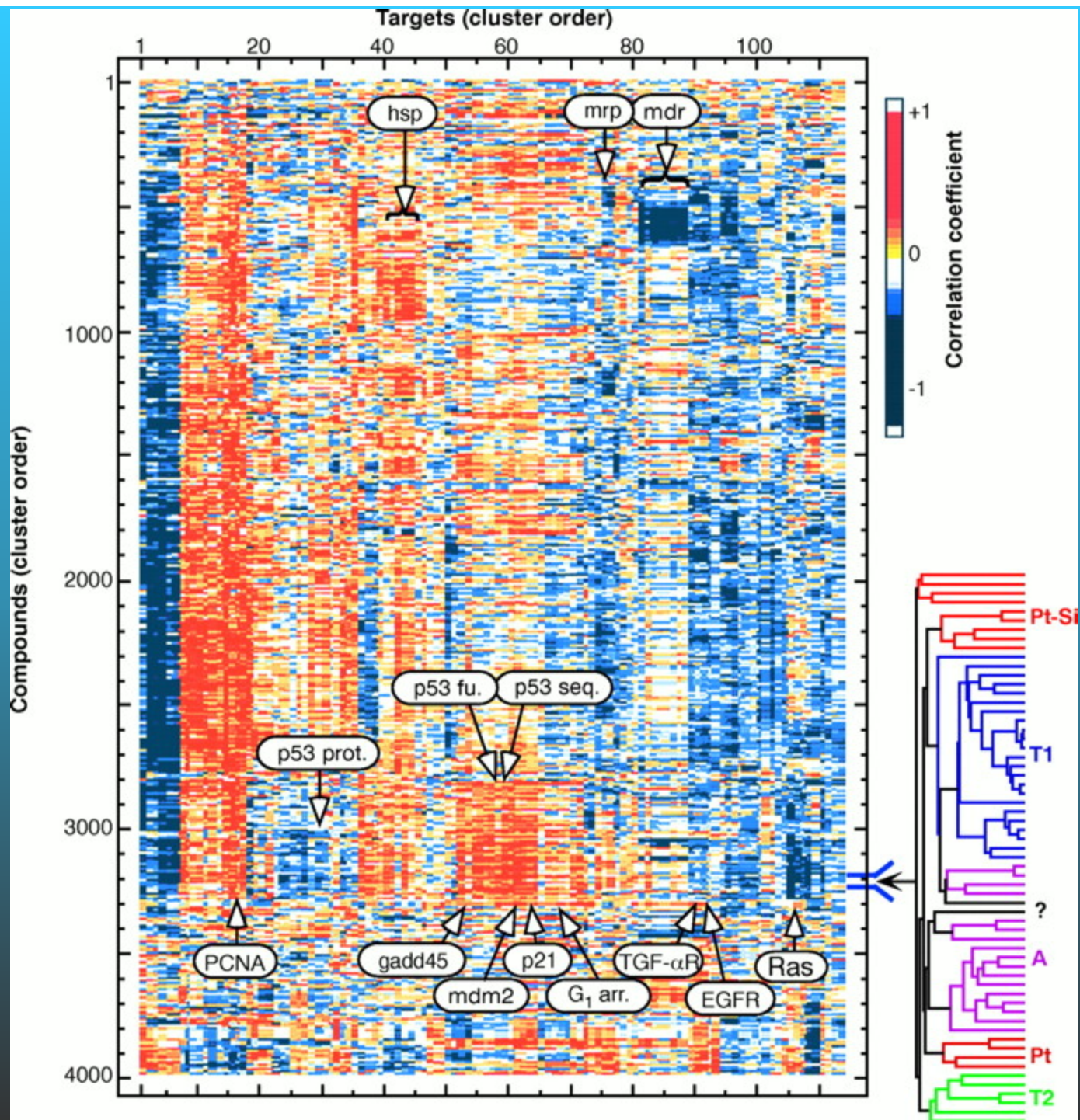
Second Paper -- Pharmacology

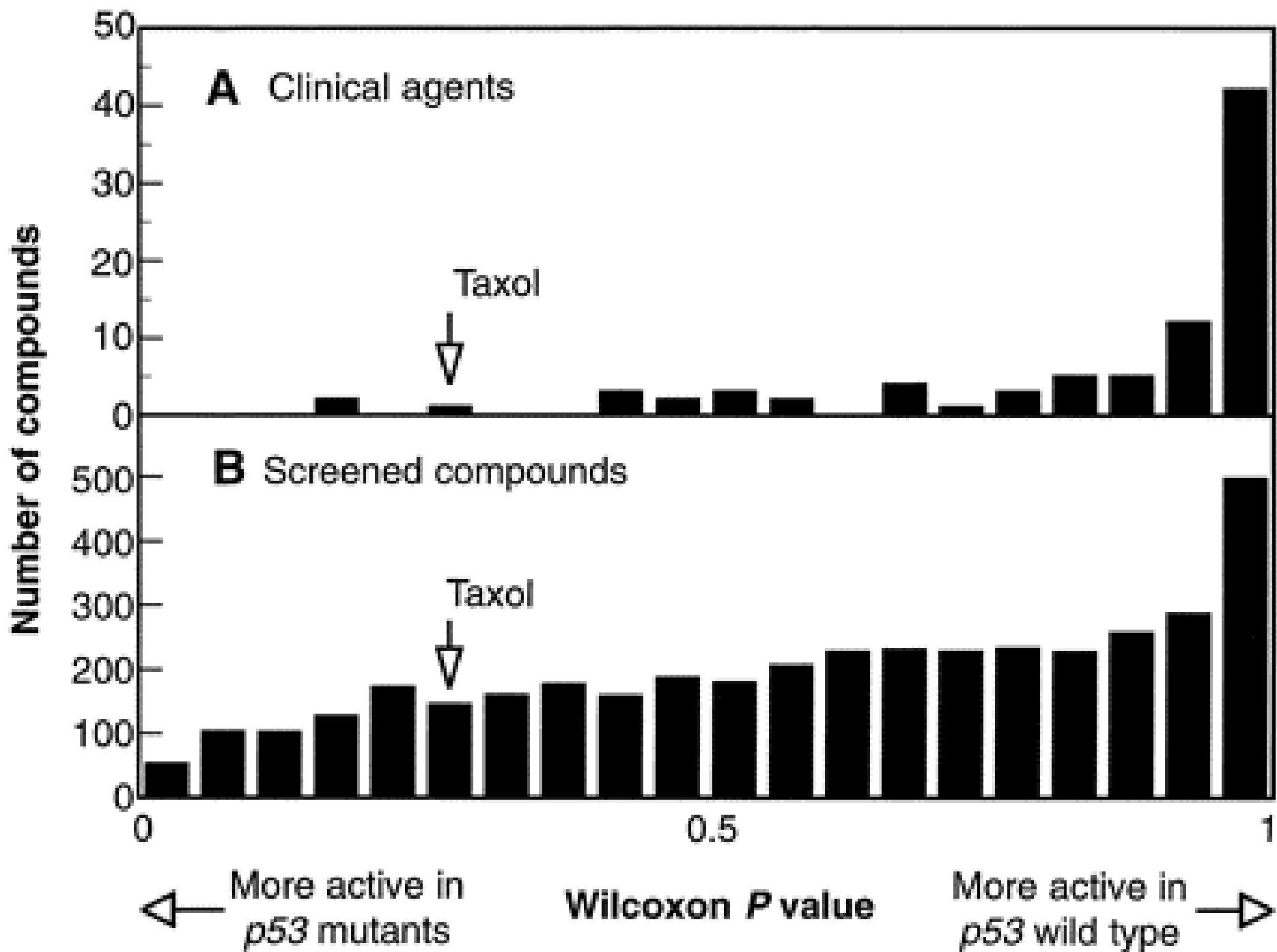
- Weinstein JN, et al took all NCI60 cell lines and treated them with each on 60,000 compounds
- They performed cluster analysis linking each cell line for each drug for each gene
- Effectively --> $60,000 \times 60 = 3.6$ million pharmacology experiments

The NCI Cancer Drug Discovery - Development Pipeline









What do we learn from drug testing?

- Identify novel agents and mechanisms for drug action
- Highlights biochemical pathways

Why is all of this good?

- Per patient treatment
 - ex. Following prognosis a drug could be prescribed that targets the molecular state of their tumors cells specifically
- Rational treatment
- Complex modeling of drug action
- Accurate categories of drugs

Why do we care about any of this
at all?

Or

Looking to the Future...

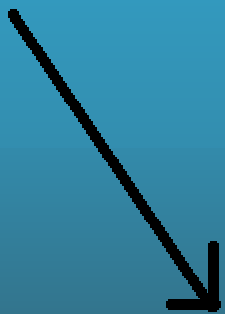
Future model for cancer treatment



A patient arrives with any kind of cancer...



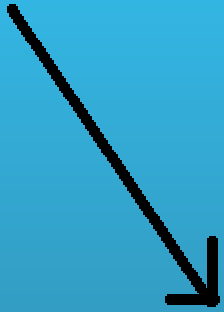
A patient arrives with any kind of cancer...



A biopsy of that tumor will be taken and will undergo Microarray analysis for expression patterns



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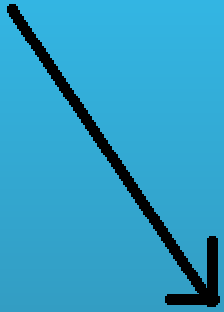


A drug cocktail will be formulated not only for their tumor type but for the individual expression patterns of their tumor.

Rational Treatment!!!



A patient arrives with any kind of cancer...



A biopsy of that tumor will be taken and will undergo Microarray analysis for expression patterns



A drug cocktail will be formulated not only for their tumor type but for the individual expression patterns of their tumor.

