

Chemogenomics and Pharmacogenomics

Team: Peer Pressure

Corban

Shivaram

What's the difference?

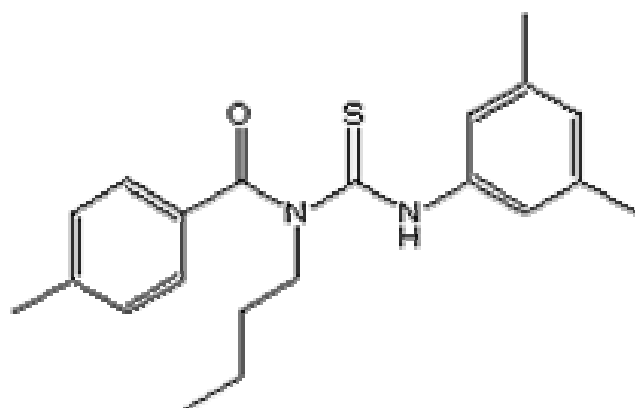
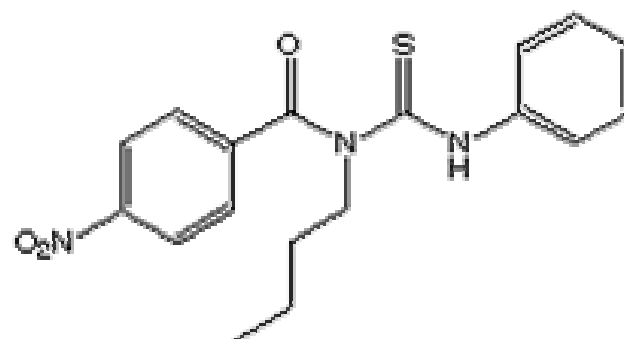
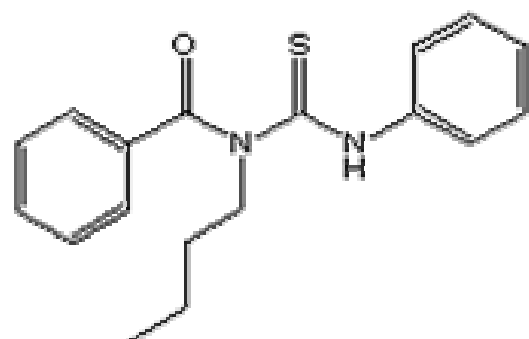
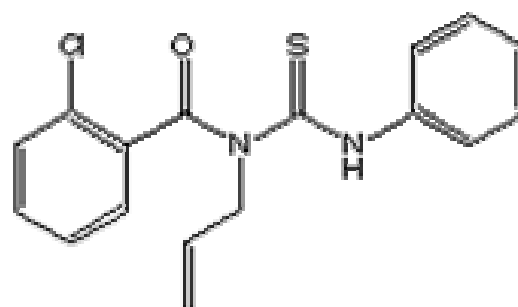
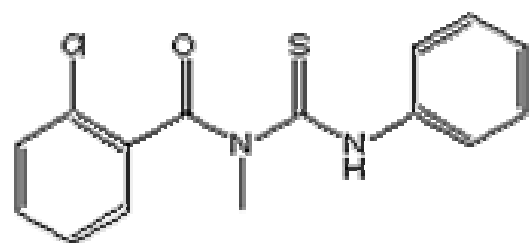
- Chemogenomics – screening a compound library to detect drug candidates
- Pharmacogenomics – investigates inherited basis for difference in drug response among individuals

Approaches to Chemogenomics

- Forward Chemogenomics
 - Example taken from Stegmaier et al.
- Reverse Chemogenomics
 - Gene Targeting
- Predictive Chemogenomics
 - Example taken from Weinstein et al.

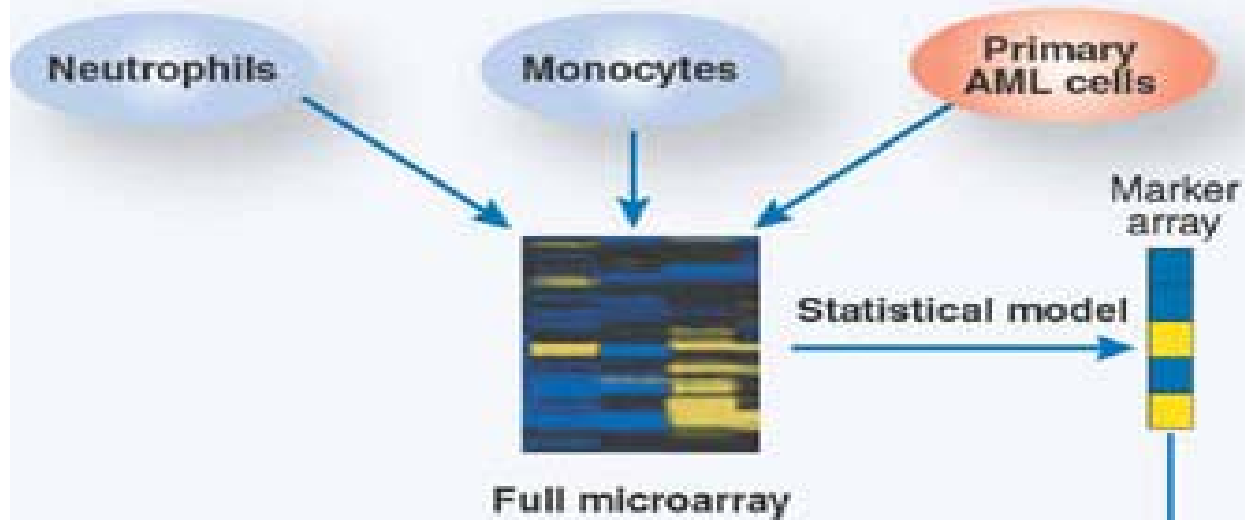
Combinatorial Chemistry

- Generates a compound library
- Generating the combination of small molecules possible by modifying a given molecular scaffold using solid state organic chemistry



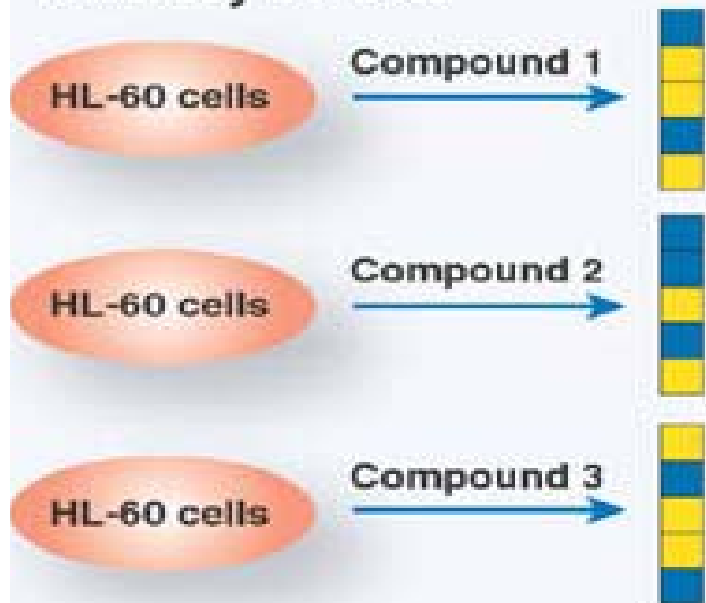
a

Definition of surrogate marker gene expression pattern



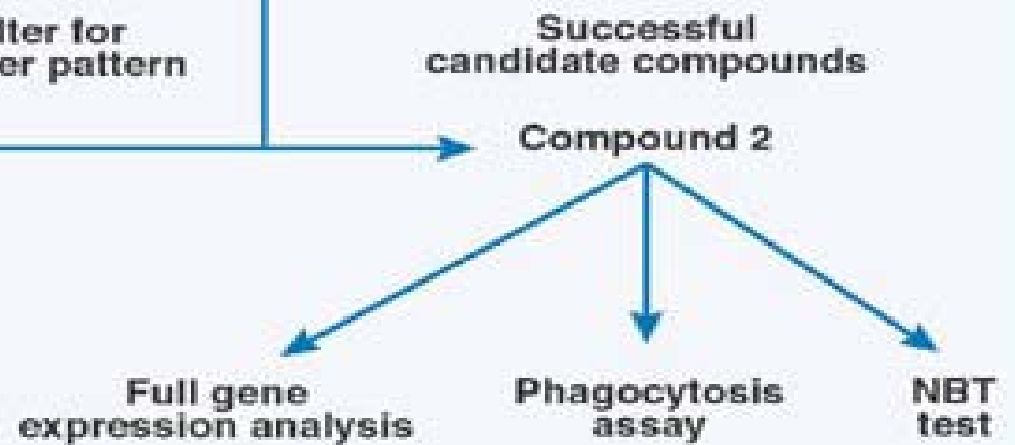
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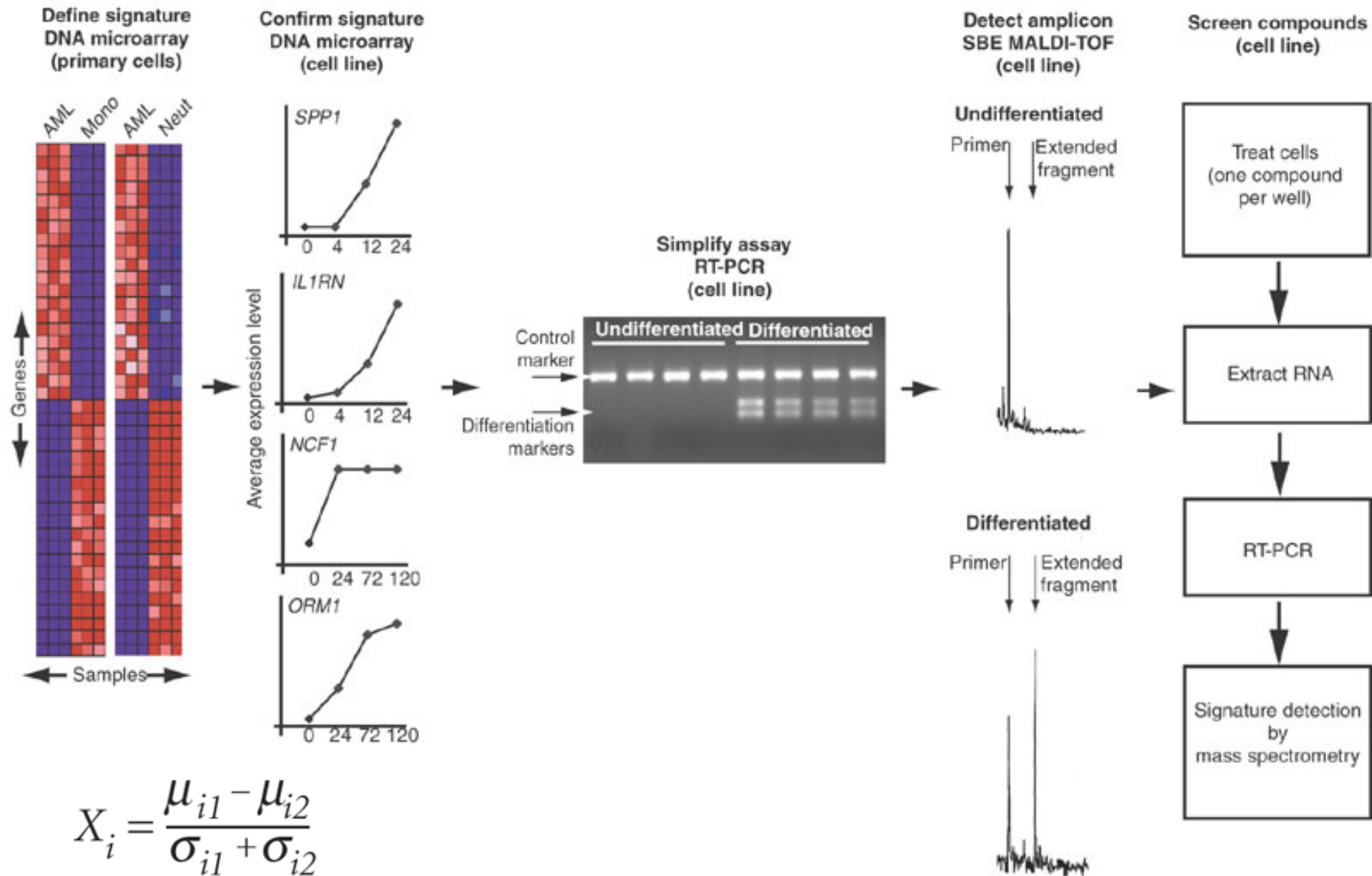
Primary screen



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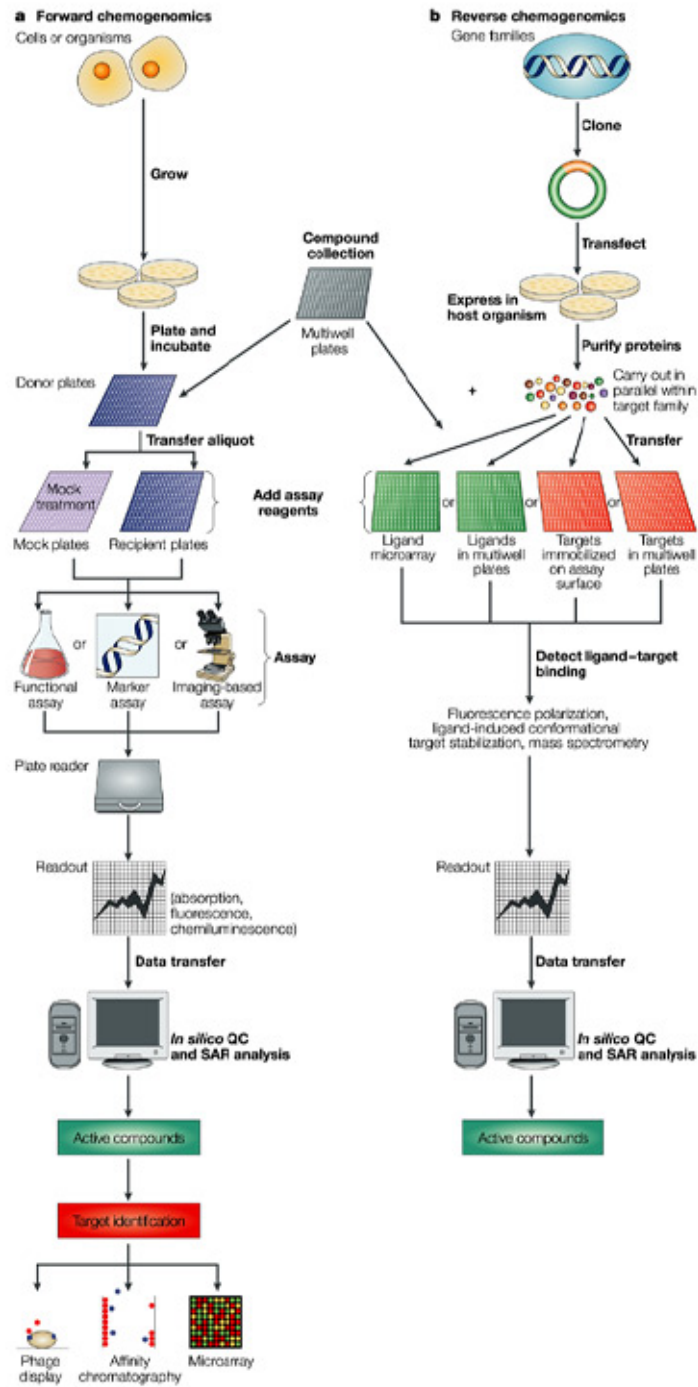
Secondary screen

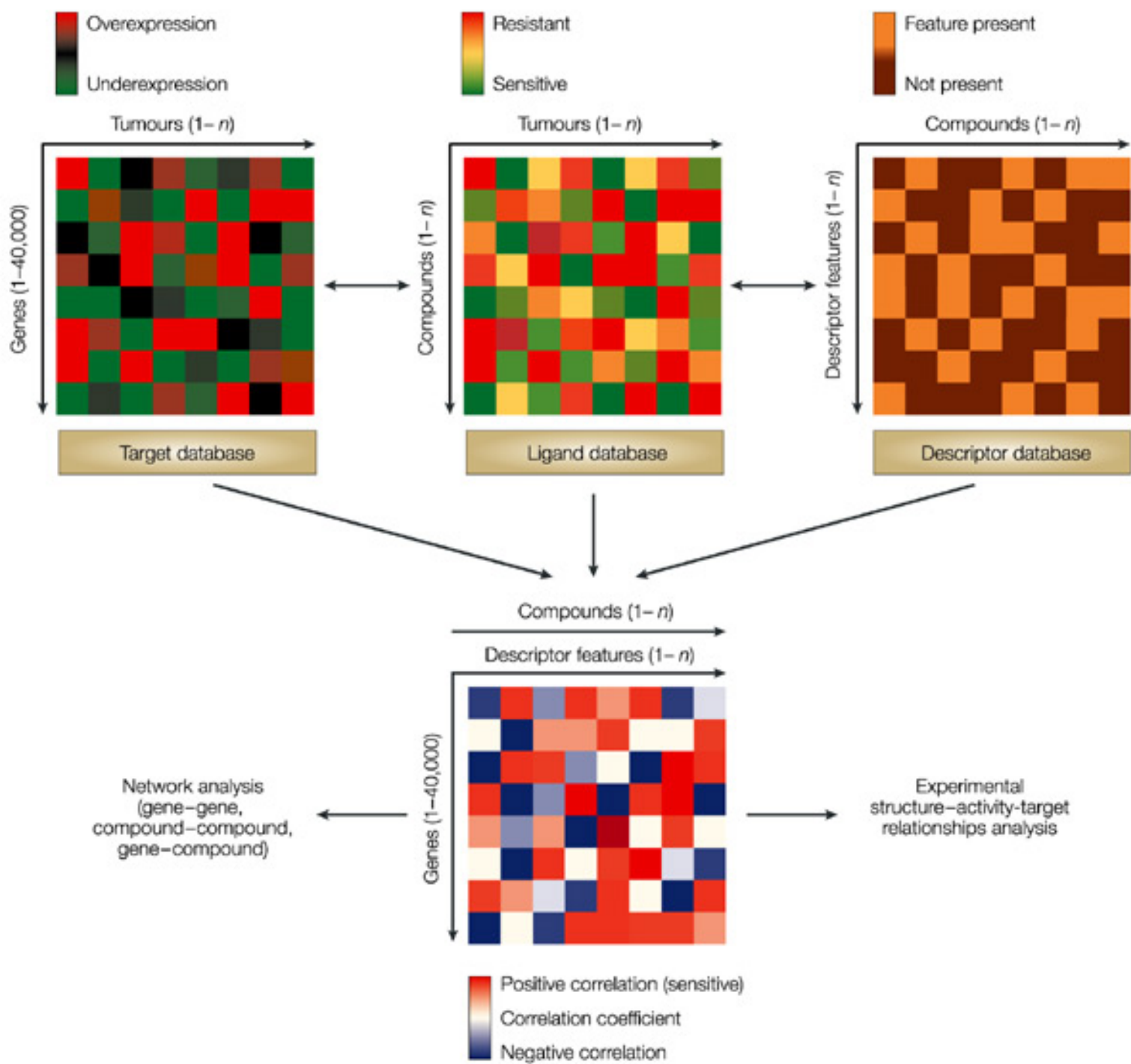


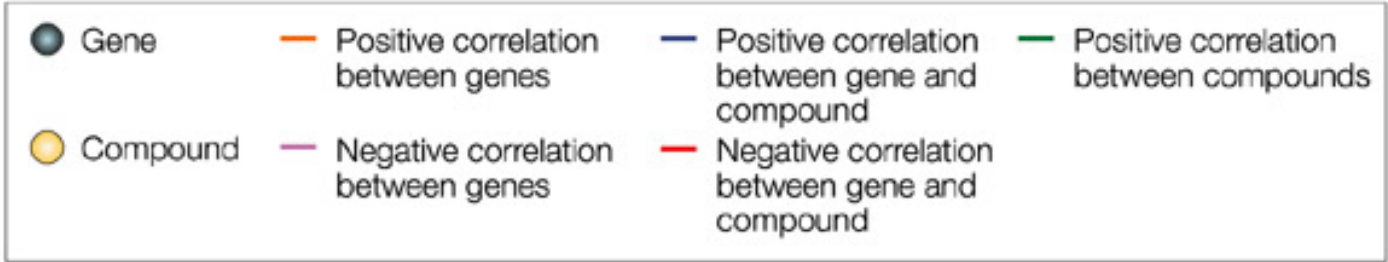
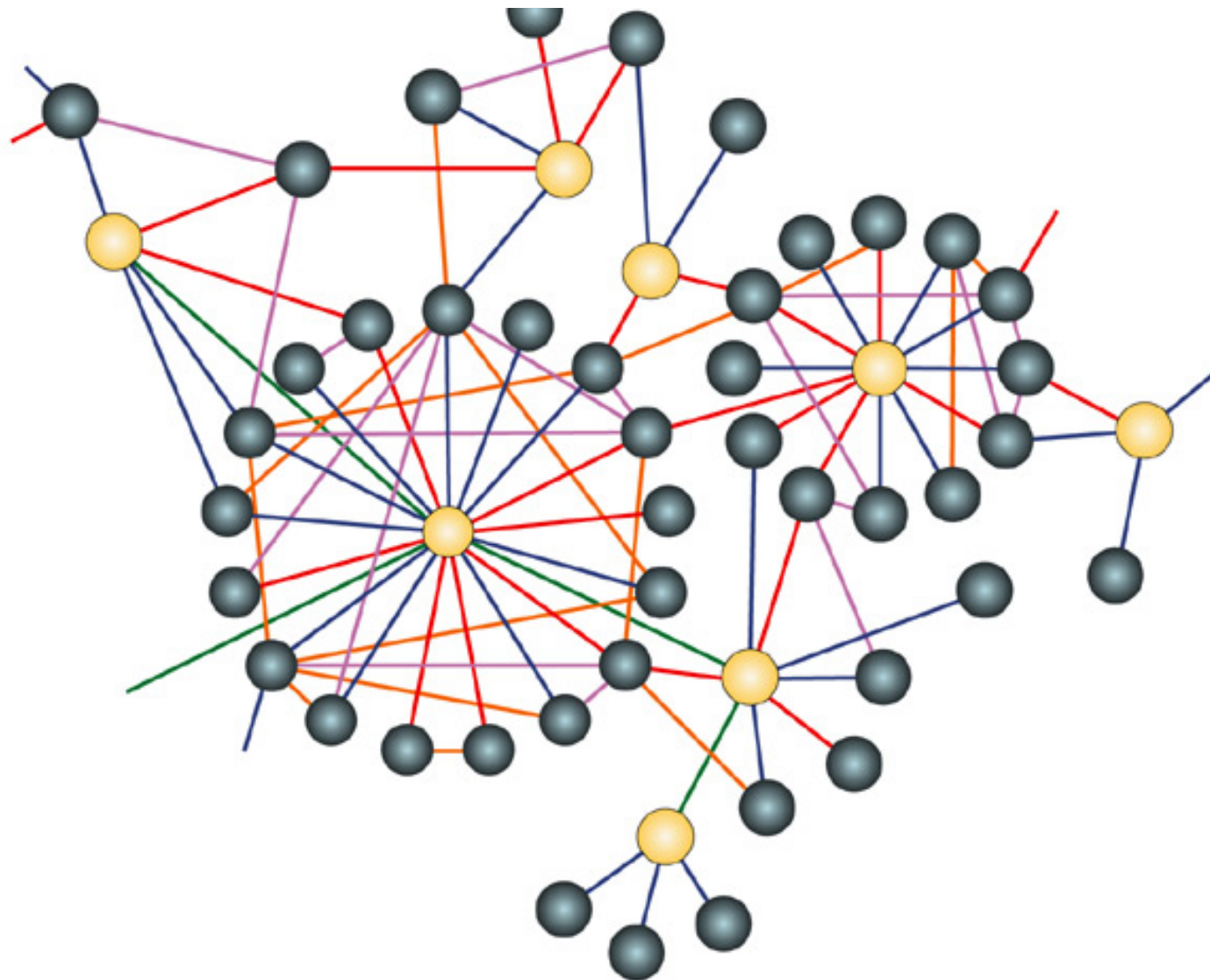


Pearson Correlation and the Mantel Test

$$R_m = \frac{\sum_{i=1}^N X_i Y_i - \frac{\sum_{i=1}^N X_i \sum_{i=1}^N Y_i}{N}}{\sqrt{\left(\sum_{i=1}^N X_i^2 - \frac{\left(\sum_{i=1}^N X_i \right)^2}{N} \right) \left(\sum_{i=1}^N Y_i^2 - \frac{\left(\sum_{i=1}^N Y_i \right)^2}{N} \right)}}$$







Pharmacogenomics

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- Different people react differently to the **same** medication.
- Factors include *genetic* and *non genetic*.
- Inherited determinants remain stable throughout the lifetime of individual.

- Pharmacogenomics: use **genome-wide means** to find out why different people react diversely in response to a drug.
- Many SNP's have been associated with the changes in the effect of the drug.

Change is mainly due to gene products influencing:

- Drug Disposition (eg: metabolizing enzymes & transporters)
- Drug targets (eg: receptors)
- Gene products may *indirectly* influence the drug action.

Treatment-specific changes in gene expression discriminate *in vivo* response in human leukemia cells

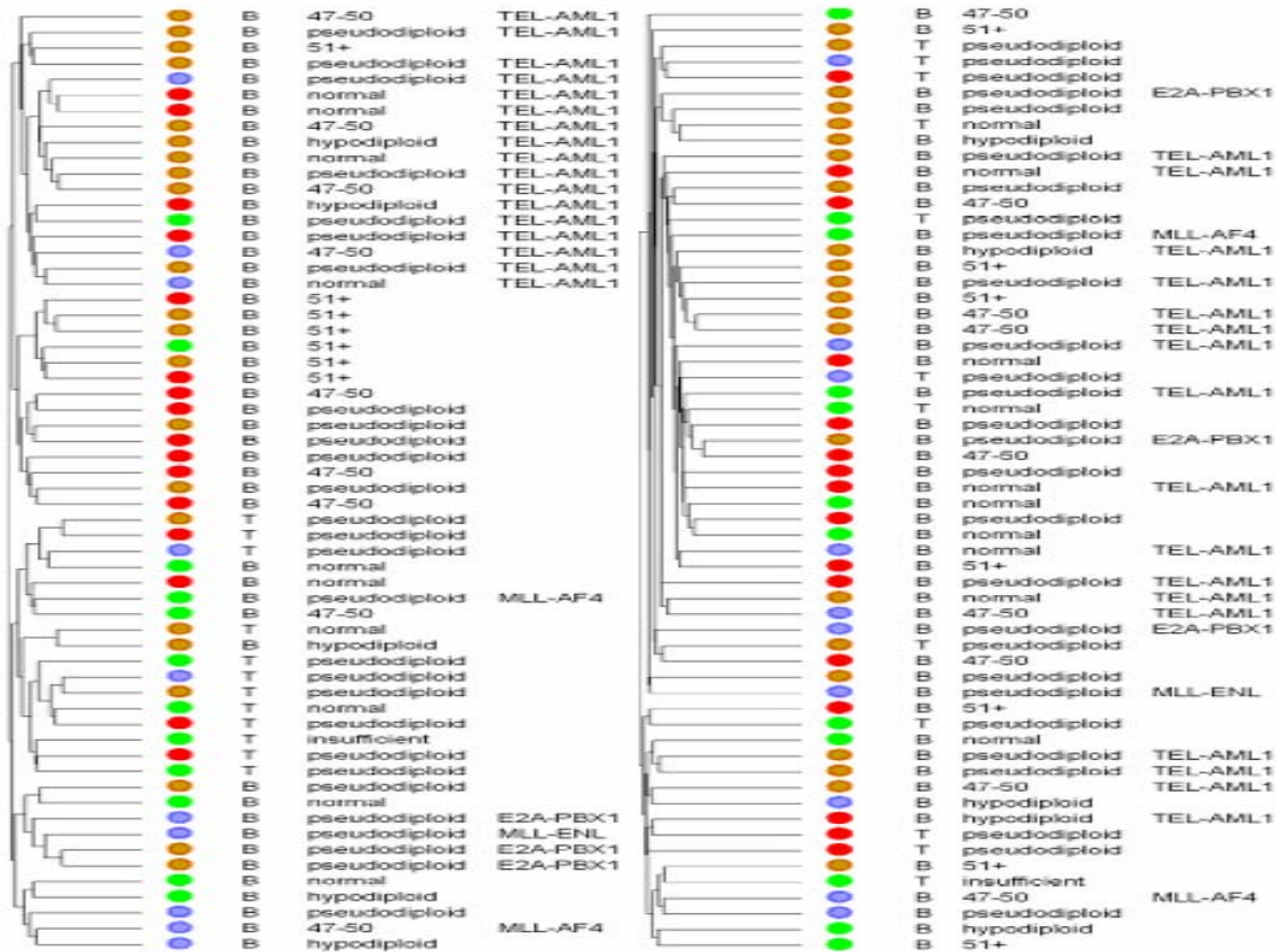
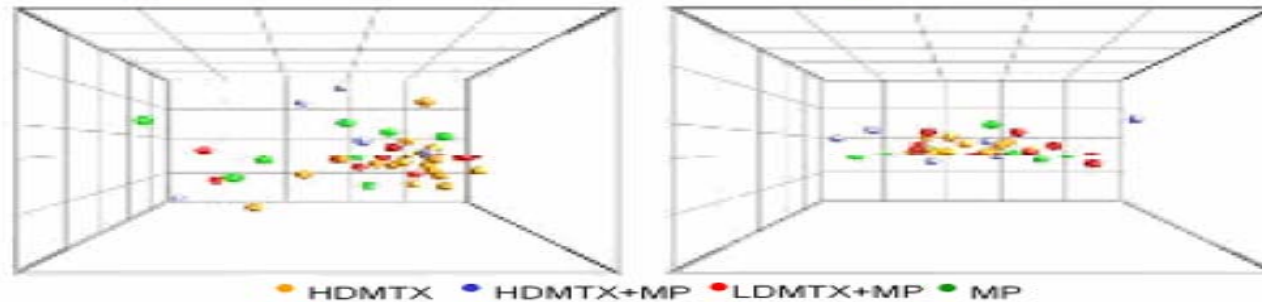
Cheok et al.

- Analysis of 9600 genes in acute lymphoblastic leukemia cells before and after in vivo treatment.
- The two drugs were given alone, as well as in combination.

The two drugs were:

- Methotrexate
 - Mercaptopurine
-
- Both affect the purine metabolism in the cell and leads to the cell death.

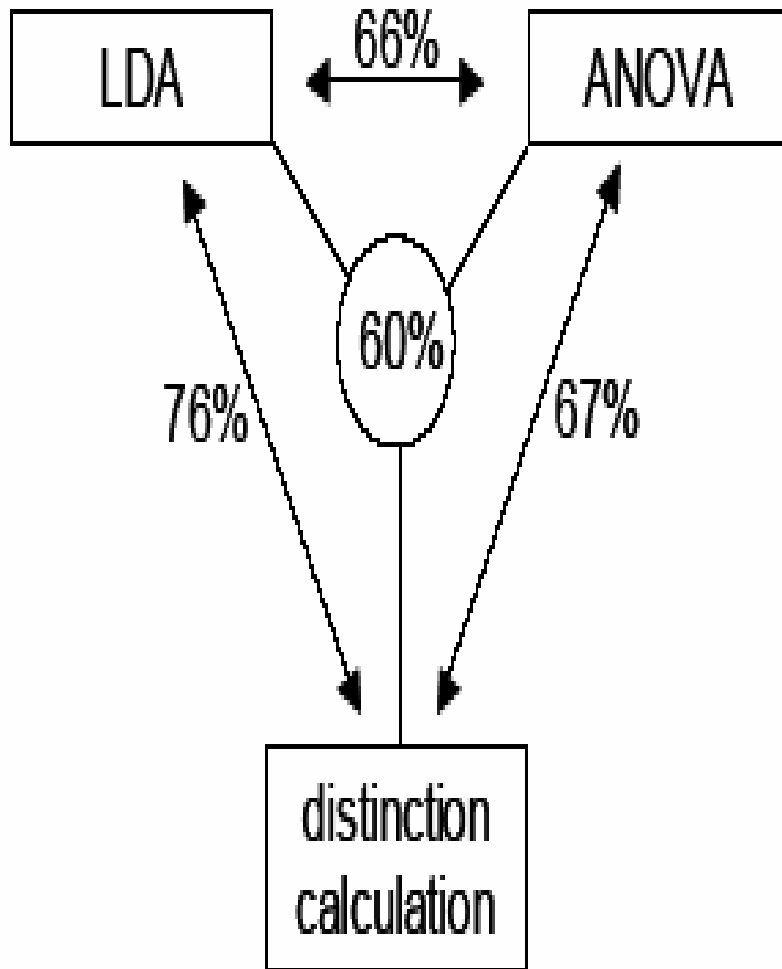
- 60 children were included in the study (training set).
- 17 additional individuals were also included in the study (test set).
- Each of the children randomly received one of the four treatments:
 1. High-dose methotrexate alone
 2. Mercaptopurine with low dose of methotrexate
 3. Mercaptopurine with high dose of methotrexate
 4. Mercaptopurine alone

a**b**

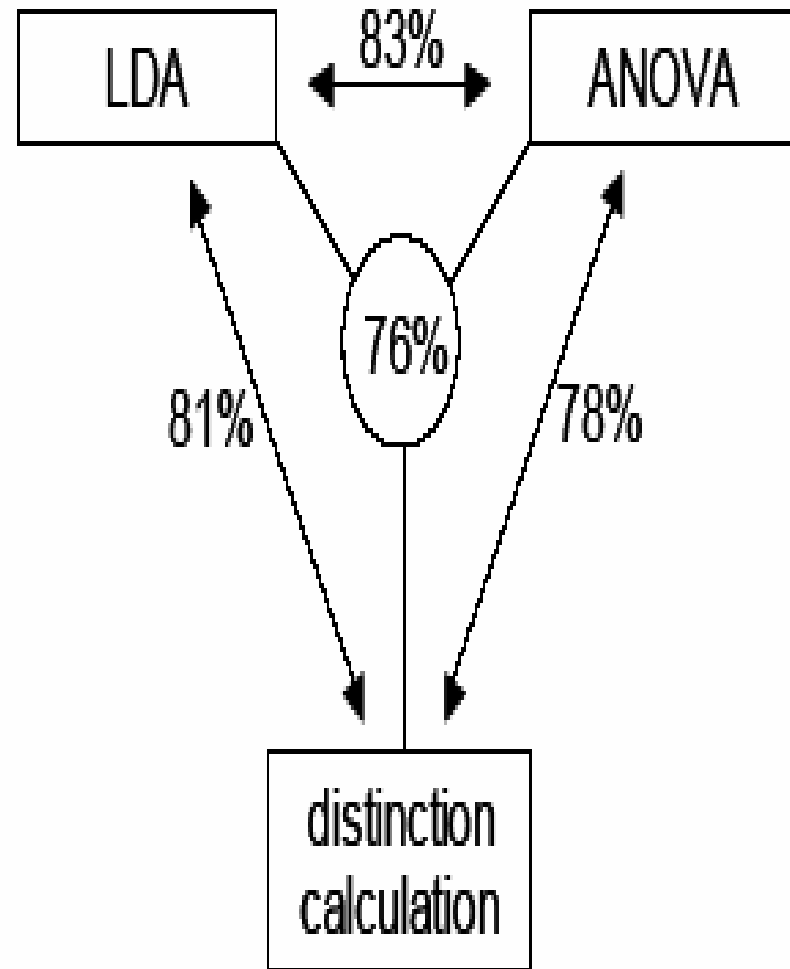
Linear Discriminant Analysis

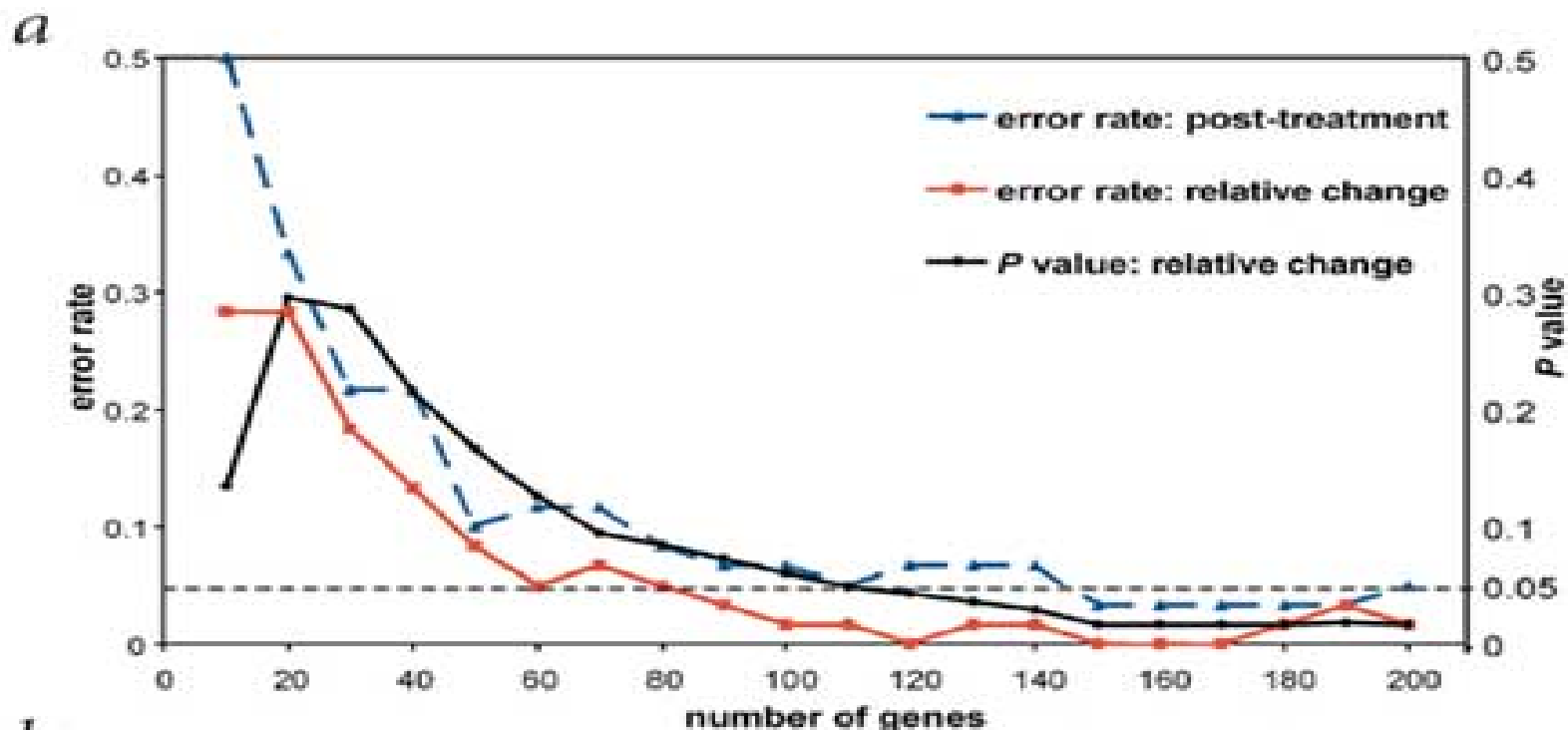
- Classify the item x at hand to one of Y groups based on measurements on p attributes.
- Linear combination of attributes of x : $y = w_1a_1 + w_2a_2 + \dots + w_p a_p$
- y we can classify into one of the Y groups.

a



b



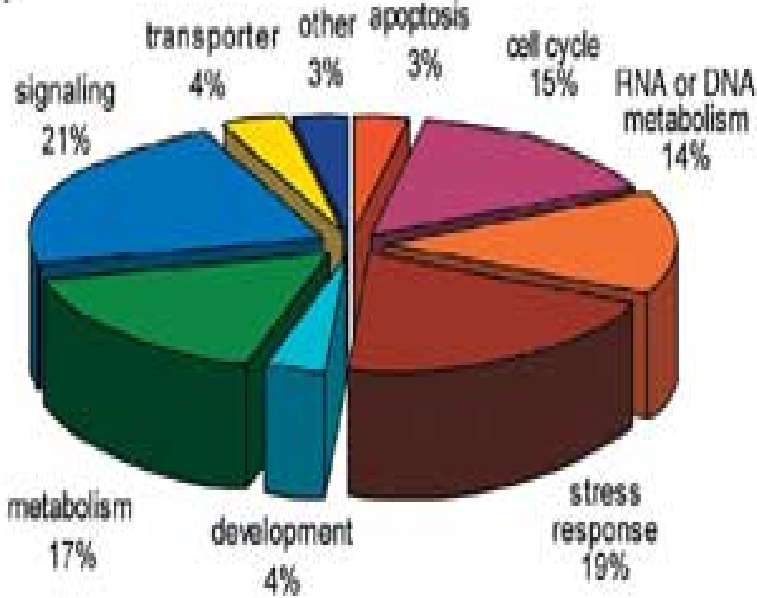


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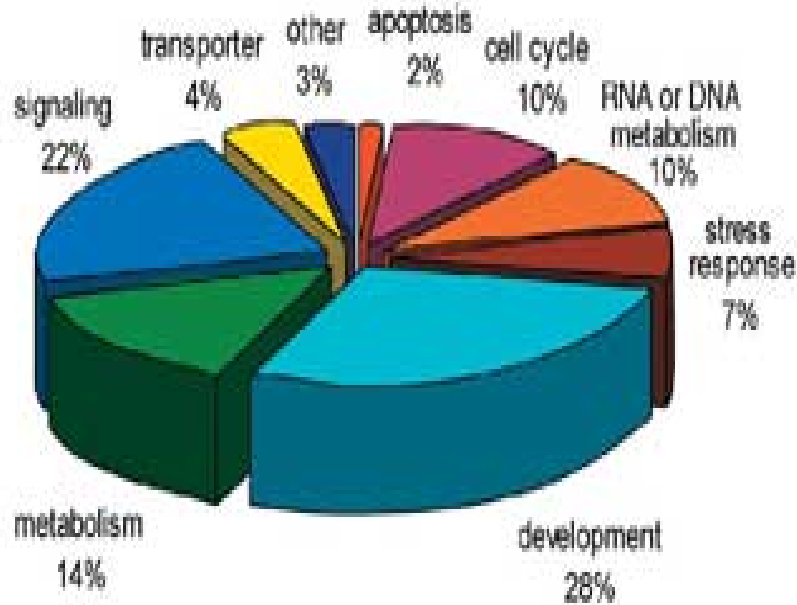
	observed \ predicted	MP	HDMTX	HDMTX+MP	LDMTX+MP
relative change	MP	12	0	0	0
	HDMTX	0	22	0	0
	HDMTX+MP	0	0	10	0
	LDMTX+MP	0	0	0	16
post-treatment	MP	11	0	0	1
	HDMTX	0	22	0	0
	HDMTX+MP	0	1	9	0
	LDMTX+MP	0	0	0	16

GO classifications of genes discriminating among treatments

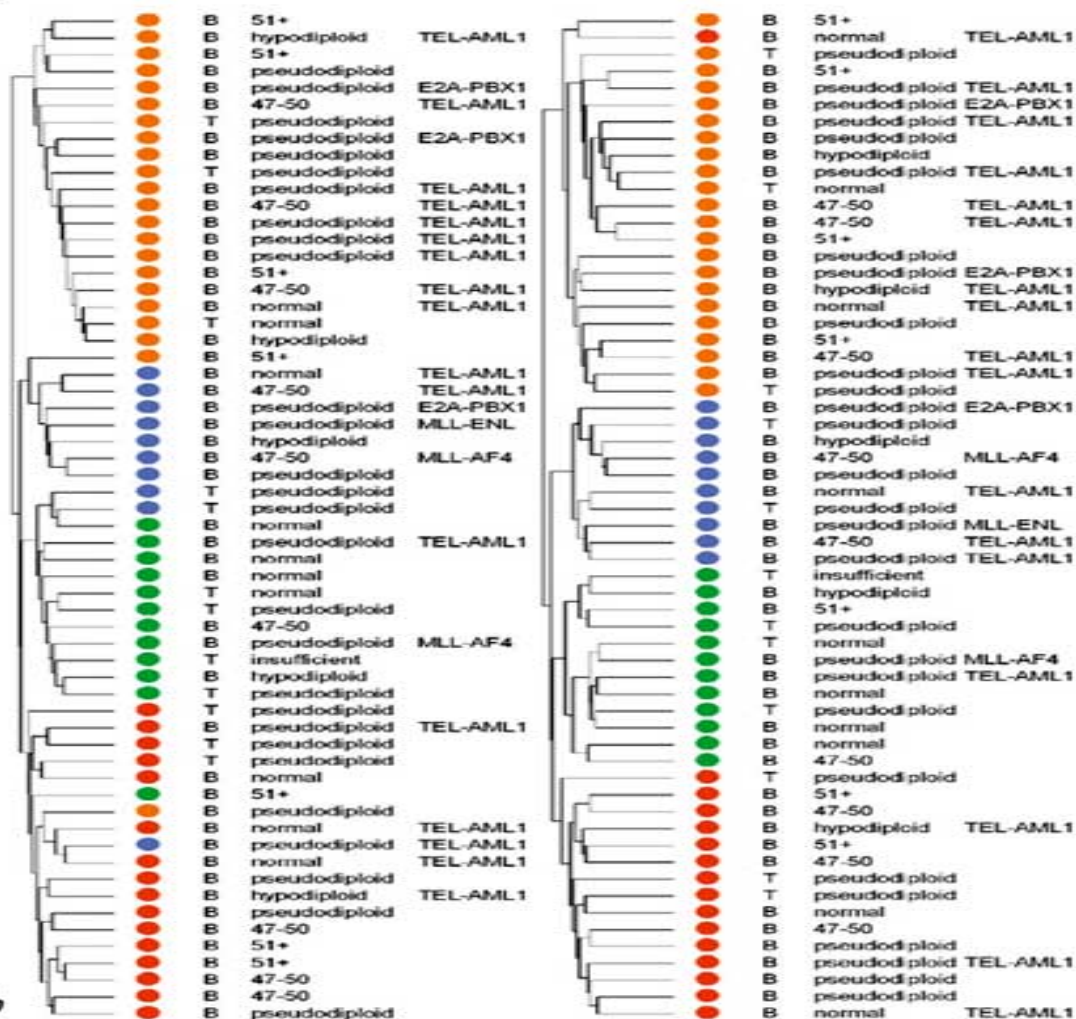
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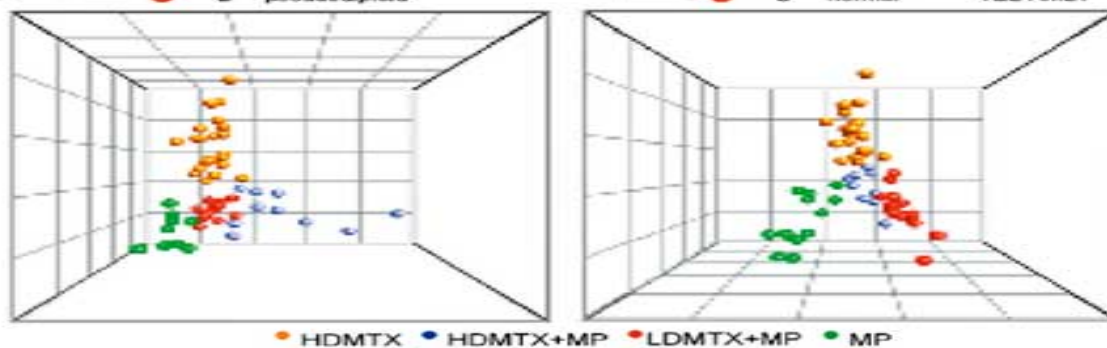
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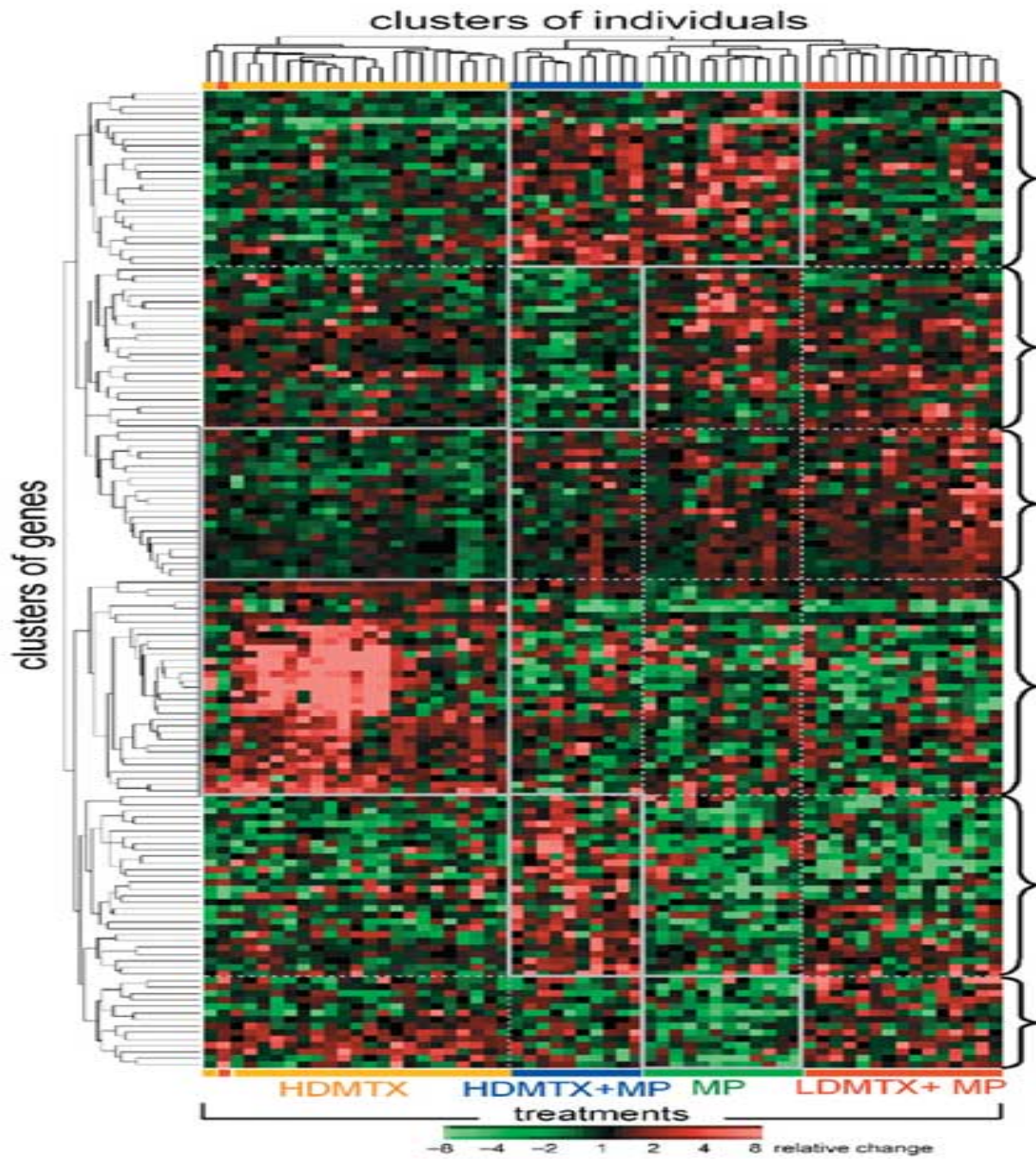


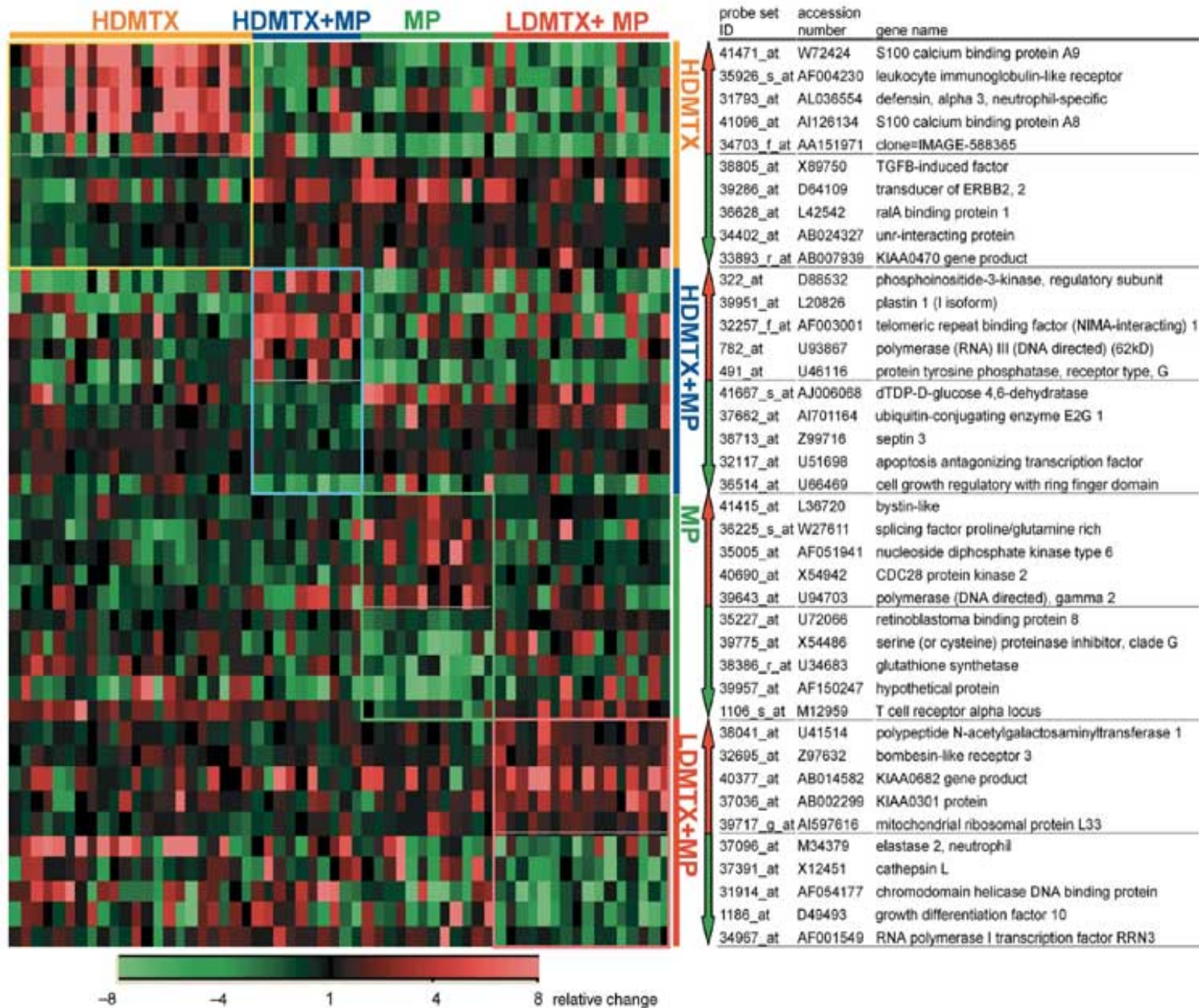
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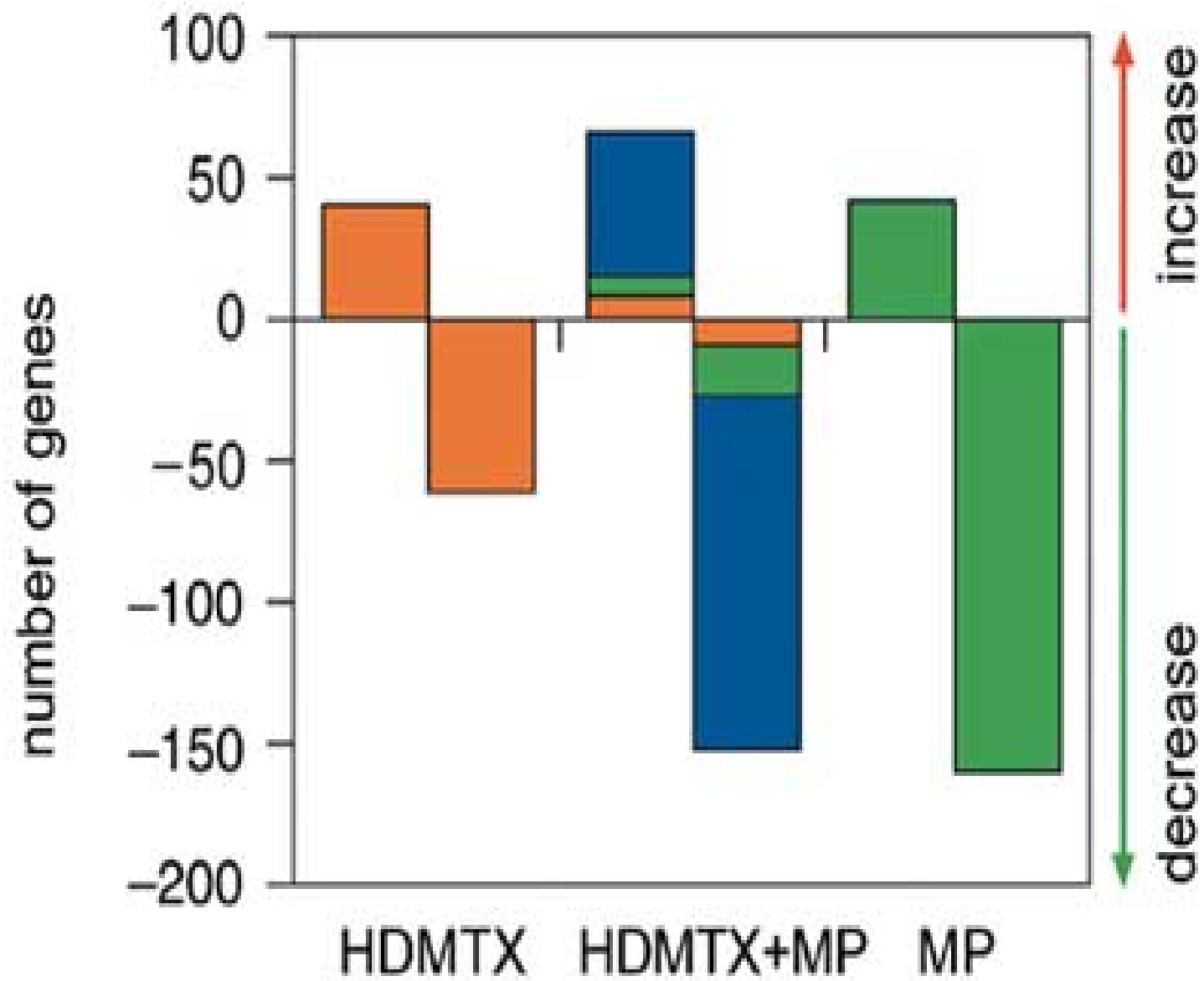


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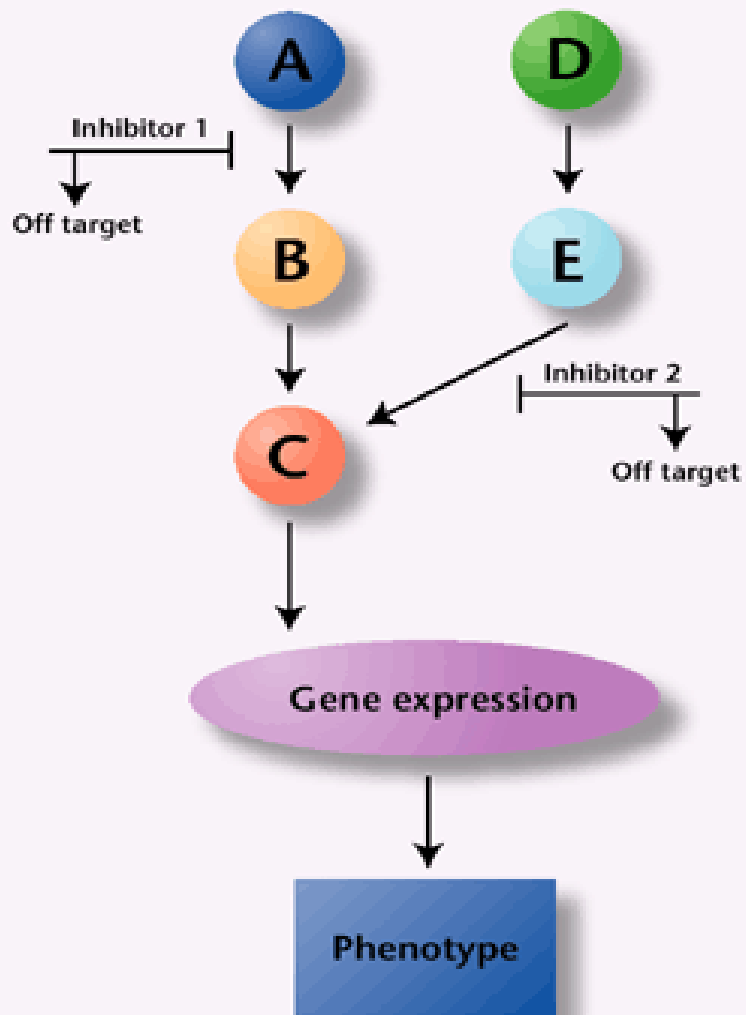




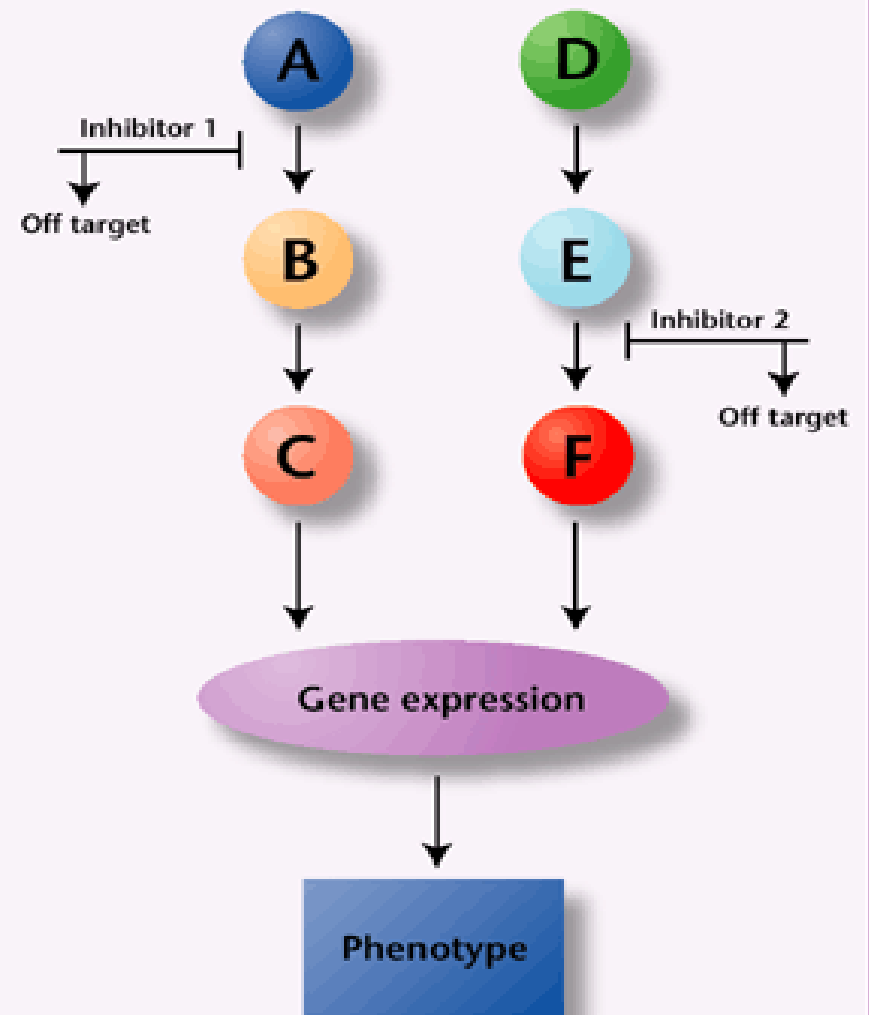
- This data supports model in which the combination is not sum of the individual effects.
- So question is whether the combination has a synergistic reaction on a single pathway or do they affect individual pathways which somehow converge.

a

Converging pathways

**b**

Parallel pathways



Thank you.