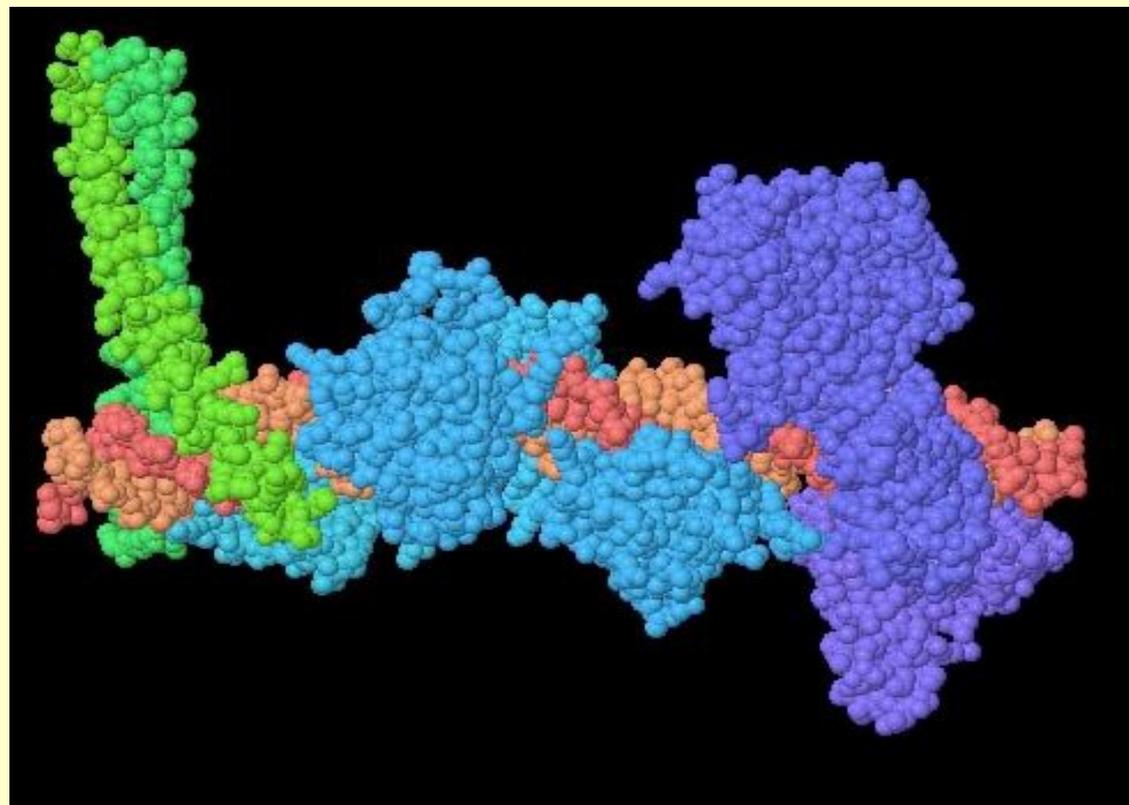


# Genomics, Bioinformatics & Medicine

<http://biochem158.stanford.edu/>

## Gene Expression and Cancer

<http://biochem158.stanford.edu/Gene%20Expression.html>



Doug Brutlag

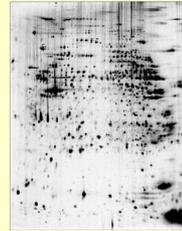
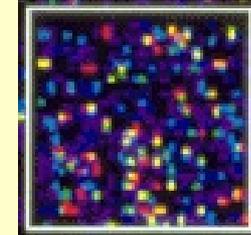
Professor Emeritus of Biochemistry & Medicine  
Stanford University School of Medicine

© Doug Brutlag 2015

# Leveraging Genomic Information

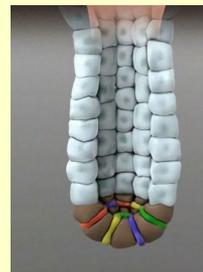
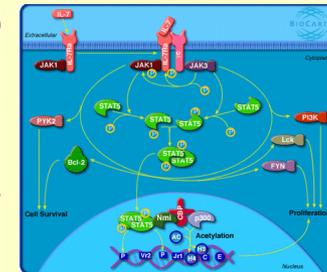
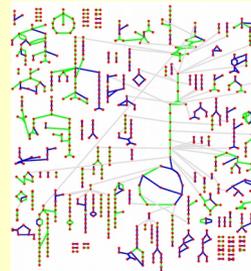
## Novel Diagnostics

DNA Microchips & Microarrays  
Gene Expression - RNA  
Proteomics - Protein



## Understanding

Metabolism  
Cell Signaling  
Differentiation  
Disease



**OMIM**  
Online Mendelian Inheritance in Man



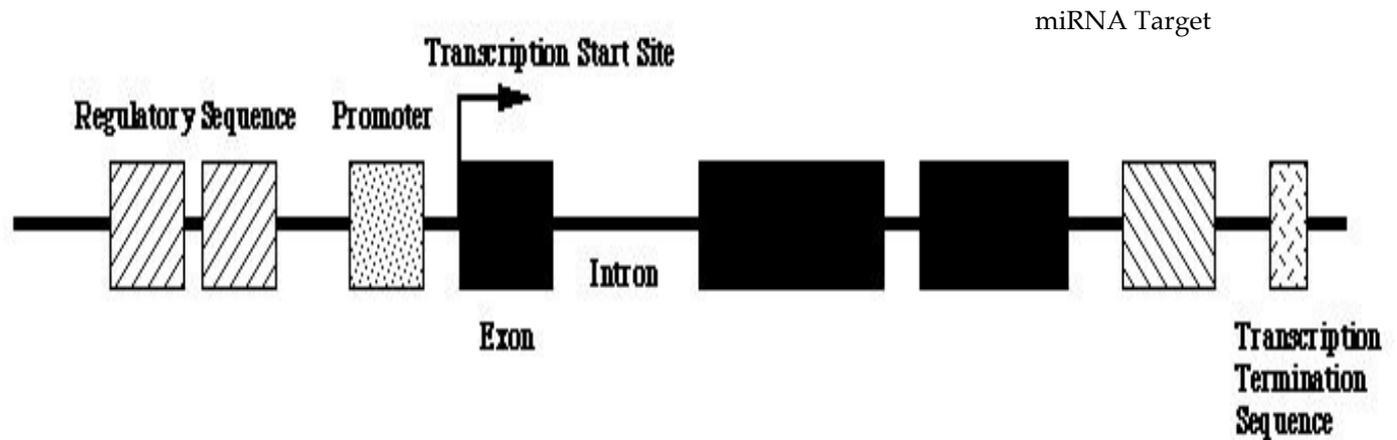
Johns  
Hopkins  
University

# Gene Regulatory Mechanisms

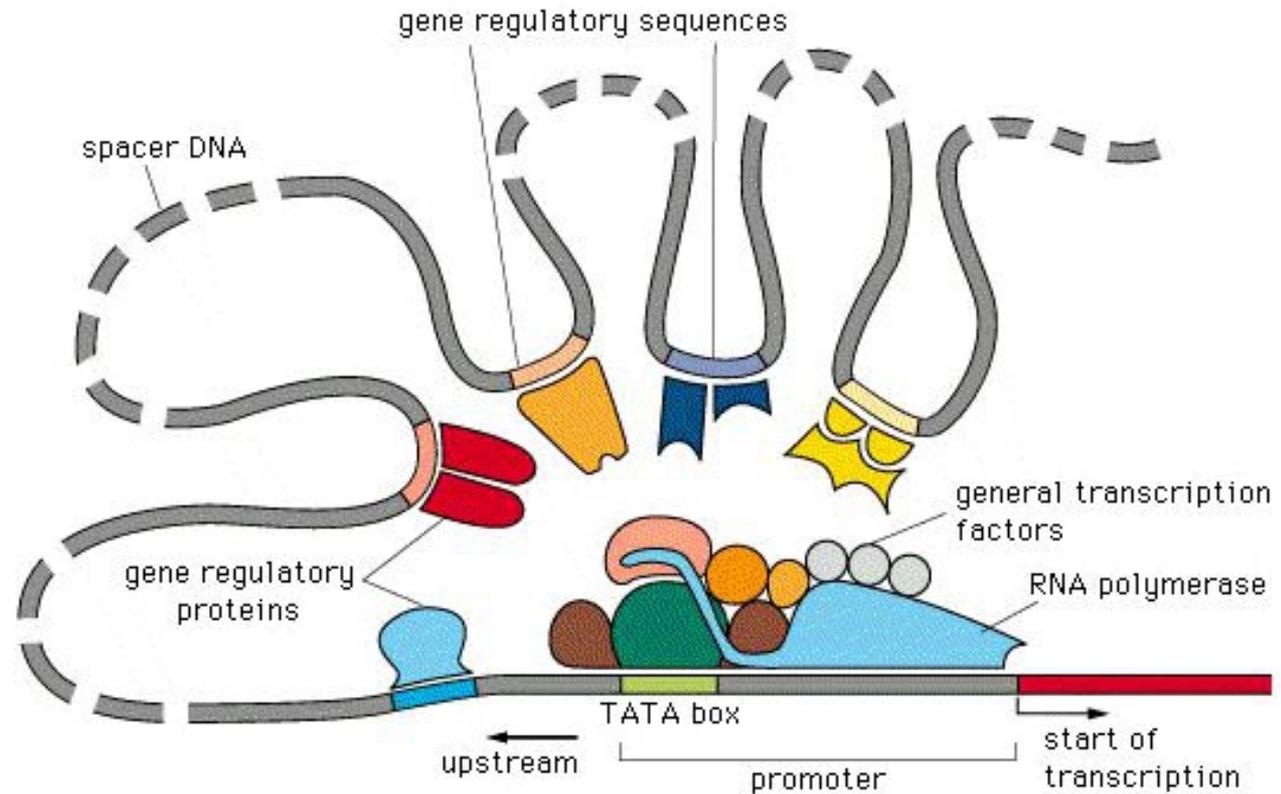
---

- Transcriptional Mechanisms
  - Type of promoters & RNA polymerase
  - Control of Transcription
  - [Transcription Factors and TFBS](#)
- RNA processing
  - Capping
  - Splicing and Alternative Splicing
  - Poly-Adenylation
  - RNA export to cytoplasm
  - RNA degradation rates
    - [Micro RNAs \(miRNAs\) inhibit translation and degrade mRNA](#)
    - [Silencer RNAs \(siRNAs or RNAi\) degrading mRNA](#)
- Epigenetic Mechanisms
  - DNA methylation
  - Histone modifications
    - Acetylation
    - Methylation
    - Phosphorylation, etc.
  - Chromatin remodeling

# Eukaryotic Gene Structure

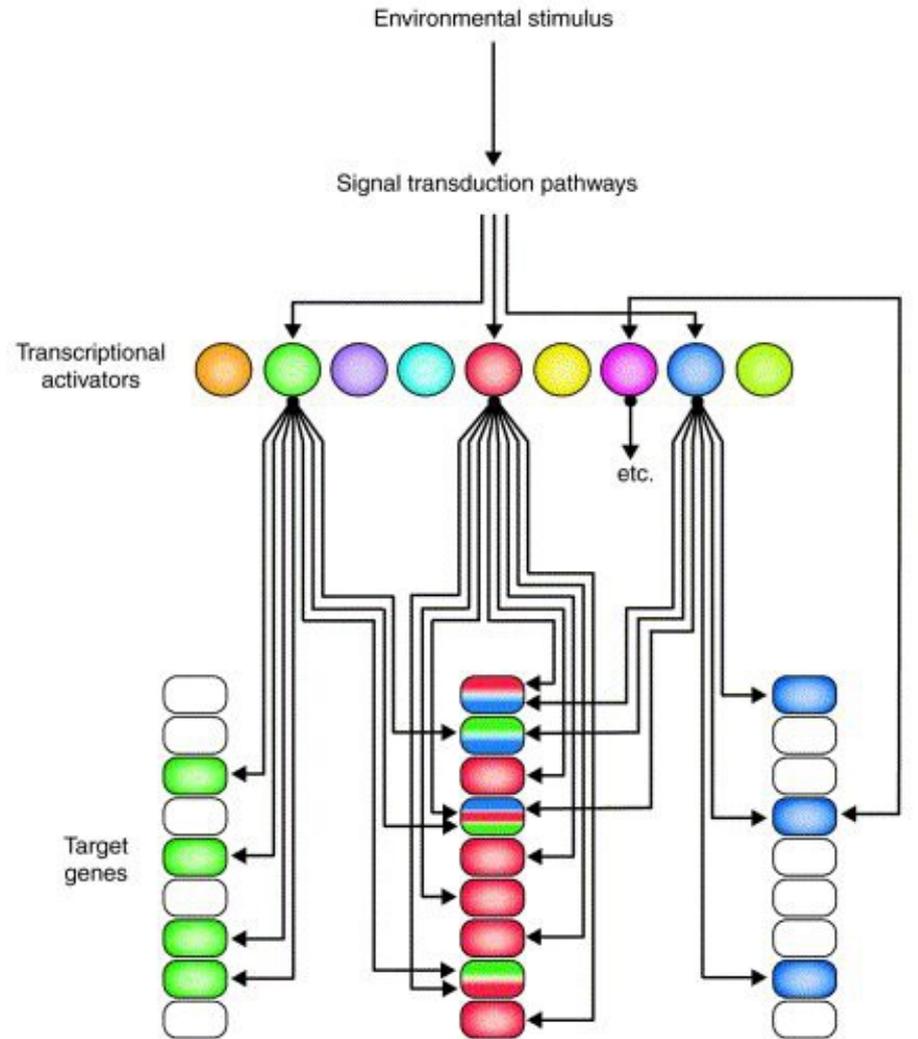


# Multiple Enhancer Sequences



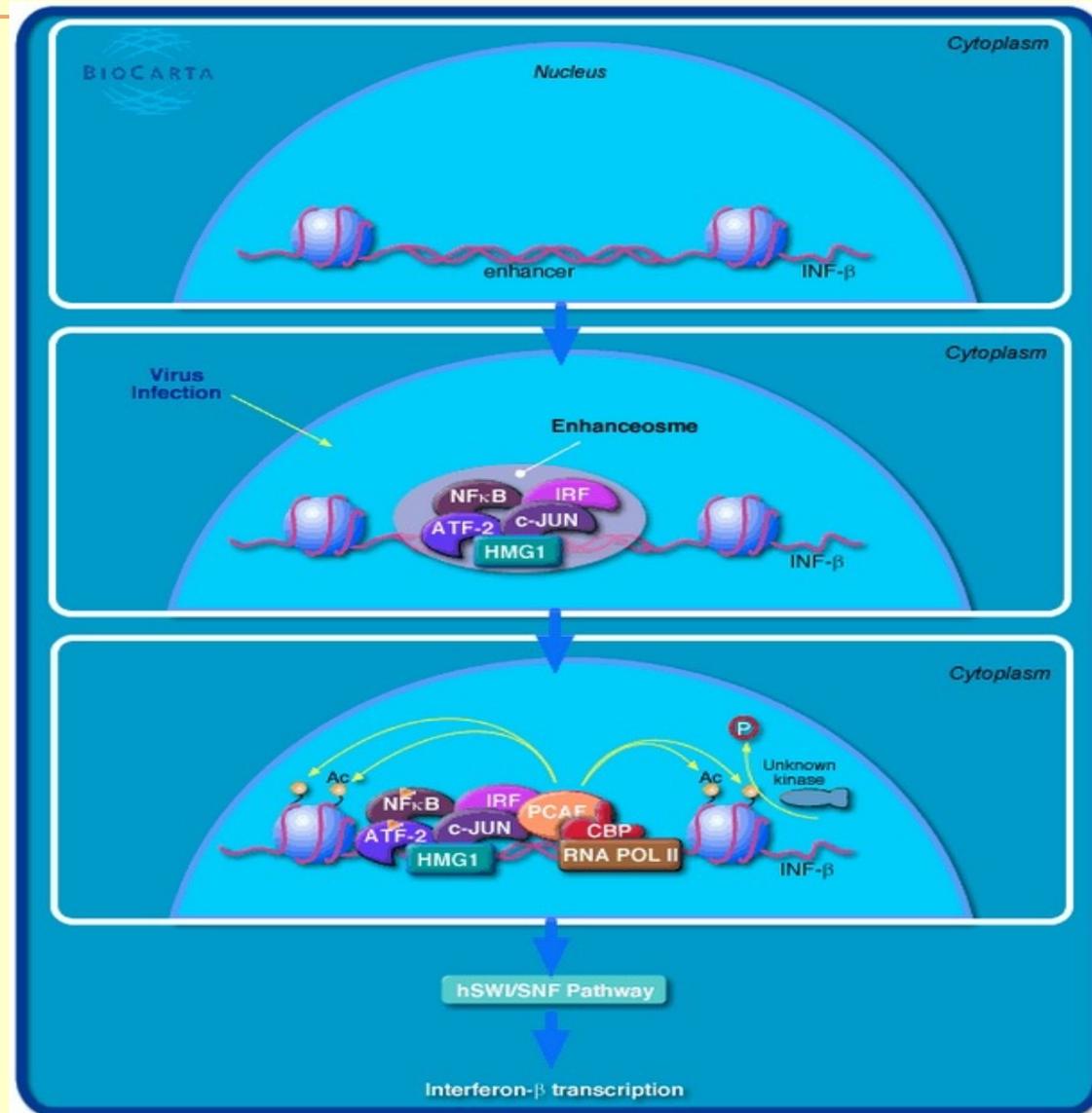
©1996 GARLAND PUBLISHING

# Gene Expression Regulatory Network



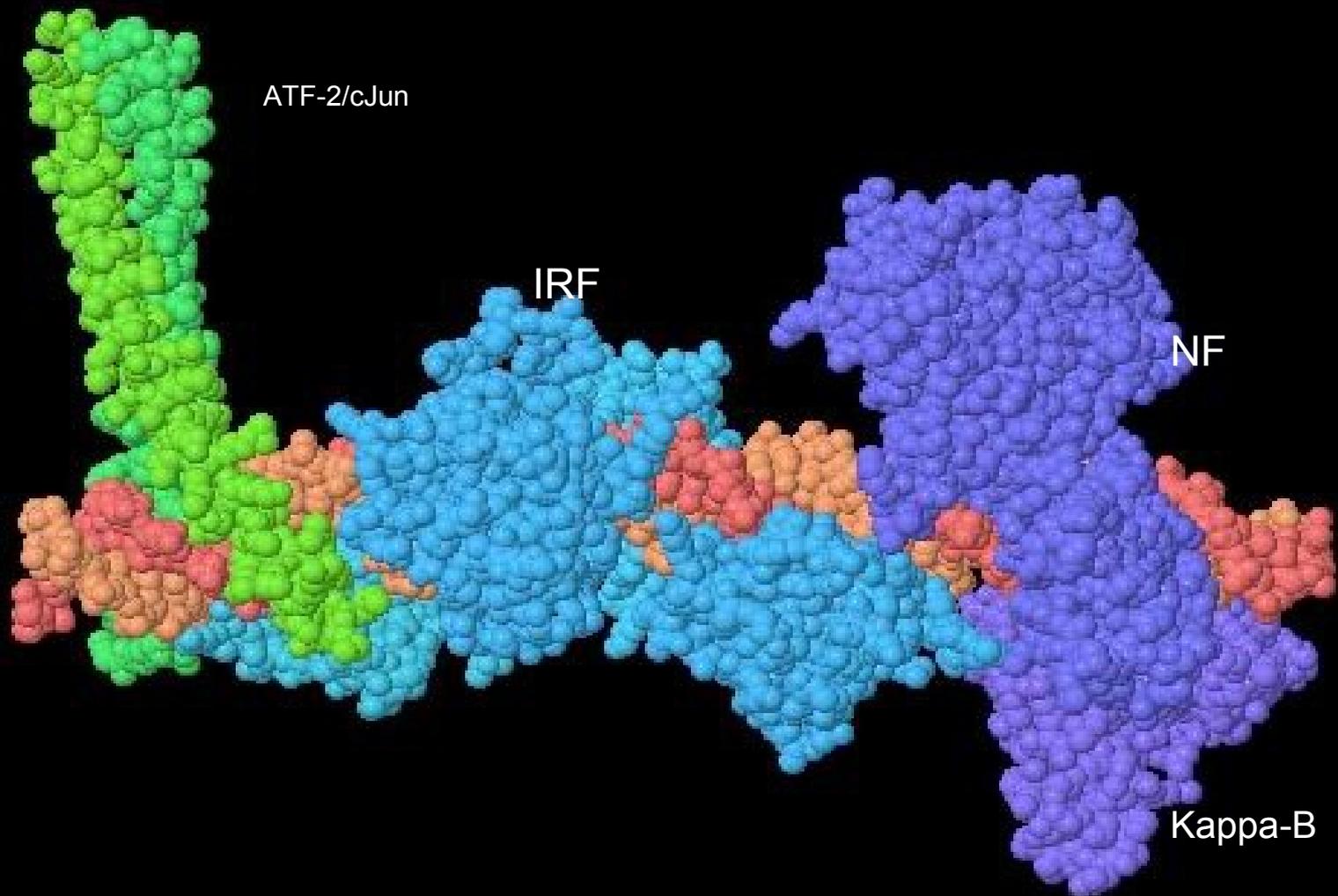
# Transcription Control at the Beta-Interferon Enhancer

[http://www.biocarta.com/pathfiles/h\\_pcafpathway.asp](http://www.biocarta.com/pathfiles/h_pcafpathway.asp)



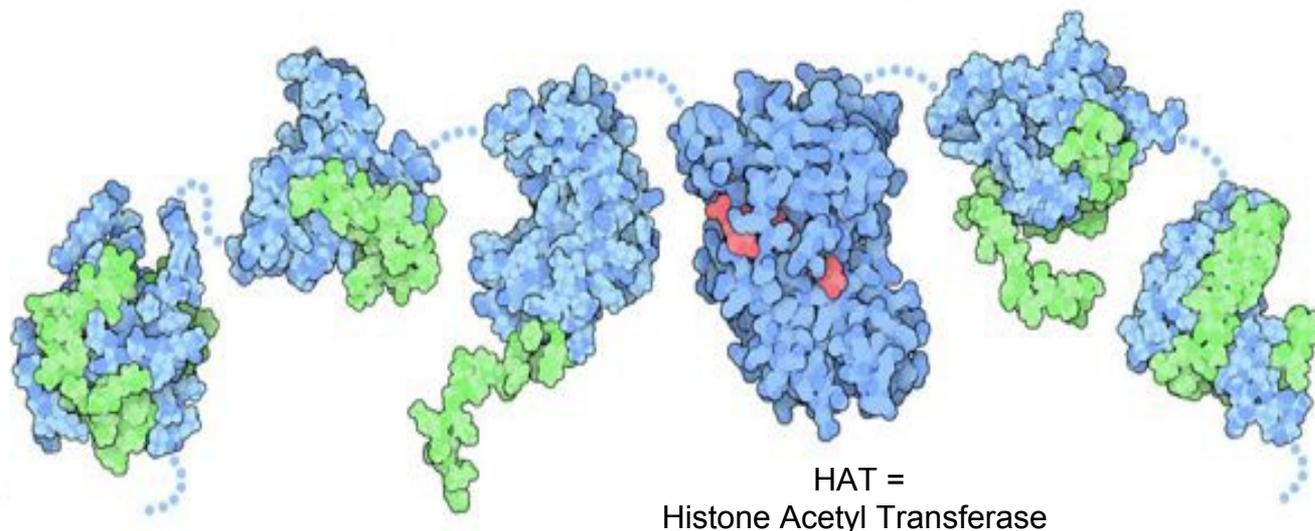
# Enhanceosome: Exploring the Structure

[http://www.rcsb.org/pdb/education\\_discussion/molecule\\_of\\_the\\_month/download/Enhanceosome.pdf](http://www.rcsb.org/pdb/education_discussion/molecule_of_the_month/download/Enhanceosome.pdf)



# Enhanceosome: Integrating the Signal

[http://www.rcsb.org/pdb/static.do?p=education\\_discussion/molecule\\_of\\_the\\_month/pdb122\\_2.html](http://www.rcsb.org/pdb/static.do?p=education_discussion/molecule_of_the_month/pdb122_2.html)



HAT =  
Histone Acetyl Transferase

## Integrating the Signal

Once the transcription factors bind to the different sites in the enhancer DNA sequence, the signal must somehow be sensed and used to activate the gene. In many cases, this is performed using CREB-binding protein or the similar protein p300. This protein is composed of many connected domains, (PDB entries **1l8c**, **1kdx**, **1jzp**, **3biy**, **2ka6** and **1kbh**), which bind to different proteins in the assembled enhanceosome. Then, a large domain in the center acts as a histone acetyltransferase, modifying histones in nucleosomes and causing them to disassemble and reveal the gene. In the interferon- $\beta$  gene, a nucleosome normally covers the start site of transcription, blocking transcription. Assembly of the enhanceosome leads to removal of this nucleosome, allowing the gene to be expressed.

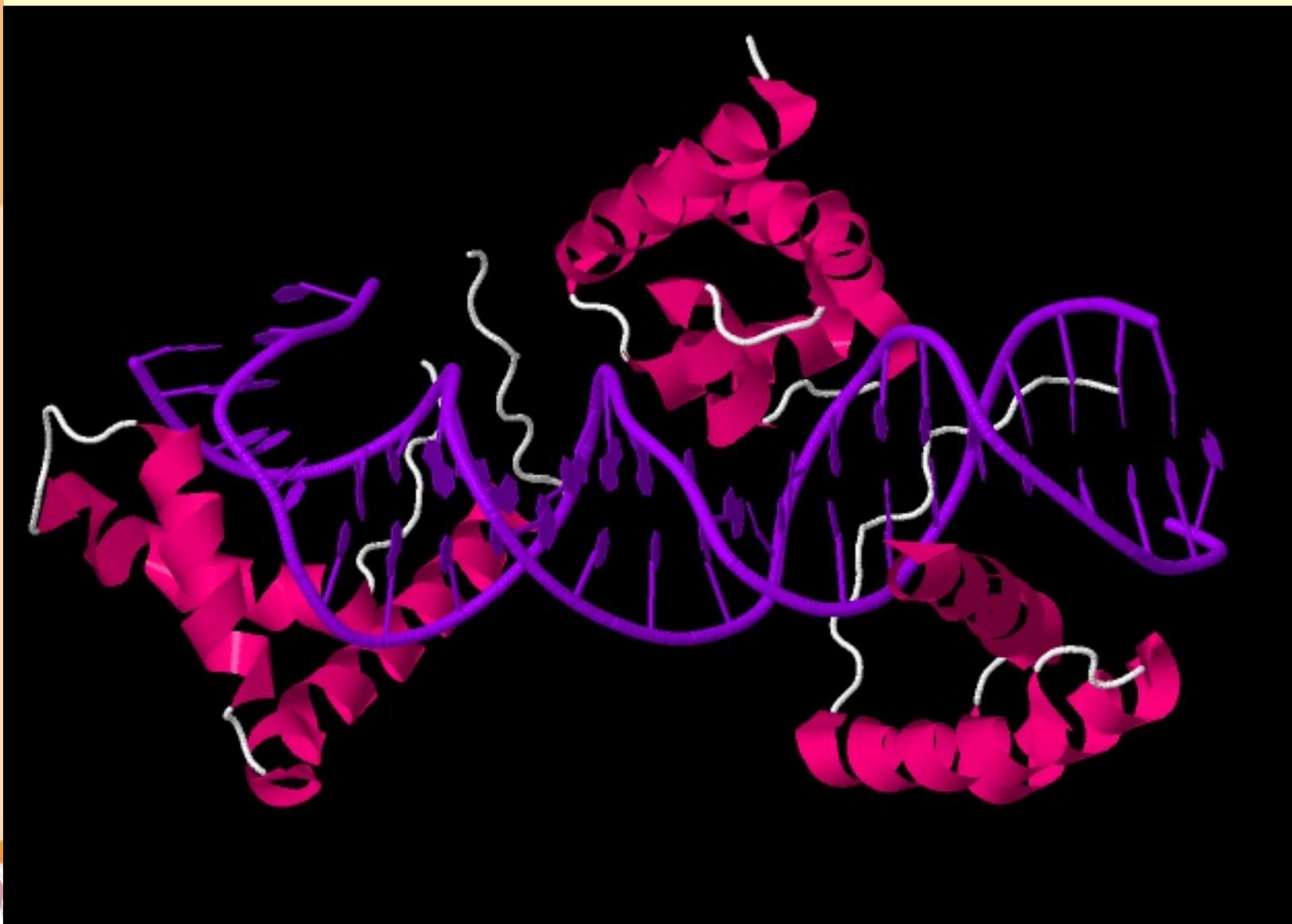
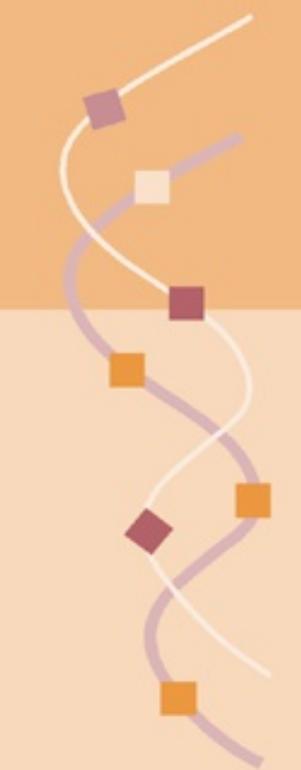
Previous: [Enhanceosome](#)

Home: [Enhanceosome](#)

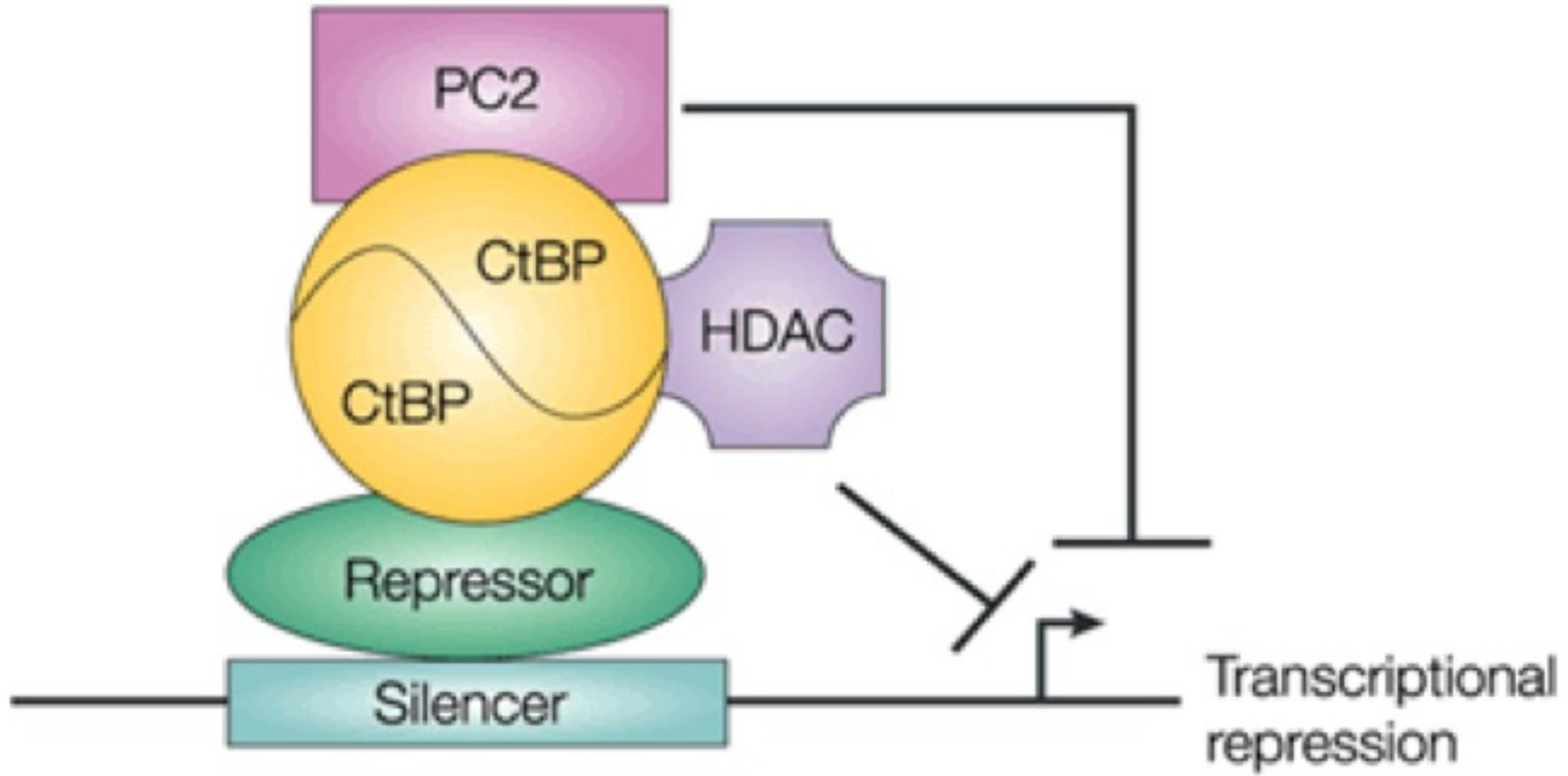
Next: [Exploring the Structure](#)

# Oct3 / 4-Sox2 bound to FGF-4 Enhancer

<http://www.pdb.org/pdb/explore/explore.do?structureId=1GT0>

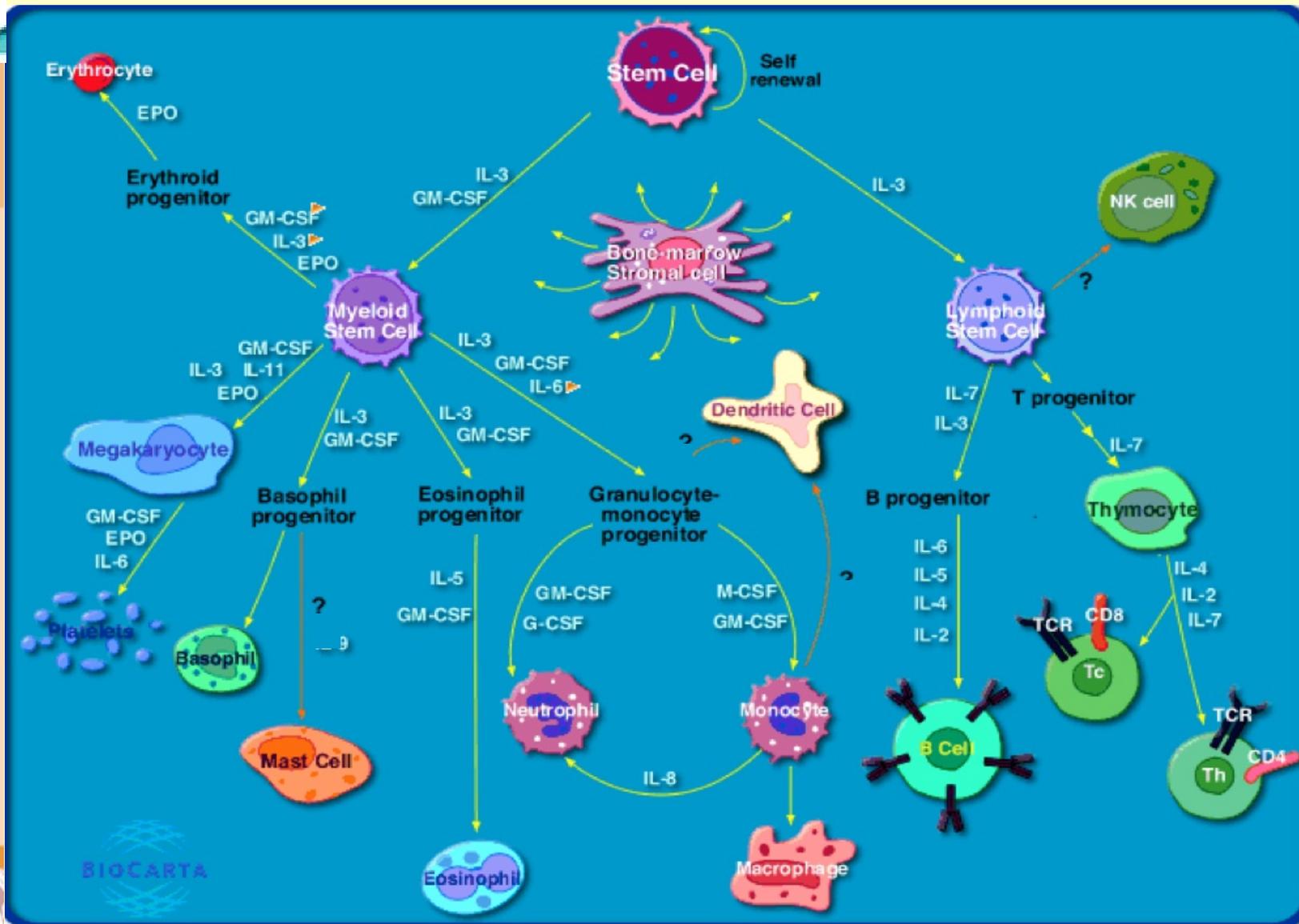


# Repressor Bound to Silencer Sites



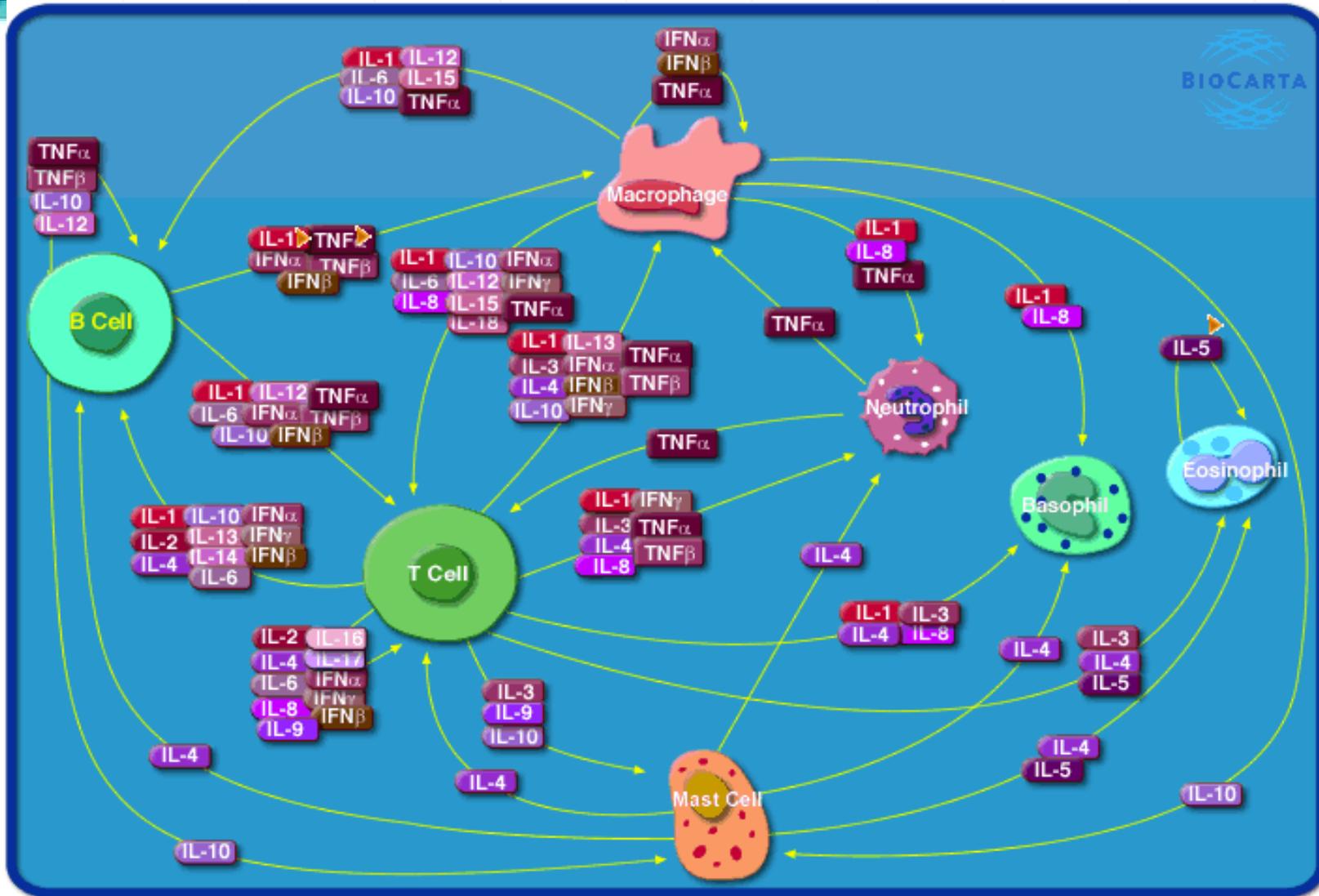
# Hematopoiesis

[http://cgap.nci.nih.gov/Pathways/BioCarta/h\\_stemPathway](http://cgap.nci.nih.gov/Pathways/BioCarta/h_stemPathway)



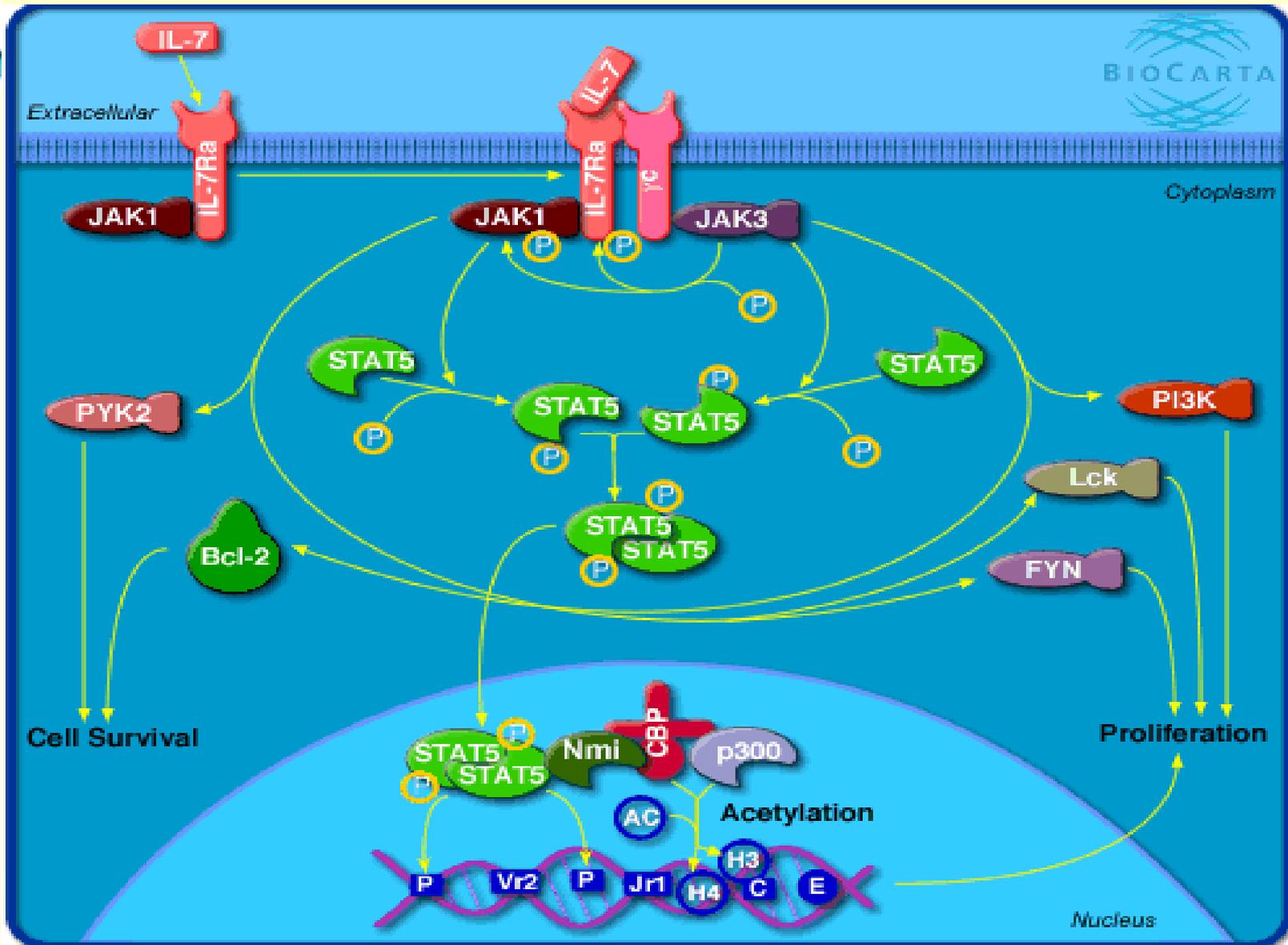
# Cytokine Network

[http://cgap.nci.nih.gov/Pathways/BioCarta/h\\_cytokinePathway](http://cgap.nci.nih.gov/Pathways/BioCarta/h_cytokinePathway)



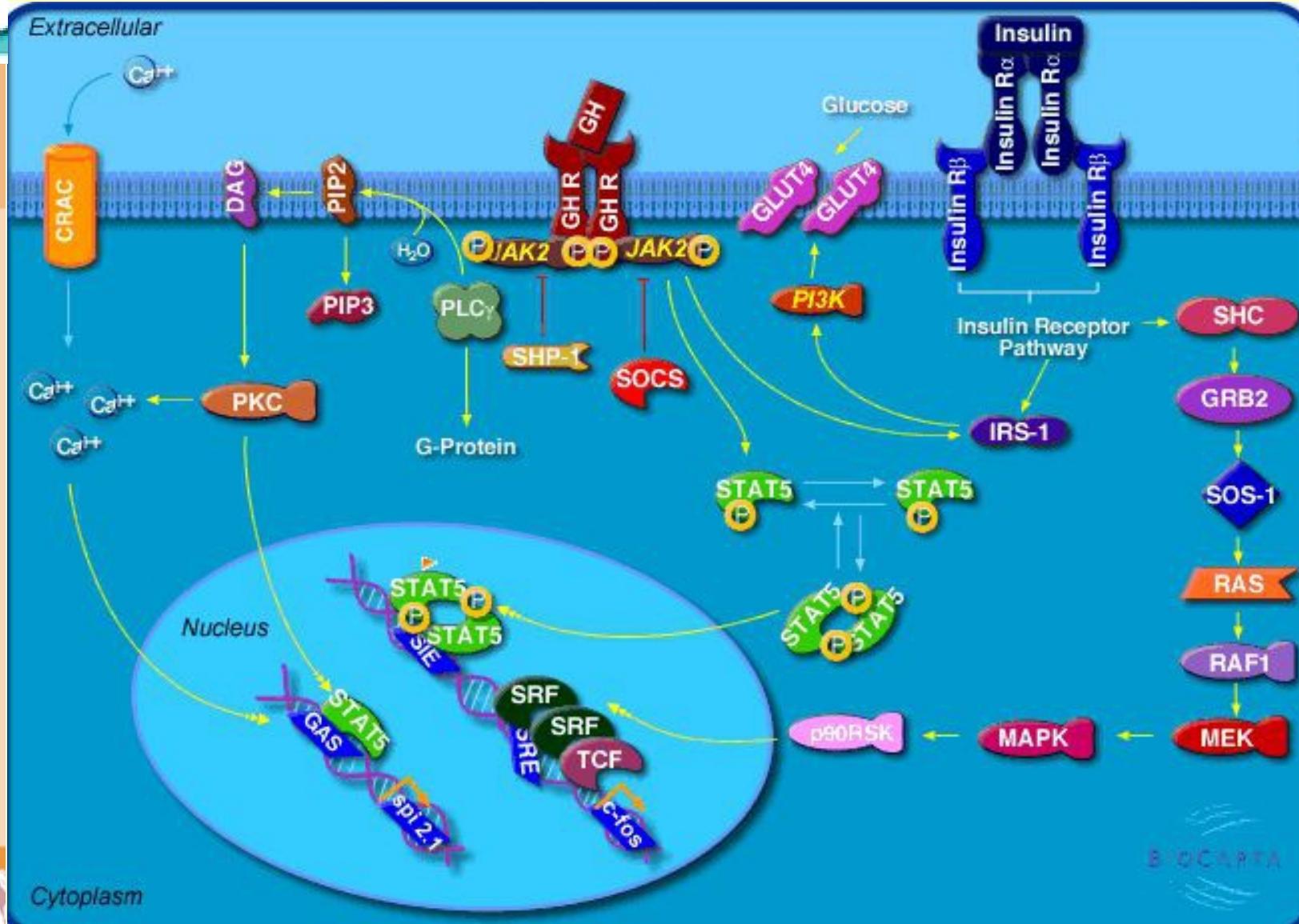
# IL7 Regulatory Pathway

[http://www.biocarta.com/pathfiles/h\\_il7Pathway.asp/](http://www.biocarta.com/pathfiles/h_il7Pathway.asp/)



# Growth Hormone Receptor Pathway

[http://www.biocarta.com/pathfiles/h\\_ghPathway.asp/](http://www.biocarta.com/pathfiles/h_ghPathway.asp/)



# DNA Microarrays & DNA Chips

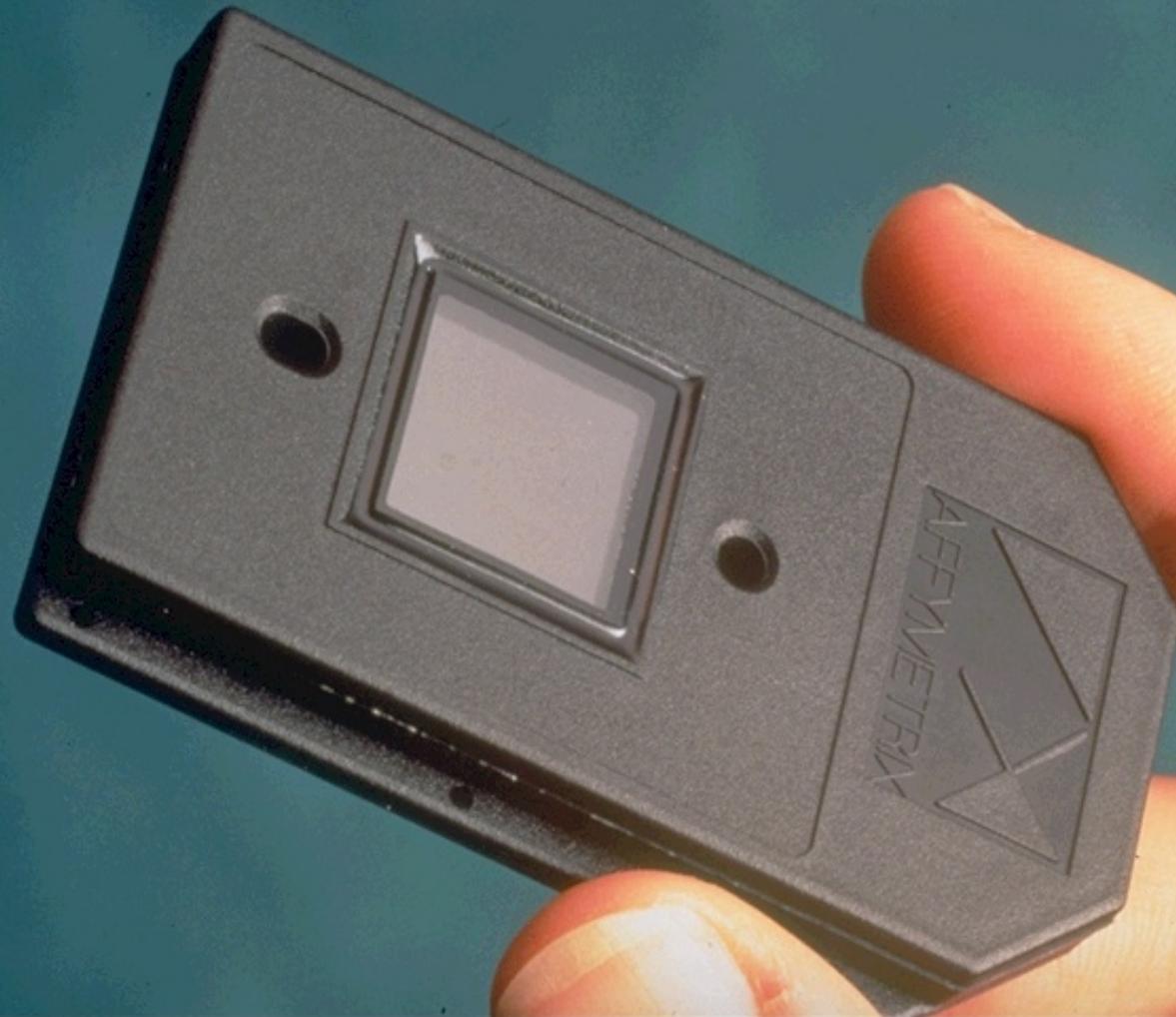
## Accelerate Gene Expression Analysis

---

- Parallel Analyses
  - Analyze entire genomes instead of single genes
  - Analyze expression of entire genome
  - Analyze genetic polymorphisms (SNPs)
- Miniaturization
- Automation

# Diagnosis Using DNA Arrays

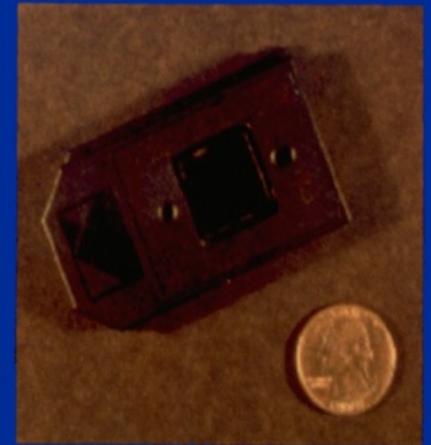
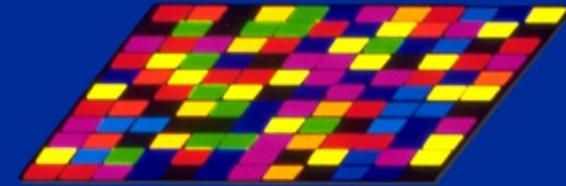
<http://www.affymetrix.com/>



# DNA Micro Arrays

---

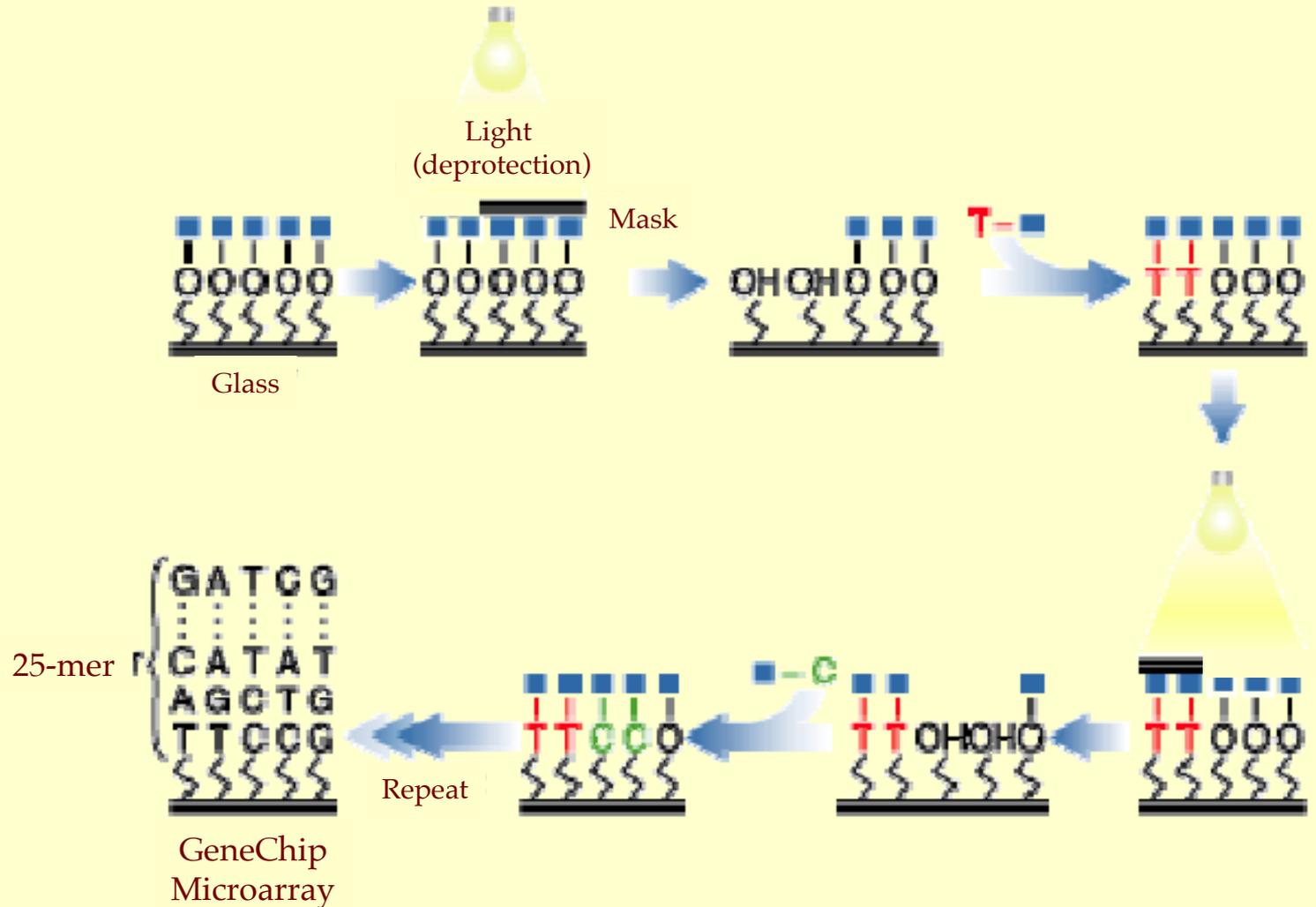
- High-density grid of DNA sequences.
- Any collection of 25mers (1,200,000) can be synthesized in 100 steps
- The location and identity of each sequence on the glass surface is known.



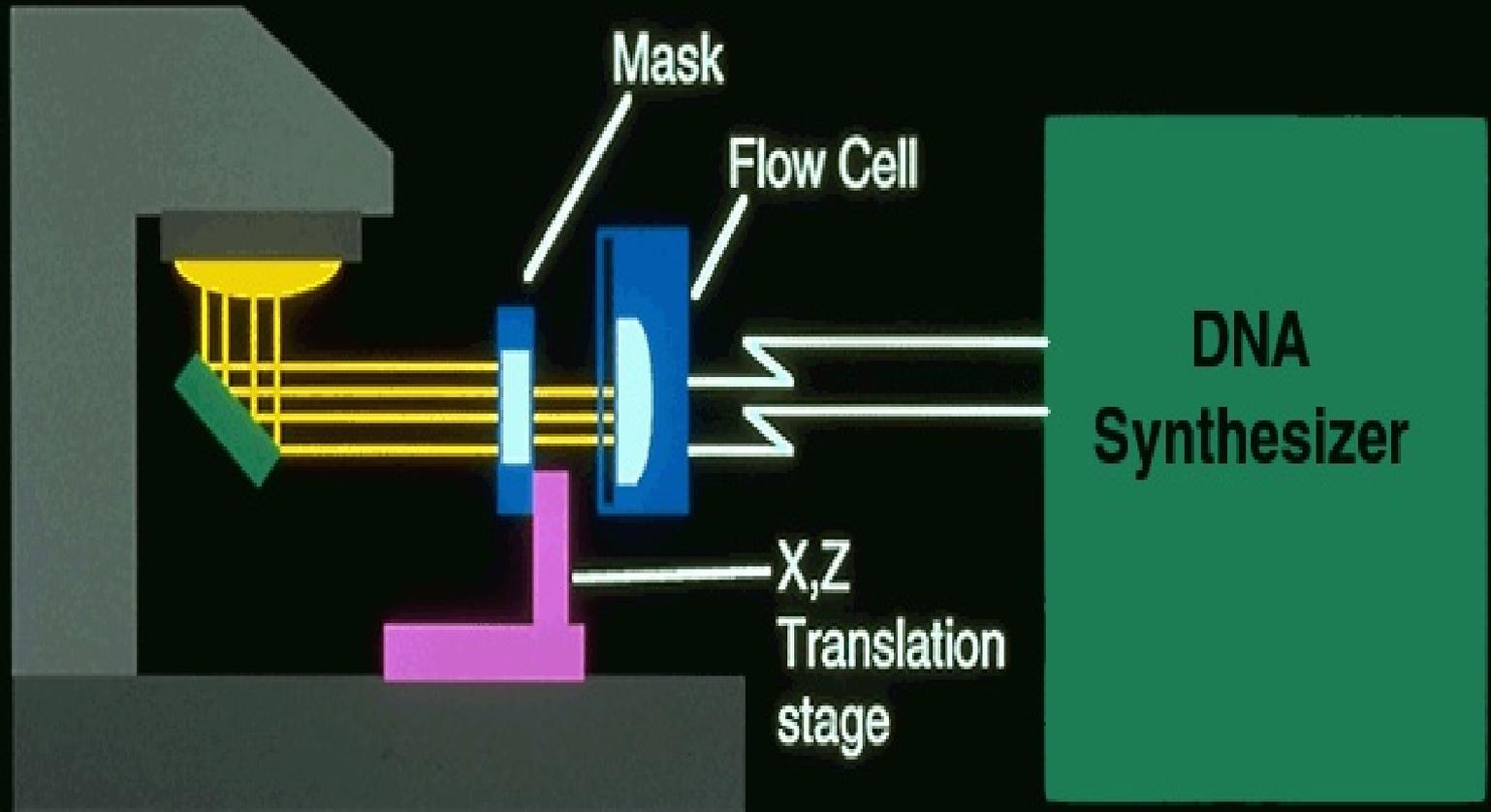
# Light Directed Oligonucleotide Synthesis

<http://www.youtube.com/watch?v=ui4BOtwJEXs&feature=related>

## Photolithography

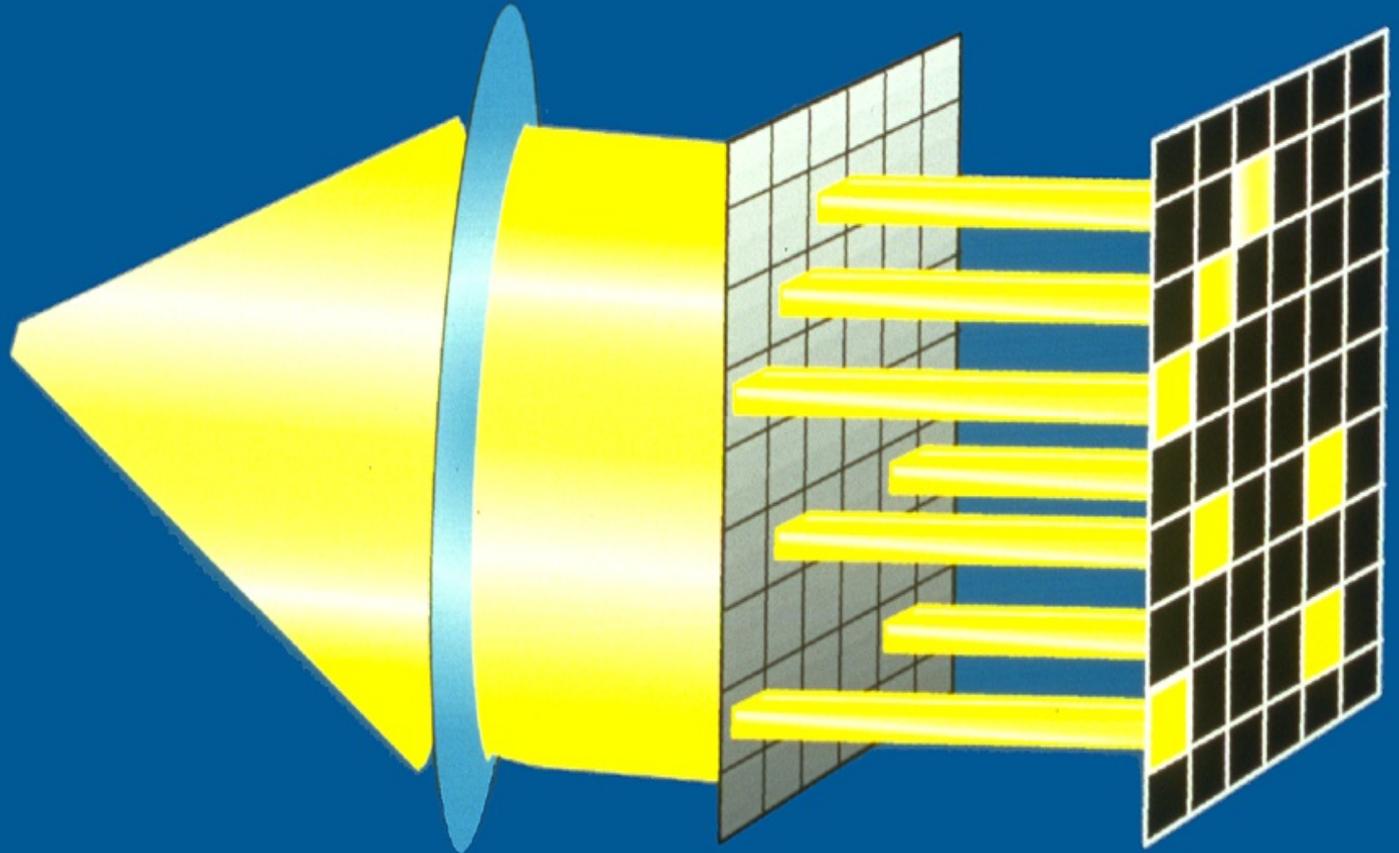


# Automated DNA Chip Synthesis

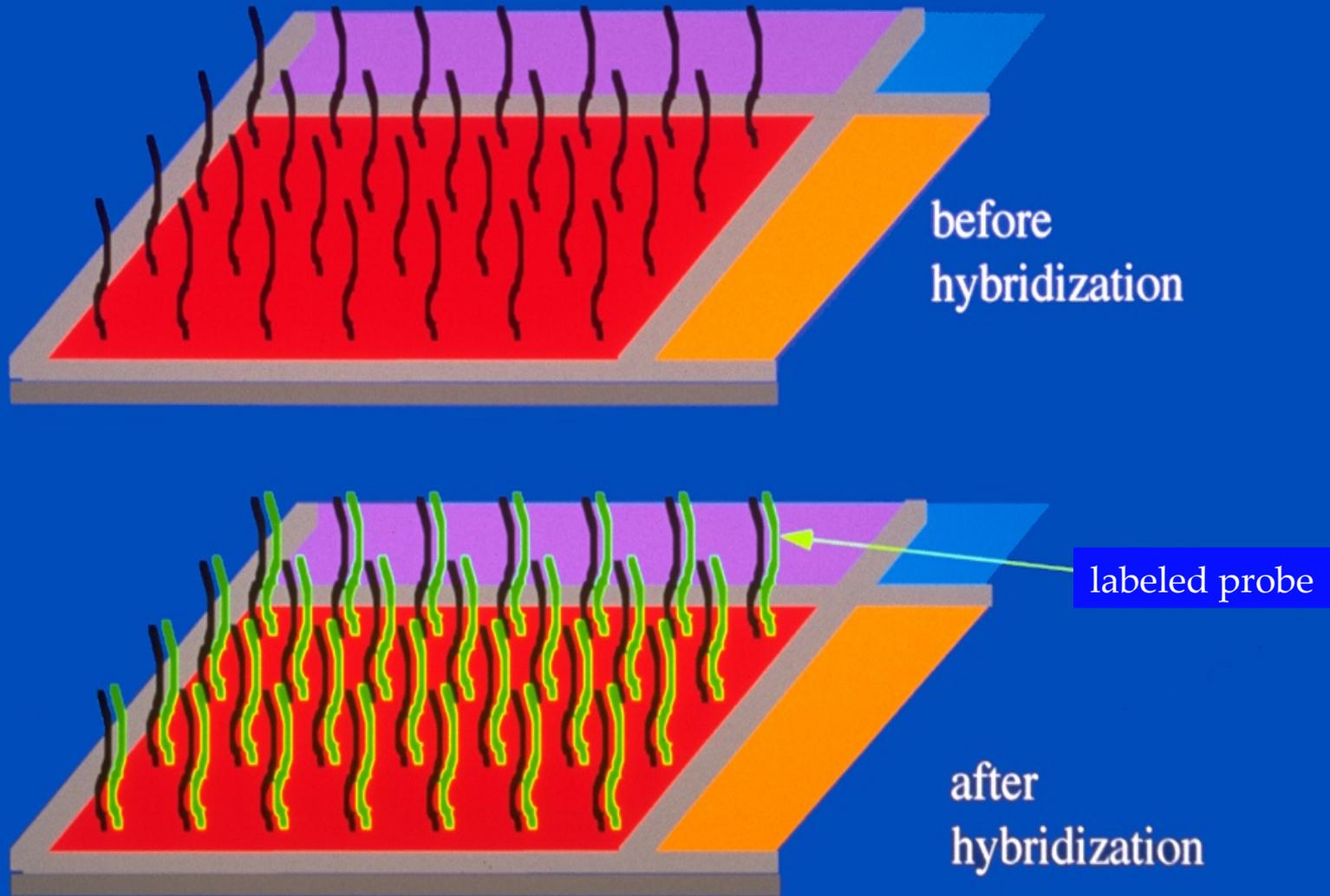


# Photolithography Masks

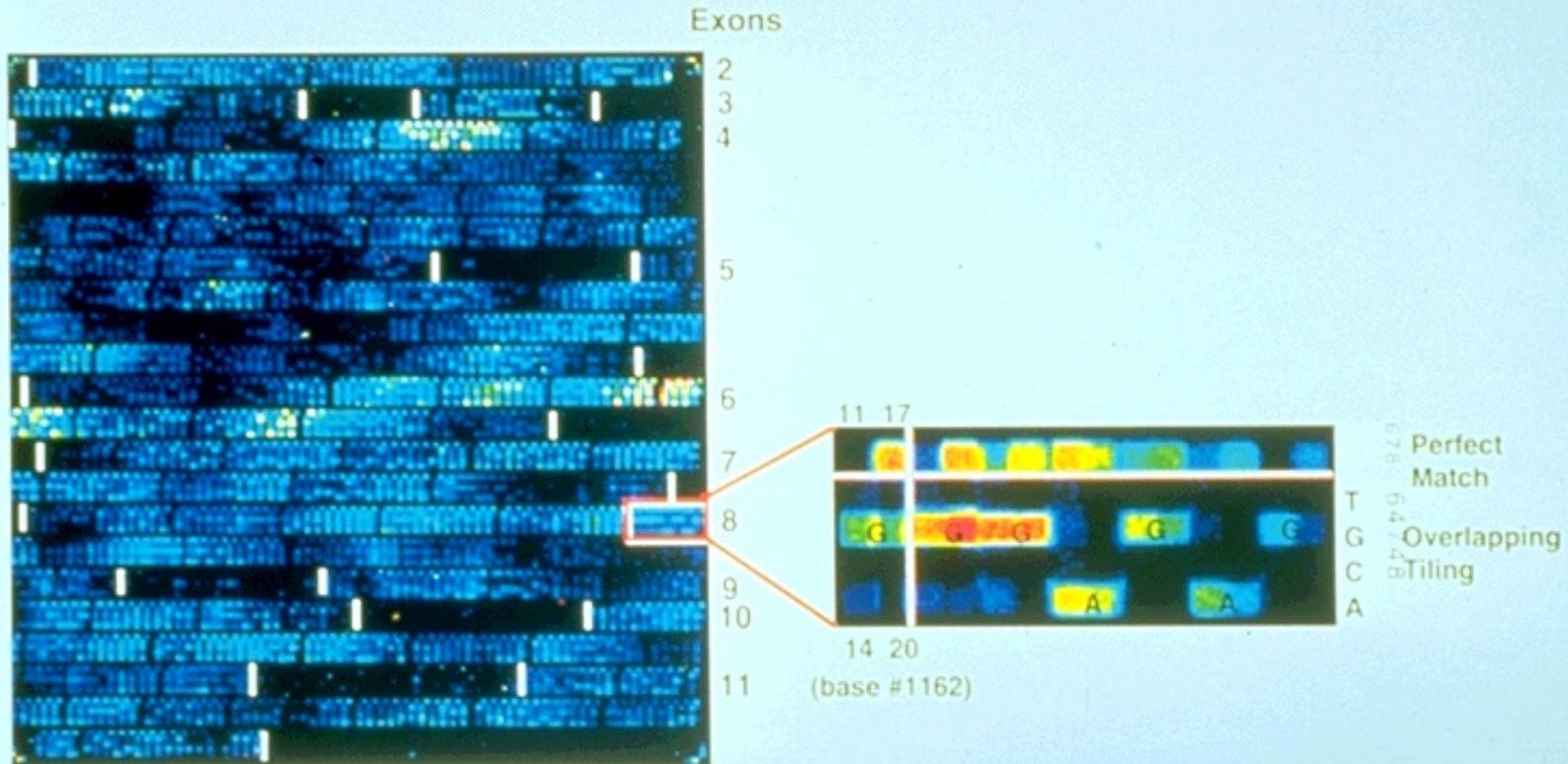
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# Hybridization & Detection



# Cystic Fibrosis Array



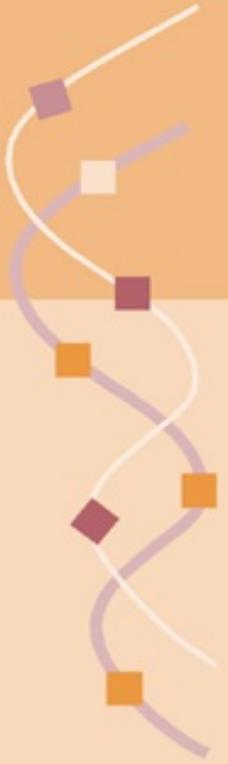
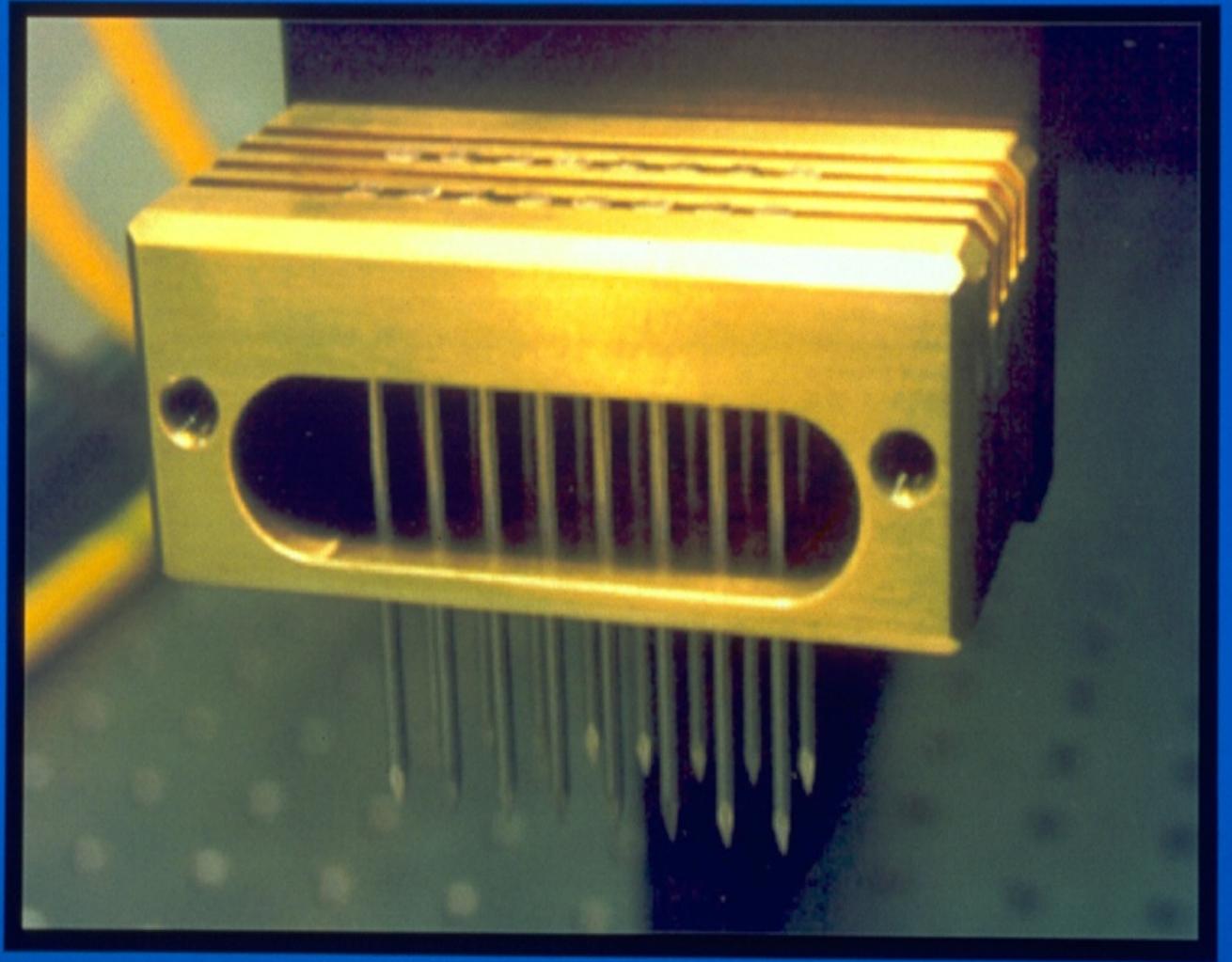
# Microarrayer in Pat Brown's Lab

<http://cmgm.stanford.edu/pbrown/>

---



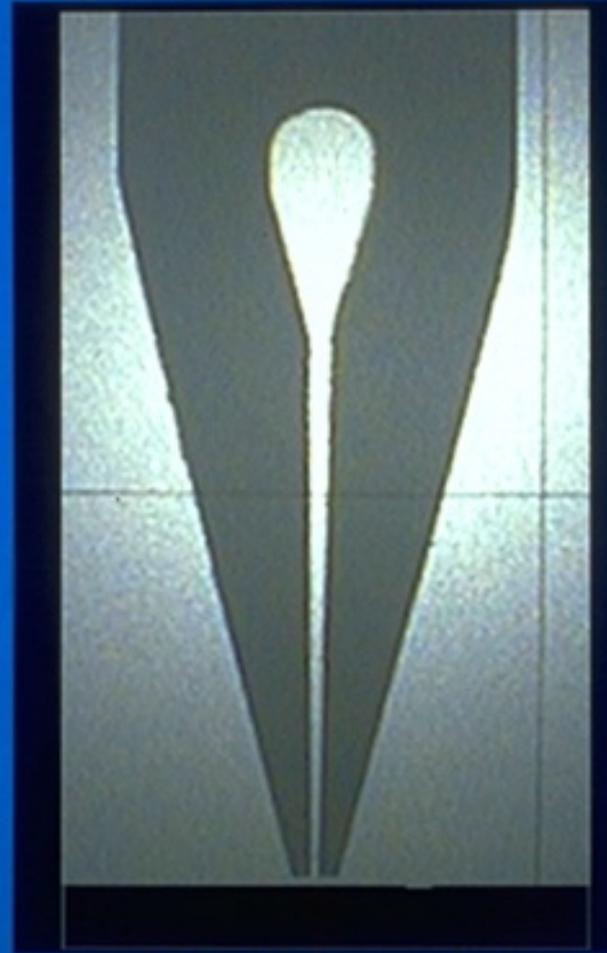
# High Precision DNA Printing



# Mechanical Spotting Microarrays

<http://www.arrayit.com/>

## Bubble Pin Technology



# DNA Chips are used to Measure Gene Expression

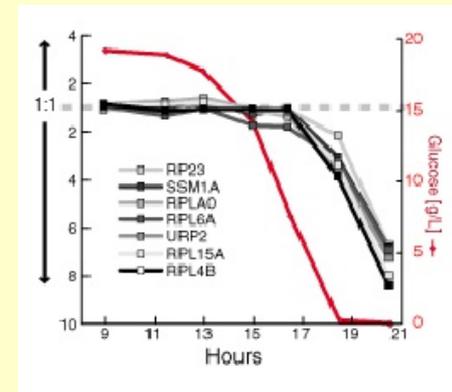
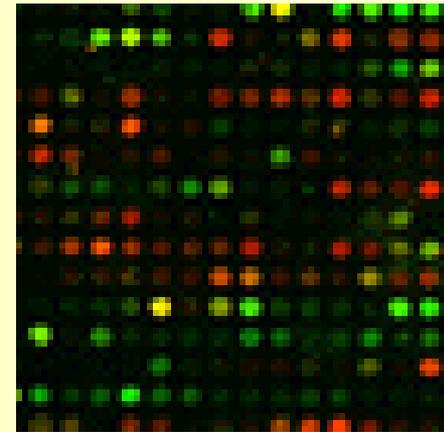
MicroArray analysis of whole genome gene expression



Clustering of genes based on their expression pattern

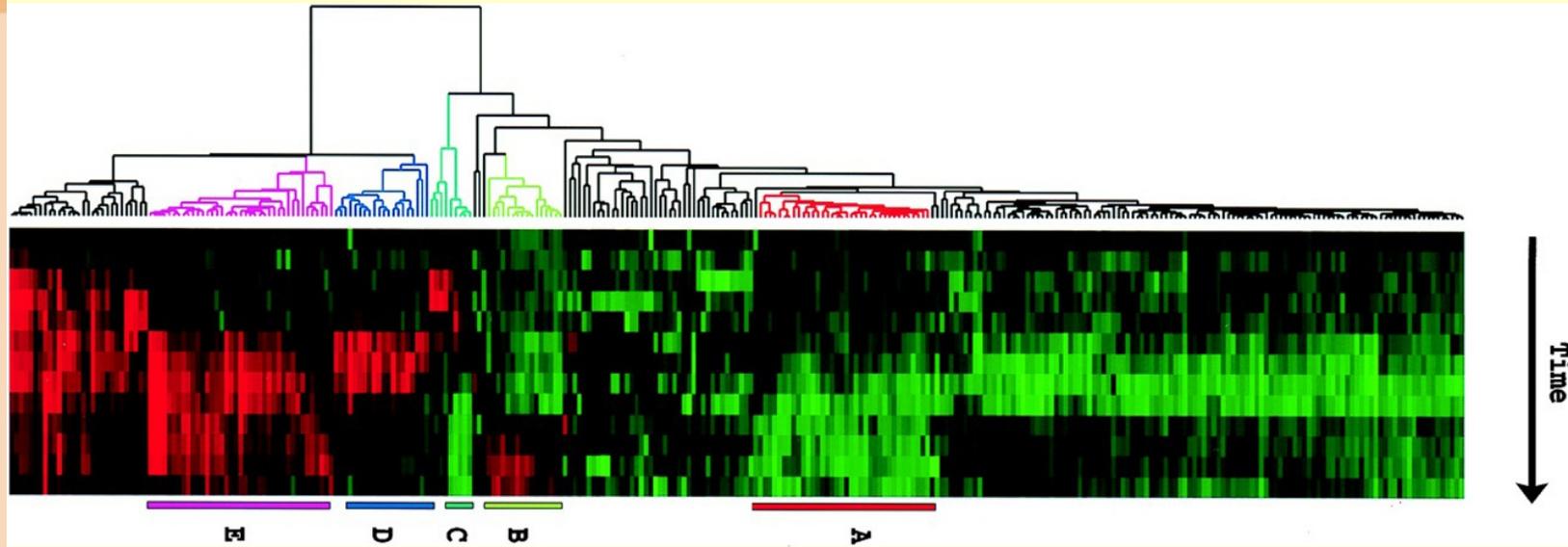


Searching for conserved sequence motifs regulating the expression



# Megacluster of Yeast Gene Expression

---



# Human Gene Expression Signatures



# Finding Transcription Factor Binding Sites

---

Upstream Regions

Co-expressed  
Genes

GATGGCTGCACCACGTGTATGC . . . ACG  
CACATCGCATCACGTGACCAGT . . . GAC  
GCCTCGCACGTGGTGGTACAGT . . . AAC  
TCTCGTTAGGACCATCACGTGA . . . ACA  
CGCTAGCCCACGTGGATCTTGA . . . AGA

Pho 5

Pho 8

Pho 81

Pho 84

Pho ...



# Finding Transcription Factor Binding Sites

---

Upstream Regions

Co-expressed  
Genes

GATGGCTGCAC**CACGTG**TATGC . . . ACG**ATGTCTCGC**  
CACATCGCAT**CACGTG**ACCAGT . . . GAC**ATGGACGGC**  
GCCTCG**CACGTG**GTGGTACAGT . . . AAC**ATGACTAAA**  
TCTCGTTAGGACCAT**CACGTGA** . . . ACA**ATGAGAGCG**  
CGCTAGCC**CACGTG**GATCTTGT . . . AGA**ATGGCCTAT**

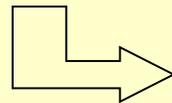
# Finding Transcription Factor Binding Sites

---

Upstream Regions

Co-expressed  
Genes

```
ATGGCTGCACCACGTTTATGC . . . ACGATGTCTCGC
CACATCGCATCACGTGACCAGT . . . GACATGGACGGC
  GCCTCGCACGTGGTGGTACAGT . . . AACATGACTAAA
TTAGGACCATCACGTGA . . . ACAATGAGAGCG
CGCTAGCCCACGTTGATCTTGT . . . AGAATGGCCTAT
```



**Pho4 binding**

# Discovering Transcription Factor Binding Sites is Difficult

---

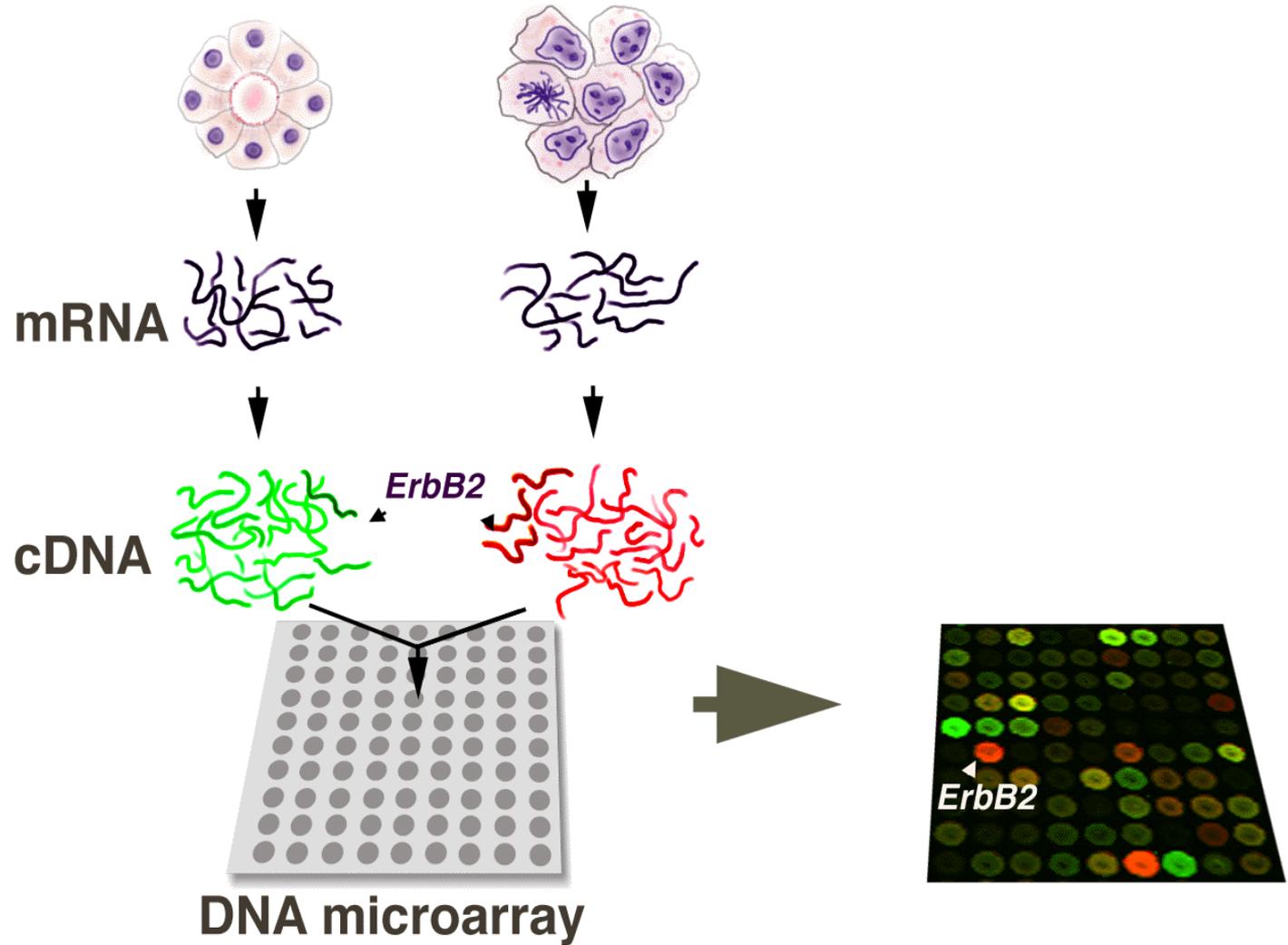
- Binding sites are short (5-15 base pairs)
- Not highly conserved (as little as 50%)
- Located in long intergenic regions (>10kb)
- Not always present (false positive genes)

# Three Algorithms

---

- **BioProspector**
  - Presented in 2000
  - Extends Gibb's sampling (stochastic method)
  - For any cluster of sequences
- **MDscan**
  - Deterministic approach
  - Enumerative
  - Very fast
  - For sequences with some ranking information
- **MotifCut and MotifScan**
  - Graph-based
  - Does not use PSSMs
  - Novel and sensitive

# cDNA Diagnostics Using DNA Microarrays

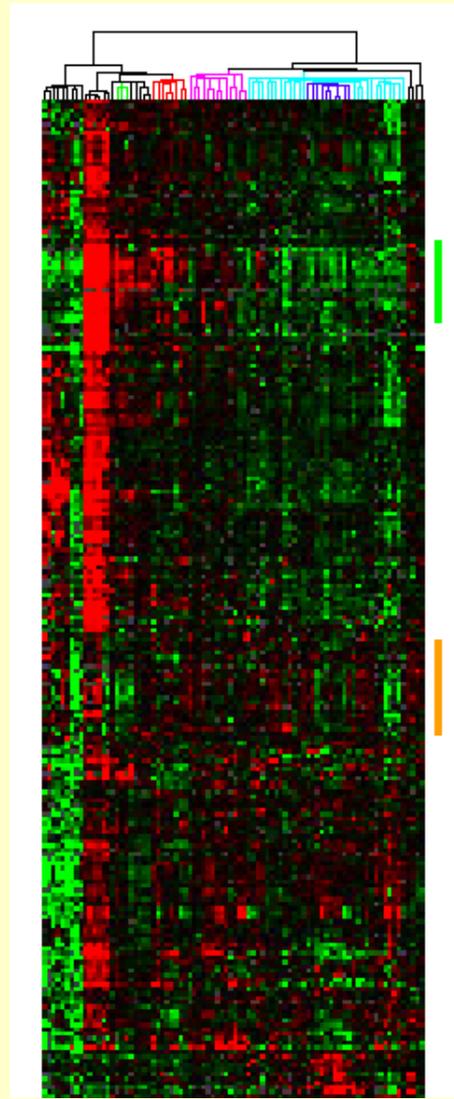


# 72 Breast Cancers Classified by 451 Gene Expression Assays

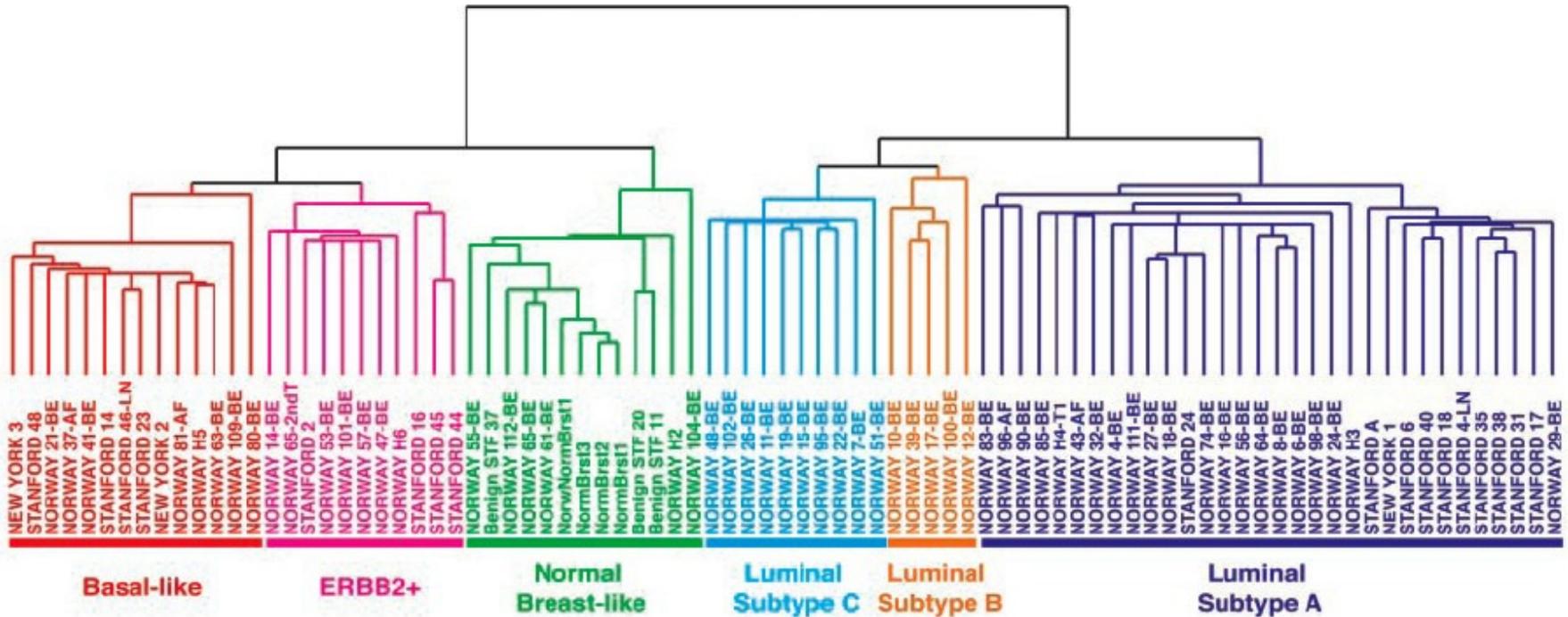


72 Patients →

↑  
451 Genes



# Breast Cancers Classified by 451 Gene Expression Assays



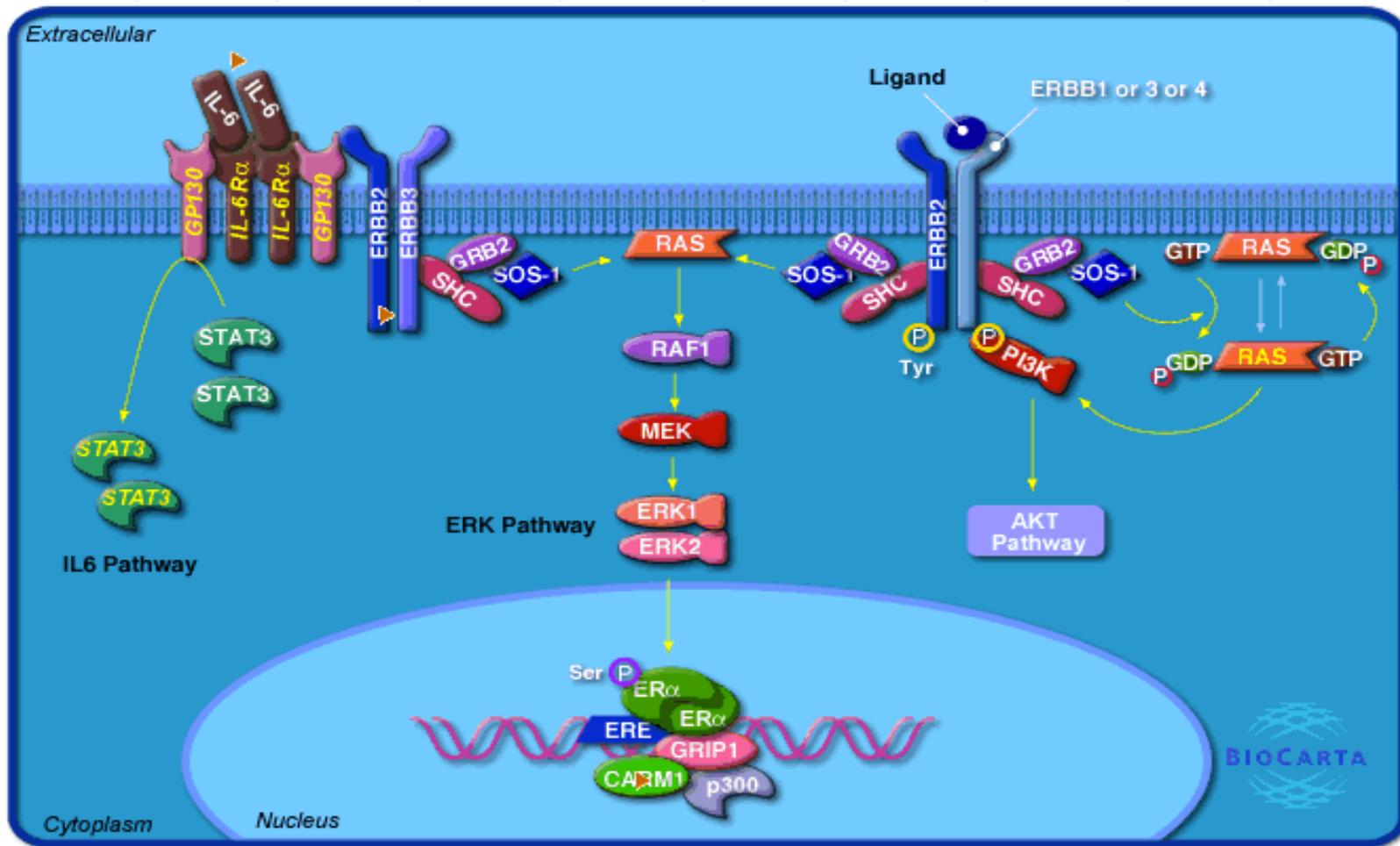
# ERB-B2 in Signal Transduction & Oncology

[http://www.biocarta.com/pathfiles/h\\_her2Pathway.asp](http://www.biocarta.com/pathfiles/h_her2Pathway.asp)

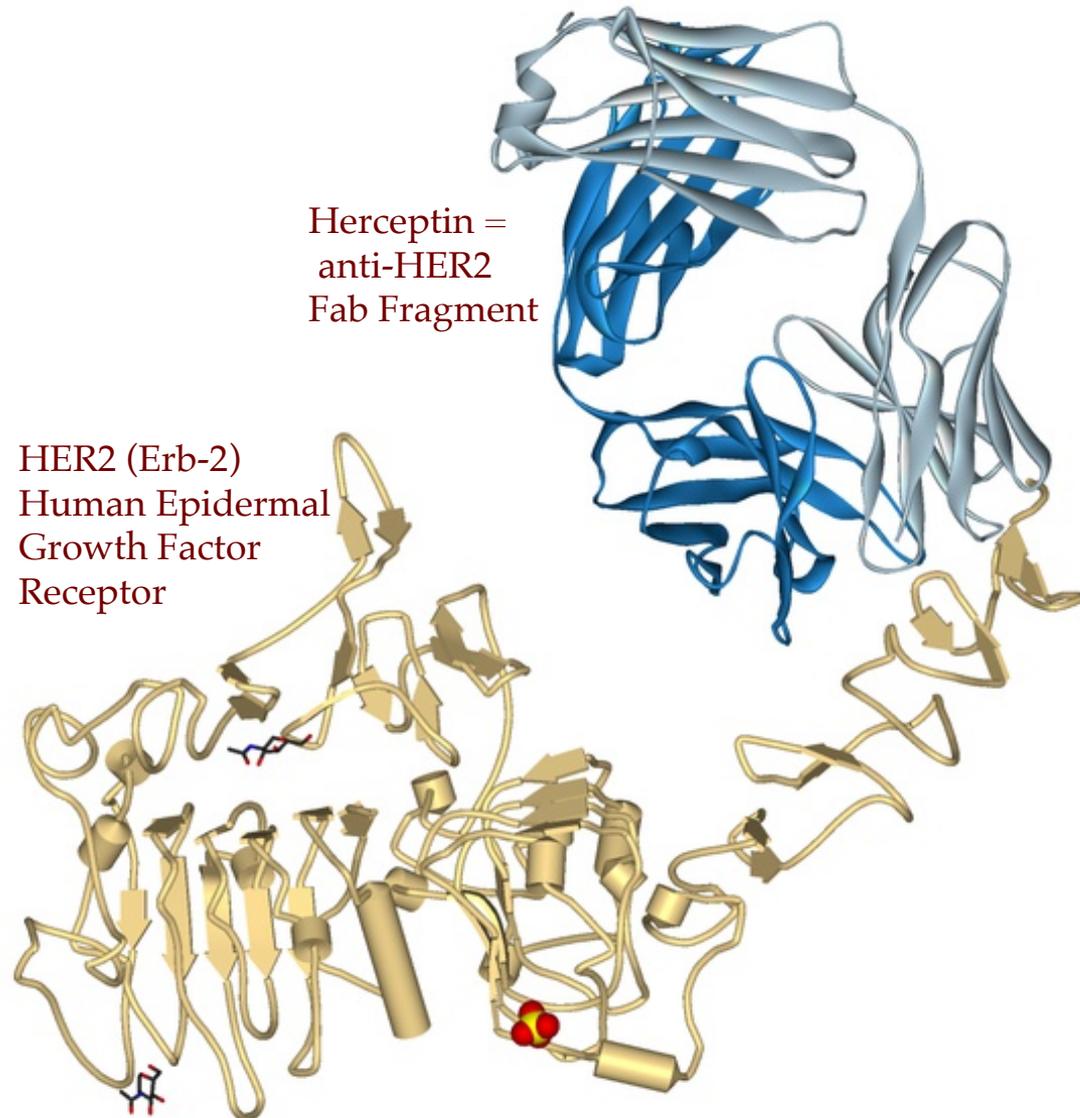
## 5 ▶ Role of ERBB2 in Signal Transduction and Oncology

Submitted by: ✉ Guru: ✉

[COMMENT ON THIS PATHWAY](#) | [DESCRIPTION](#) | [CONTRIBUTORS](#) | [SAVE THIS LINK](#) | [SUBMIT](#) | [LEGEND](#)

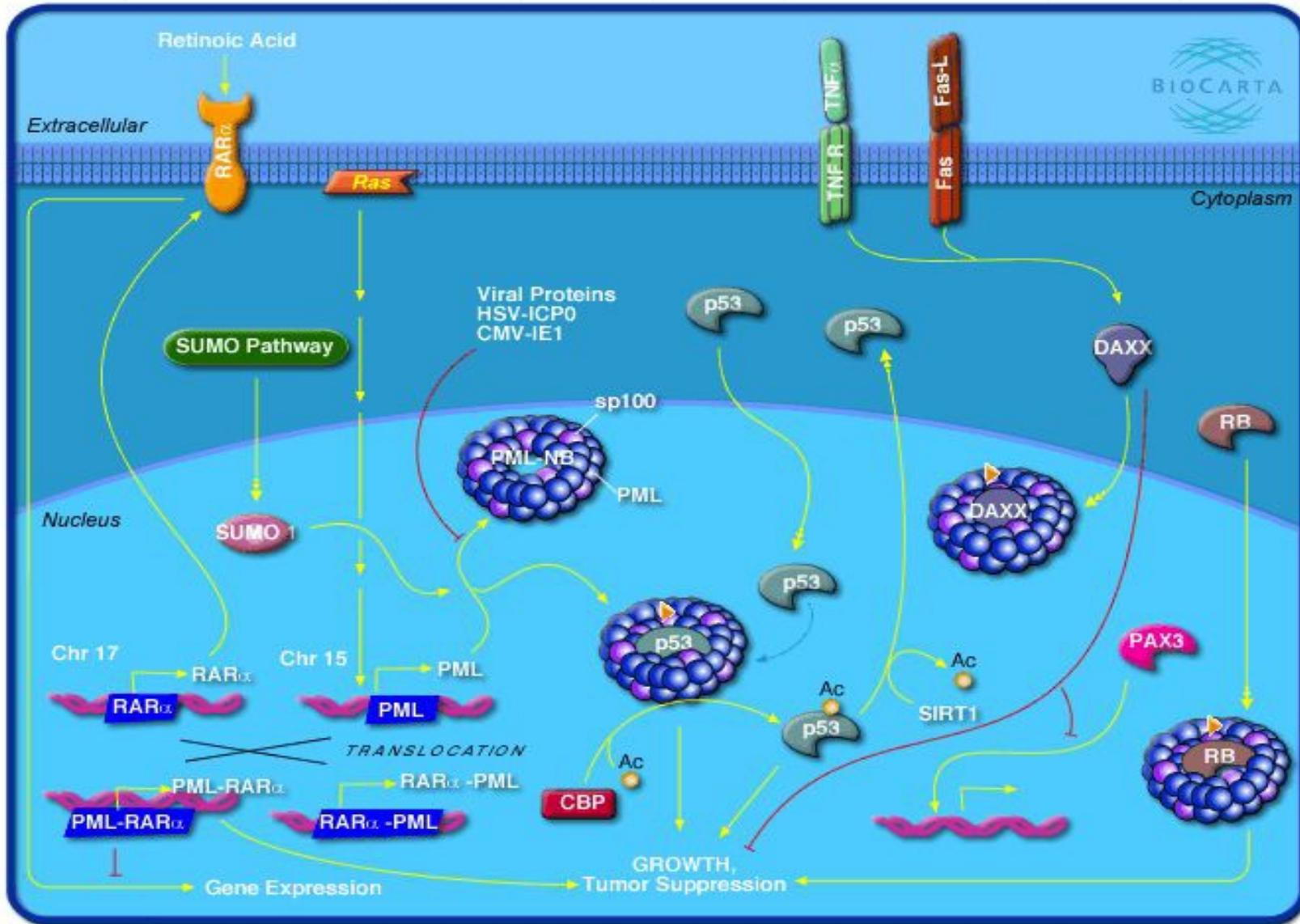


# Herceptin binds to ERB-B2 (HER-2) Blocking Cell Growth



# Regulation of transcriptional activity by PML

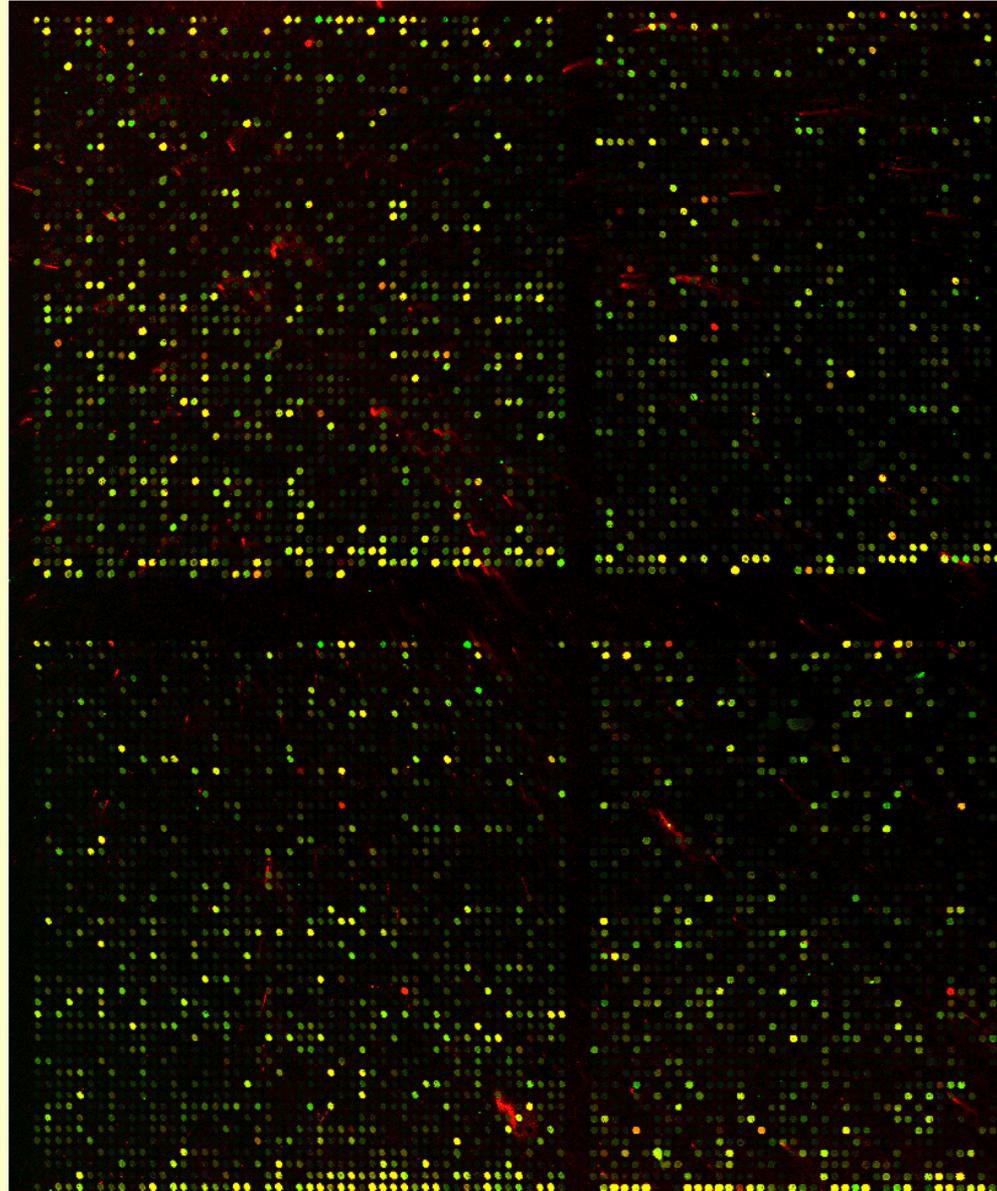
[http://www.biocarta.com/pathfiles/h\\_pmlPathway.asp](http://www.biocarta.com/pathfiles/h_pmlPathway.asp)



# Acute Promyelocytic Leukemia

Tumor cDNA + Retinoic Acid (24 hr)

(Doug Ross & Pat Brown)



# Three strikes to cancer

## Breakthrough phase

A single cell develops a specific driver-gene mutation and begins to divide abnormally

Melanoma      Pancreatic ductal adenocarcinoma      Cervical carcinoma      Colorectal carcinoma

*BRAF*

*KRAS*

*TP53*  
*RB*

*APC*

## Expansion phase

A cell develops an additional driver-gene mutation that gives rise to a benign tumor

*TERT*

*CDK2NA*

*PIK3CA*

*KRAS*

## Invasive phase

A cell develops an additional driver-gene mutation in at least one of the indicated pathways, enabling it to invade surrounding tissues

*CDK2NA*  
*TP53*  
*PIK3CA*

*SMAD4*  
*TP53*

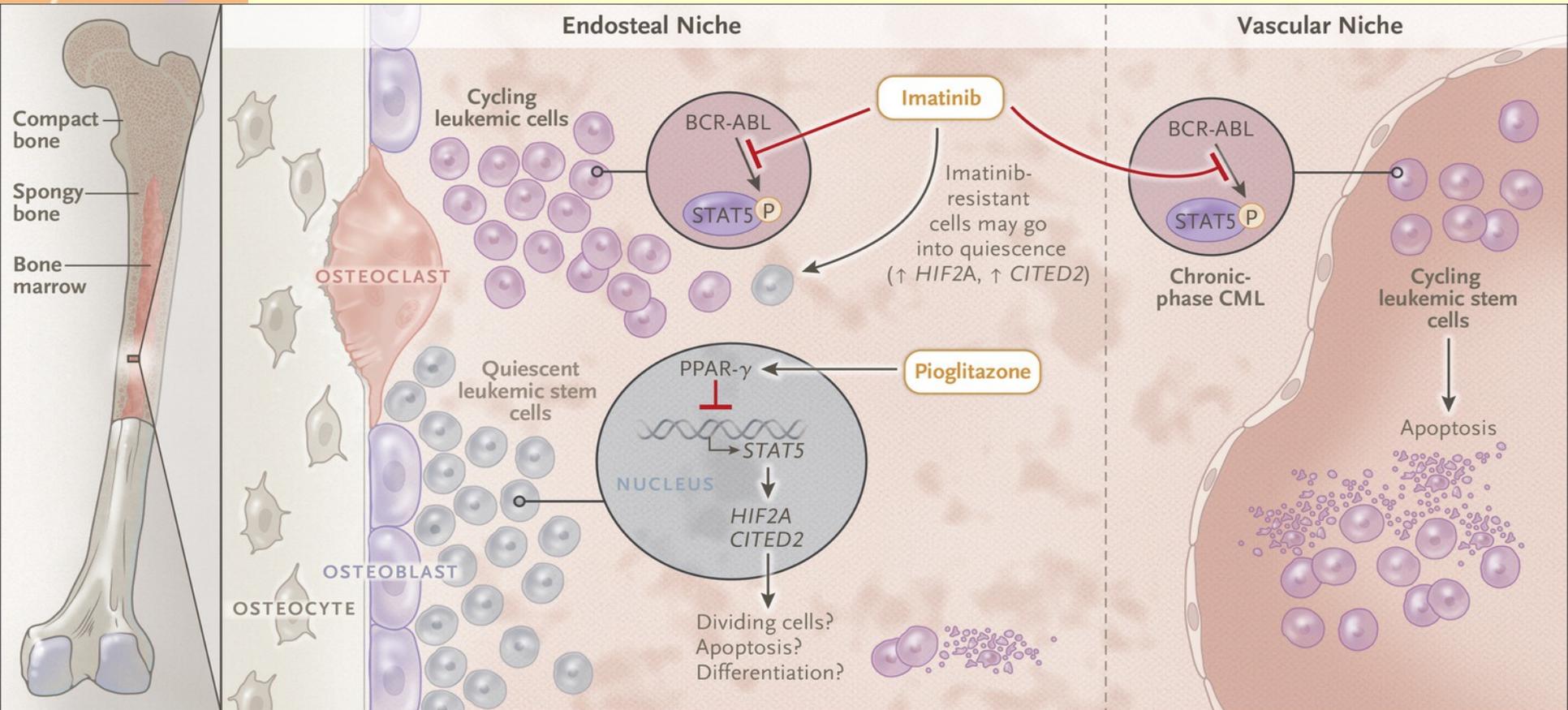
*MAPK1*  
*STRK11*  
*FBXW7*

*SMAD4*  
*TP53*  
*PIK3CA*  
*FBXW7*

Metastasis

Examples of the genetic alterations leading to four representative cancer types are shown. Each gene symbol denotes a pathway. For example, APC denotes the pathway regulated by APC. A "mutation" in a pathway can be achieved by genetic or epigenetic inactivation of both alleles of a tumor-suppressor gene or by genetic activation of an oncogene in that pathway. Pathogenic strains of human papillomavirus initiate the breakthrough phase by disabling both the TP53 and RB pathways

# Targeting Chronic Myeloid Leukemia (CML) Cells with a Double Whammy.



# Predicting Site of Origin for Cancers of Unknown Primary

---

- 1844 tumors tested one at a time versus all 18 tissues of origin
- Retrospective study on well characterized patient samples
- Uses PathChip (functionally similar to Affymetrix HU-133A GeneChip)
  - 604 specimens used for training
  - 636 specimens used for test
  - 604 specimens in reserve for final validation
- Reproducibility from lab to lab
- Performance based on sensitivity (> 70%) & accuracy (> 95%)

# Predicting Site of Origin for Cancers of Unknown Primary

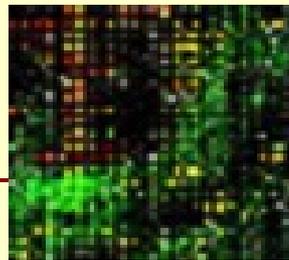
Sample



## Clinical Laboratory

- ❖ Receive sample
- ❖ Process specimen, mRNA extraction and microarray hybridization
- ❖ Submit data file to PathWork for processing

Microarray data file



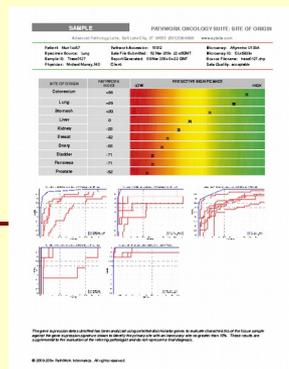
I  
N  
T  
E  
R  
N  
E  
T

- ❖ Receive microarray data file
- ❖ Check file and data quality

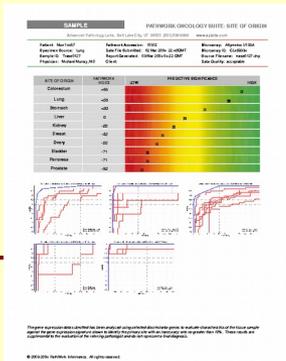
- ❖ Run model against microarray data file

- ❖ Generate report file
- ❖ Deliver report file back to clinical lab

- ❖ Deliver report to oncologist



PDF Report

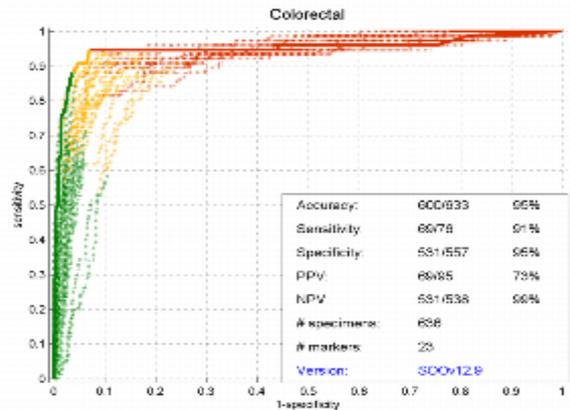


**DEMONSTRATION  
EXAMPLE REPORT**

**PATHWORK ONCOLOGY SUITE: SITE OF ORIGIN  
GENE EXPRESSION-BASED MOLECULAR DIAGNOSTIC**

Patient ID: Liv18350	Client Name:	Data Quality: Acceptable
Specimen Source: Liver	Client ID:	Microarray: Affymetrix U133A
Medical Record:	Order Pathologist:	Microarray ID: CL18350hg133a11
Case Number:	Treating Physician:	Source Filename: 18350hg133a11.cel
PathWork Accession: SOO7982	Date/Time Processed: 29.Jul.2005 11:54PDT	Version: SOOv12.9

SITE OF ORIGIN	PPV	NPV	SIMILARITY SCORE	NEGATIVE	SIMILARITY SCORE	POSITIVE
Colorectal	73%	99%	92			
Hepatocellular	100%	100%	57			
Gastroesophageal	48%	98%	-37			
Pancreatic	88%	99%	-40			
Non-Small Cell Lung Cancer	85%	98%	-48			
Ovarian	98%	98%	-72			
Breast	93%	98%	-74			
Malignant Pleural Mesothelioma	100%	100%	-80			
Kidney	97%	99%	-81			
Squamous	48%	100%	-86			
Thyroid	95%	100%	-88			
Bladder	67%	99%	-89			
Prostate	91%	100%	-89			
Central Nervous System	100%	100%	-95			
Germ Line	88%	100%	-96			
Non Hodgkin's Lymphoma	91%	100%	-100			
Melanoma	91%	100%	-100			
Soft Tissue-Sarcoma	39%	99%	-100			



**KEY**

Sample Site: Liver  
 Primary Site: CO  
 Percent Tumor: 50-75  
 Pathology Morphology: Adenocarcinoma  
 Sample Description: PARTIAL  
 HEPATECTOMY; METASTATIC  
 ADENOCARCINOMA PRIMARY IN  
 COLON, STATUS POST  
 CHEMOTHERAPY.

*For use by CLIA-certified clinical laboratories only. The clinical interpretation of the results should be made in context of the patient's clinical history and other diagnostic tests performed by a qualified individual.*

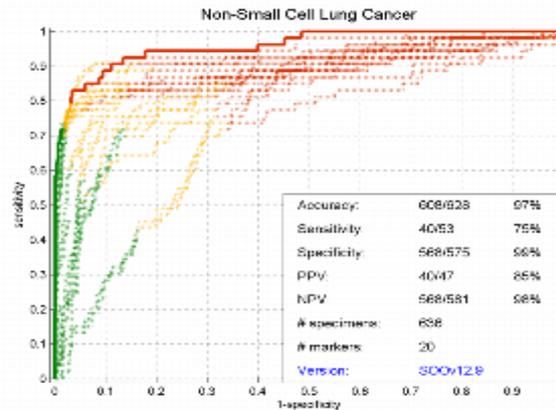
Advanced Pathology Labs  
 123 Diagnostic Drive, Multiplex, CA 99212 (800) 555-1212

**DEMONSTRATION  
EXAMPLE REPORT**

**PATHWORK ONCOLOGY SUITE: SITE OF ORIGIN  
GENE EXPRESSION-BASED MOLECULAR DIAGNOSTIC**

Patient ID: Lun31878	Client Name:	Data Quality: Acceptable
Specimen Source: Lung	Client ID:	Microarray: Affymetrix U133A
Medical Record:	Order Pathologist:	Microarray ID: CL31878hg133a11
Case Number:	Treating Physician:	Source Filename: 31878hg133a11.cel
PathWork Accession: SOO6030	Date/Time Processed: 29.JUL.2005 11:54PDT	Version: SOOV12.9

SITE OF ORIGIN	PPV	NPV	SIMILARITY SCORE	NEGATIVE	SIMILARITY SCORE	POSITIVE
Non-Small Cell Lung Cancer	85%	98%	98			
Colorectal	73%	99%	2			
Gastroesophageal	48%	98%	-43			
Non Hodgkin's Lymphoma	91%	100%	-56			
Pancreatic	86%	99%	-57			
Kidney	97%	99%	-65			
Squamous	48%	100%	-68			
Melanoma	91%	100%	-70			
Bladder	67%	99%	-71			
Ovarian	96%	98%	-71			
Malignant Pleural Mesothelioma	100%	100%	-73			
Thyroid	95%	100%	-74			
Breast	93%	98%	-75			
Central Nervous System	100%	100%	-79			
Prostate	91%	100%	-89			
Hepatocellular	100%	100%	-90			
Germ Line	88%	100%	-91			
Soft Tissue-Sarcoma	39%	99%	-93			



**KEY**

Sample Site: Lung  
 Primary Site: CO  
 Percent Tumor: 25-50  
 Pathology Morphology: Adenocarcinoma  
 Sample Description: LULLUNG WEDGE BIOPSY; METASTATIC ADENOCARCINOMA C/W COLONIC PRIMARY DIAGNOSED 7 YEARS PRIOR; STAGING AT TIME OF ORIGINAL DIAGNOSIS UNKNOWN.

*For use by CLIA-certified clinical laboratories only. The clinical interpretation of the results should be made in context of the patient's clinical history and other diagnostic tests performed by a qualified individual.*

Advanced Pathology Labs  
 123 Diagnostic Drive, Multiplex, CA 99212 (800) 555-1212

# Response Genetics

## RESPONSE GENETICS

Client services: (888)700-7110

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- ResponseDX: Tissue of Origin Test

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- Case Study: History of Multiple Primary Cancers

- Case Study: Breast, Axilla, & Lung Lesions in a Young Woman

- Case Study: FNA of

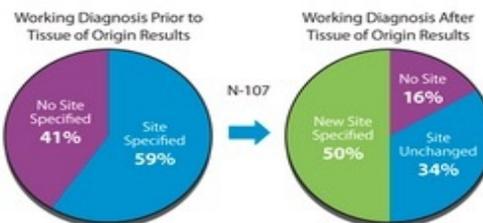
## ResponseDX: Tissue of Origin Test

The ResponseDX: Tissue of Origin Test is a microarray-based gene expression test that aids in identifying challenging tumors, including metastatic, poorly differentiated, and undifferentiated cancers.

- 2000 genes, covering 15 tumors types and 90% of all solid tumors<sup>1</sup>
- Only FDA-cleared test of its type, Medicare-approved
- Performed on FFPE tissue at our CLIA certified, CAP accredited laboratory
- Extensive analytical and clinical validation
- Statistically significant improvement in accuracy over other methods, including IHC<sup>2</sup>

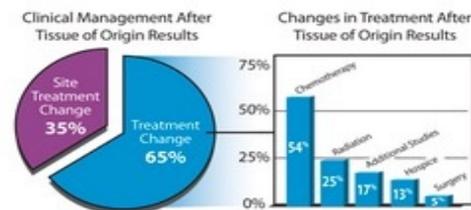
### CHANGE IN DIAGNOSIS

Confirms a working diagnosis 34% of the time  
Identifies a new site 50% of the time<sup>3</sup>



### CHANGE IN THERAPY

Leads to a change in treatment 65% of the time<sup>3</sup>



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# Response Genetics

## ResponseDX: Tissue of Origin™ Test

In challenging cancers that require a second round of IHC, the ResponseDX: Tissue of Origin Test increases diagnostic accuracy and confidence in site-specific treatment decisions.<sup>1</sup>

### 1. A MULTICENTER STUDY DIRECTLY COMPARING THE DIAGNOSTIC ACCURACY OF GENE EXPRESSION PROFILING AND IMMUNOHISTOCHEMISTRY FOR PRIMARY SITE IDENTIFICATION IN METASTATIC TUMORS

*CR Handorf, A Kulkarni, JP Grenert, L Weiss, W Rogers, O Kim, F Monzon, M Halks-Miller, G Anderson, M Walker, R Pillai, WD Henner. Am J Surg Pathol; 2013;37:1067-1075*

Subgroup Analysis	IHC	Gene Expression Profiling	P-value
Well-differentiated (N=106)	85%	87%	0.52
Poorly-differentiated (N=51)	79%	94%	0.016
Poorly-differentiated carcinomas (N=33)	71%	91%	0.023
Overall (N=157)	83%	89%	0.013

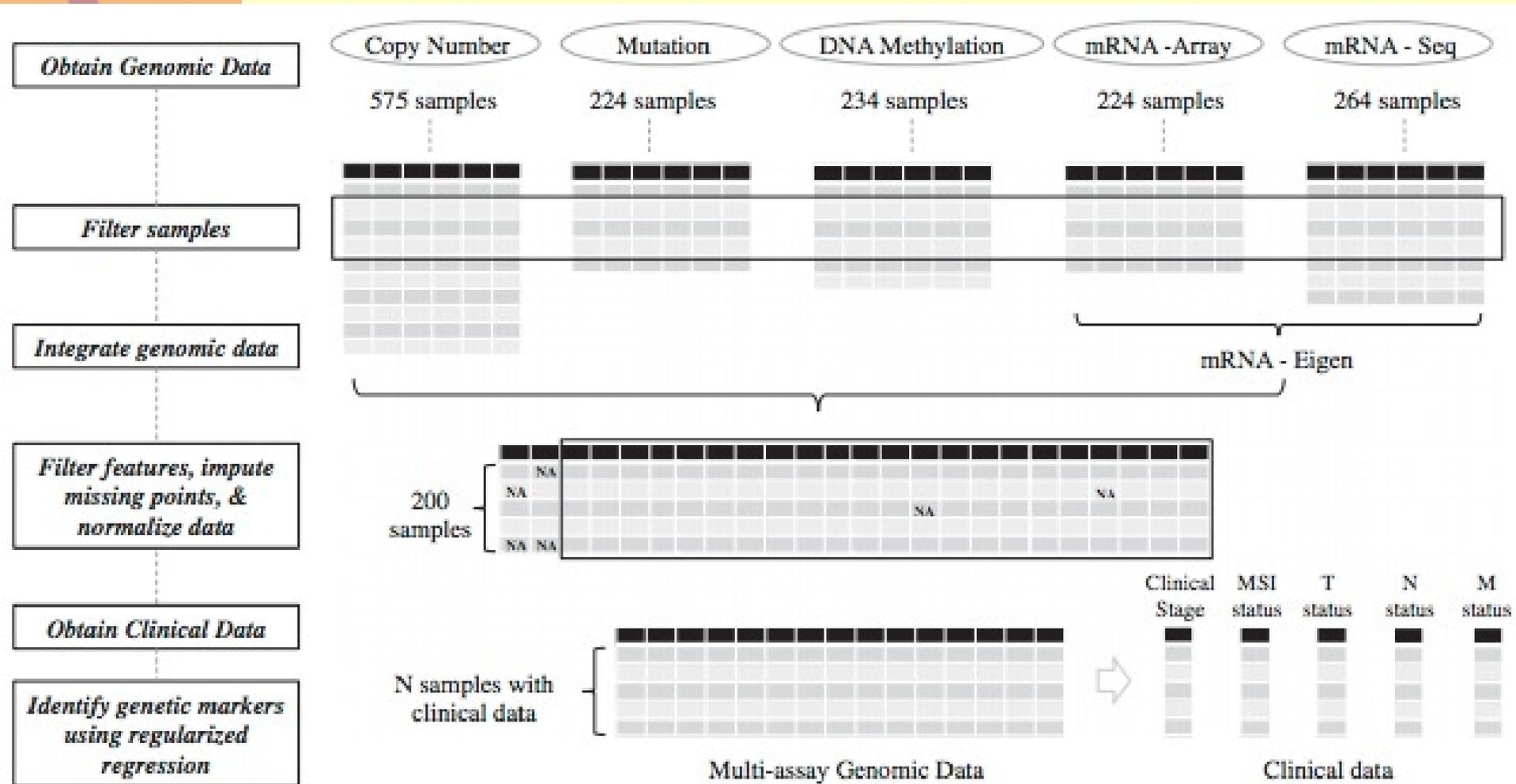
# Tumor Sequence Heterogeneity

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- Hanlee Ji: Suppressor and Oncogene variations in early stage tumors  
2013
- Jay Shendure: Sequence variations in various sections of the genome  
2014
- Stanford Cancer Center Tumor Heterogeneity Symposium 2014
  - Videos
- Hanlee Ji The Genetics of Personalized Cancer Medicine  
2012

# Genes Associated with Colorectal Cancer

<http://www.biomedcentral.com/content/pdf/1755-8794-6-54.pdf>



# Genes Associated with Colorectal Cancer

<http://www.biomedcentral.com/content/pdf/1755-8794-6-54.pdf>

Genomic assay	Direct association	Inverse association
Copy number	Increase with advanced stage	Decrease with advanced stage
Mutation	More frequent in advanced stage	Less frequent in advanced stage
Gene expression	Higher expression in advanced stage	Lower expression in advanced stage
Methylation	Hyper-methylation in advanced stage	Hypo-methylation in advanced stage
Examples	<p>A B C</p>	<p>D E F</p>

# Genes Associated with Colorectal Cancer

<http://www.biomedcentral.com/content/pdf/1755-8794-6-54.pdf>

Copy Number			
Rank	Gene	Chr	Sign
1	<i>FUBP1*</i>	1p31.1	↓
2	<i>CUX1</i>	7q22.1	↑
3	<i>WRN*</i>	8p12	↓
4	<i>MALT1*</i>	18q21.32	↓
5	<i>ERCC5*</i>	13q33.1	↑
6	<i>HOXA13*</i>	7p15.2	↑
7	<i>HOXA11*</i>	7p15.2	↑
8	<i>HOXA9*</i>	7p15.2	↑
9	<i>IPO5</i>	13q32.2	↑

9 out of 9 genes

Mutations		
Rank	Gene	Sign
1	<i>GNAS*</i>	↑
2	<i>ESRRA</i>	↑
3	<i>RUNX1T1*</i>	↓
4	<i>KAT6B*</i>	↓
5	<i>GPHN*</i>	↓
6	<i>STIL*</i>	↓
7	<i>PALB2*</i>	↓

7 out of 7 genes

Methylation		
Rank	Gene	Sign
1	<i>WRN*</i>	↑
2	<i>FOXP4</i>	↓
3	<i>HSD3B7</i>	↓
4	<i>SYK*</i>	↓
5	<i>PRELP</i>	↓
6	<i>MUC1*</i>	↑
7	<i>NTRK1*</i>	↑
8	<i>RNF113A</i>	↑
9	<i>GPR125</i>	↓
10	<i>MGMT</i>	↓

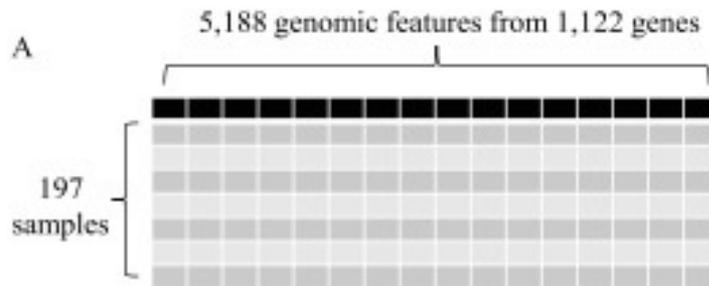
10 out of 33 genes

mRNA		
Rank	Gene	Sign
1	<i>PDK4</i>	↑
2	<i>REEP5</i>	↑
3	<i>TH</i>	↑
4	<i>DDX5*</i>	↓
5	<i>CYP26B1</i>	↓
6	<i>SLC22A11</i>	↓
7	<i>WRN*</i>	↓
8	<i>OR51E2</i>	↑
9	<i>TNFAIP3*</i>	↓
10	<i>DDIT3*</i>	↑

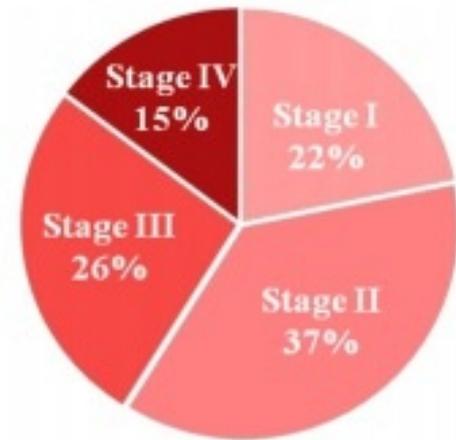
10 out of 65 genes

# Genes Associated with Colorectal Cancer

<http://www.biomedcentral.com/content/pdf/1755-8794-6-54.pdf>



Clinical stage

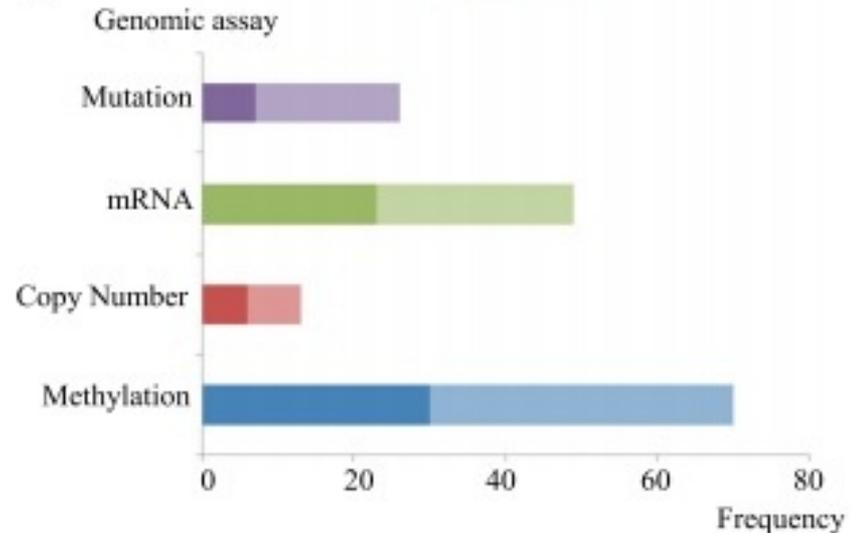


B

Rank	Gene	Assay	Chr	Sign
1	<i>FOXP4</i>	Methyl	6p21.1	↓
2	<i>REEP5</i>	mRNA	5q22.2	↑
3	<i>PDK4</i>	mRNA	7q21.3	↑
4	<i>OR51E2</i>	mRNA	11p15.4	↑
5	<i>WRN</i>	CN	8p12	↓
6	<i>SYK</i>	Methyl	9q22.2	↓
7	<i>S100P</i>	mRNA	4p16.1	↓
8	<i>HIP1</i>	mRNA	7q11.23	↑
9	<i>SDHC</i>	mRNA	1q23.3	↑
10	<i>DDIT3</i>	mRNA	12q13.3	↑
11	<i>ADRA2C</i>	mRNA	4p16.3	↑
12	<i>DDX5</i>	mRNA	17q23.3	↓
13	<i>SYK</i>	mRNA	9q22.2	↓
14	<i>FCRL4</i>	mRNA	1q23.1	↓
15	<i>SLC22A11</i>	mRNA	11q13.1	↓

Top 15 out of 158 selected features

C



# Genes Associated with Colorectal Cancer

**Table 3 Top 25 candidates associated with advanced clinical stage**

Gene	Chr	Score	Elastic-net Feature Rank			
			Copy Number	Gene Expression	Methylation	Mutation
<i>WRN*</i>	8p12	27.03	5 ↓	106 ↓	29 ↑	
<i>SYK*</i>	9q22.2	24.09		13 ↓	6 ↓	
<i>DDX5*</i>	17q23.3	18.94	70 ↓	12 ↓		
<i>ADRA2C</i>	4p16.3	18.13		11 ↑	81 ↓	
<i>GNAS*</i>	20q13.32	16.9			39 ↓	68 ↑
<i>SEMA3B</i>	3p21.31	16.66		82 ↓	28 ↓	
<i>HSD17B2</i>	16q23.3	14.45	17 ↑	120 ↑		
<i>TTN</i>	2q31.2	13.72		80 ↓		66 ↓
<i>FHIT*</i>	3p14.2	13.56			71 ↑	77 ↓
<i>HIST1H4I*</i>	6p22.1	12.82		35 ↑	122 ↓	
<i>FOXP4</i>	6p21.1	12.74			1 ↓	
<i>REEP5</i>	5q22.2	12.66		2 ↑		
<i>PDK4</i>	7q21.3	12.58		3 ↑		
<i>OR51E2</i>	11p15.4	12.49		4 ↑		
<i>S100P</i>	4p16.1	12.25		7 ↓		
<i>HIP1*</i>	7q11.23	12.17		8 ↑		
<i>ZNF570</i>	19q13.12	12.09		50 ↑		116 ↓
<i>SDHC*</i>	1q23.3	12.09		9 ↑		
<i>DDIT3*</i>	12q13.3	12		10 ↑		
<i>CRTC1*</i>	19p13.11	11.92			130 ↑	38 ↓
<i>FCRL4*</i>	1q23.1	11.84		14 ↓	155 ↓	
<i>SLC22A11</i>	11q13.1	11.6		15 ↓		
<i>FLT1</i>	13q12.2	11.51		16 ↑		
<i>CYP26B1</i>	2p13.2	11.35		18 ↓		
<i>RNF113A</i>	Xq24	11.27			19 ↑	

# The Genetics of Personalized Cancer Medicine

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## The Genetics of Personalized Cancer Medicine

Quicktime

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