# Principles of Chemotherapy and Other Agents

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## Principles of Chemotherapy and Other Agents
Agenda

- A historical perspective: Cancer in Context
- How does one develop a drug for cancer?
- How can we target the unique biology that makes a cancer cell a cancer cell?
- Examples:
  - Turning genes on and Off
  - Teaching Cancer Cells How to Die
  - Targeting the Molecular Roots of Lymphoma

## Fundamental Defects in Cancer Cells
## Shifting the Balance Between of Survival & Growth

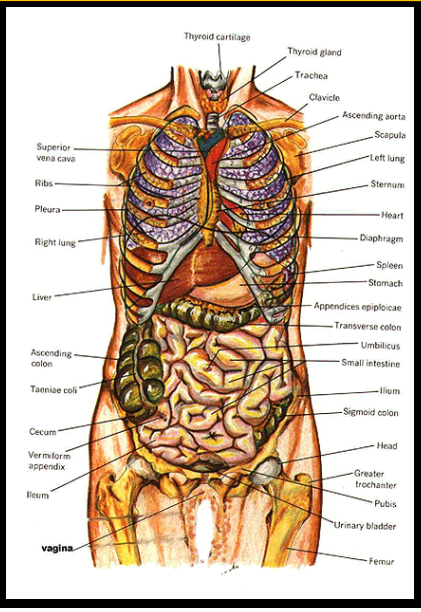
*Growth*

- Cells grow when they shouldn't – the accelerator is always turned-on
- The breaks to inhibit growth are turned-off

*Survival*

- Those signals that tell a cell to die when something is not right are turned-off
- Those signals that instruct a cell to survive are always turned-on

## Cancer is Not One Disease
## It May be Hundreds to Thousands




Organ
(lung, breast, skin, colon, bone, blood)

↓

Tissue
(epithelial, hematopoietic, mesenchymal)

↓

Type of Cell
(squamous, columnar, lymphocyte)

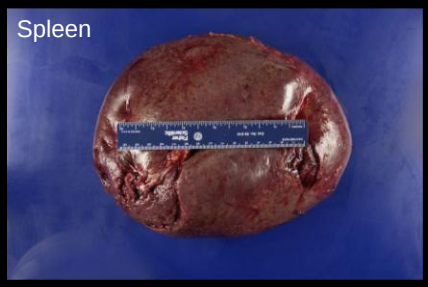
↓

Features of Cell
(B-cell vs T-cell, ER, ras, Her-2Neu)

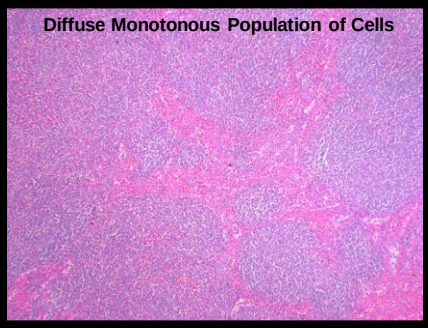
↓

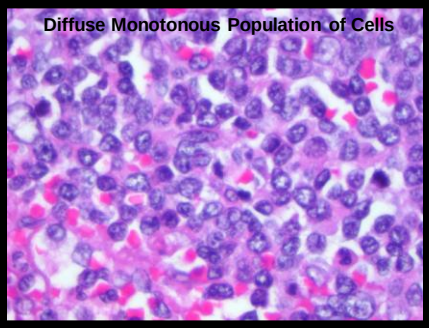
Molecular Sub-type
(Genetic profile)

## DIAGNOSIS HAS EVOLVED FROM EMPHASIS ON THE ORGAN & MORPHOLOG

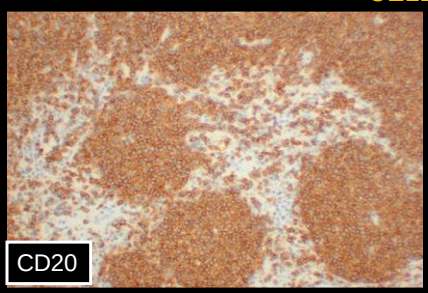


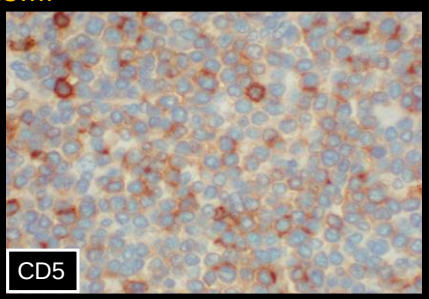


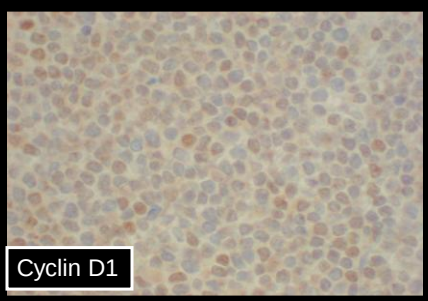


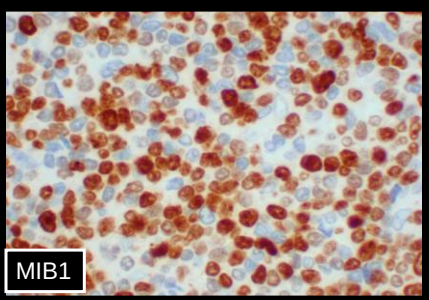




## .....TO INCLUDE BIOLOGICAL FEATURES OF CELLS BASED ON THE DIFFERENTIAL EXPRESSION OF PROTEINS IN OR ON CANCER CELLS....

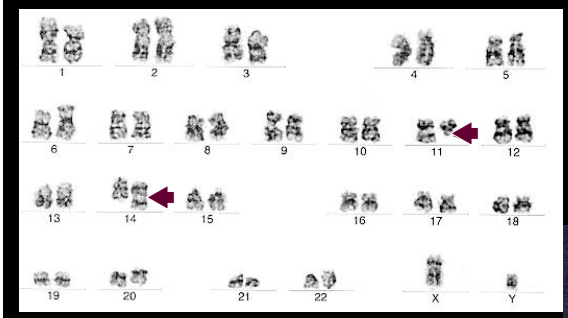


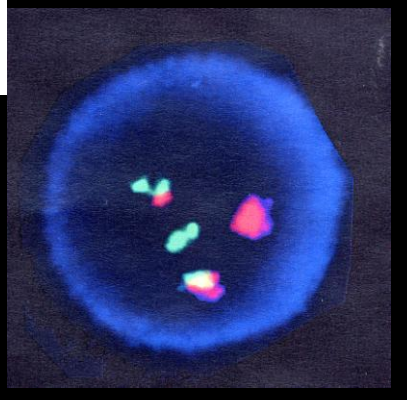



## ……AND CHARACTERIZATION OF THE GROSS AND MOLECULAR CHANGES IN WHOLE CHROMOSOMES.....



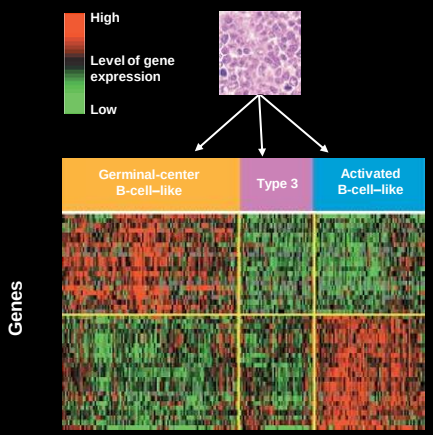
Karyotype of patient with mantle cell lymphoma showing the classic t(11:14) chromosomal translocation)

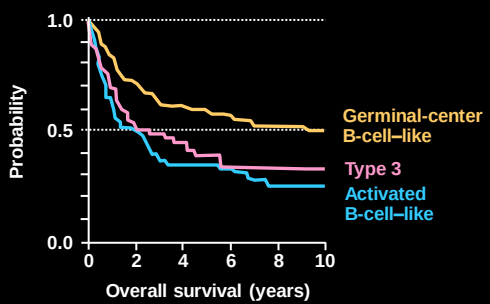


Floursence In-situ Hybridization Showing the t(11:14) translocation

## …….To The Detailed Determination of Which Genes are Turned On or Turned Off in Different Patients with the 'Same Disease' ……

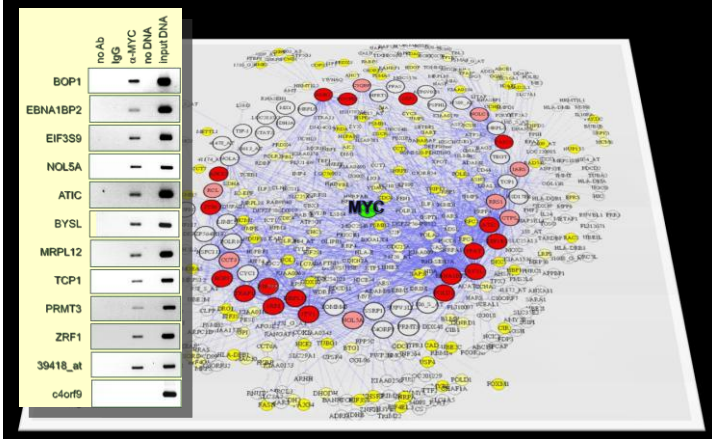
In what was thought to be one disease (DLBCL) we now have three different disease, each with a different prognosis




Rosenwald A et al. *N Engl J Med*. 2002;346:1937-1947.

## ……To Now Defining Cancer Cell Signaling Networks - Using Systems Biology – To Understand Which Genes Talk to Whom……..





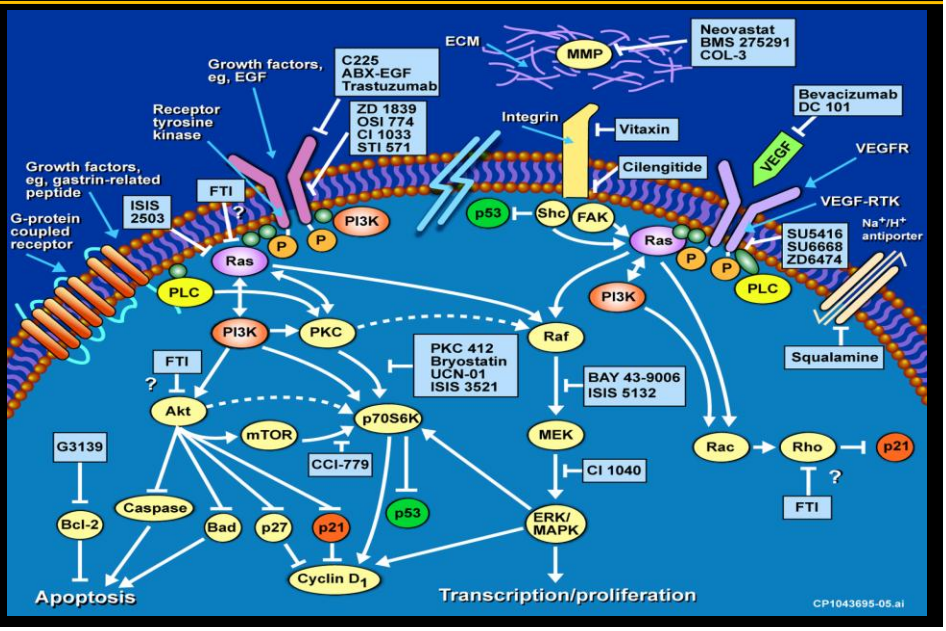
**>50% of known direct MYC targets**

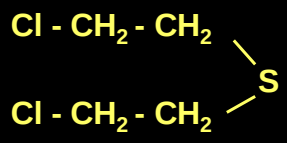
**>90% of new targets validated by ChIP**

**Scale free, hierarchical control structure**

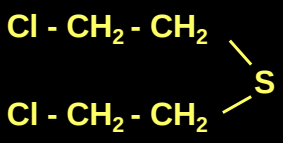
Basso K et al. (2005), Nat Genet.;37(4):382-90.
Margolin AA et al. (2006), Nature Protocols; 1(2): 662-671

## ……All of Which is Leading To a New Diagnostic, Prognostic and Molecular View of Cancer.






| | |
|---|---|
| **1854** | Synthesized |
| **1887** | Vesicant properties noted: eye, lungs and skin |
| **1914 - 1945** | World War I and II - Agent classified and developed as chemical warfare agent |
| **1919** | Krumbhaar & Krumbhaar note leukopenia, aplasia of the bone marrow, dissolution of lymphoid tissue in autopsies |
| **1931** | Clinical trials show no benefit, excess toxicity |
| **1942** | Auerbach and Robson describe very first evidence of chemical mutagenesis in Drosophila |




**Bis (2-Chloroethyl) sulfide**

**[Mustard Gas, Yperite]**

| | |
|---|---|
| **1854** | Synthesized |
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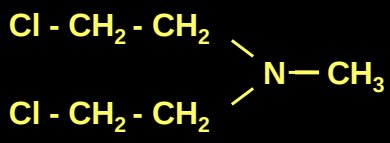
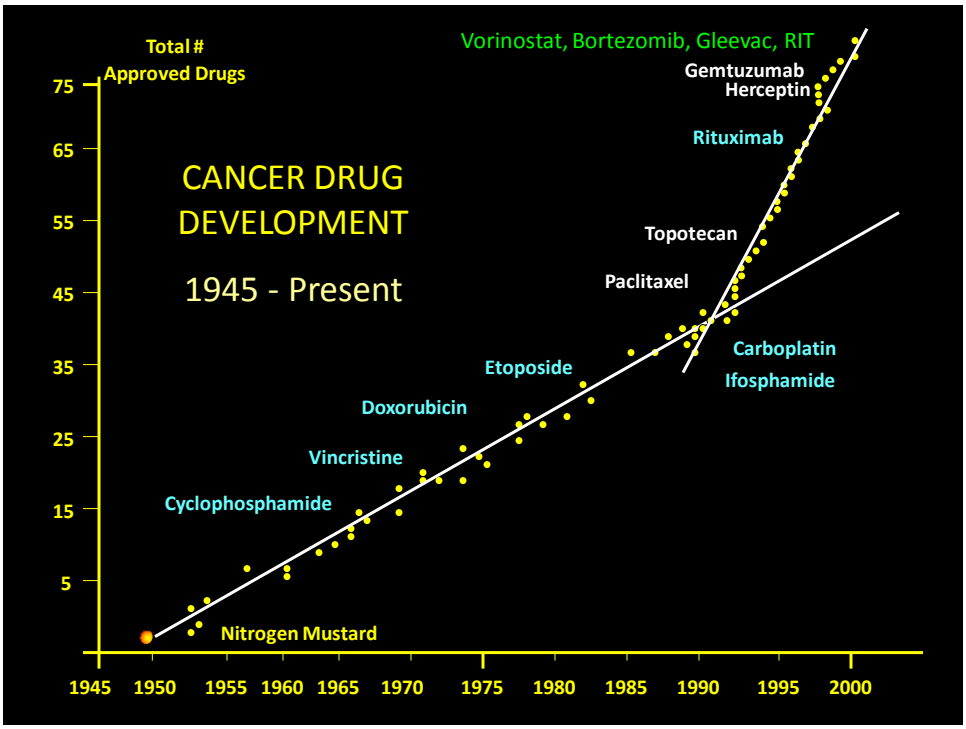



**Methyl-bis (2-Chloroethyl) amine**

**[Nitrogen Mustard, Mechlorethamine]**

| | |
|---|---|
| **1914 - 1945** | During WW I & II - New less toxic agents synthesize as part of chemical warfare development – secrecy restrictions |
| **1940's** | Goodman and colleagues show effect of nitrogen mustard on lymphosarcoma in mice |
| **1946** | 3 Clinical trials in patients with Hodgkin's Disease, Non-Hodgkin's Lymphoma and leukemia show clinical benefit of nitrogen mustard – declassified & approved |

**THE ERA OF MODERN CHEMOTHERAPY IS LAUNCEHD**



## NOVEL CHEMOTHERAPY TARGETS & AGENTS

Most Effect Cancer Cell Specific Pathways of Growth and Survival

**GENE EXPRESSION**

- HDAC Inhibitors
- Proteasome Inhibitors
- Antisense Molecules
- Hypomethylating Agents

**SIGNAL TRANSDUCTION**

- G-proteins, RAS
- Farnesyl transferase inhibitors
- PKC (β)

**ONCOGENES**

- bcr-abl

**APOPTOSIS**

- Oblimersen
- AT-101
- ABT-787
- Anti-TRAIL

**CELL CYCLE**

- cdk Inhibitors

**NEW DERIVATIVES**

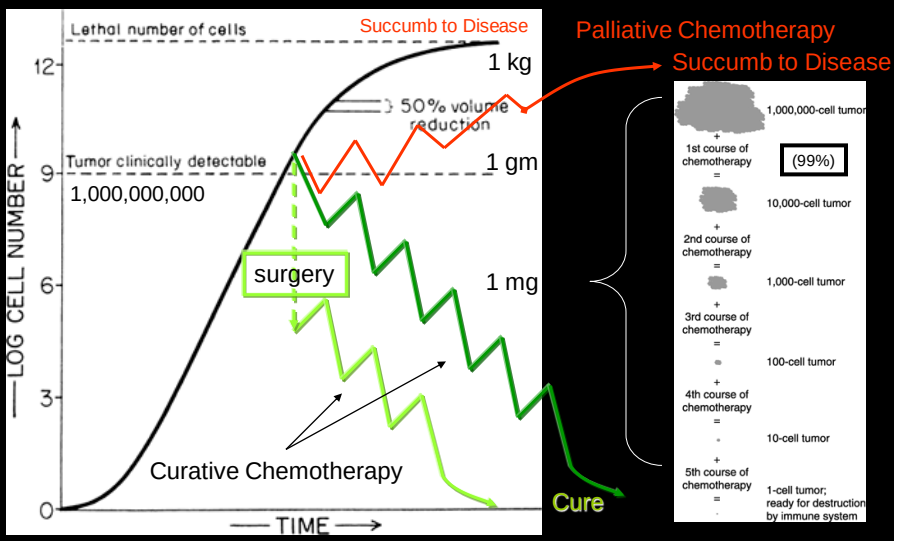
- Pralatrexate
- Liposomal Preparations

Most Anticancer Drugs Used

Today Broadly

Affect How Cells Divide

# Effects of Treatment on Tumor Burden




Frei, 1984

1,000,000,000

First cycle of therapy → Kill 99%

1,000,000

Second cycle of therapy → Kill 99%

10,000

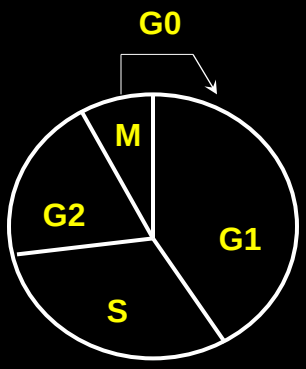
Third cycle of therapy → Kill 99%

100

Fourth cycle of therapy → Kill 99%

1

# EFFECTS OF CANCER DRUGS ON THE CELL CYCLE




THE CELL CYCLE

## CELL CYCLE NON-SPECIFIC AGENTS

- ***Cis*-Platin**
- **Alkylating agents**
- **Nitrosoureas**

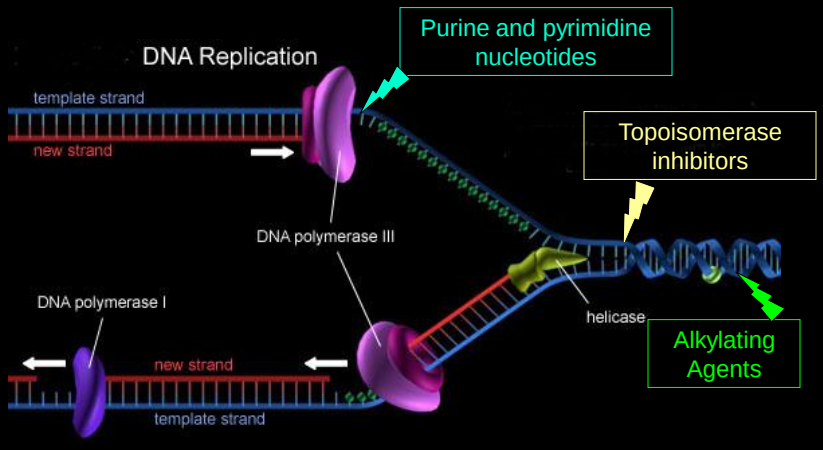
**Effective for both low and high growth fraction tumors**

## CELL CYCLE SPECIFIC AGENTS

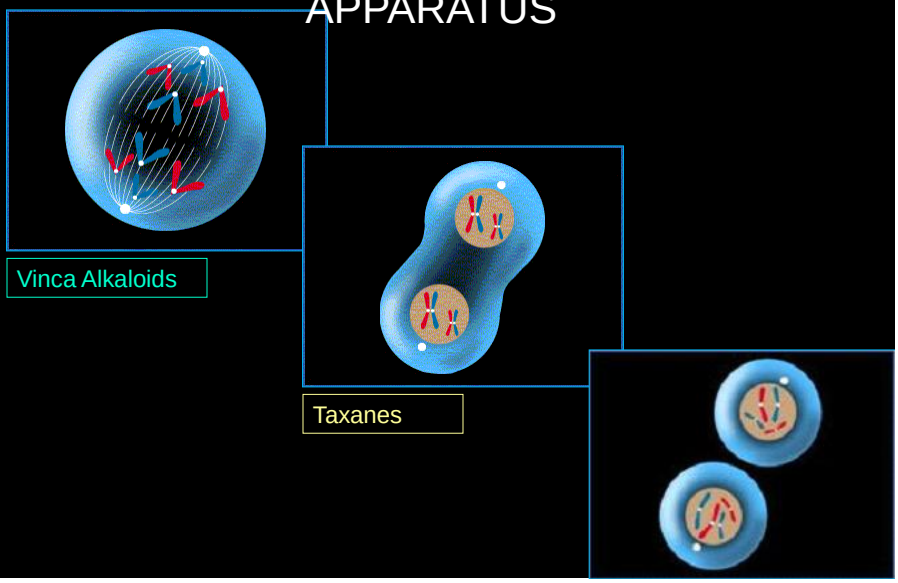
- **Antimetabolites**
- **Bleomycin**
- **Vinca Alkaloids**

**Effective for high growth fraction malignancies (eg: hematologic cancers)**

# 30 YEARS OF DRUG DEVELOPMENT…….
## DISRUPTING DNA SYNTHESIS



## ALSO INCLUDING TARGETS……
## DISRUPTING THE MITOTIC APPARATUS




## TRADITIONAL CHEMOTHERAPY TARGETS
Most Effect DNA in a Non-Specific Manner

**DNA DAMAGE**
- Alkylating Agents

**Broadly Modifies DNA**

**MITOTIC SPINDLE POISONS**
- Vinca alkaloids
- Taxanes

**Broadly inhibit proteins than cause one cell to become two**

**DNA SYNTHESIS**
- Purine antimetabolites
- Pyrimidine antimetabolites
- Antifolates

**Broadly Act as Fraudulent Mimics of Normal DNA Components**

- Ribonucleotide reductase inhibitors
- DNA polymerase inhibitors

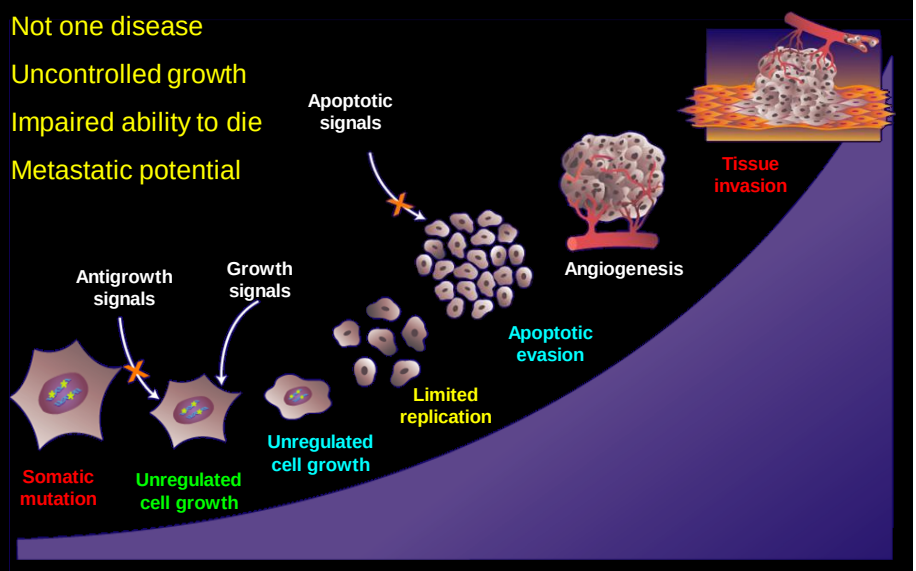
**Broadly inhibit enzymes necessary for making new DNA**

## Major Question:
How Can We Affect Tumor Cells More Selectively?

## The Answer:
Target That Biology Present in Only the Tumor

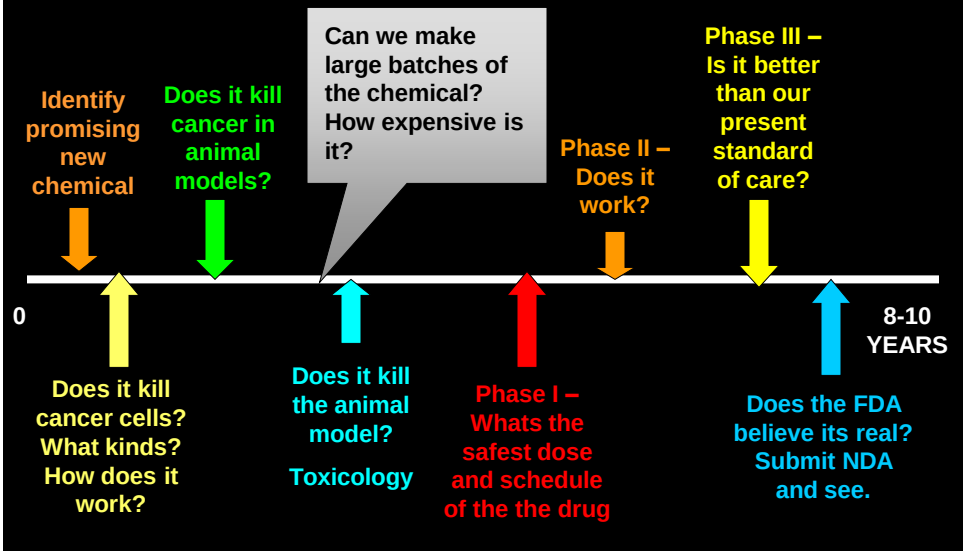
# THE HALLMARKS OF CANCER

- Not one disease
- Uncontrolled growth
- Impaired ability to die
- Metastatic potential



# THE PROCESS OF DRUG DEVELOPMENT

**A DECADE LONG PROCESS FOR ONLY $800 MILLION TO $1 BILLION**




All things are poisons; there is none which is not a poison

The right **dose** differentiates a poison from a remedy.

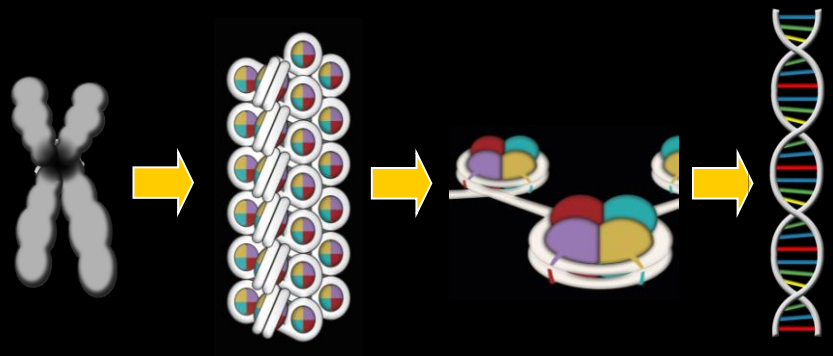
*Paracelsus*

## Epigenetics
## Identical Mice with Variable Hair Color

- DNA methylation
- Histone modifications (Histone code)
- Switches that turn the genes on and off differ slightly


Morgan *et al. Nat Genetics* 23, 314 (1999)

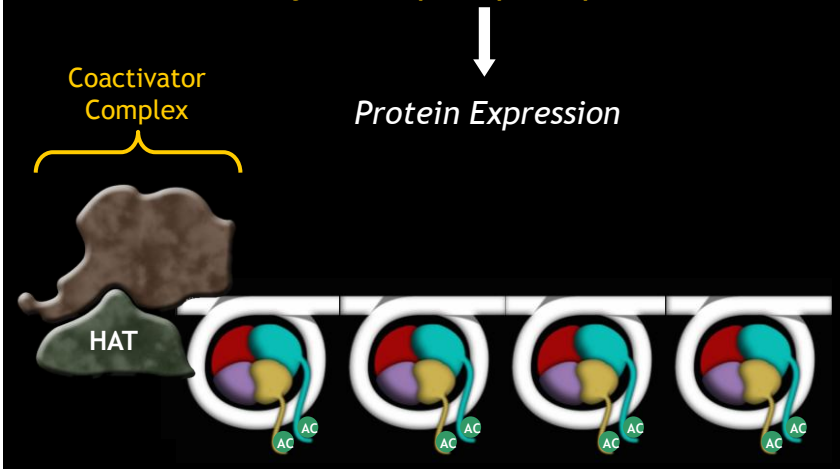
## Chromatin Structural Composition



Chromosome Solenoid Nucleosome DNA

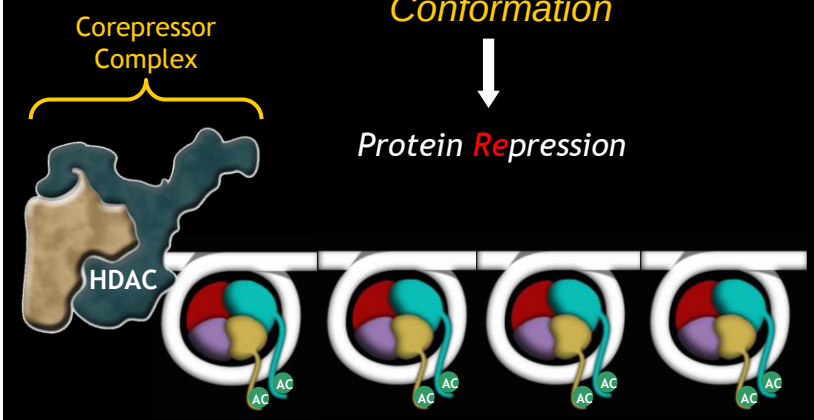
# Acetylation of Histones Allows Transcription

*Histone Acetylation (HAT) = Open Conformation*



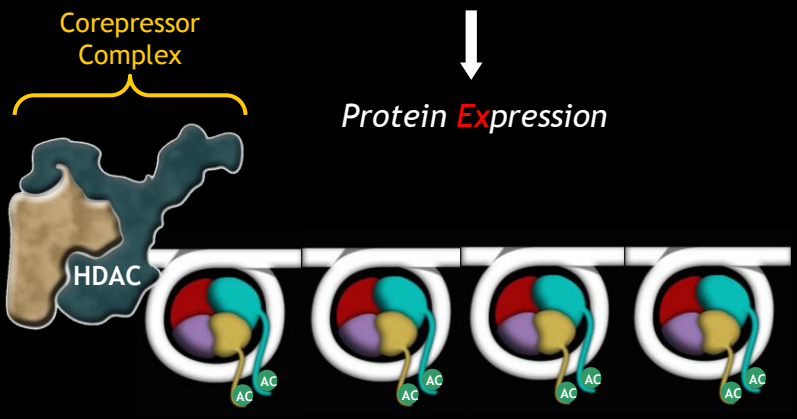

# Deacetylation of Histones Blocks Transcription

*Histone Deacetylation (HDAC) = Closed Conformation*



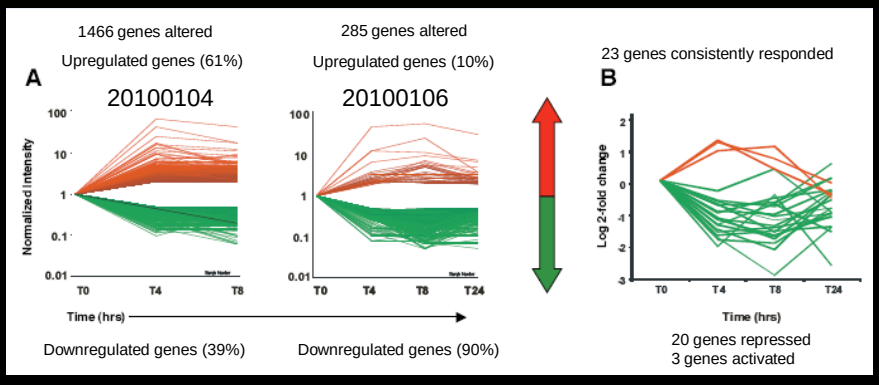
# Inhibition of HDACs Blocks Deacetylation of Histones

*Histone Deacetylation (HDAC) = Closed Conformation*



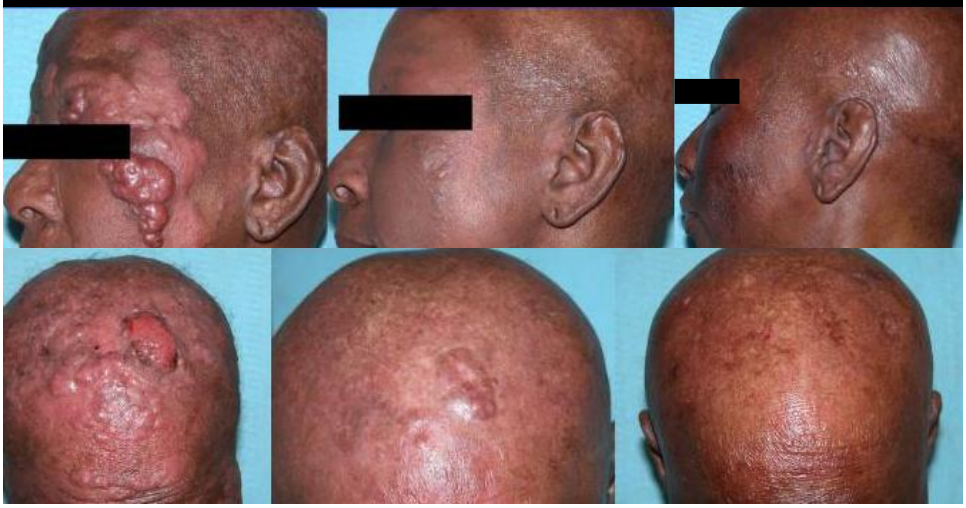

# Differential Gene Expression Changes in Response to LBH589

- LBH589 induces rapid (by 4 hours) and robust changes in tumor cell gene expression
- Persisted for at least 8 hours for most genes
- Consistent with cell line data
- 1- 4% of genes were significantly altered with the majority of genes down regulated
- Combined data identified 23 genes that were altered in all patients

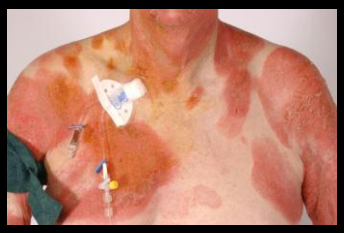


## Cohort 1: Partial Response in Stage IVB with Transformed MF (6 prior therapies including TBSEB, CVP, Ontak, and Bexarotene) – Duvic et al., 2005

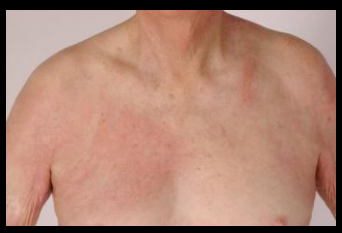
Baseline | Week 8 | Week 24



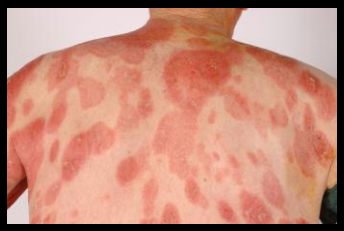
## Depsipeptide Response in CTCL:

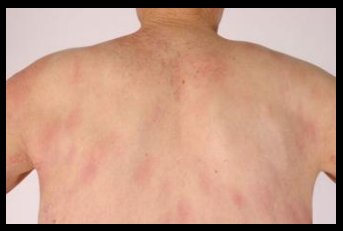


**1/22/04**



**2/18/04**





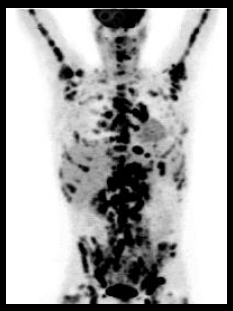
Piekarz R, et al. Oral Presentation ASH 2005 Annual Meeting; *Blood* 2005 106: Abstract 231

# MGCD0103 Clinical Activity in Hodgkin's Lymphoma: Case Study 1

31-Year-old female with extensive prior therapy

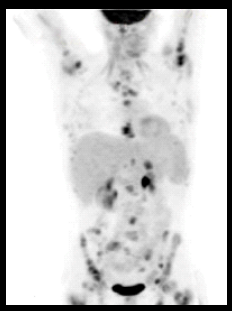
| Regimen | Best Response |
|---|---|
| ABVD | PR |
| XRT | Not Eval |
| DHAP | PR |
| Auto SCT | Not Eval |
| IGEV | Progression |
| DHAP | Progression |
| Fludarabine/ Melphalan | Progression |
| Allo SCT | Progression |
| Donor Lymphocyte | Progression |
| MOPP | Not Eval |
| ESHAP | Progression |
| IEV | Progression |

Baseline



788 mm

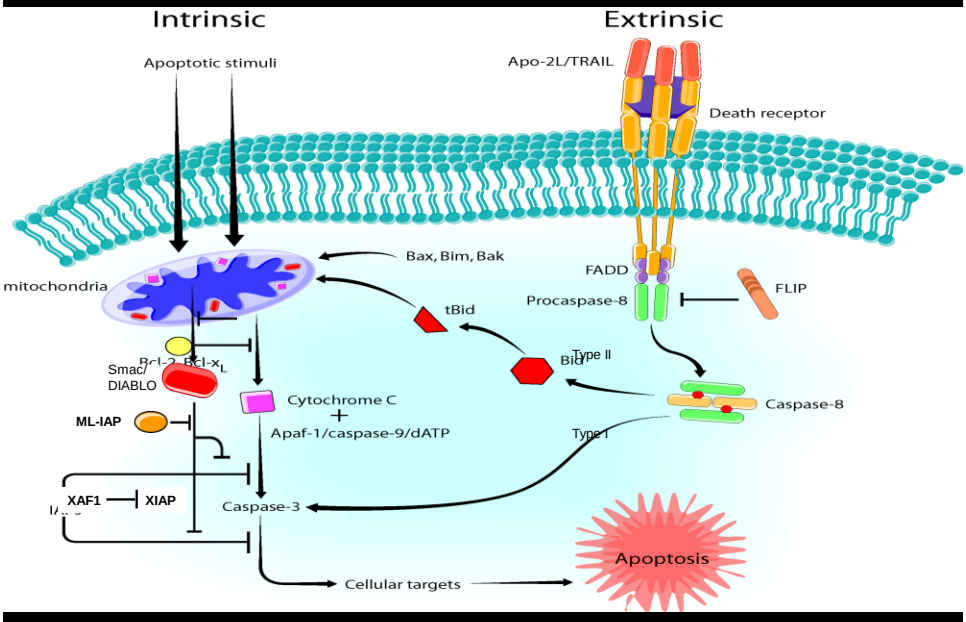
Months



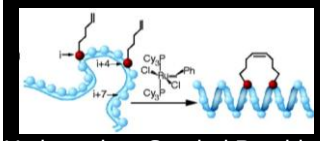
378 mm

Younes, A, et al. ASCO 2007, abstract 8000

# TEACHING CANCER CELLS HOW TO DIE



# Strategies Directed Towards Bcl-2 Inhibition

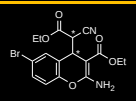


Hydrocarbon Stapled Peptides

$K_i$ = 39 nM (Bcl-2)
Walensky et al., Science, 2004, 305, 1466

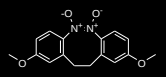
Genasense™ (Ph III)
Klasa et al., Anitsense Nucl. Acid Drug Devel., 2002, 12, 193

Antisense



HA14-1

$K_i$ = 9.0 μM (Bcl-2)
Wang et al., PNAS, 2000, 97, 7124



BL-11

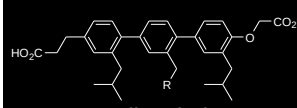
$K_i$ = 9-10 μM (Bcl-2, $X_L$)
Enyedy et al., J. Med. Chem, 2001, 44, 4313

Structure-based design

Proteo-mimetics

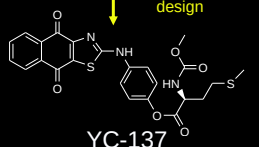
Virtual screening

Library screening



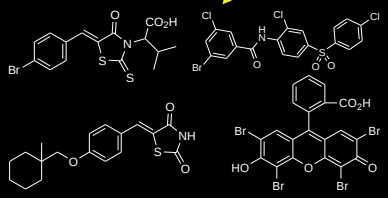
α-Helix Mimicry

$K_i$ = 0.11 μM (Bcl-$X_L$)
Kutzki et al., J. Am. Chem. Soc., 2002, 124, 11838



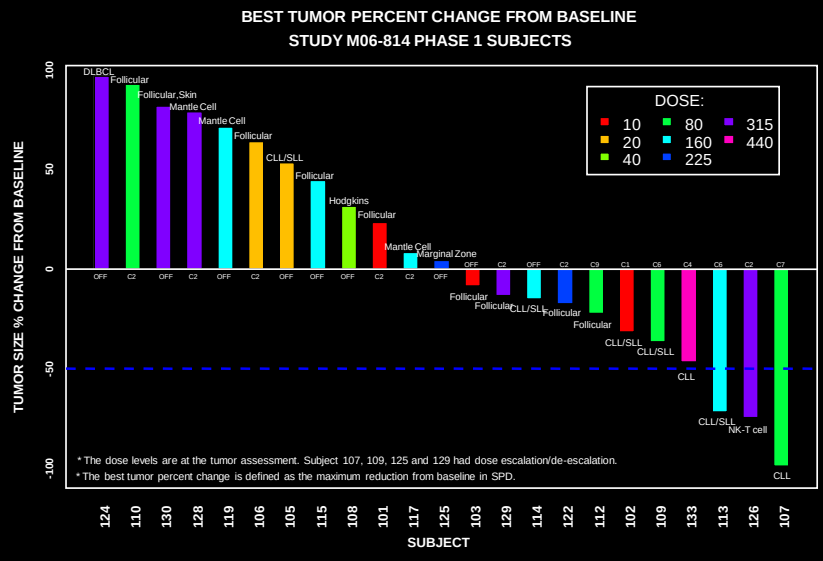
YC-137

$K_i$ = 1.3 μM (Bcl-2)
Real et al., Cancer Res., 2004, 64, 7947



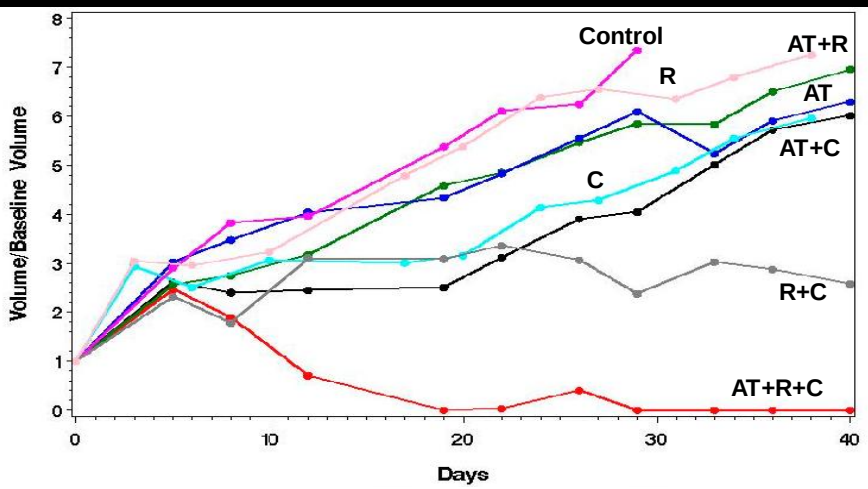
$K_i$ = 2-22 μM (Bcl-2,$X_L$)
Degterev et al., Nat. Cell Biol., 2001, 3, 173
Shiau et al., Cancer Res., 2005, 65, 1561
Tan et al., J. Cancer Res. Clin. Oncol., 2003, 129, 437

# PROMISING SINGLE AGENT ACTIVITY OF ABT-263 IN NHL



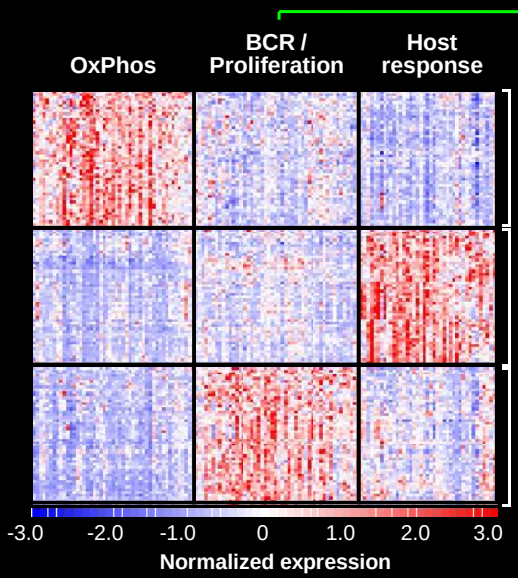

O'Connor et al., 2008, Lugano

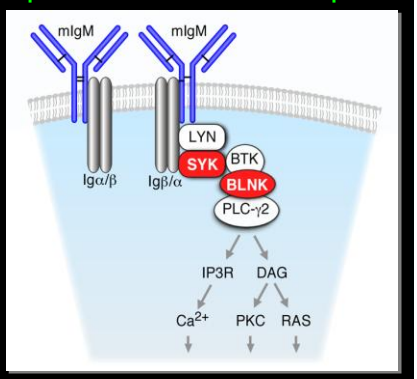
## In Vivo Activity of AT-101 in a SCID Beige Model of B-cell Lymphoma (RL): AUC per day analysis




**The triplet combination demonstrated statistical significant shrinkage of the tumor volume compared to any other treatment group in a multiple comparison model.**

## INCREASINGLY, OUR TARGETS COME FROM MINING THE GENOME: DLBCL IS NOT A SINGLE DISEASE




BCR Lymphomas have increased expression of the BCR components

# Phase I/II Trial: Fostamatinib in Relapsed/Refractory B-Cell NHL

- Phase I (N=13)
  - DLBCL (N=3), FL (5), MCL (3), CLL/SLL (2)
  - Fostamatinib 200 mg (N=6) or 250 mg (N=7) BID
  - Dose-limiting toxicities: neutropenia, thrombocytopenia, diarrhea
- Phase II (N=68)
  - DLBCL (N=23), FL (21), CLL/SLL (11), MCL (9), LPL (1), MZL (3)
  - 200 mg BID

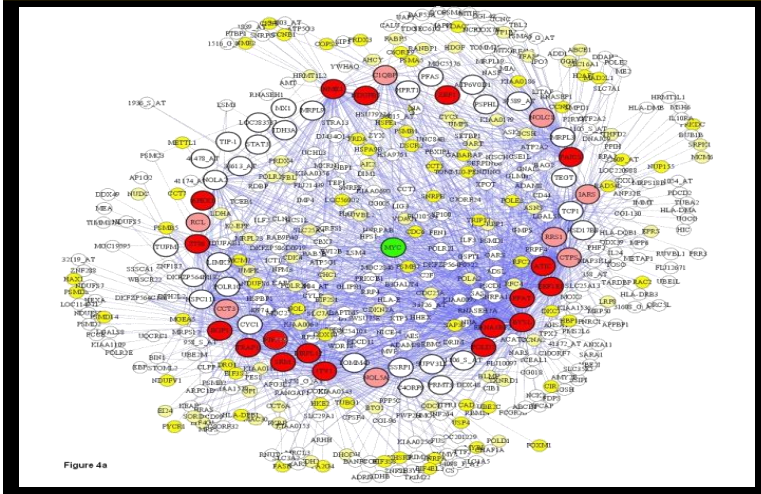
| Response | | | |
|---|---|---|---|
| **Group** | **N** | **ORR** | **CR** |
| DLBCL | 23 | 24% | 1 |
| FL | 21 | 10% | 0 |
| CLL/SLL | 11 | 55% | 0 |
| MCL | 9 | 11% | 0 |

| **AE** | **All Grades** | **Grade 3/4** |
|---|---|---|
| Diarrhea | 41% | 0 |
| Fatigue | 41% | 0 |
| Neutropenia | 31% | 18% |
| Anemia | 27% | 7% |
| Thrombocytopenia | 24% | 3% |
| Hypertension | 22% | 6% |

Friedberg. *Blood, 2010; 115 (13)*

# The Future of Drug Discovery – A Systems Biology Approach to Understanding Cancer Signaling Networks

## Reverse Engineering of The B-Cell





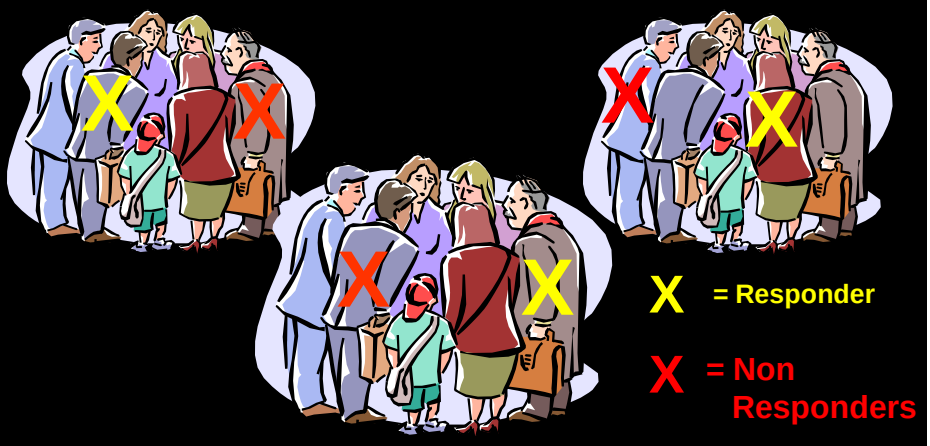
Basso K et al. (2005), Nat Genet. 37(4):382-90. / Margolin AA et al. (2006), Nature Protocols; 1(2): 662-671

## THE EMPIRIC STRATEGY FOR DRUG THERAPY

**Treat All Patients with the Same Diagnosis with the Same Medications**

## INDIVIDUALIZING TREAMENT STRATEGY FOR SPECIFIC PATIENTS AND DISEASES

**Tailor Treatment to the Patients Host and Tumor Genetics**



# FUTURE TRENDS AND OUTLOOK

- We are witness to the greatest renaissance ever in the treatment of cancer
- Understanding cancer biology has directly translated into new opportunities for treatment
- New therapies unlikely to supplant old
- The Challenge, integrating new agents into the conventional treatment paradigms to improve the results
- What can you do?

ENROLL ON A CLINICAL TRIAL WHERE EVER FEASIBLE

# THANK YOU!!