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

<table>
<thead>
<tr>
<th>Organ</th>
<th>Tissue</th>
<th>Type of Cell</th>
<th>Features of Cell</th>
<th>Molecular Sub-type</th>
</tr>
</thead>
<tbody>
<tr>
<td>(lung, breast, skin, colon, bone, blood)</td>
<td>(epithelial, hematopoietic, mesenchymal)</td>
<td>(squamous, columnar, lymphocyte)</td>
<td>(B-cell vs T-cell, ER, ras, Her-2Neu)</td>
<td>(Genetic profile)</td>
</tr>
</tbody>
</table>
DIAGNOSIS HAS EVOLVED FROM EMPHASIS ON THE ORGAN & MORPHOLOGY 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.

>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.

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

......All of Which is Leading To a New Diagnostic, Prognostic and Molecular View of Cancer.
**Cl - CH₂ - CH₂**

**Cl - CH₂ - CH₂**

\[ \text{S} \]

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

---

**Cl - CH₂ - CH₂**

**Cl - CH₂ - CH₂**

\[ \text{S} \]

Bis (2-Chloroethyl) sulfide

[Mustard Gas, Yperite]

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Methyl-bis (2-Chloroethyl) amine

Cl - CH₂ - CH₂

Cl - CH₂ - CH₂

N — CH₃

[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 LAUNCHED

CANCER DRUG DEVELOPMENT
1945 - Present

Total # Approved Drugs

Nitrogen Mustard
Cyclophosphamide
Vincristine
Etoposide
Paclitaxel
Carboplatin
Ifosfamide
Topotecan
Gemtuzumab
Herceptin
Rituximab
Vorinostat, Bortezomib, Gleevec, RIT

Paclitaxel
Gemtuzumab
Herceptin
Rituximab
Vorinostat, Bortezomib, Gleevec, RIT
### NOVEL CHEMOTHERAPY TARGETS & AGENTS
Most Effect Cancer Cell Specific Pathways of Growth and Survival

<table>
<thead>
<tr>
<th>GENE EXPRESSION</th>
<th>APOPTOSIS</th>
</tr>
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<tbody>
<tr>
<td>• HDAC Inhibitors</td>
<td>• Oblimersen</td>
</tr>
<tr>
<td>• Proteasome Inhibitors</td>
<td>• AT-101</td>
</tr>
<tr>
<td>• Antisense Molecules</td>
<td>• ABT-787</td>
</tr>
<tr>
<td>• Hypomethylating Agents</td>
<td>• Anti-TRAIL</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SIGNAL TRANSDUCTION</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• G-proteins, RAS</td>
<td></td>
</tr>
<tr>
<td>• Farnesyl transferase inhibitors</td>
<td></td>
</tr>
<tr>
<td>• PKC (β)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ONCOGENES</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• bcr-abl</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NEW DERIVATIVES</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Pralatrexate</td>
<td></td>
</tr>
<tr>
<td>• Liposomal Preparations</td>
<td></td>
</tr>
</tbody>
</table>

Most Anticancer Drugs Used

Today Broadly

Affect How Cells Divide
Effects of Treatment on Tumor Burden

Succumb to Disease

Curative Chemotherapy

Surgery

Palliative Chemotherapy

Frei, 1984

1,000,000,000

1,000,000

10,000

100

1

First cycle of therapy

Second cycle of therapy

Third cycle of therapy

Fourth cycle of therapy

Kill 99%
EFFECTS OF CANCER DRUGS ON THE CELL CYCLE

THE CELL CYCLE

G0

M

G2

S

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

DNA Replication

Purine and pyrimidine nucleotides

Topoisomerase inhibitors

Alkylating Agents
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

Somatic mutation
Unregulated cell growth
Antigrowth signals
Growth signals
Unregulated replication
Apoptotic signals
Angiogenesis
Apoptotic evasion
Tissue invasion
THE PROCESS OF DRUG DEVELOPMENT
A DECADE LONG PROCESS FOR ONLY $800 MILLION TO $1 BILLION

Identify promising new chemical

Does it kill cancer in animal models?

Phase III – Is it better than our present standard of care?

Can we make large batches of the chemical? How expensive is it?

Phase II – Does it work?

Does it kill the animal model? Toxicology

Phase I – What’s the safest dose and schedule of the drug

Does it kill cancer cells? What kinds? How does it work?

Does the FDA believe it’s real? Submit NDA and see.

8-10 YEARS

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


Chromatin Structural Composition

Chromosome → Solenoid → Nucleosome → DNA
Acetylation of Histones Allows Transcription

Histone Acetylation (HAT) = Open Conformation

Coactivator Complex

Protein Expression

Deacetylation of Histones Blocks Transcription

Histone Deacetylation (HDAC) = Closed Conformation

Corepressor Complex

Protein Repression
Inhibition of HDACs
Blocks Deacetylation of Histones

Histone Deacetylation (HDAC) = Closed Conformation

Corepressor Complex

Protein Expression

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

A

1466 genes altered
Upregulated genes (61%)

20100104

285 genes altered
Upregulated genes (10%)

20100106

B

23 genes consistently responded

20 genes repressed
3 genes activated
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
## MGCD0103 Clinical Activity in Hodgkin’s Lymphoma: Case Study 1

<table>
<thead>
<tr>
<th>31-Year-old female with extensive prior therapy</th>
<th>Baseline</th>
<th>Months</th>
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<tbody>
<tr>
<td>Regimen</td>
<td>Best Response</td>
<td></td>
</tr>
<tr>
<td>ABVD</td>
<td>PR</td>
<td></td>
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<tr>
<td>XRT</td>
<td>Not Eval</td>
<td></td>
</tr>
<tr>
<td>DHAP</td>
<td>PR</td>
<td></td>
</tr>
<tr>
<td>Auto SCT</td>
<td>Not Eval</td>
<td></td>
</tr>
<tr>
<td>IGEV</td>
<td>Progression</td>
<td></td>
</tr>
<tr>
<td>DHAP</td>
<td>Progression</td>
<td></td>
</tr>
<tr>
<td>Fludarabine/Meplhalan</td>
<td>Progression</td>
<td></td>
</tr>
<tr>
<td>Allo SCT</td>
<td>Progression</td>
<td></td>
</tr>
<tr>
<td>Donor Lymphocyte</td>
<td>Progression</td>
<td></td>
</tr>
<tr>
<td>MOPP</td>
<td>Not Eval</td>
<td></td>
</tr>
<tr>
<td>ESHAP</td>
<td>Progression</td>
<td></td>
</tr>
<tr>
<td>IEV</td>
<td>Progression</td>
<td></td>
</tr>
<tr>
<td></td>
<td>788 mm</td>
<td>378 mm</td>
</tr>
</tbody>
</table>

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

## TEACHING CANCER CELLS HOW TO DIE

### Intrinsic
- Apoptotic stimuli
- Mitochondria
- Smac/DIABLO
- ML-IAP
- XIAP
- XAF1
- Cytochrome C
- Apaf-1/Caspase-9/dATP
- Caspase-3
- Cellular targets
- Apoptosis

### Extrinsic
- Apo-2L/TRAIL
- Death receptor
- FADD
- Procaspase-8
- Caspase-8
- Bax, Bim, Bak
- FLIP
- BID
- Apoptosis
Strategies Directed Towards Bcl-2 Inhibition

**Hydrocarbon Stapled Peptides**

K_i = 39 nM (Bcl-2)
Walensky et al., Science, 2004, 305, 1468

**α-Helix Mimicry**

K_i = 0.11 µM (Bcl-X_l)

**Proteo-mimetics**

**Antisense**

**Virtual screening**

**Structure-based design**

**YC-137**

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

**Genasense™ (Ph III)**

Klasa et al., AntiSense Nucl. Acid Drug Devel., 2002, 12, 193

**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)

**YC-137**

K_i = 2.22 µM (Bcl-2, X_l)
Shiau et al., Cancer Res., 2005, 65, 1581

**Protéo-mimetics**

**α-Helix Mimicry**

K_i = 0.11 µM (Bcl-X_l)

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**PROMISING SINGLE AGENT ACTIVITY OF ABT-263 IN NHL**

**BEST TUMOR PERCENT CHANGE FROM BASELINE**

**STUDY M06-814 PHASE 1 SUBJECTS**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Tumor % Change</th>
<th>Tumor Size</th>
<th>Study</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>105</td>
<td>-100</td>
<td>-100</td>
<td>CLL/SLL</td>
<td>10</td>
</tr>
<tr>
<td>106</td>
<td>-100</td>
<td>-100</td>
<td>CLL/SLL</td>
<td>20</td>
</tr>
<tr>
<td>107</td>
<td>-100</td>
<td>-100</td>
<td>CLL/SLL</td>
<td>40</td>
</tr>
<tr>
<td>108</td>
<td>-100</td>
<td>-100</td>
<td>CLL/SLL</td>
<td>80</td>
</tr>
<tr>
<td>109</td>
<td>-100</td>
<td>-100</td>
<td>CLL/SLL</td>
<td>160</td>
</tr>
<tr>
<td>110</td>
<td>-100</td>
<td>-100</td>
<td>CLL/SLL</td>
<td>225</td>
</tr>
<tr>
<td>111</td>
<td>-100</td>
<td>-100</td>
<td>CLL/SLL</td>
<td>315</td>
</tr>
</tbody>
</table>

* The dose levels are at the tumor assessment. Subject 107, 109, 125 and 129 had dose escalation/de-escalation.

* The best tumor percent change is defined as the maximum reduction from baseline in SPD.

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

<table>
<thead>
<tr>
<th>Response</th>
<th>N</th>
<th>ORR</th>
<th>CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLBCL</td>
<td>23</td>
<td>24%</td>
<td>1</td>
</tr>
<tr>
<td>FL</td>
<td>21</td>
<td>10%</td>
<td>0</td>
</tr>
<tr>
<td>CLL/SLL</td>
<td>11</td>
<td>55%</td>
<td>0</td>
</tr>
<tr>
<td>MCL</td>
<td>9</td>
<td>11%</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AE</th>
<th>All Grades</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>41%</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>41%</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>31%</td>
<td>18%</td>
</tr>
<tr>
<td>Anemia</td>
<td>27%</td>
<td>7%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>24%</td>
<td>3%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>22%</td>
<td>6%</td>
</tr>
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</table>

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

THE EMPIRIC STRATEGY FOR DRUG THERAPY
Treat All Patients with the Same Diagnosis with the Same Medications

INDIVIDUALIZING TREATMENT STRATEGY FOR SPECIFIC PATIENTS AND DISEASES
Tailor Treatment to the Patients Host and Tumor Genetics

X = Non Responders
X = Responder
X = Non Responders
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!!