Targeted Therapy - Fundamentals

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Regional Cancer Centre.
Mustard Gas (Yperite)

Use – WW1 Germany
Onset - 12 Hs.
Effect - skin blisters, bleeds
Death - 4-5 wks / painful
Other - Lymphopenia, Aplasia
Chemotherapy

Target - DNA
1. Alkylators
2. Platinum derivatives
3. Anti metabolites
4. DNA intercalators
5. Topoisomerase inh

Problems
1. Toxicity
2. Non Specific
3. Low Ti
4. Resistance
5. SMN/Late effects

Look Out for New Targets
Concept - “Chemotherapia specifica”

Ehrlich’s first magic bullet

Salvarsan – syphilis (1909)
Cell signaling

- Intercellular
  1. Direct – CAM
  2. Indirect –
     - Endocrine
     - Paracrine
     - Autocrine

- Trans & Intra cellular

Signal transduction
Signal Transduction

**Types of Ligand**

<table>
<thead>
<tr>
<th>Type</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Permeable</td>
<td>Estrogen, Testosterone</td>
</tr>
<tr>
<td>Impermeable</td>
<td>Neurotransmitters</td>
</tr>
<tr>
<td>Physical</td>
<td>Pressure, Temp</td>
</tr>
</tbody>
</table>

**Receptors**

- G protein coupled
- Protein Kinase
- Ion Channels
- Trans Membrane Scaffold
- Guanylyl cyclase
- Nuclear receptors

**Cellular response**

- Cell Division
- Cell Death
Why such complexity

1. Evolution
2. Amplification
3. Frugality
4. Coordination
Novel Targets

**Self sufficiency in growth Signals**

**Evading Apoptosis**

**Insensitivity to Anti growth signals**

**Sustained Angiogenesis**

**Tissue Invasion & Metastasis**

**Limitless Replication**

1. Gr fact/signal transduction
2. Angiogenesis
3. Invasion/mets
4. DNA repair
5. Telomerase
6. Cell cycle regulators
7. Control of apoptosis
8. Gene silencing

Hanahan and Weinberg, Cell, Vol. 100, 57–70, 2000
Levels of Interference

Mo Ab –Receptor - EGFR ,ERB b2
Small Molecule TKI –EGFR TKI
Signal Tr Path – RAK.MEK inh

GF
Mo Ab- VEGF

Cell Membrane
Cytoplasm
Nucleus

Cellular response
Ideal Target

1. Sufficient
2. Specific
3. Spare(Nor Cell)
4. Should be critical
5. Not –Shed, shared, Lost
6. Not Circulate/mutate
Classes

1. Monoclonal Antibodies
2. Tyrosine Kinase Inhibitors
3. Proteasome Inhibitors
4. Parp Inhibitors
5. Vaccines
1- Monoclonal Antibodies

Innovators

Niels K. Jerne
Georges J.F. Köhler
César Milstein

Hybridoma

Nobel Prize in Physiology or Medicine 1984
# 1- Monoclonal Antibodies

## Mechanism Of Action

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antagonism</td>
<td>Infliimab</td>
</tr>
<tr>
<td>Signalling</td>
<td>TGN412</td>
</tr>
<tr>
<td>CDC</td>
<td>RT;Alemtu</td>
</tr>
<tr>
<td>ADCC</td>
<td>RT;Alemtu</td>
</tr>
</tbody>
</table>
1 - Monoclonal Antibodies

**Obstacles**

1. Non uniform distribution
2. Inadequate trafficking
3. Ag Heterogeneity
4. Shedding
5. Rapid Clearance
6. Immunogenicity

**Disadvantages**

<table>
<thead>
<tr>
<th>Immune</th>
<th>Anaphylactic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>Tb, HBV, PMFLE, JCV</td>
</tr>
<tr>
<td>Platelet &amp; Thr dis</td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Autoimmune</td>
<td>Lupus, AI colitis</td>
</tr>
</tbody>
</table>
# Monoclonal Antibodies

## Unconjugated

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Target</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituimab</td>
<td>CD20</td>
<td>NHL</td>
</tr>
<tr>
<td>Trasutzumab</td>
<td>HER 2</td>
<td>Breast</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>CD52</td>
<td>CLL</td>
</tr>
<tr>
<td>Cetuimab</td>
<td>EGFR</td>
<td>CRC</td>
</tr>
</tbody>
</table>

## Immunoconjugate

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Target</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mylotarg</td>
<td>CD33</td>
<td>AML</td>
</tr>
<tr>
<td>Ibrutomomab</td>
<td>CD20</td>
<td>NHL</td>
</tr>
<tr>
<td>Tositumomab</td>
<td>CD20</td>
<td>NHL</td>
</tr>
</tbody>
</table>
2- Tyrosine Kinase Inhibitors

Tyrosine kinase

Mechanism Of Action

Types

<table>
<thead>
<tr>
<th>Receptor TK</th>
<th>Non receptor Tk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell sur trans memb</td>
<td>Cytoplasmic</td>
</tr>
<tr>
<td>Enzymic activity</td>
<td>&lt;&lt;</td>
</tr>
<tr>
<td>Act –Ligand Binding</td>
<td>Complex</td>
</tr>
<tr>
<td>EGFR, PGDFR, FGF</td>
<td>SRC, ABC,</td>
</tr>
</tbody>
</table>

Phosphorylation of tyrosine residue
2 - Tyrosine kinase Inhibitors

**Why Target it**

**How to target it**

<table>
<thead>
<tr>
<th>Method</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small Mol tki</td>
<td>Imatinib, Dasatinib</td>
</tr>
<tr>
<td>Mo Ab</td>
<td>Trasutzumab</td>
</tr>
<tr>
<td>Chaperone Inhibitors</td>
<td>CDDP, Novobiocin</td>
</tr>
<tr>
<td>Ab drug conjugate</td>
<td>Tositumomab</td>
</tr>
<tr>
<td>Angiogenesis inh</td>
<td>Avegf</td>
</tr>
</tbody>
</table>
3 - Proteasome Inhibitors

Proteasome

Protein Complex
Eukaryotes
Nucleus & Cytoplasm
Degrades misfolded protein

Degradation

Degrades misfolded protein
<table>
<thead>
<tr>
<th>Effects of Inhibition</th>
<th>Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. NFkB inhibition</td>
<td>1. Bortezomib – MM, MCL</td>
</tr>
<tr>
<td>2. Pro Apoptotic protein</td>
<td>2. Carfilizomib – MM</td>
</tr>
<tr>
<td>3. ER Stress</td>
<td>3. ON–O912 – Solid tumors</td>
</tr>
<tr>
<td>4. Cell cycle Arrest</td>
<td></td>
</tr>
<tr>
<td>5. Angiogenesis inh</td>
<td></td>
</tr>
<tr>
<td>6. Imp DNA damage repair</td>
<td></td>
</tr>
</tbody>
</table>
4 –PARP Inhibitors

DNA damage repair

**Mechanism**

**Single Stranded Break**
- Base Excision Repair
- Neucleo Excision Repair
- Mismatch Repair

**Double Stranded Break**
- Homologous Recomb
- Non Hom EJ

4 - PARP Inhibitors

Role of BRCA 1 & 2

4 – PARP Inhibitors

**Concept**

**Synthetic lethality**

<table>
<thead>
<tr>
<th>Gene X</th>
<th>Gene Y</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>+</td>
<td>No effect</td>
</tr>
<tr>
<td>−</td>
<td>+</td>
<td>No effect</td>
</tr>
<tr>
<td>+</td>
<td>−</td>
<td>No effect</td>
</tr>
<tr>
<td>−</td>
<td>−</td>
<td>Death</td>
</tr>
</tbody>
</table>

Mutation of either gene - viability
Mutation of both - death

Ashworth A JCO 2008; 26: 3785-3790
4 - PARP Inhibitors

Drugs

1. Olaparib
2. AG014699
3. BSI-201
4. ABT-888

Questions

1. Who will benefit
2. Sequence
3. Pharmacodynamics
4. Long term
5 - Cancer Vaccines

Key Players

1. Dendritic Cell
   Processes Ag,
   Presents Ag
2. T Cell
   Mediates Response

Technique (Dendritic Vac0)

Monocyte
   IL-4 +GMcSF
   Dendr Cell
   Cancer Cell
   Act Dr Cell
   Intra der inj
# 5 - Cancer Vaccines

<table>
<thead>
<tr>
<th>Source</th>
<th>Type</th>
<th>Malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor cell</td>
<td>Auto/Allogenic</td>
<td>Melanoma</td>
</tr>
<tr>
<td>Dendritic Cell</td>
<td>Exposure/ Gene therapy</td>
<td>Melanoma</td>
</tr>
<tr>
<td>Antigen</td>
<td>Single Epitope</td>
<td>Ovary</td>
</tr>
<tr>
<td>Anti Idiotypic</td>
<td>Ab acts as antigen</td>
<td>Lymphoma</td>
</tr>
<tr>
<td>DNA</td>
<td>Coated</td>
<td>Leukemia/Prostate</td>
</tr>
</tbody>
</table>
Future

1. Cancer - Chronic illness
2. Era - Personalized Medicine
3. Toxicity - Minimum
4. QOL - Ultimate
“Only in the darkness can you see the stars.”

Martin Luther King Jr.