Targeted Therapy - Fundamentals

Dr Sreejith Nair,
Dept of Medical Oncology,
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

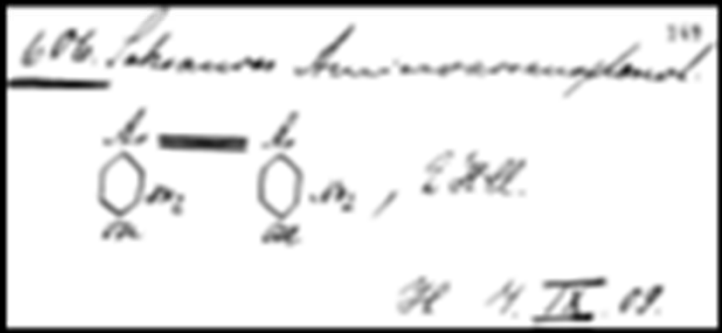
Problems

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

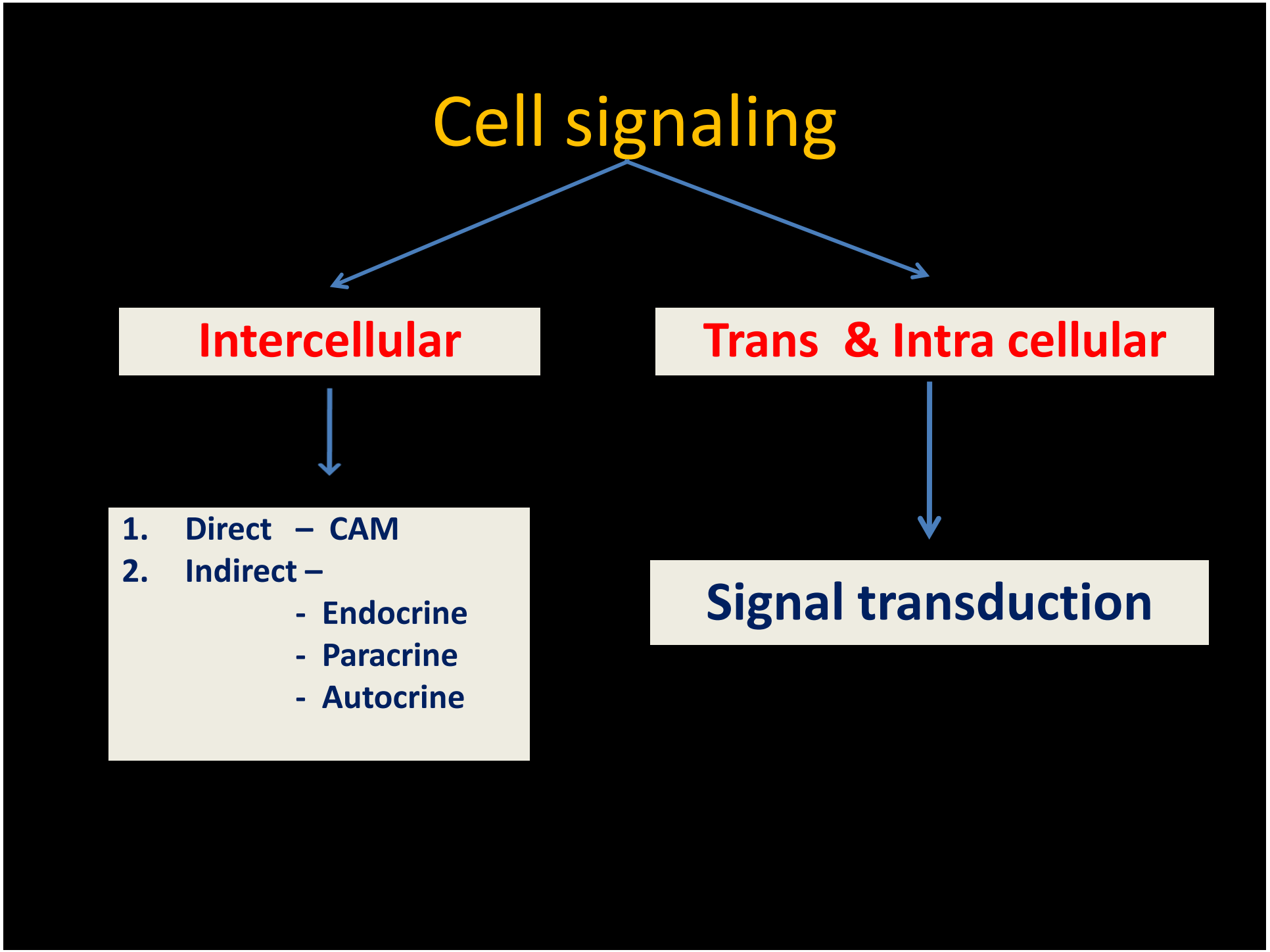
Look Out for New Targets

Concept - *"Chemotherapia specifica"*

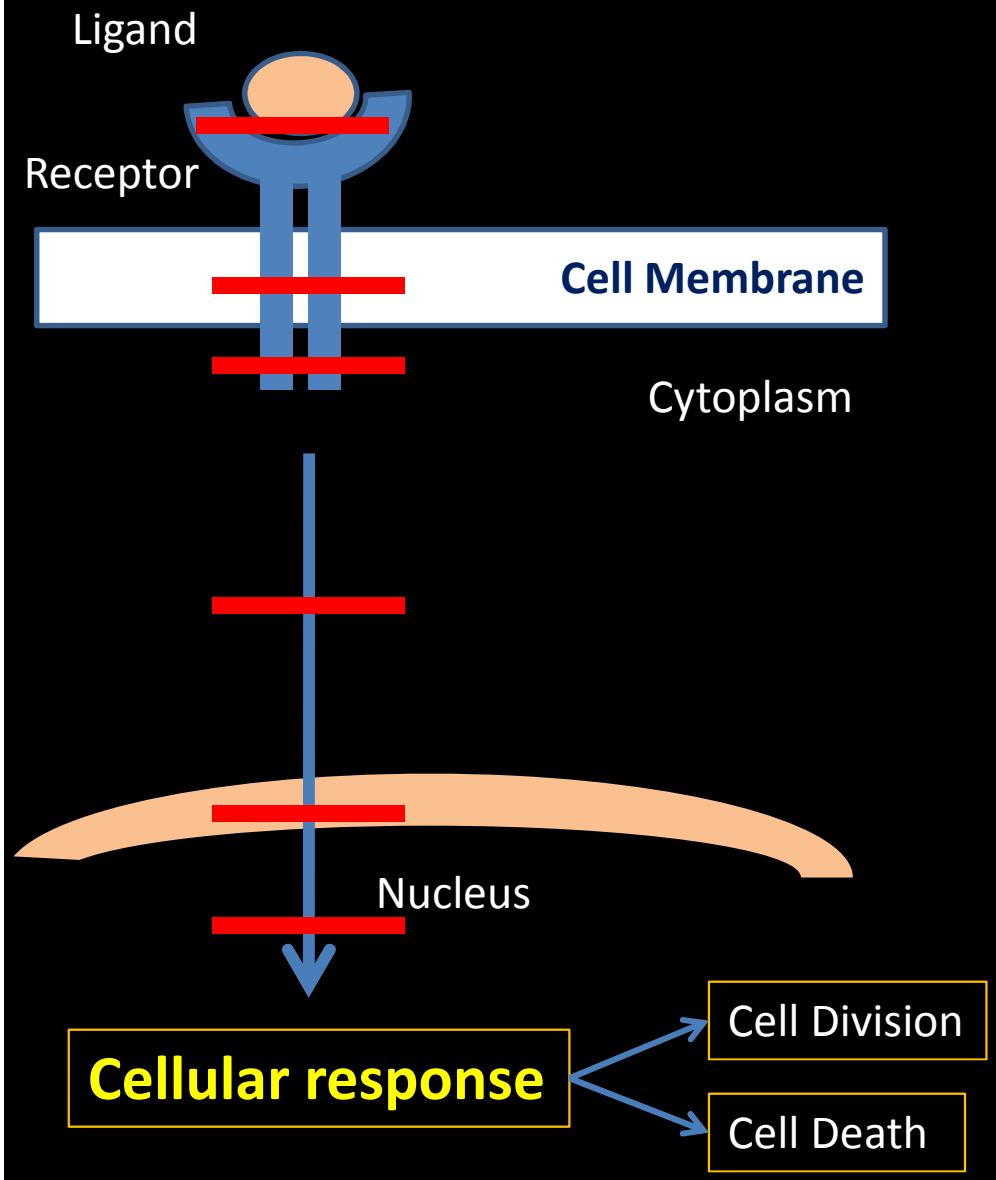
Ehrlich's first magic bullet



Salvarsan – syphilis (1909)


Cell signaling
Intercellular
Trans & Intra cellular
1. Direct – CAM
2. Indirect –
- Endocrine
- Paracrine
- Autocrine
Signal transduction

Signal Transduction



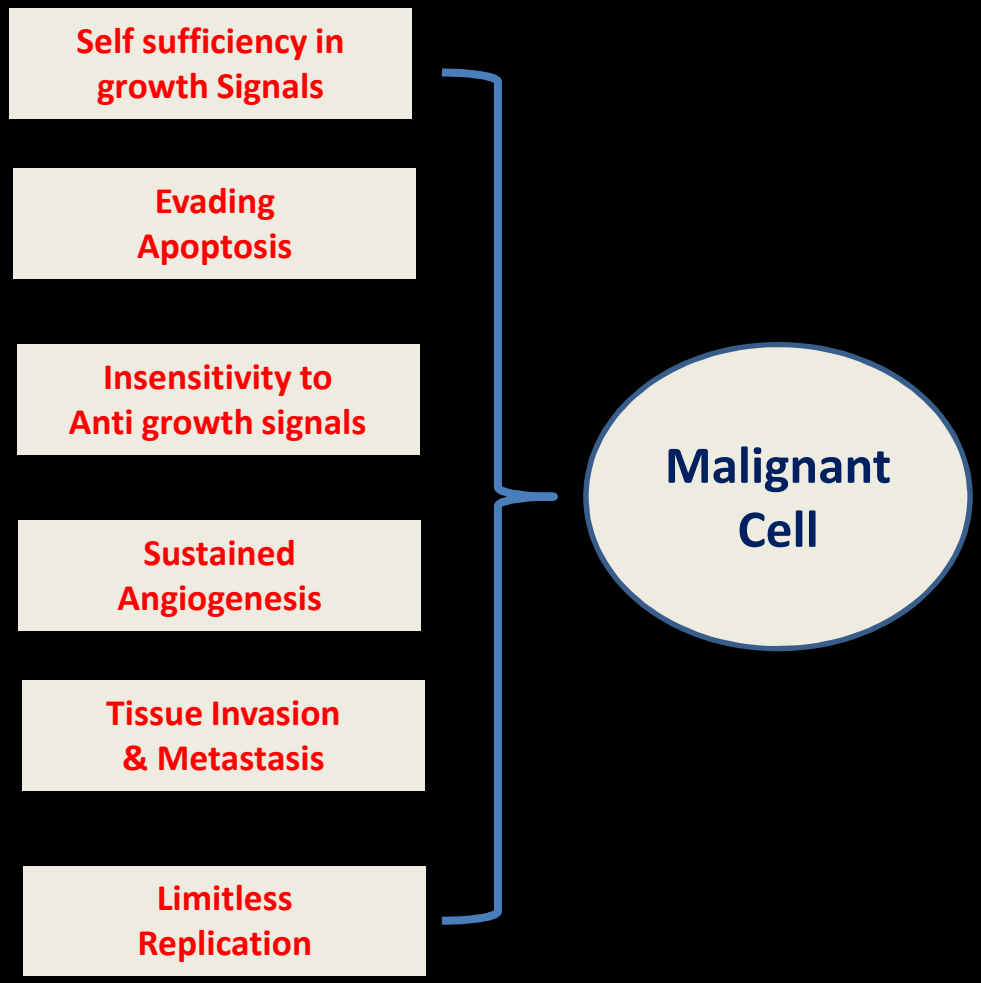
Types of Ligand	
Permeable	Estrogen,Testosne
Impermeable	Neurotransmitters
Physical	Pressure, Temp

Receptors
G protein coupled
Protein Kinase
Ion Channels
Trans Memb Scaff
Guanyl cyclase
Nuclear receptors

Why such complexity

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

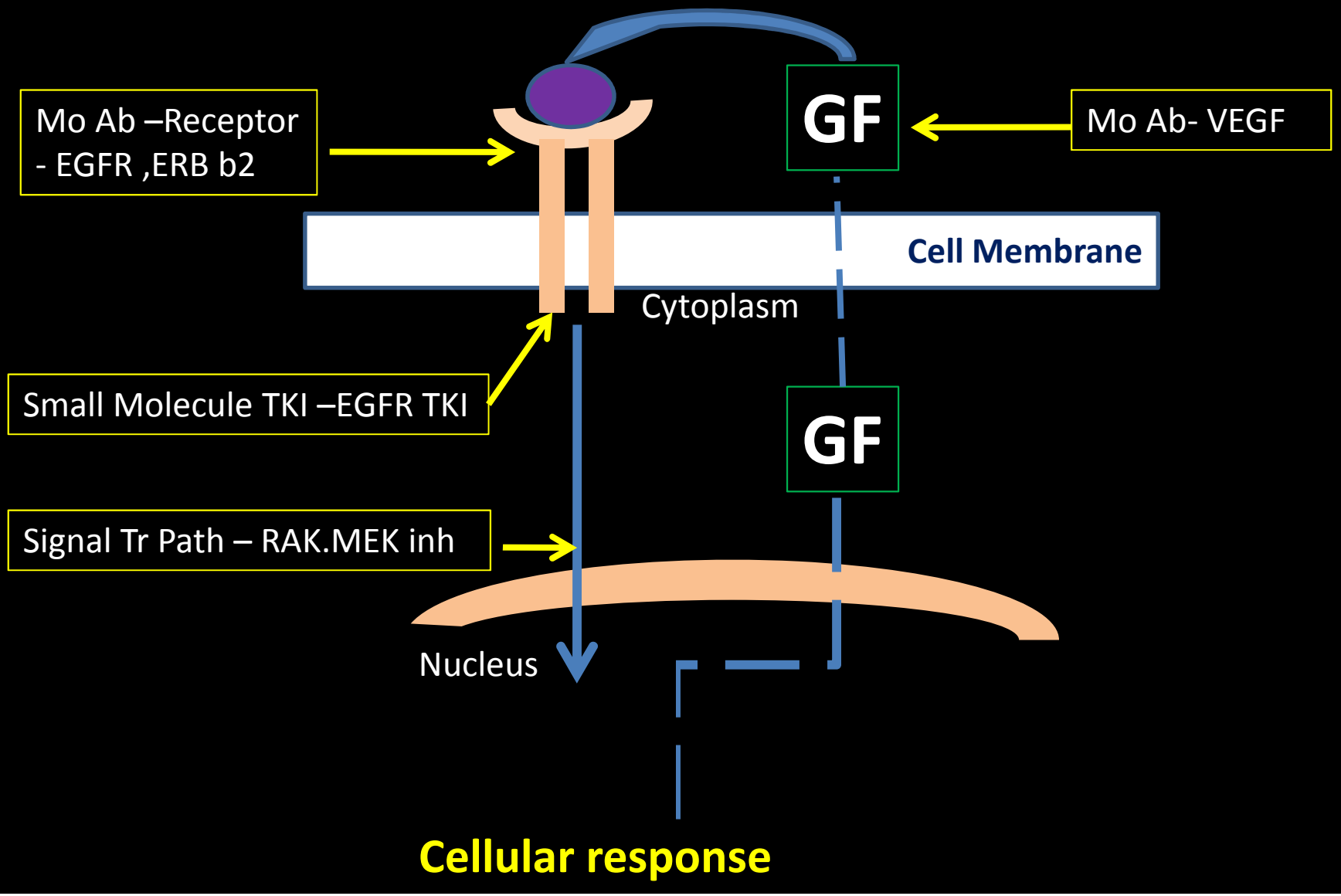
Novel Targets



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



Ideal Target

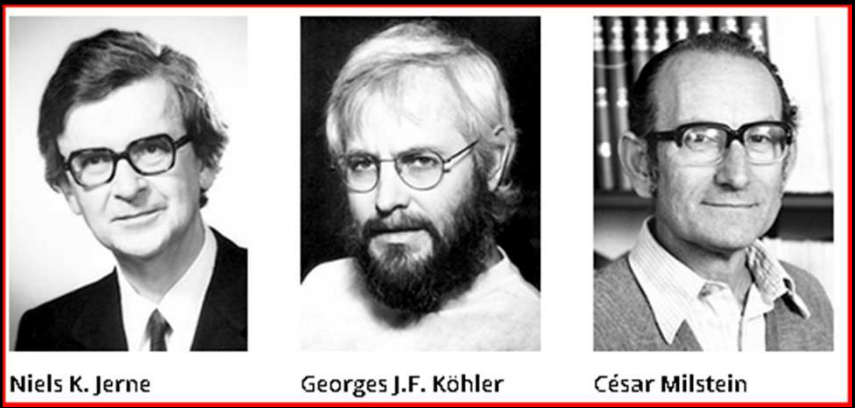
1. Sufficient
2. Specific
3. Spare(Nor Cell)
4. Should be critical
5. Not –Shed, shared, Lost
6. Not Circulate/mutate

Classes

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

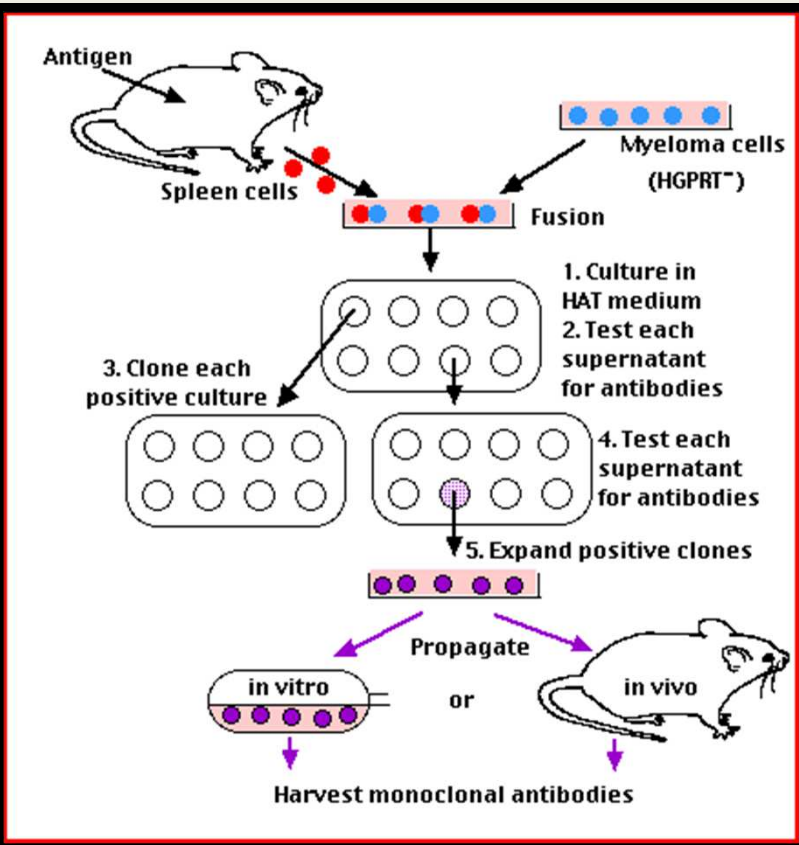
1- Monoclonal Antibodies

Innovators



Nobel Prize in Physiology or Medicine 1984

Hybridoma



1- Monoclonal Antibodies

Mechanism Of Action

Mechanism	Agent
Antagonism	Infliimab
Signalling	TGN412
CDC	RT;Alemtu
ADCC	RT;Alemtu

1 -Monoclonal Antibodies

Obstacles

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

Disadvantages

Immune	Anaphylactic
Infection	Tb,HBV,PMFLE,JCV
Platelet&Thr dis	Thrombocytopenia
Autoimmune	Lupus,AI colitis

1 -Monoclonal Antibodies

Unconjugated

Rituimab	CD20	NHL
Trasutzumab	HER 2	Breast
Alemtuzumab	CD52	CLL
Cetuimab	EGFR	CRC

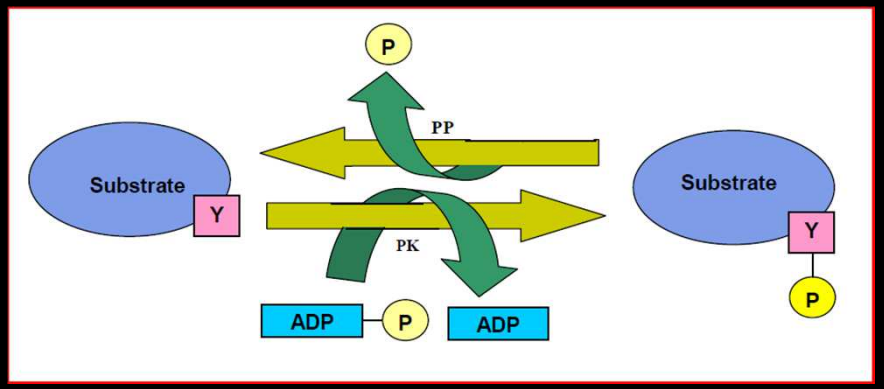
Immunoconjugate

Mylotarg	CD33	AML
Ibrutomomab	CD20	NHL
Tositumomab	CD20	NHL

2- Tyrosine Kinase Inhibitors

Tyrosine kinase

Mechanism Of Action



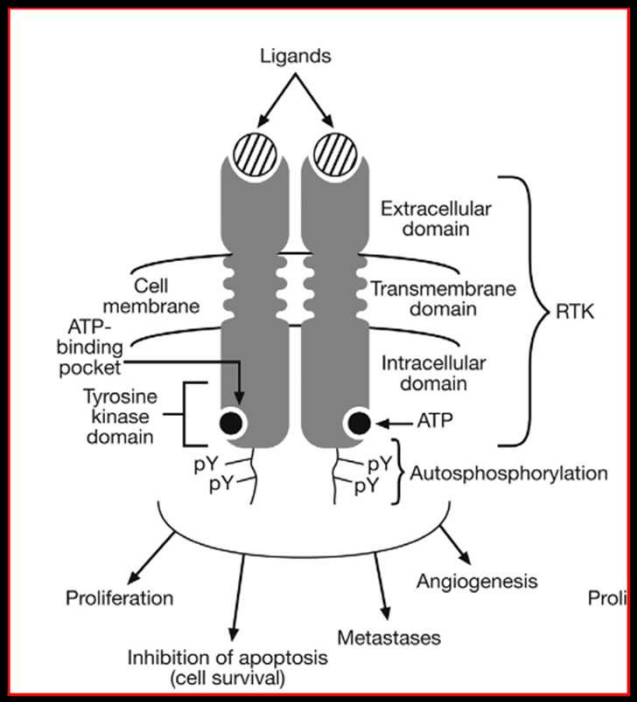
Phosphorylation of tyrosine residue

Types

Receptor TK	Non receptor Tk
Cell sur trans memb	Cytoplasmic
Enzymic activity	<<
Act –Ligand Binding	Complex
EGFR,PGDFR,FGF	SRC,ABC,

2 - Tyrosine kinase Inhibitors

Why Target it

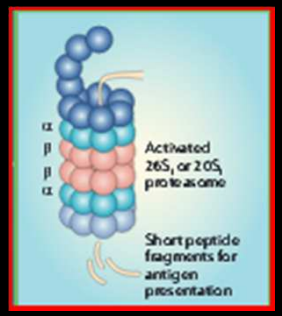


How to target it

Method	Drug
Small Mol tki	Imatinib,Dasatinib
Mo Ab	Trasutzumab
Chaperone Inhibitors	CDDP.Novobiocin
Ab drug conjugate	Tositumomab
Angiogenesis inh	Avegf

3 - Proteasome Inhibitors

Proteasome



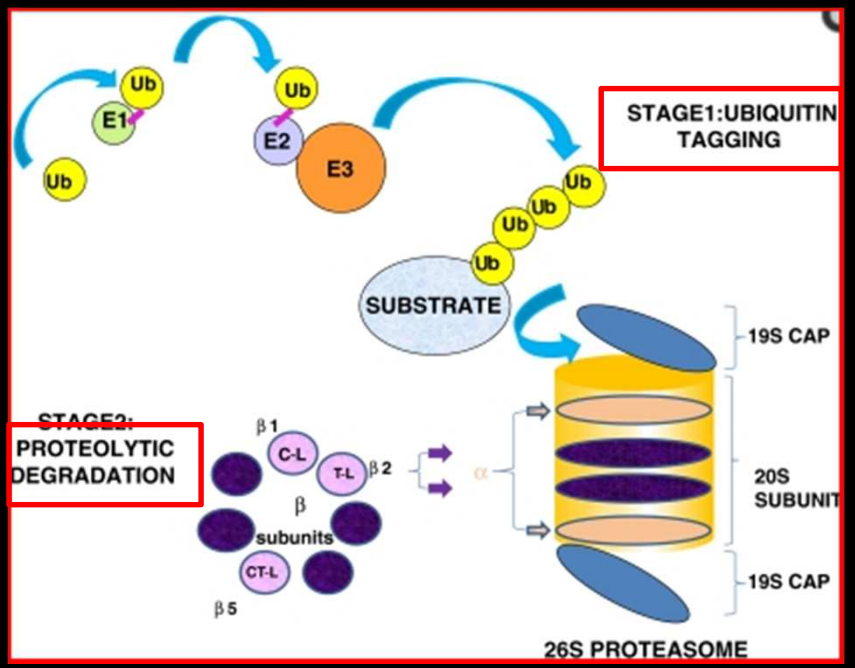
Protein Complex

Eukaryotes

Nucleus & Cytoplasm

Degrades misfolded protein

Degradation



3 - Proteasome Inhibitors

Effects of Inhibition	Agents
1. NFk B inhibition	1. Bortezomib – MM, MCL
2. Pro Apoptotic protein	2. Carfilizomib – MM
3. ER Stress	3. ON –O912 - Solid tumors
4. Cell cycle Arrest	
5. Angiogenesis inh	
6. Imp DNA damage repair	

4 –PARP Inhibitors

DNA damage repair

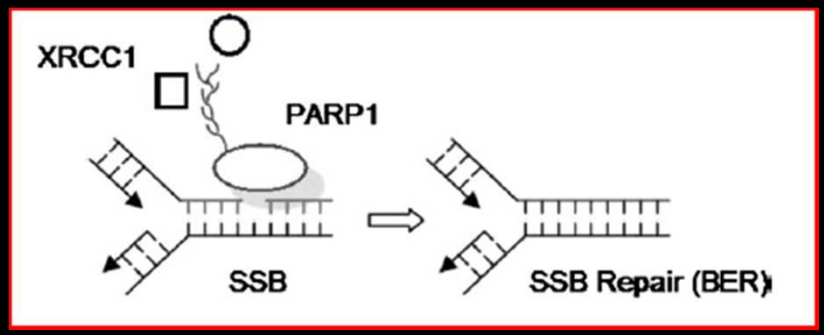
Mechanism

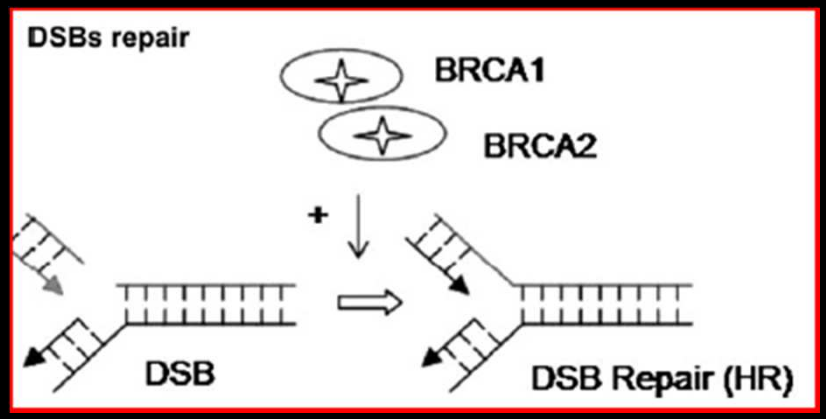
Single Stranded Break

- Base Excision Repair
- Neucleo Excision Repair
- Mismatch Repair

Double Stranded Break

- Homologous Recomb
- Non Hom EJ

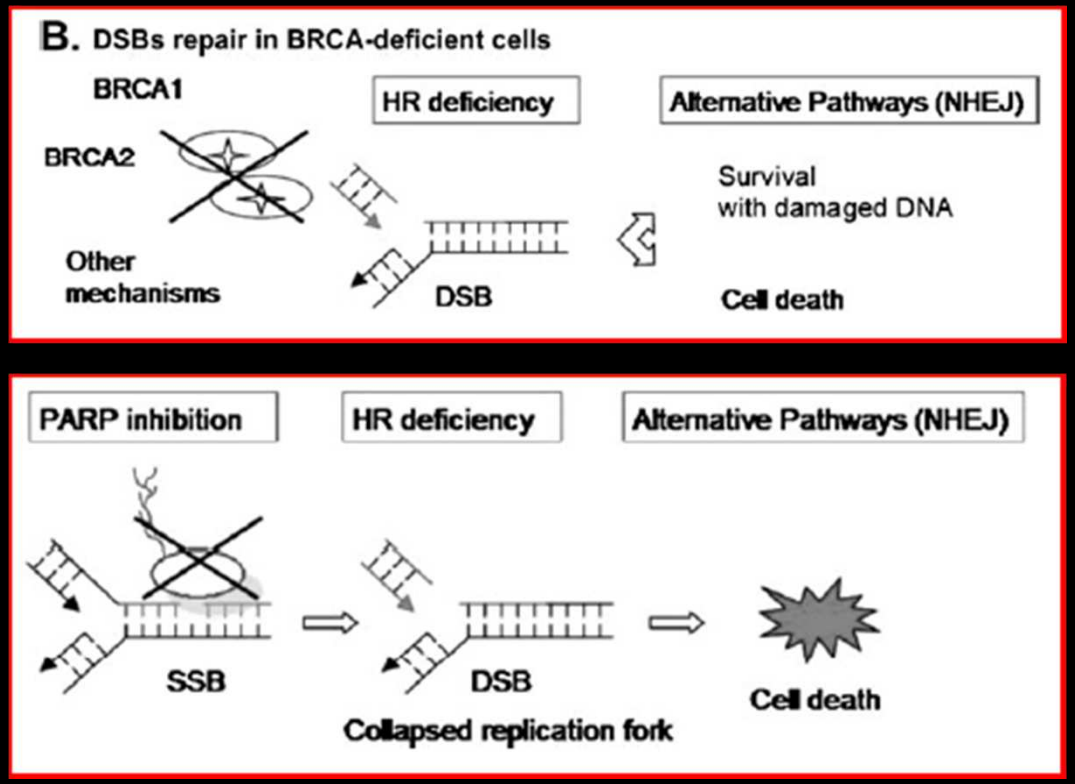




Annals of Oncology 22: 268–279, 2011

4 –PARP Inhibitors

Role of BRCA 1 & 2



Annals of Oncology 22: 268–279, 2011

4 –PARP Inhibitors

Concept

Synthetic lethality

Gene *X*	Gene *Y*	
+	+	No effect
–	+	No effect
+	–	No effect
–	–	Death

Mutation of either gene - viability
Mutation of both - death

Ashworth A JCO 2008; 26: 3785-3790

4 - PARP Inhibitors

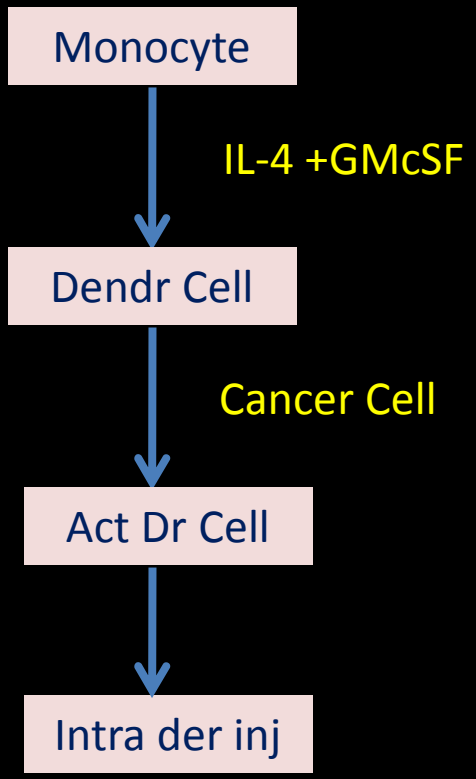
Drugs	Questions
1. Olaparib 2. AG014699 3. BSI-201 4. ABT-888	1. Who will benefit 2. Sequence 3. Pharmacodynamics 4. Long term

5 - Cancer Vaccines

Key Players

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

Technique (Dendritic Vac0



5 - Cancer Vaccines

Source	Type	Malignancy
Tumor cell	Auto/Allogenic	Melanoma
Dendritic Cell	Exposure/ Gene therapy	Melanoma
Antigen	Single Epitope	Ovary
Anti Idiotypic	Ab acts as antigen	Lymphoma
DNA	Coated	Leukemia/Prostate

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.

Thank You