



UNIwersYTET JAGIELLOŃSKI  
COLLEGIUM MEDICUM



Szpital  
Uniwersytecki  
w Krakowie

# INTRODUCTION TO CLINICAL ONCOLOGY



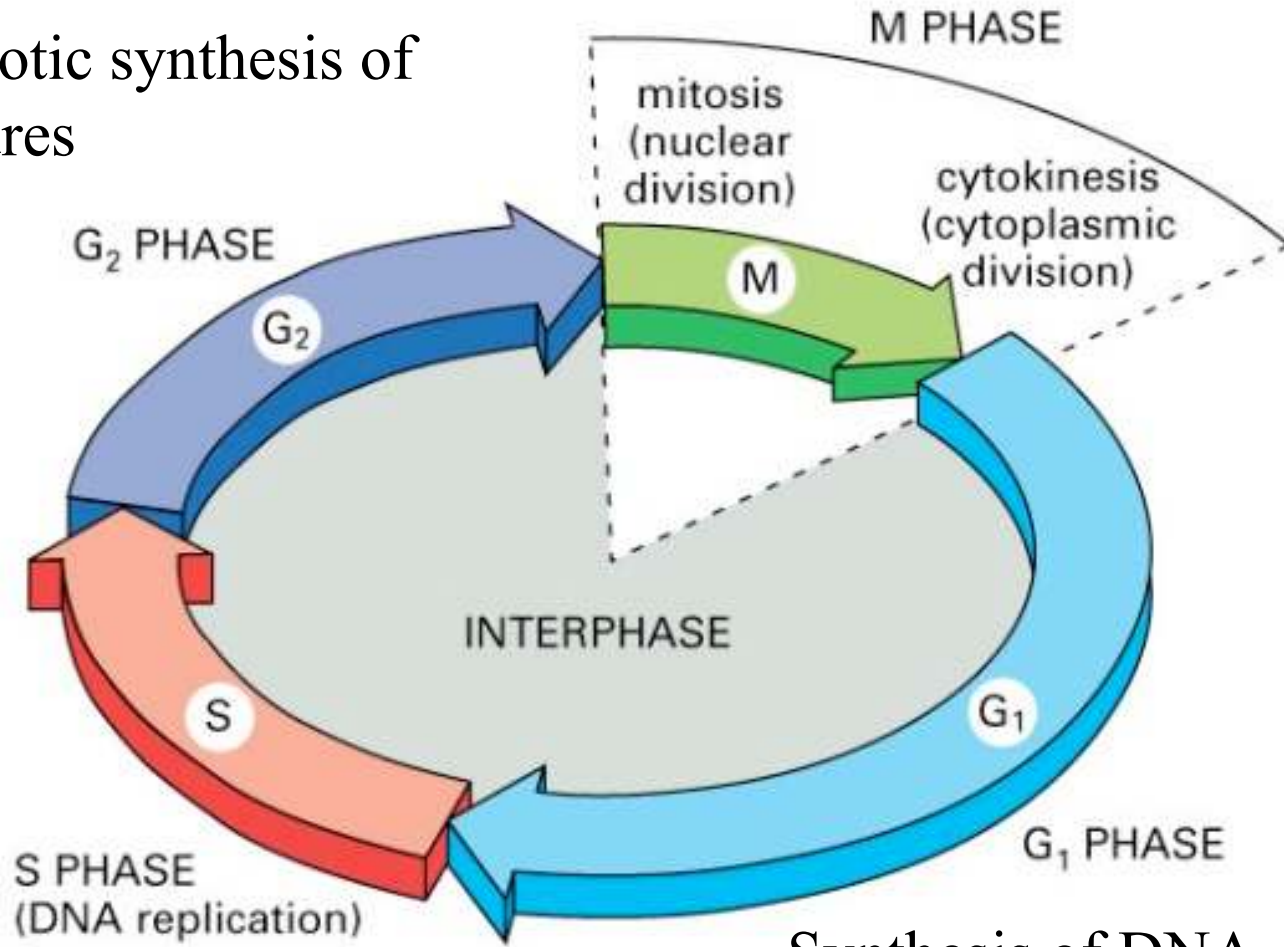
# AGENDA

- CHEMOTHERAPY
- ENDOCRINE THERAPY
- TARGETED THERAPIES
- PERSONALIZATION OF ONCOLOGY
- IMMUNOTHERAPY



# Cell Cycle Phases

Premitotic synthesis of structures



Synthesis of DNA precursors, proteins, etc.



# Uncontrolled Proliferation

- Result of action of proto-oncogenes or inactivated tumor suppressor genes
  - Change in growth factors, receptors
    - increased growth factors production
  - Change in growth factor pathways
  - Change in cell cycle transducers
    - Cyclins, Cdk' s, Cdk inhibitors

# Anticancer Drugs are Antiproliferative



- Affect cell division
  - Active on rapidly dividing cells
- Most effective during S phase of cell cycle
  - Many cause DNA damage
- Damage DNA → initiation of apoptosis



- Side effects greatest in other rapidly-dividing cells
  - Bone marrow toxicity
  - Impaired wound healing
  - Hair follicle damage
  - GI epithelium damage
  - Growth in children
  - Gametes
  - Fetus
- May themselves be carcinogenic



# Difficulties in Chemotherapy Effectiveness

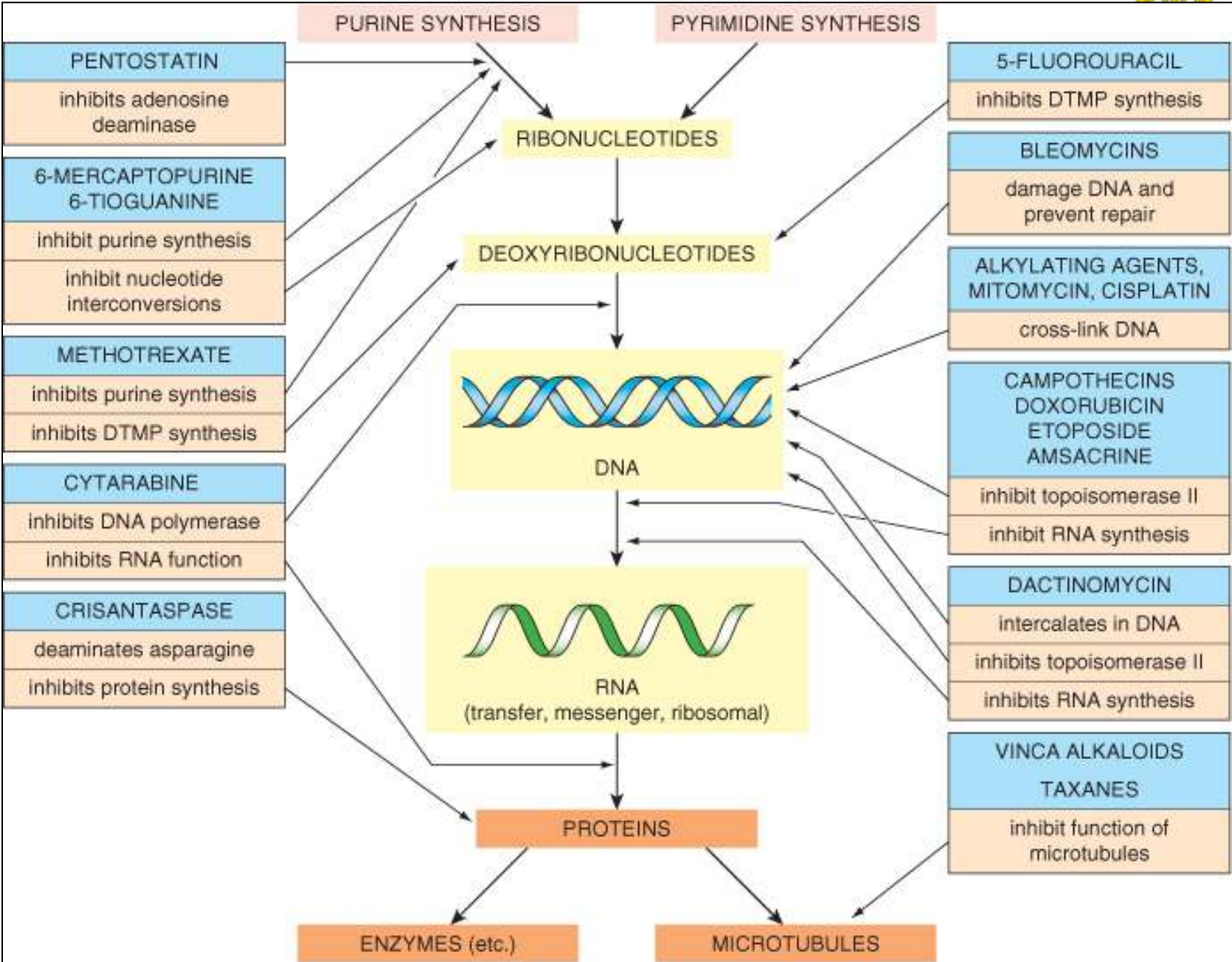
- Solid tumors
  - Growth rate decreases as neoplasm size increases
    - Outgrows ability to maintain blood supply AND
    - Not all cells proliferate continuously
  - Compartments
    - Dividing cells (may be ~5% tumor volume)
      - Only population susceptible to most anticancer drugs
    - Resting cells (in G0); can be stimulated → G1
      - Not sensitive to chemotherapy, but activated when therapy ends
    - Cells unable to divide but add to tumor bulk



# Drugs Used in Cancer Chemotherapy

- Cytotoxic Agents
  - Alkylating Agents
  - Antimetabolites
  - Cytotoxic antibiotics
  - Plant derivatives

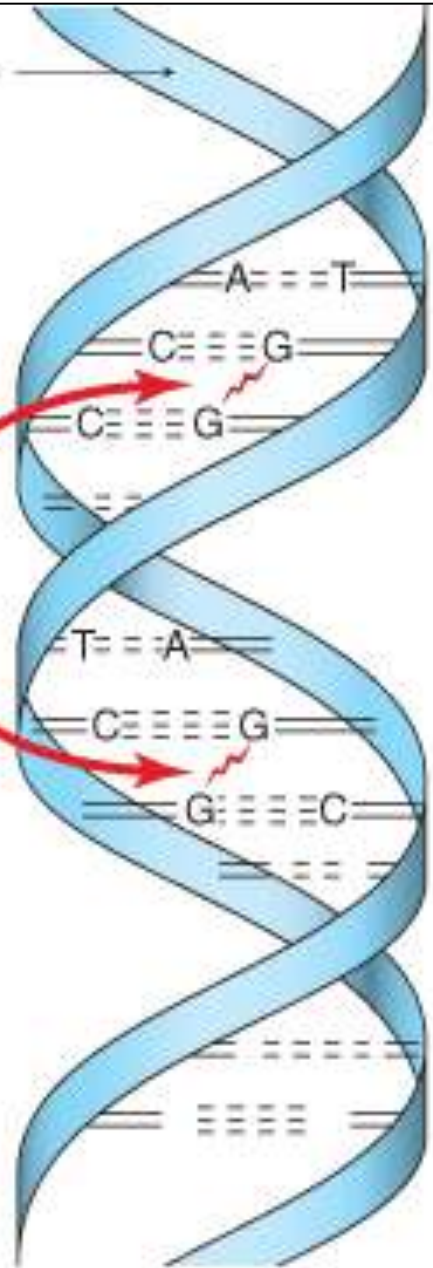






Sugar-phosphate backbone

**Bifunctional alkylating agents can cause intrastrand linking and cross-linking**





# Antimetabolites

- Mimic structures of normal metabolic mol' s
  - Inhibit enzymes competitively OR
  - Incorporated into macromolecules → inappropriate structures
- Kill cells in S phase
- Three main groups
  - Folate antagonists
  - Pyridine analogs
  - Purine analogs

## M Phase Specific

### **Antimicrotubule Agents**

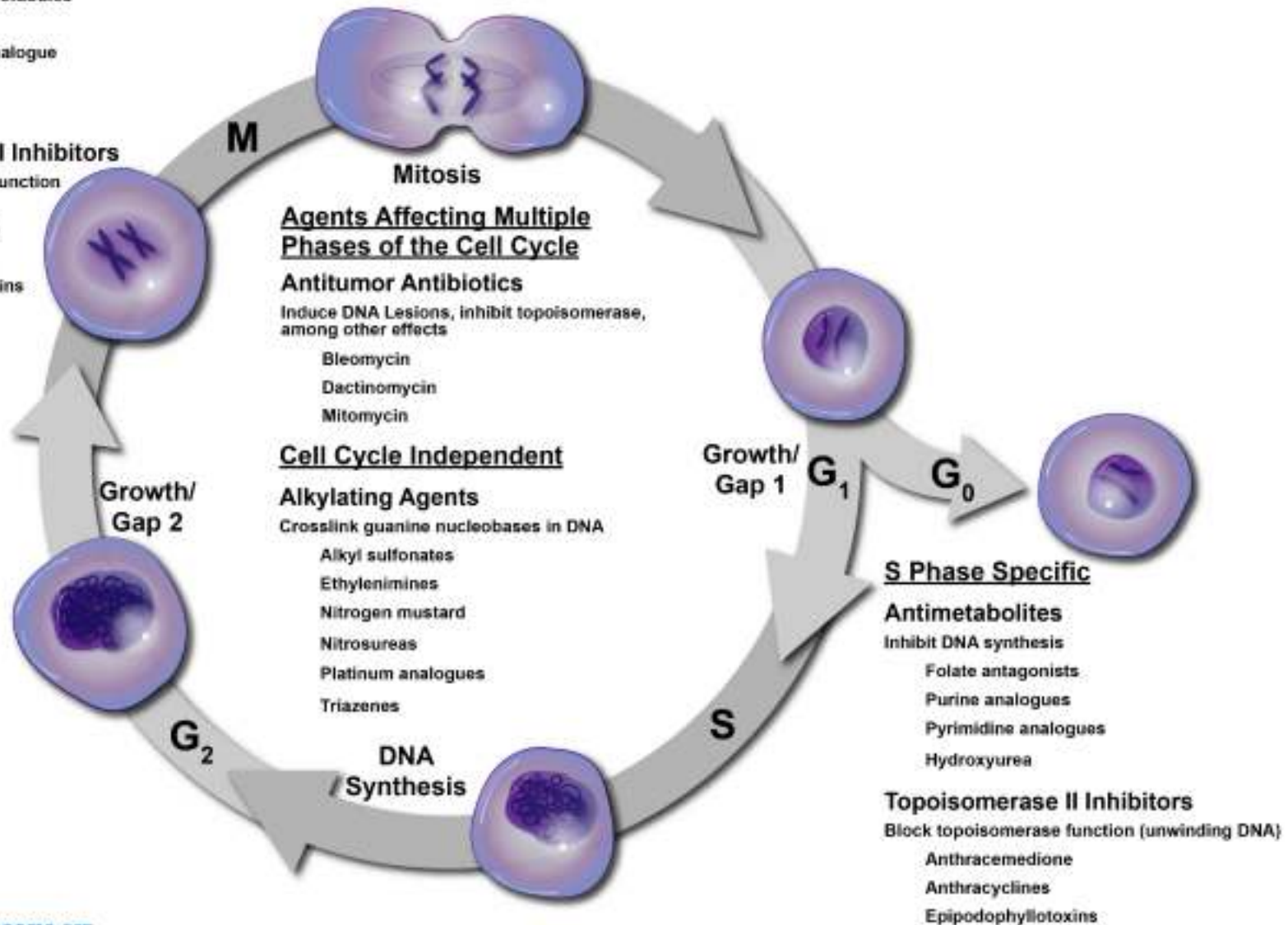
Inhibit function of microtubules

- Epothilones
- Halichondrin B analogue
- Taxanes
- Vinca alkaloids

### **Topoisomerase II Inhibitors**

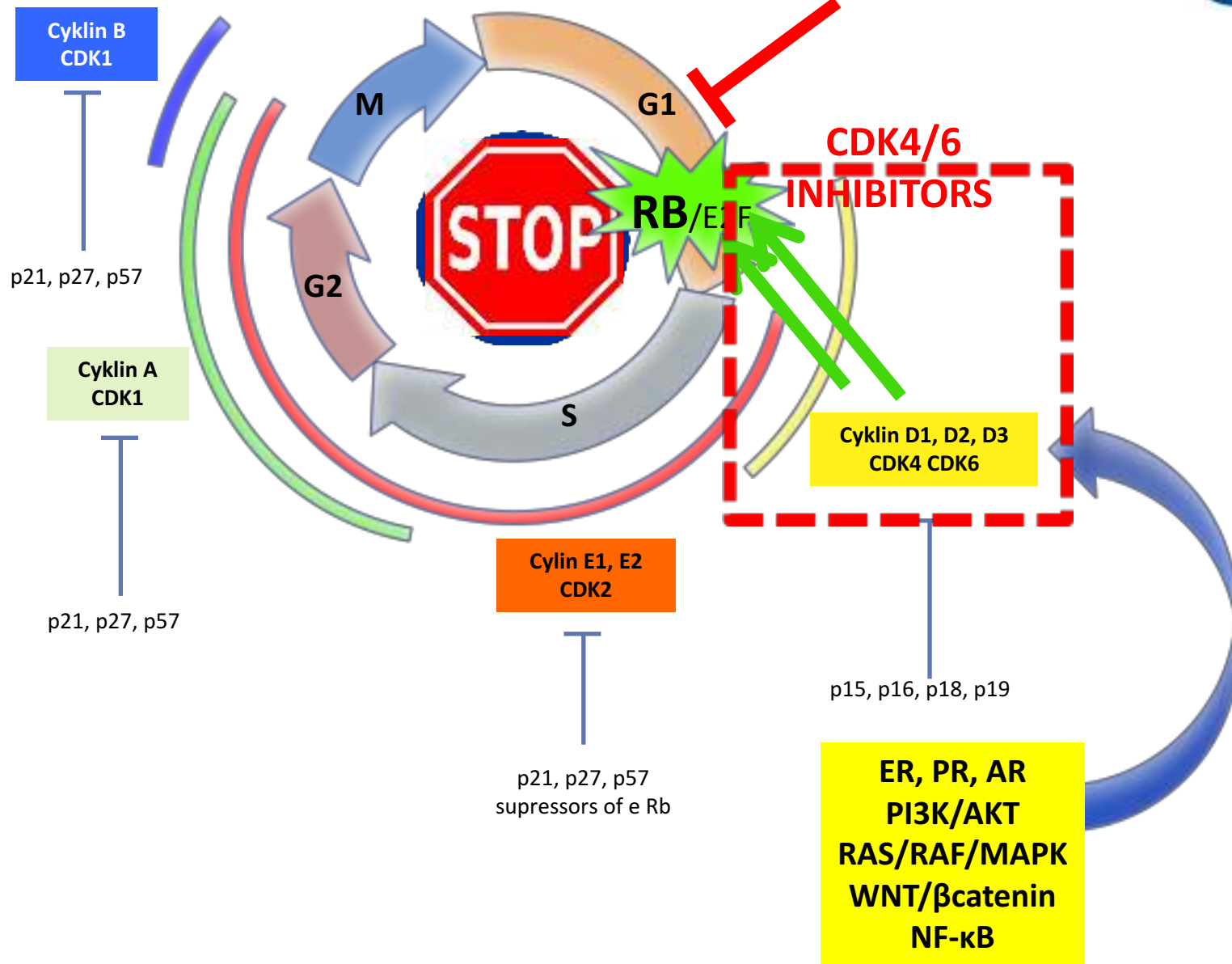
Block topoisomerase function (unwinding DNA)

- Anthracedione
- Anthracyclines
- Epipodophyllotoxins





ENDOCRINE THERAPY



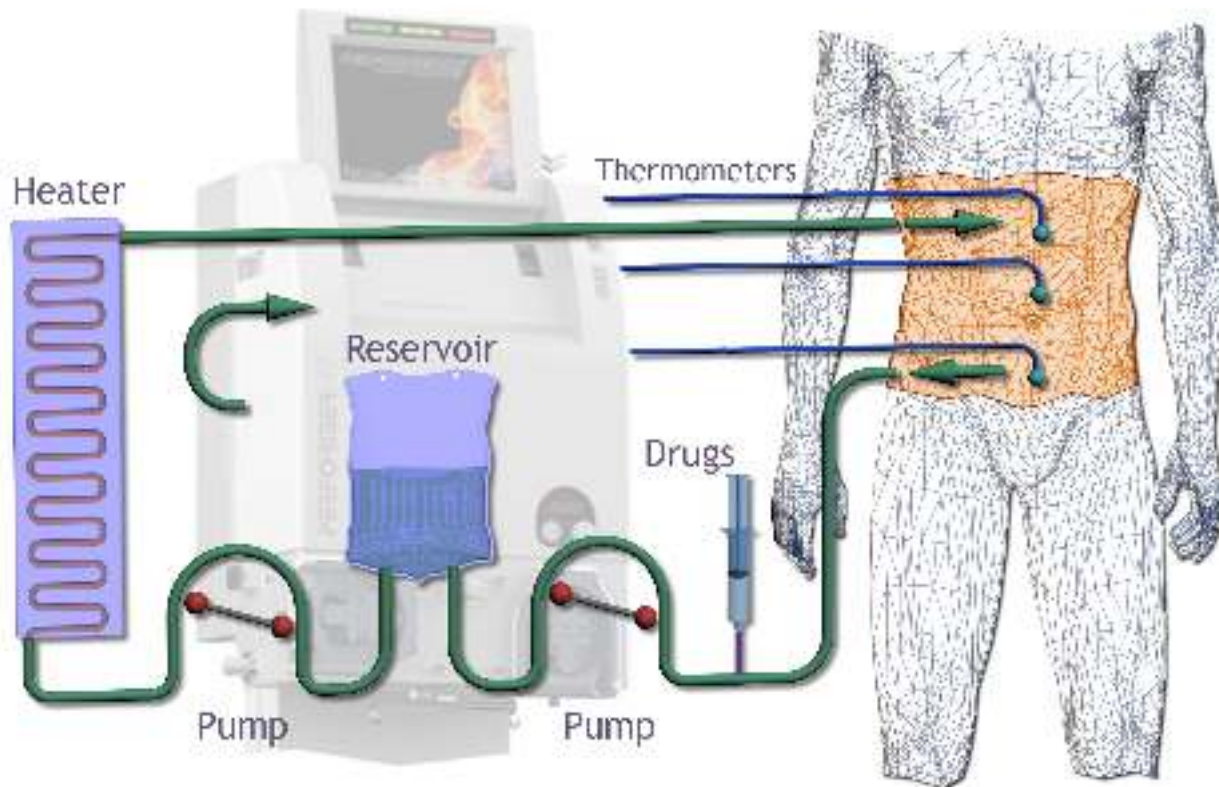
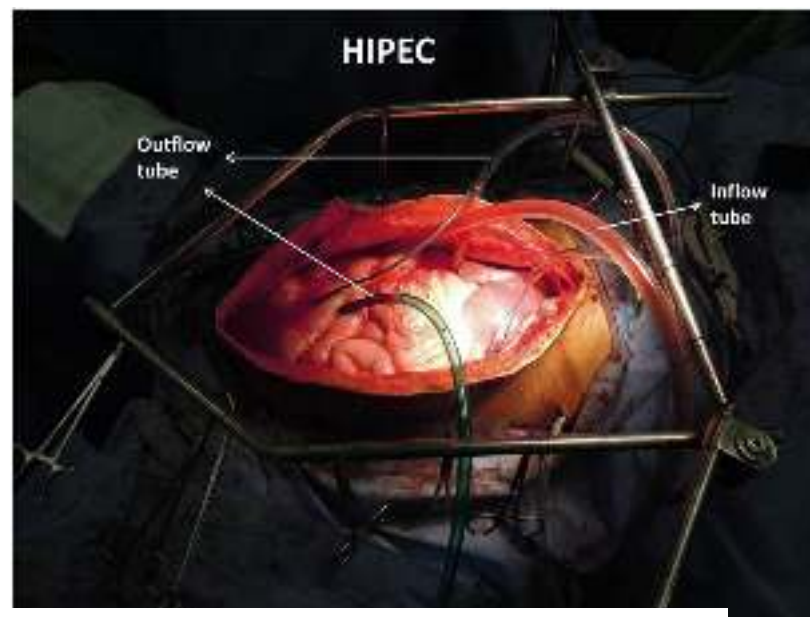
# ROUTES OF CHEMOTHERAPY ADMINISTRATION



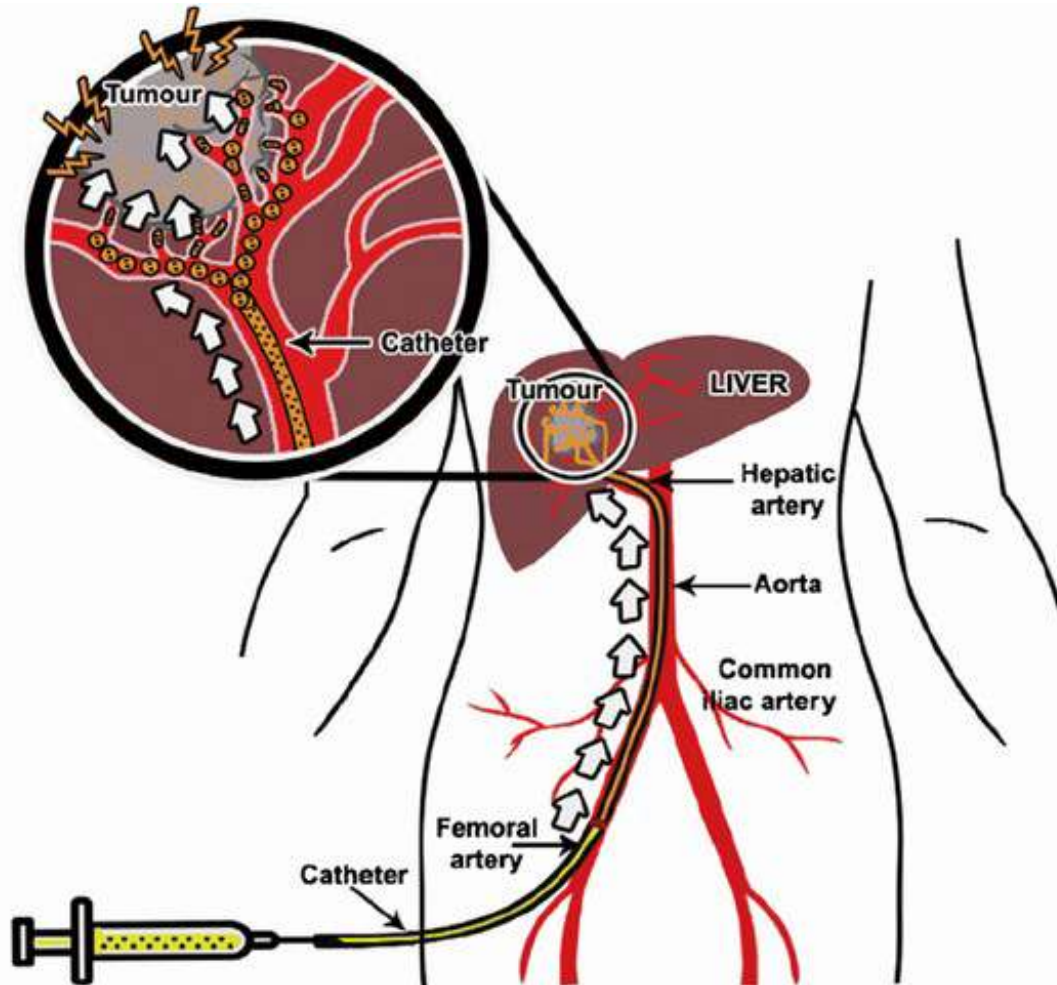
- INTRAVENOUS
  
- ORAL
  - ANTIMETABOLITES
  - ALKYLATING AGENTS
  - MITOTIS SPINDLE POISONS
  
- INTRAPERITONEAL
  
- INTRATUMORAL (TRANSARTERIAL CHEMOEMBOLIZATION)

# HIPEC

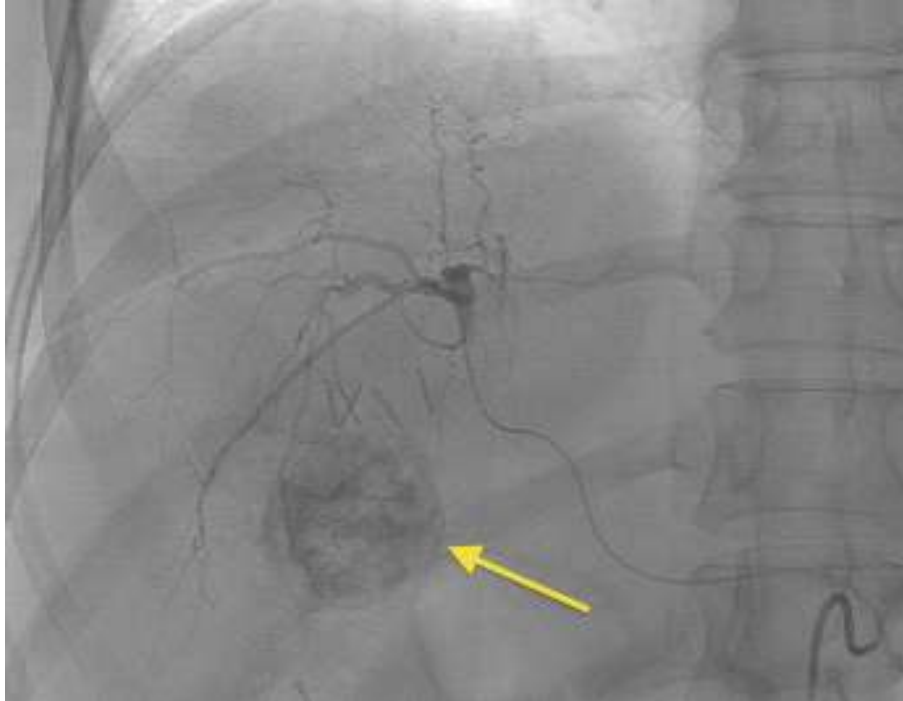
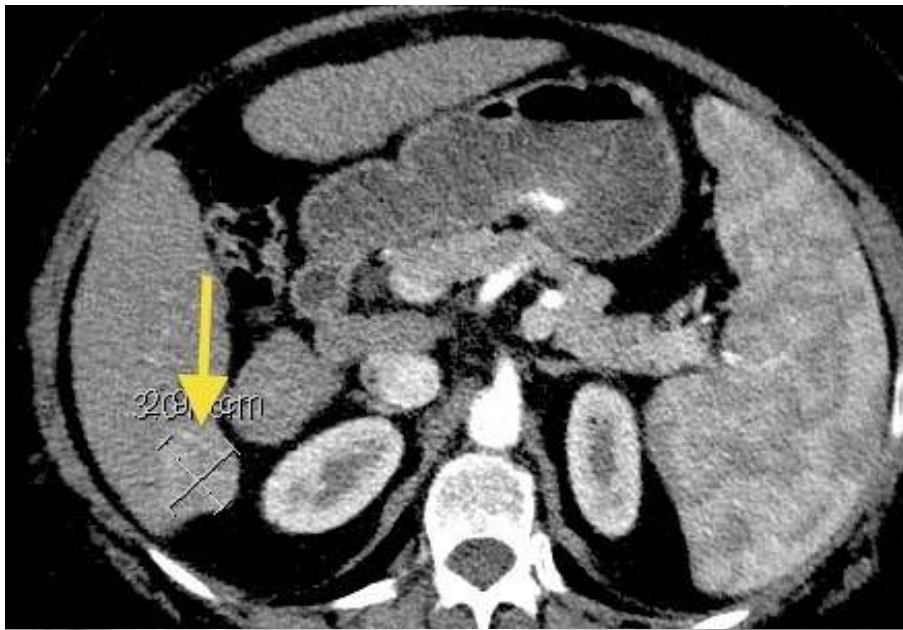
HYPERTHERMIC  
INTRA-PERITONEAL  
CHEMOTHERAPY



# TRANSARTERIAL CHEMOEMBOLIZATION







## Case Example 1: Chemoembolization of Hepatocellular Carcinoma

This 60 year-old cirrhotic female has a 3 cm mass in the posterior right segment of the liver diagnosed on pre-procedure CT scan (1a arrow). She was referred for chemoembolization. The arteriogram demonstrates the targeted mass (1b arrow). Follow-up imaging demonstrates complete tumor necrosis (1c arrow). The patient went on to liver transplant 6 months later.



# ENDOCRINE THERAPY





# Hormones

- Tumors derived from tissues responding to hormones may be hormone-dependent
  - Growth inhibited by hormone antagonists OR other hormones w/ opposing actions OR inhibitors of relevant hormone
- Glucocorticoids
  - Inhibitory on lymphocyte proliferation
  - Used against leukemias, lymphomas



## ■ ESTROGEN RECEPTOR

- breast, ovarian, endometrial cancers
- drugs
  - ER blockers – tamoxifen, fulvestrant
  - estrogen synthesis blockers – aromatase inhibitors
  - estrogen deprivation – aGnRH agonists/antagonists

## ■ ANDROGEN RECEPTOR

- prostate, breast cancer
- drugs
  - androgen deprivation – aLHRH agonists/antagonists
  - AR blockers – flutamide, bicalutamide, enzalutamide
  - androgen synthesis blocker – abiraterone

## ■ PROGESTERONE RECEPTOR

- specific drugs in development
- progestogens

# ENDOCRINE THERAPY IN BREAST CANCER



**E**

**ER**





**E**

**ER**

**CoA**

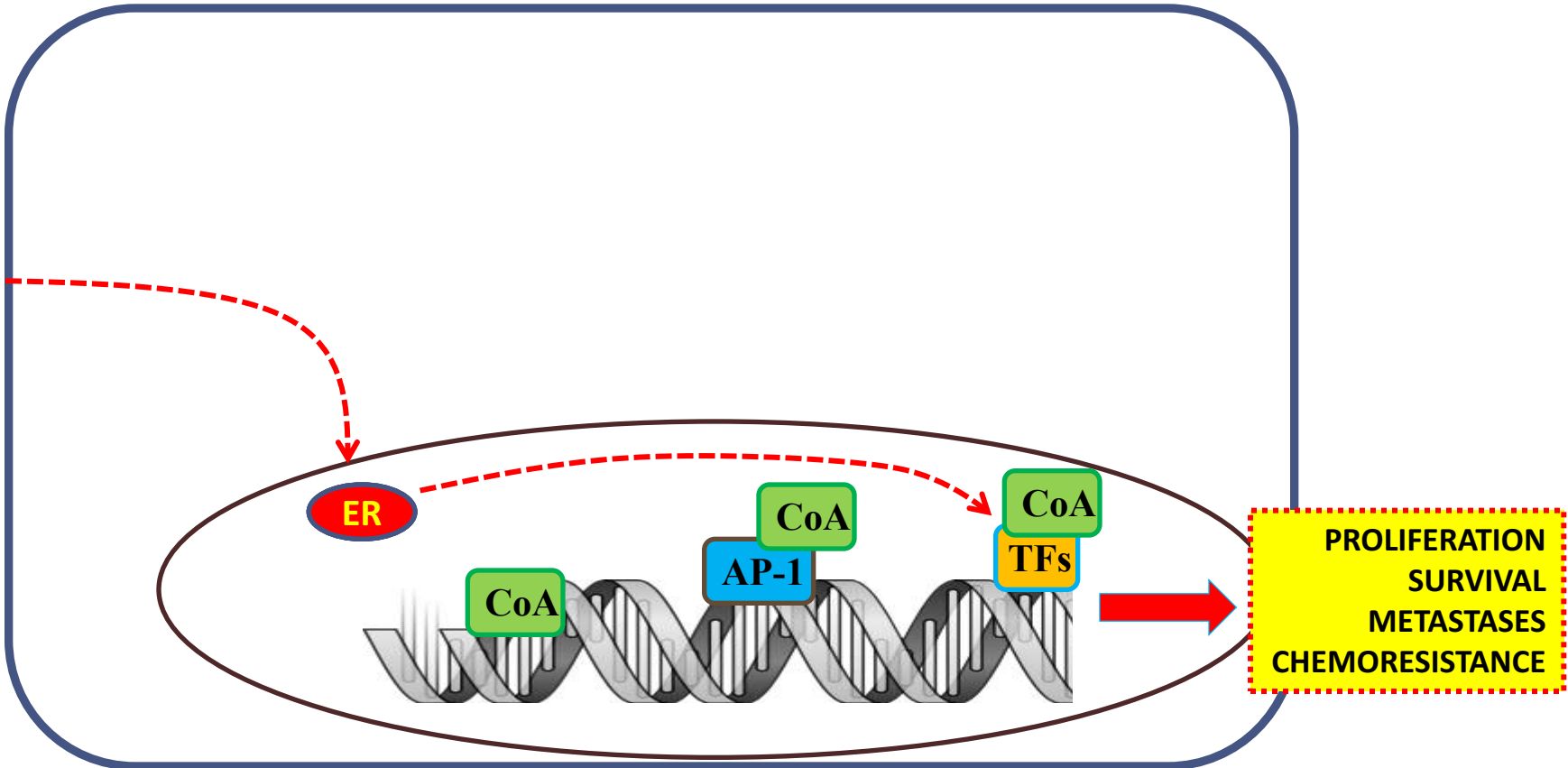
**AP-1**

**CoA**

**CoA**

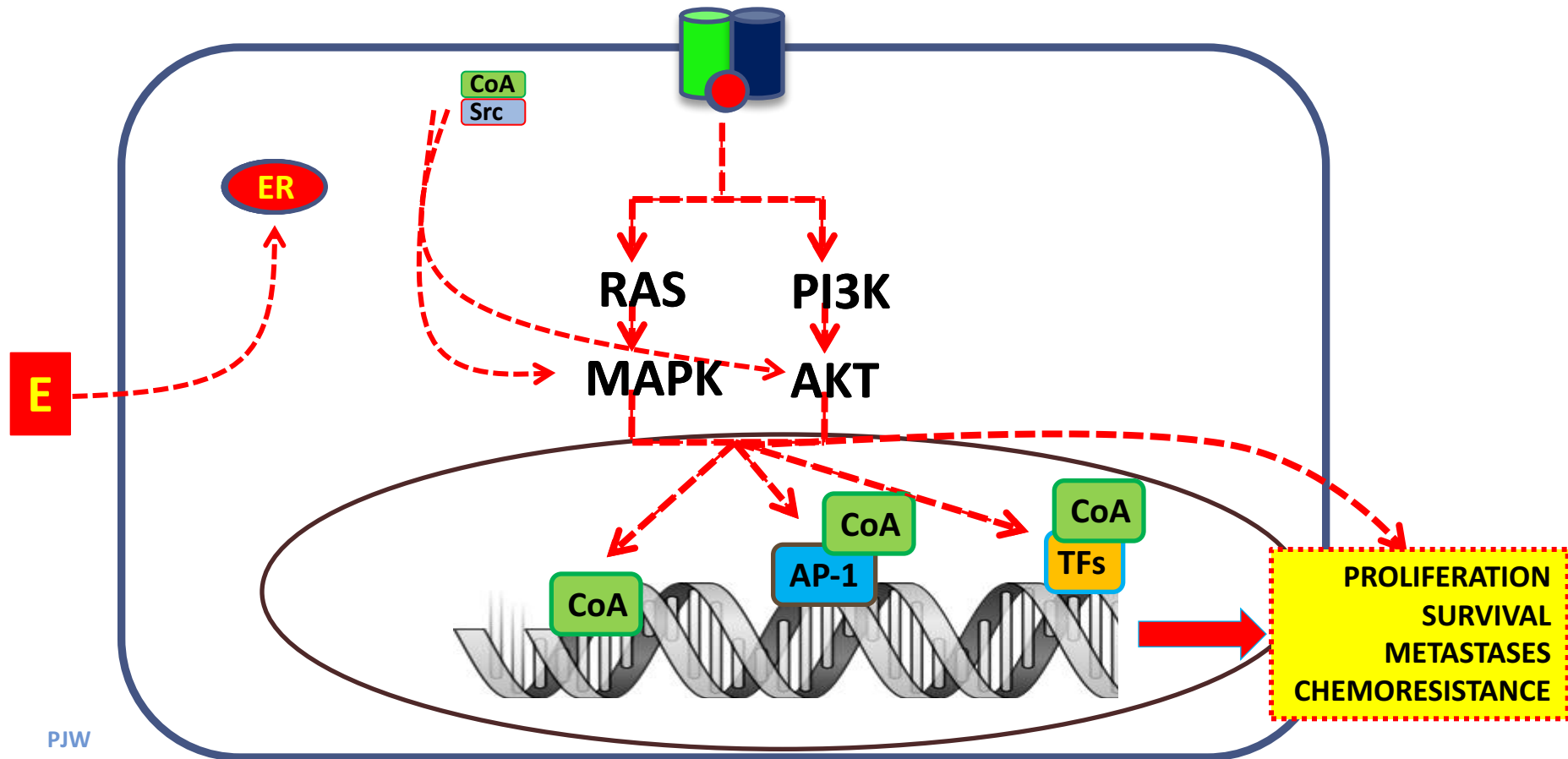
**TFs**

**PROLIFERATION  
SURVIVAL  
METASTASES  
CHEMORESISTANCE**



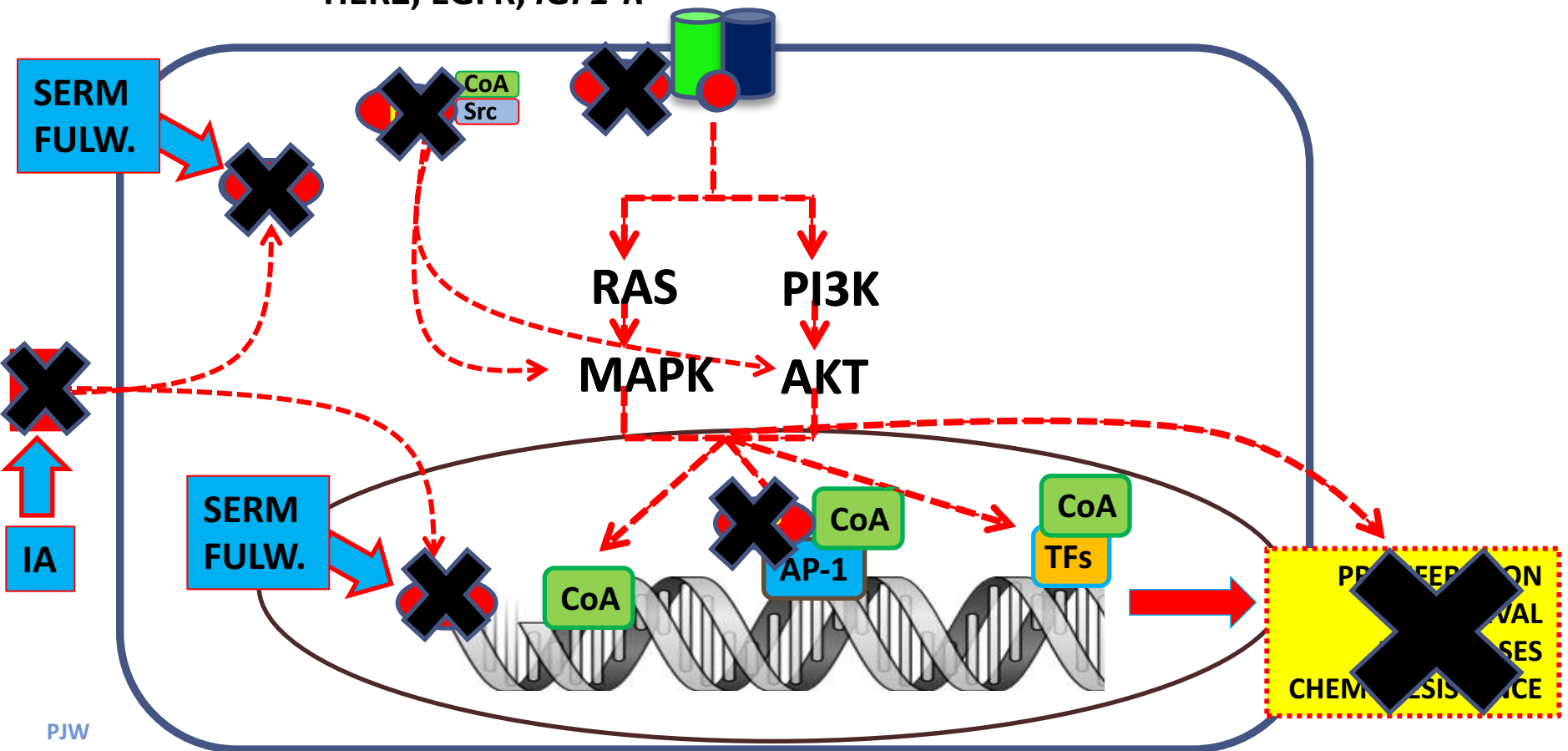


## HER2, EGFR, IGF1-R





HER2, EGFR, IGF1-R





# MALE ENDOCRINE SYSTEM



HYPOTHALAMUS

GONADOTROPIN  
RELEASING  
HORMONES

PITUARY GLAND

GONADOLIBERIN  
• AGONISTS  
• ANTAGONISTS

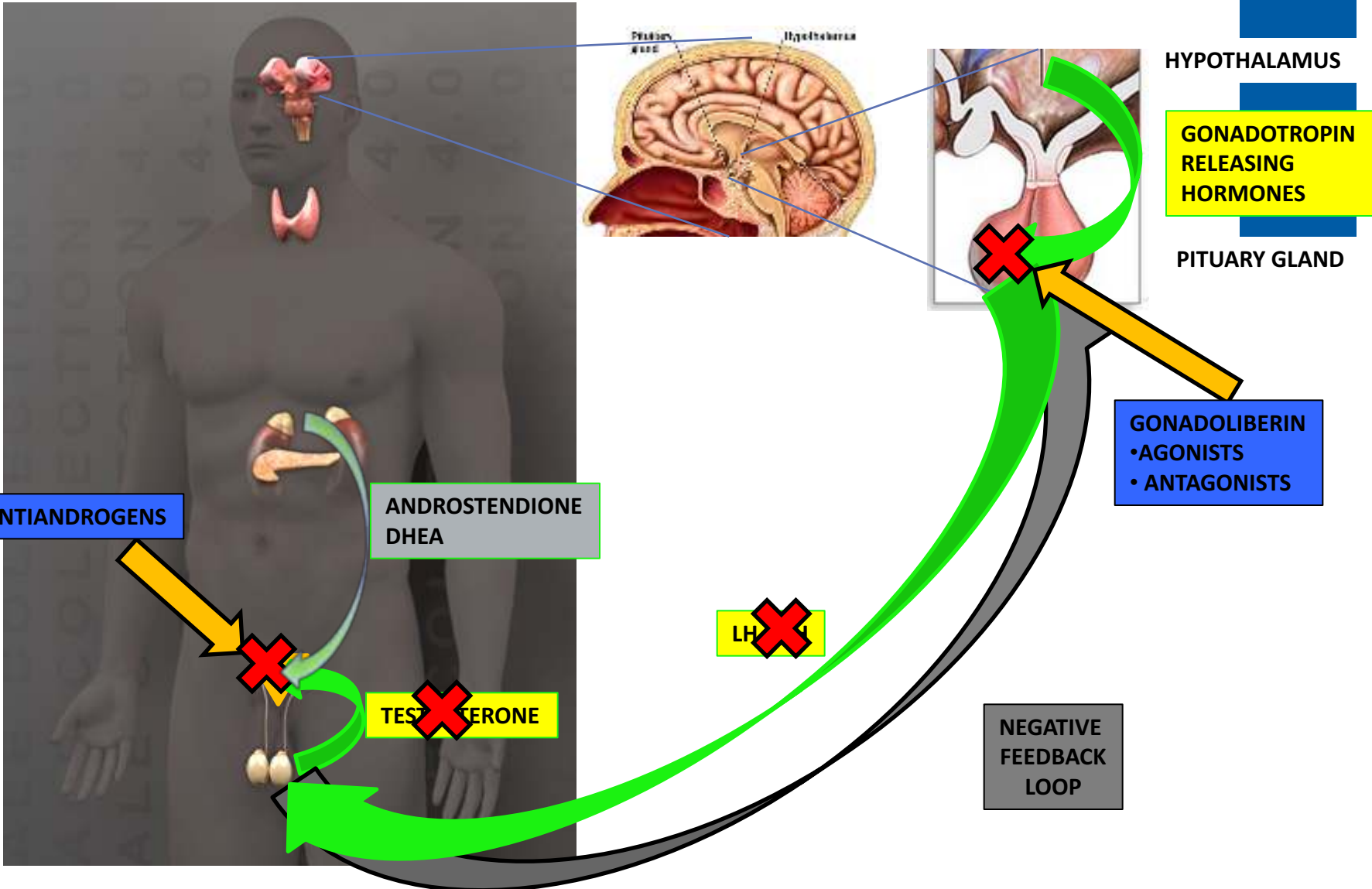
ANDROSTENDIONE  
DHEA

TESTOSTERONE

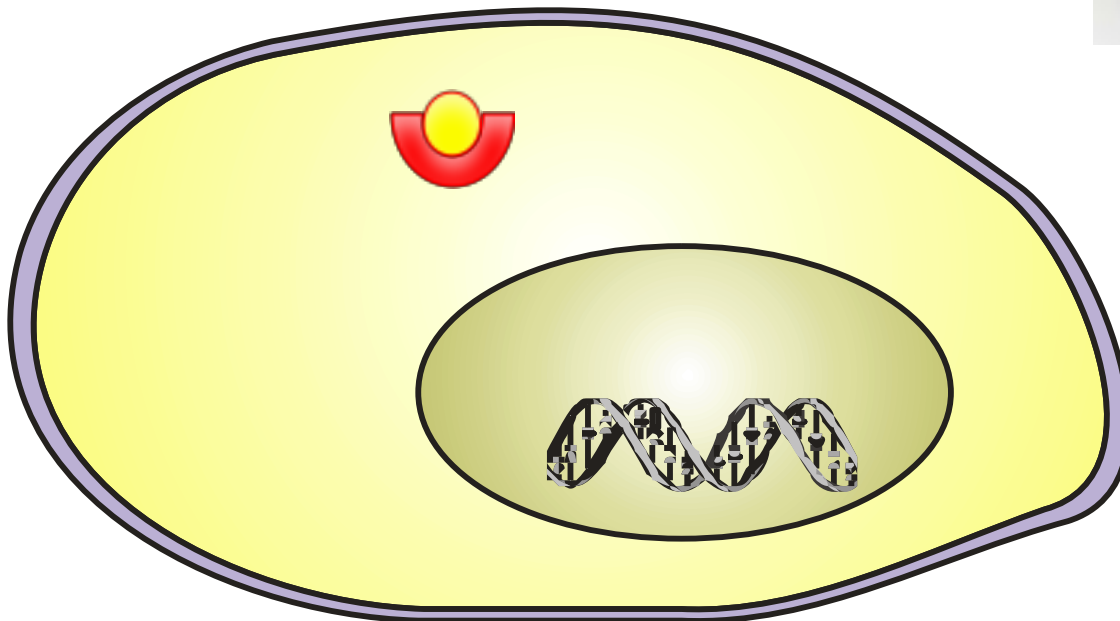
LH

NEGATIVE  
FEEDBACK  
LOOP

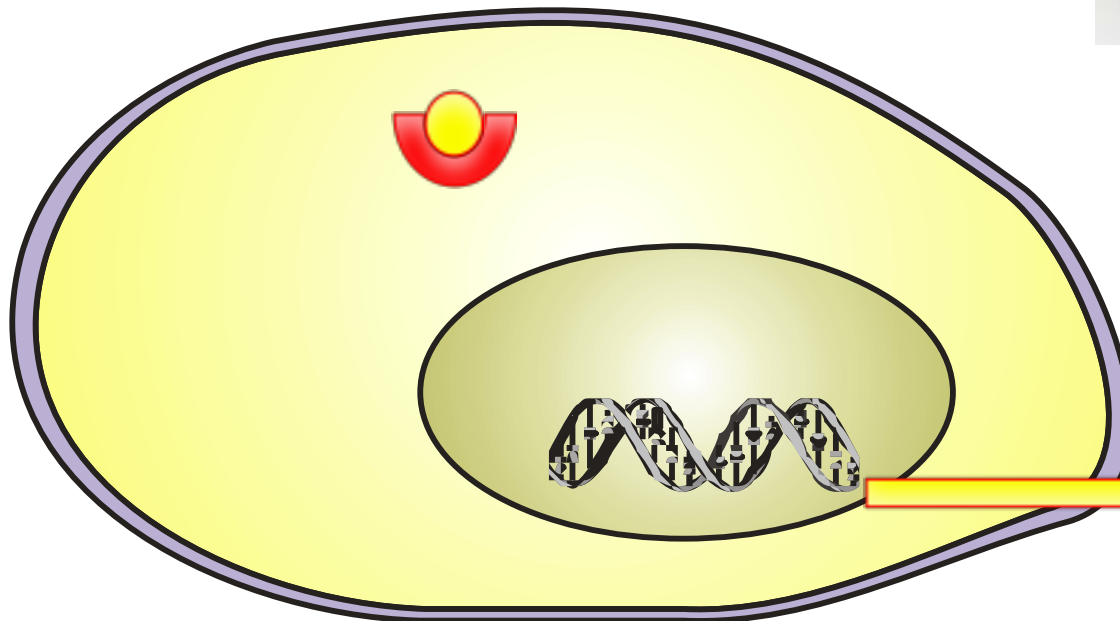
ANTIANDROGENS



# HORMONE SENSITIVITY OF PROSTATE CANCER



# HORMONE SENSITIVITY OF PROSTATE CANCER



SURVIVAL  
PROLIFERATION  
ANGIOGENESIS  
METASTASIS

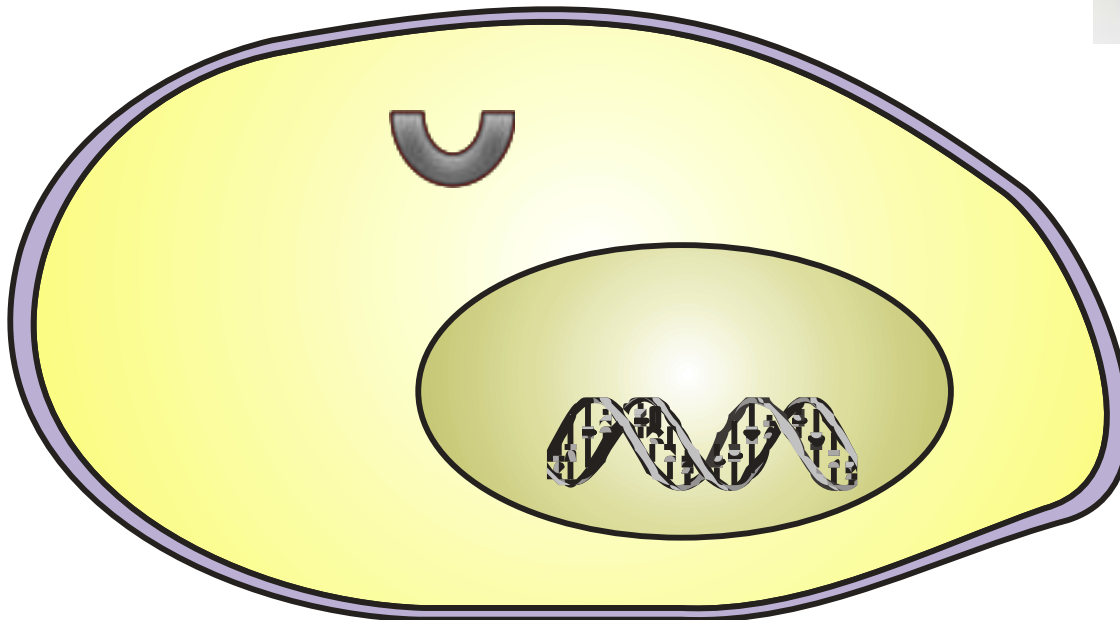
# ENDOCRINE THERAPY OF PROSTATE CANCER



## ANTIANDROGENS

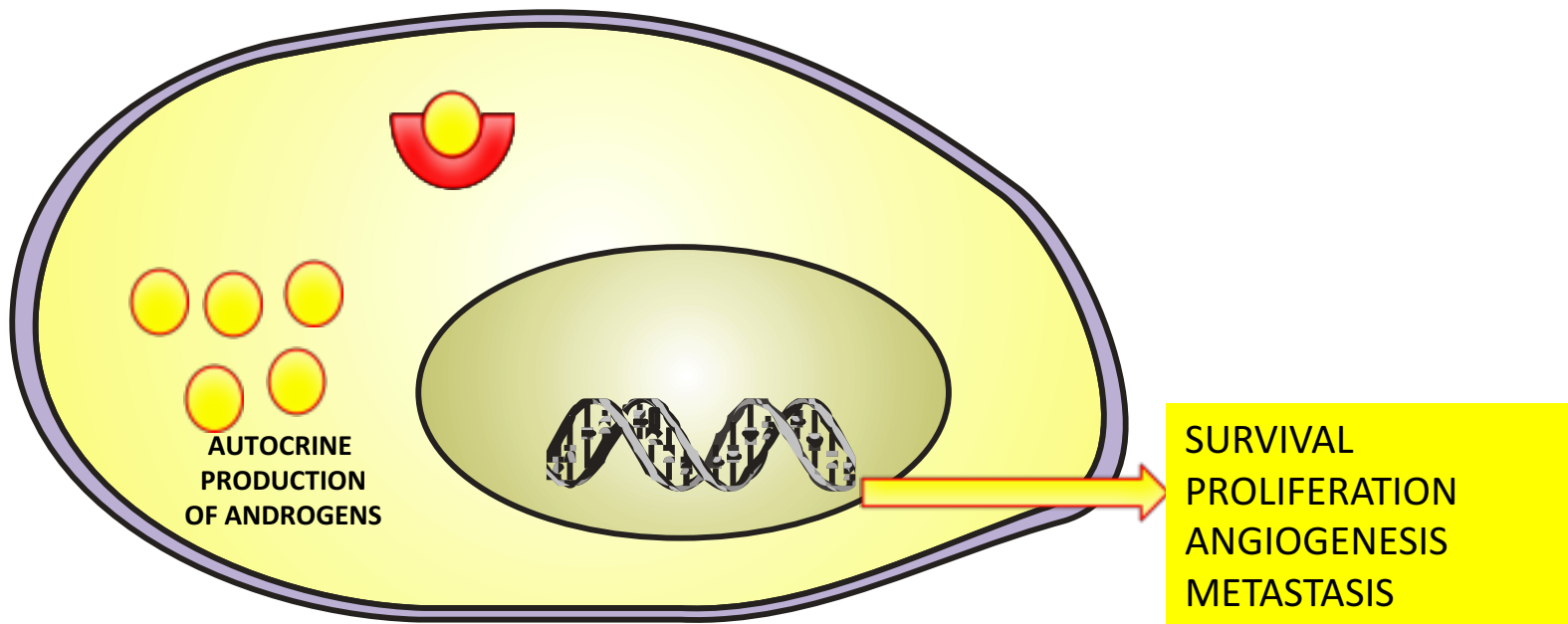
*FLUTAMIDE*

*BIKALUTAMIDE*



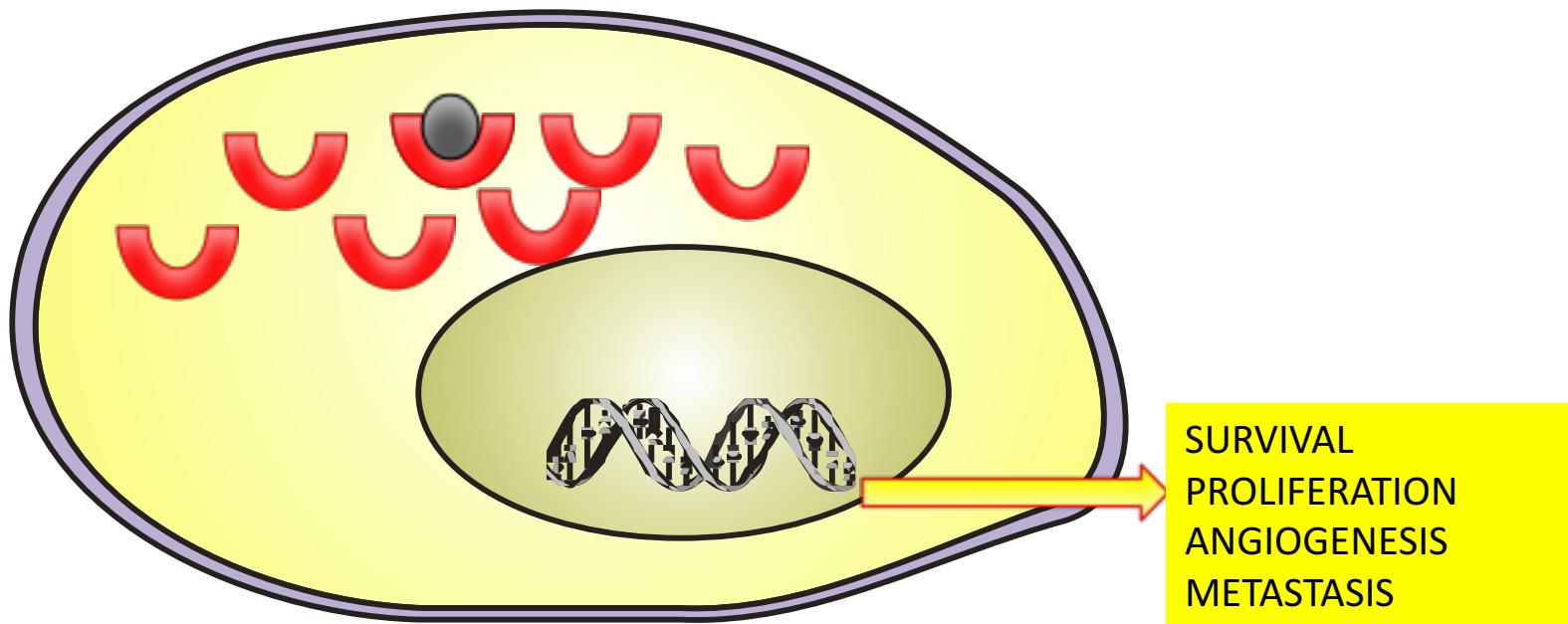
castration  
surgical  
pharmacological  
aGnRH

# RESISTANCE TO CASTRATION AUTOCRINE PRODUCTION OF ANDROGENS



# RESISTANCE TO CASTRATION

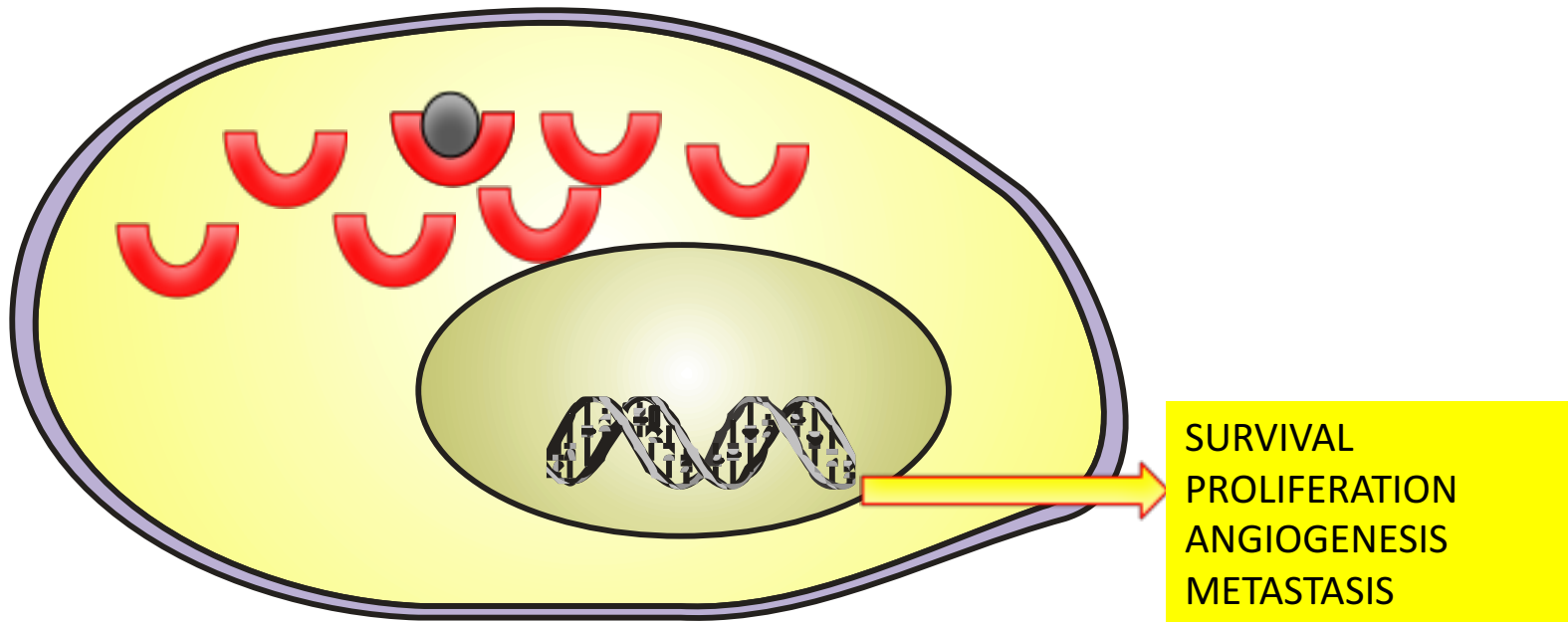
## *AR* amplification





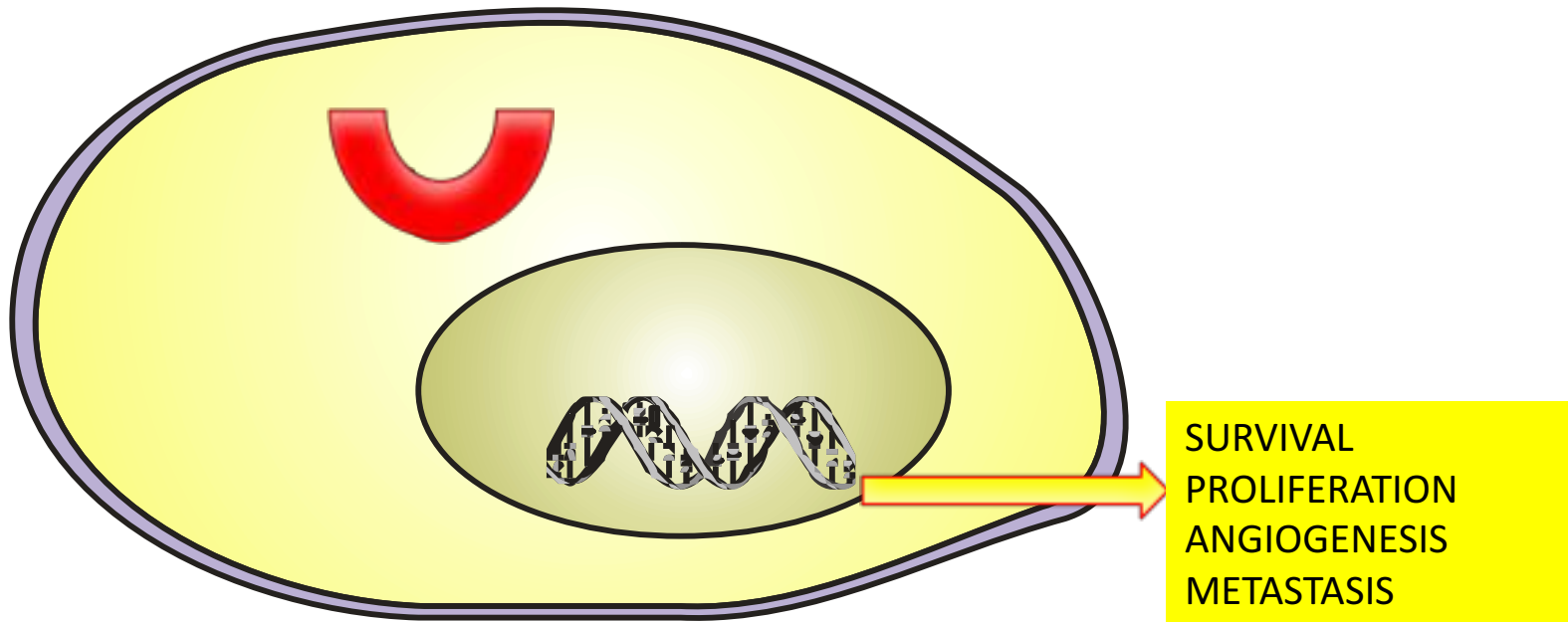
# RESISTANCE TO CASTRATION

## AR overexpression



# RESISTANCE TO CASTRATION

## hypersensitivity of AR

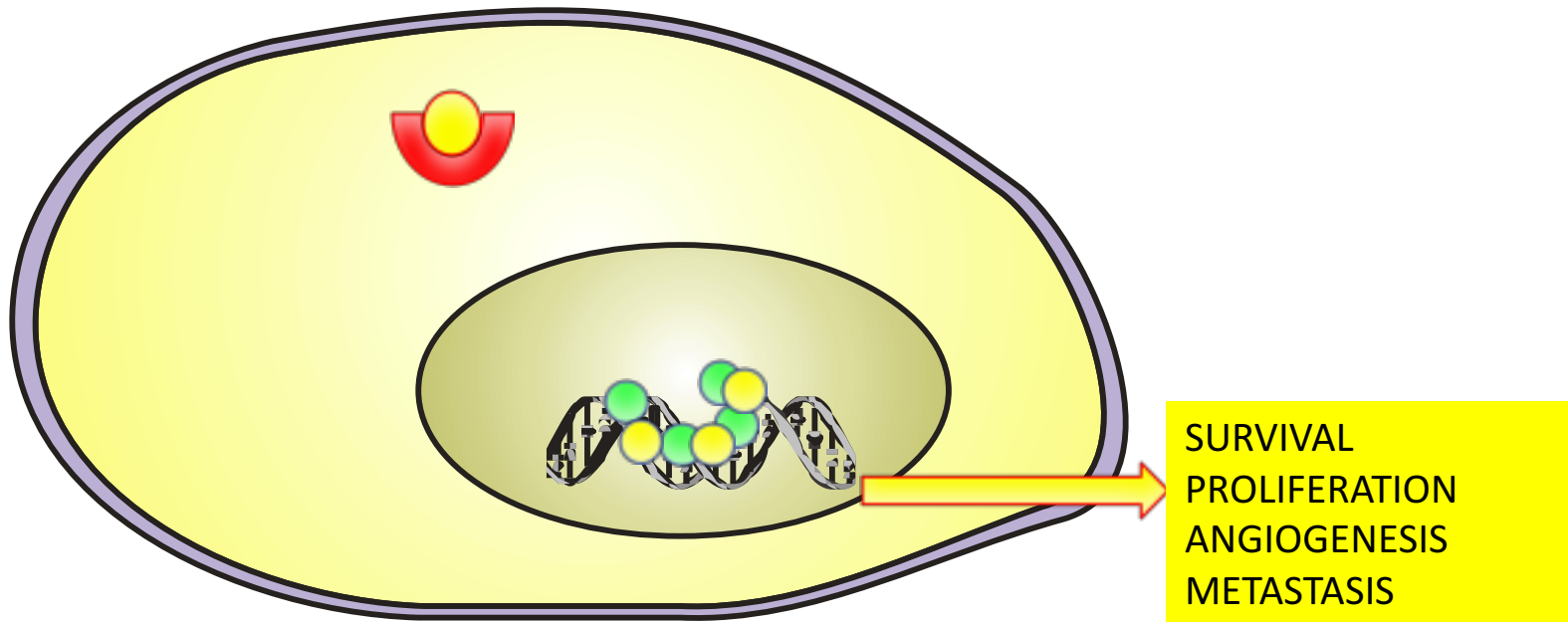






# RESISTANCE TO CASTRATION

## co-regulators

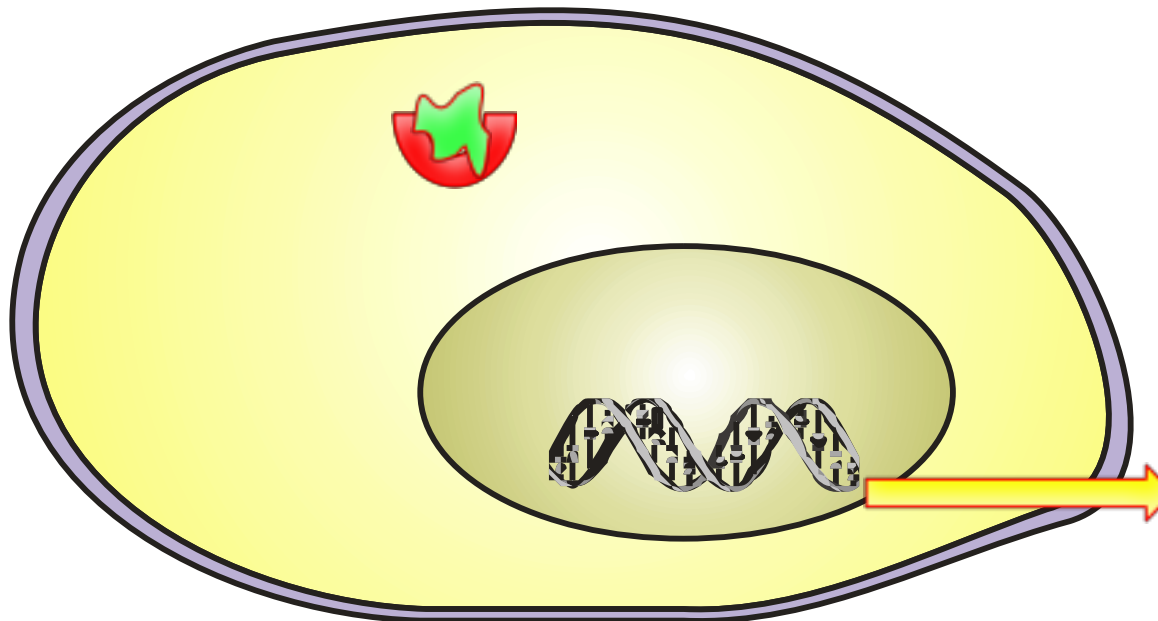




# RESISTANCE TO CASTRATION

## activation of AR by other factors

- prolactin
- growth hormone



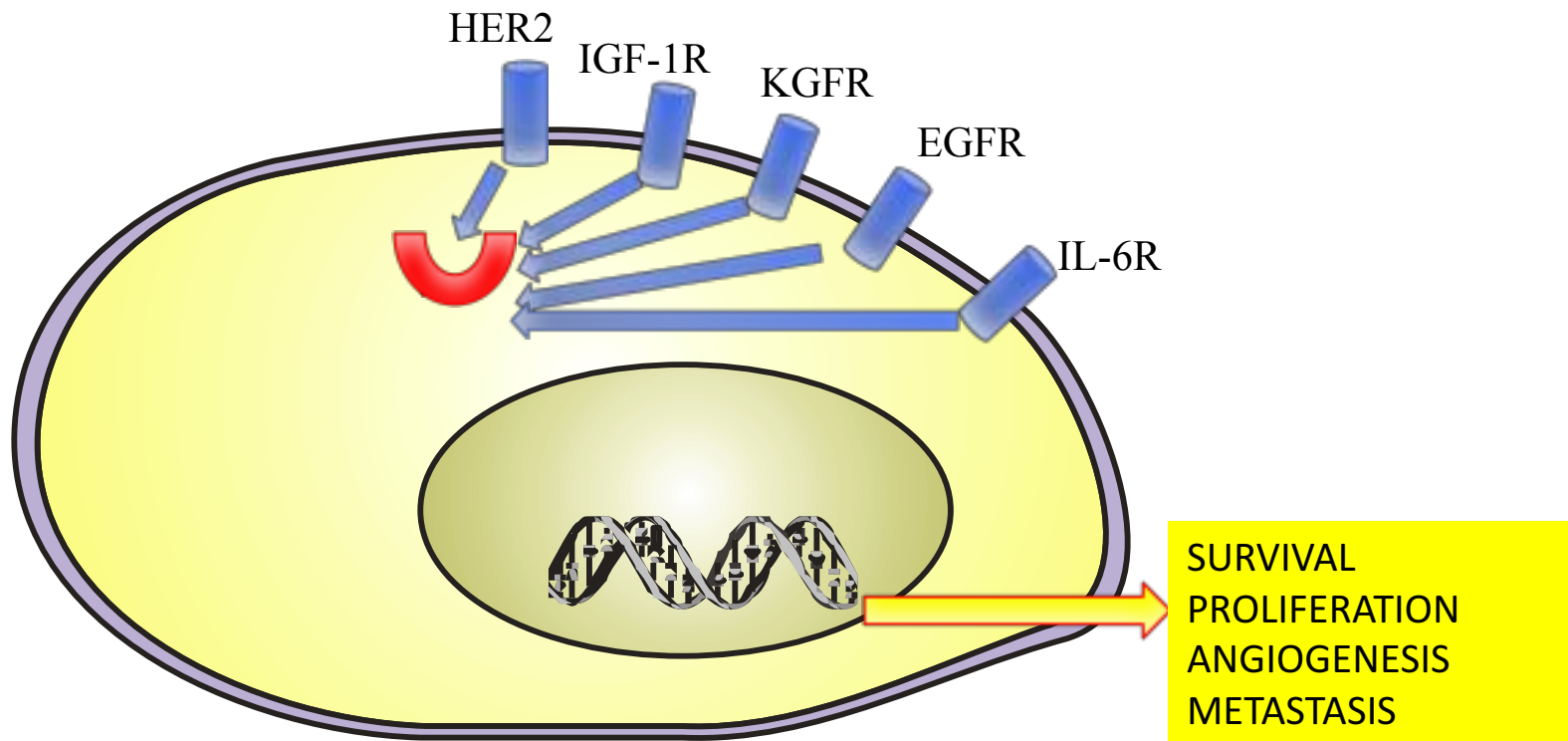
PRZEŻYCIE  
PROLIFERA  
CJA  
ANGIOGEN

# RESISTANCE TO CASTRATION

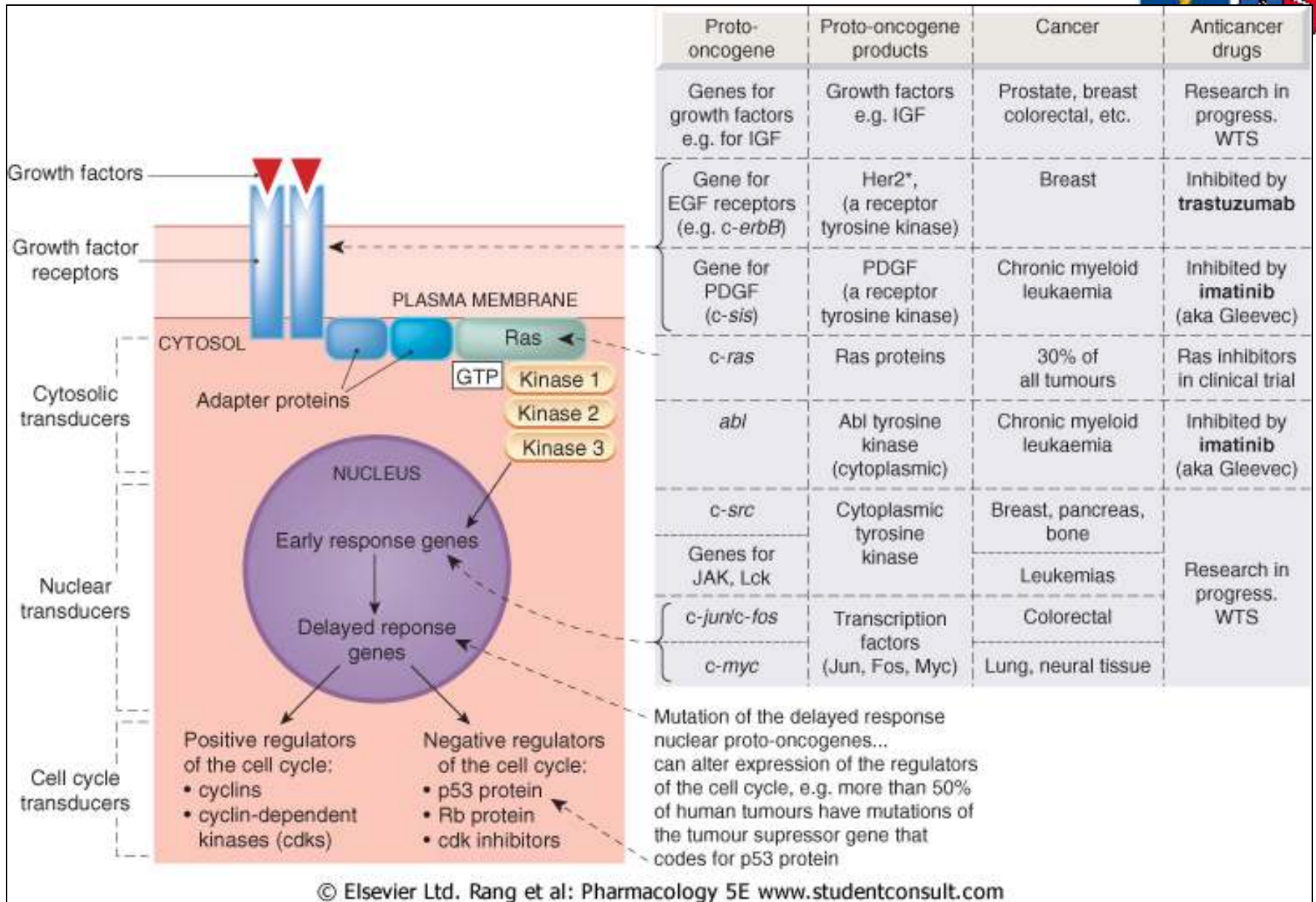
## activation of AR via various signalling pathways



- IGF-1
- KGF
- TGF
- IL-6
- IL-8



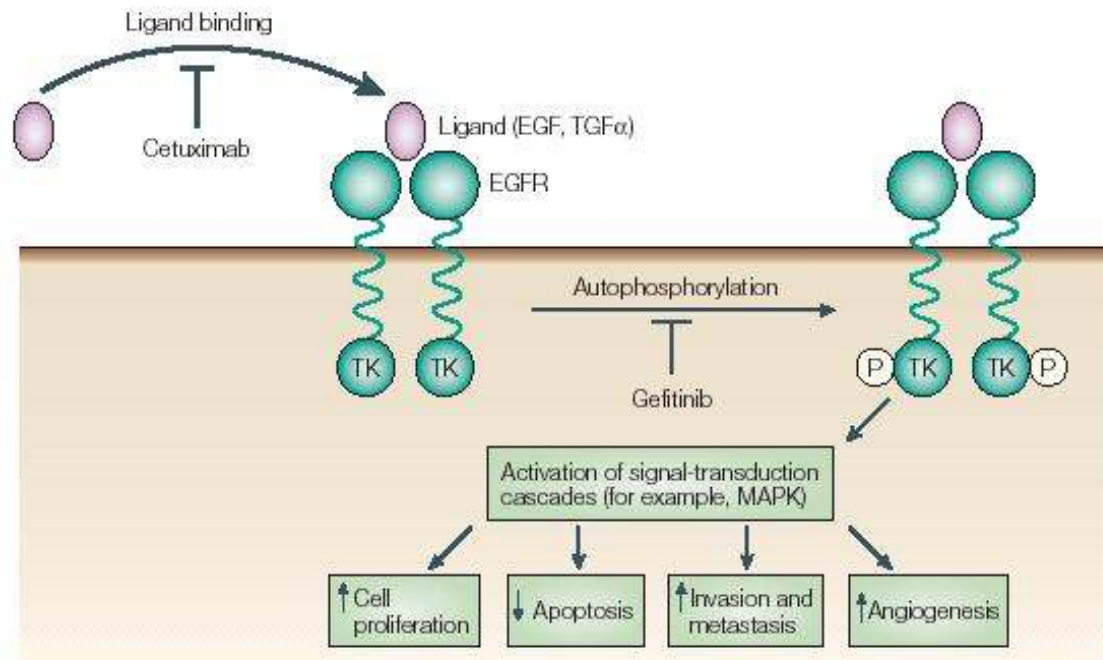
# Antitumor Agents Working through Cell Signalling



# Drugs Targeting Growth Factor Receptors



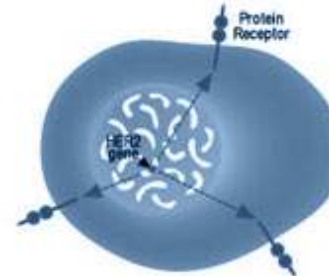
- Cetuximab, Panitumumab
  - Monoclonal Ab directed against EGFR
- Erbitux –anti-EGFR Ab





## ■ Trastuzumab

- “Humanized” mouse monoclonal Ab
- Binds HER2
  - Membrane protein structurally similar to EGFR
  - Has integral tyrosine kinase activity
  - Important in breast cancer cells
- May also induce p21 and p27
  - Cell cycle inhibitors

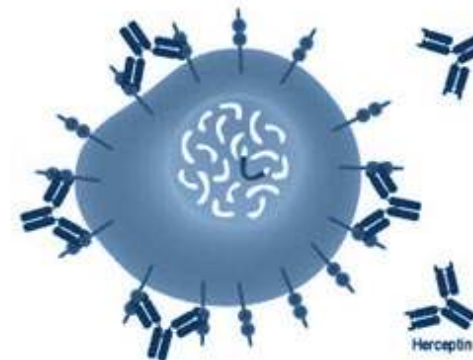


### Normal Cell

In normal breast tissue cells, the HER2 gene produces a protein receptor on the cell surface. These growth factor-like receptors are thought to play a role in normal cell growth by signaling the cell to divide and multiply.

### HER2 Overexpressing Cancer Cell

Cancerous breast tissue cells that overexpress (or overproduce) the HER2 gene produce extra protein receptors on the cell surface. The higher density of receptors triggers the cell to divide and multiply at an accelerated rate, thus contributing to tumor growth. Approximately 25-30% of all women with metastatic breast cancer overexpress the HER2 protein.



### Herceptin® (Trastuzumab)

It is thought that Herceptin (a HER2 antibody) binds to numerous HER2 receptor sites found on the cell surface, blocking the receptor sites and possibly preventing further growth by interrupting the growth signal. As a result, the HER2 antibody may slow progression of the disease.



# PERSONALIZED HEALTHCARE IN ONCOLOGY

*- WE ARE NOT THERE YET-*



**CANCER**

CANCER

*CANCER*

CANCER

*CANCER*

CANCER





# Tailoring Treatment?



**prof. Ian Tannock**  
**PMH University of Toronto**

- „If I go to my tailor to buy a new suit, I do not ask for a suit for a group of Caucasian men with white hair—
  - I expect to be measured for the suit so that it fits me alone
- It's important to differentiate between treatment that is tailored individually....
  - ....and treatment that is tailored to a group (e.g. women with breast cancer whose cells express HER2)“



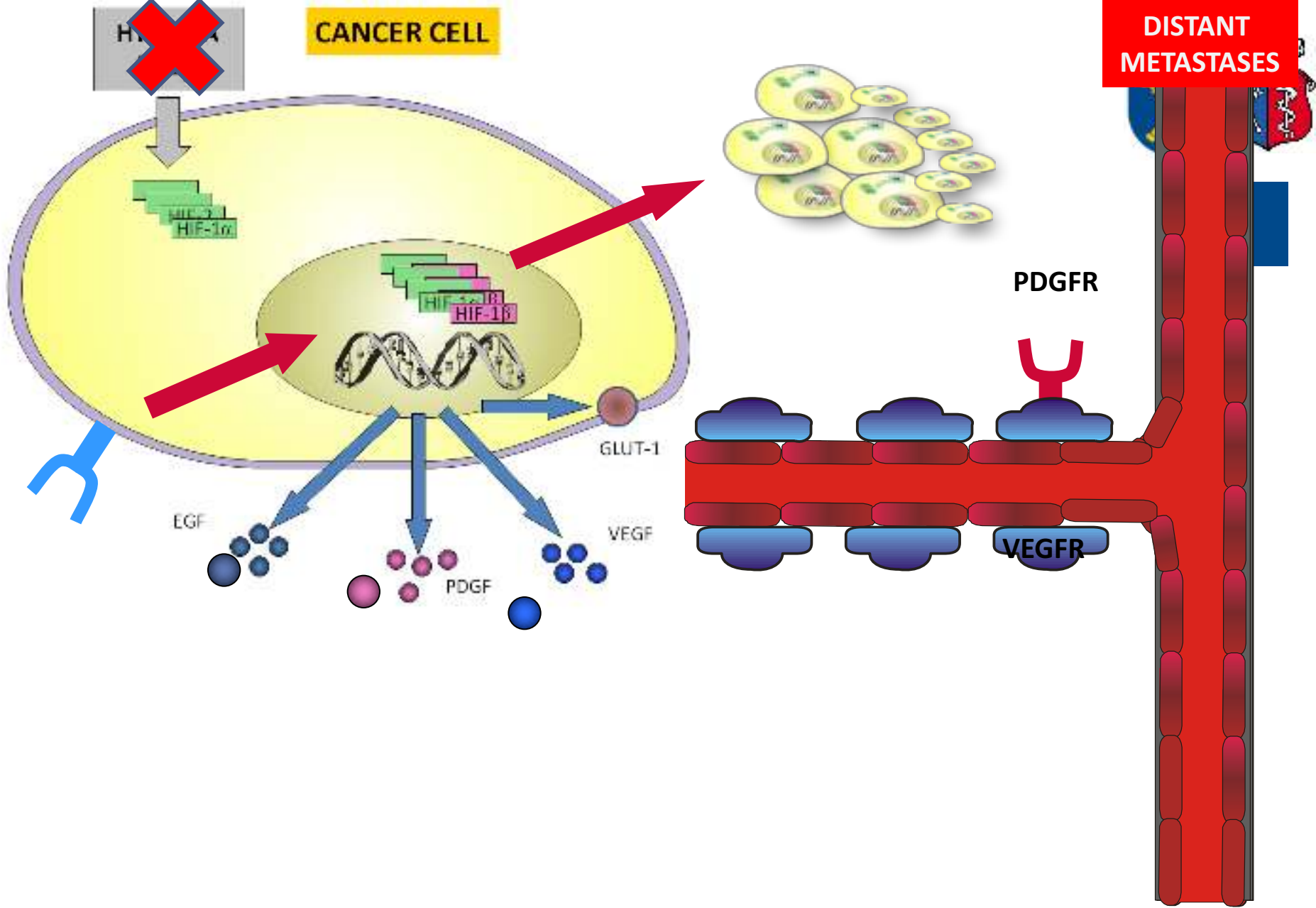
# BIOMARKERS

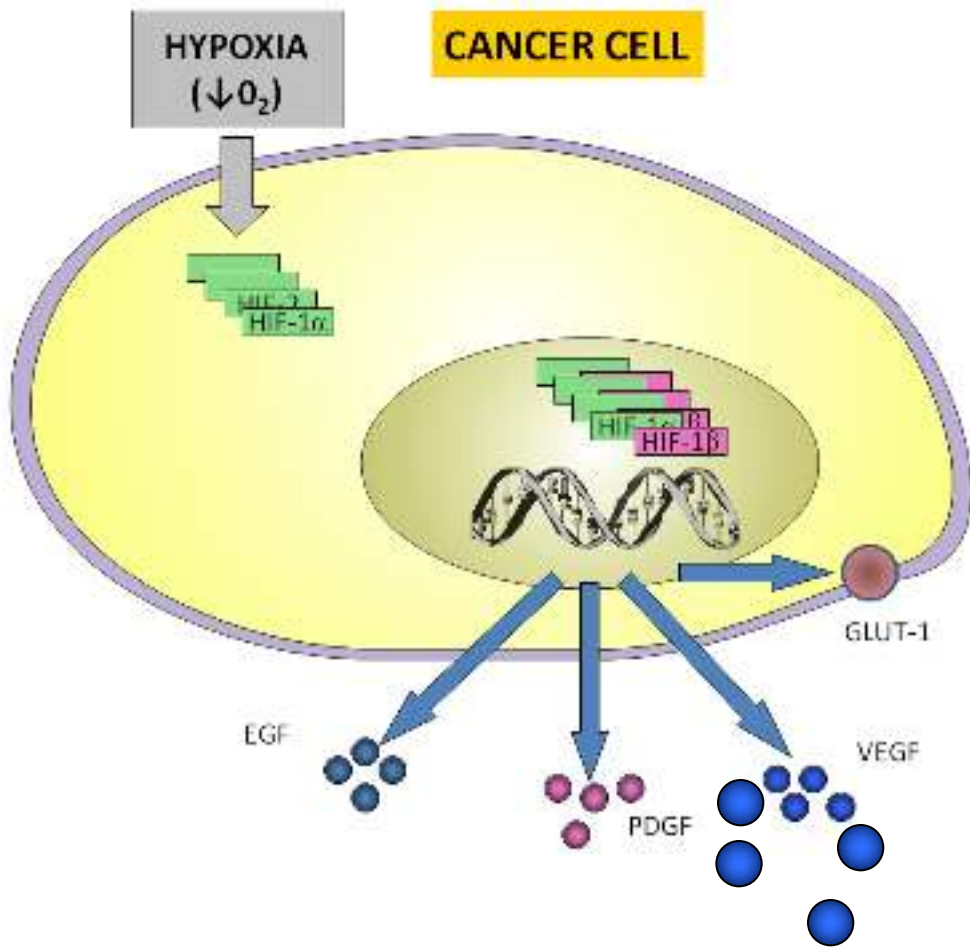
BIOMARKER = BIOLOGICAL MARKER THAT CAN BE DEFINED ON GENOMIC OR MOLECULAR LEVEL

- BIOLOGICAL PROGNOSTIC FACTORS
- BIOLOGICAL PREDICTIVE FACTORS
- BIOLOGICAL SIGNS OF TREATMENT EFFICACY (RESPONSE)
- BIOLOGICAL MARKERS DEMONSTRATING RESISTANCE TO TREATMENT

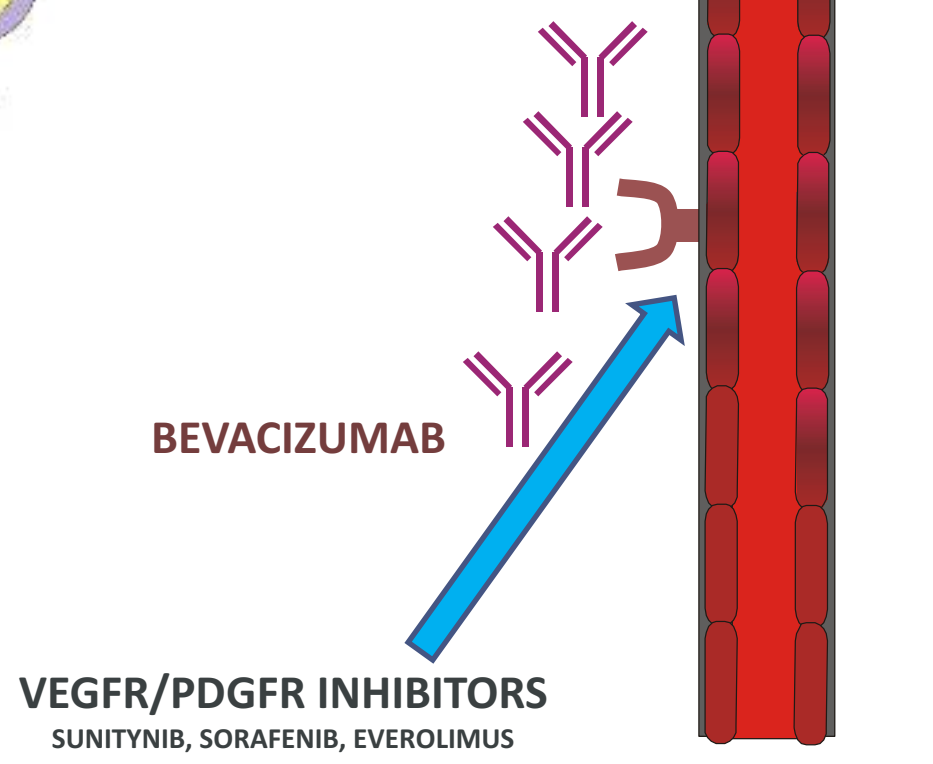


# NOVEL antiangiogenic THERAPIES— are there any biomarkers?





**INHIBITION OF ANGIOGENESIS**





# BEVACIZUMAB

VEGF – KEY FACTOR IN TUMOR-INDUCED ANGIOGENESIS

VEGF – IMMUNOSUPPRESSIVE FACTOR

VEGF – PROGNOSTIC FACTOR

BUT

VEGF – PREDICTIVE FACTOR FOR BEVACIZUMAB EFFICACY???

VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, PlGF, sVEGFR??

# ANTIANGIOGENIC THERAPIES USED FOR TREATMENT OF RENAL CANCER



## TYROSINE KINASE INHIBITORS

- SORAFENIB – VEGFR-1, VEGFR-2, VEGFR-3, PDGFR- $\beta$ , RAF
- SUNITYNIB – VEGFR-1, VEGFR-2, VEGFR-3, PDGFR- $\alpha$ , PDGFR- $\beta$

## SERINE-THREONINE KINASE (mTOR ) INHIBITORS

- TEMSIROLIMUS
- EVEROLIMUS

## VEGF NEUTRALIZATION

- BEVACIZUMAB

**BUT**  
**THERE IS NO SINGLE PREDICTIVE FACTOR**



# HER2 AND TARGETED THERAPIES IN BREAST CANCER





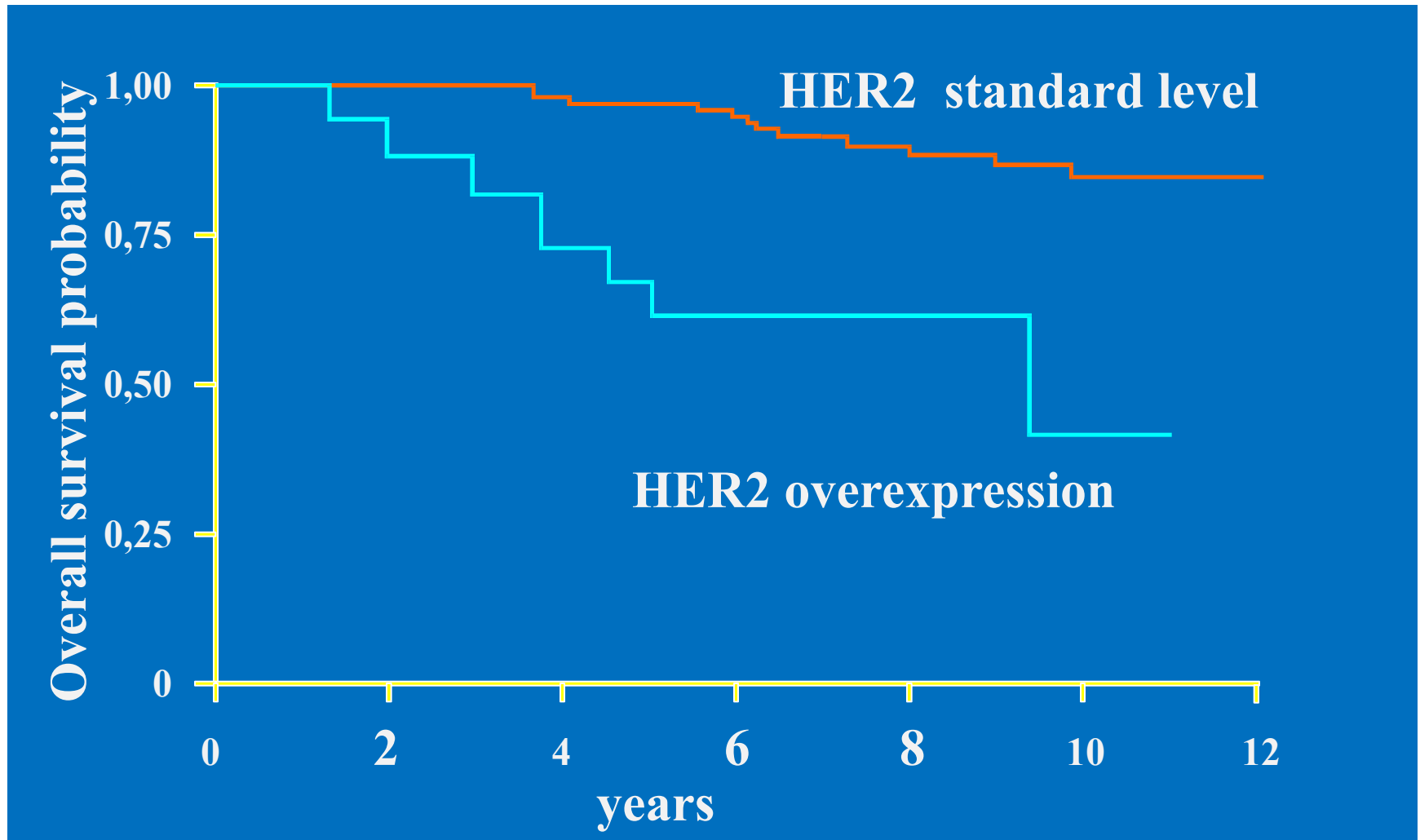
# HER2 (ErbB2)

## MEMBER OF EPIDERMAL GROWTH FACTOR RECEPTOR FAMILY



- OVEREXPRESSION OF HER2 – prognostic biomarker in breast cancer
- OVEREXPRESSION OF HER2 – negative predictive biomarker for response to hormonal treatment in breast cancer
- OVEREXPRESSION OF HER2 – predictive biomarker for therapies targeting this receptor (trastuzumab and lapatinib)

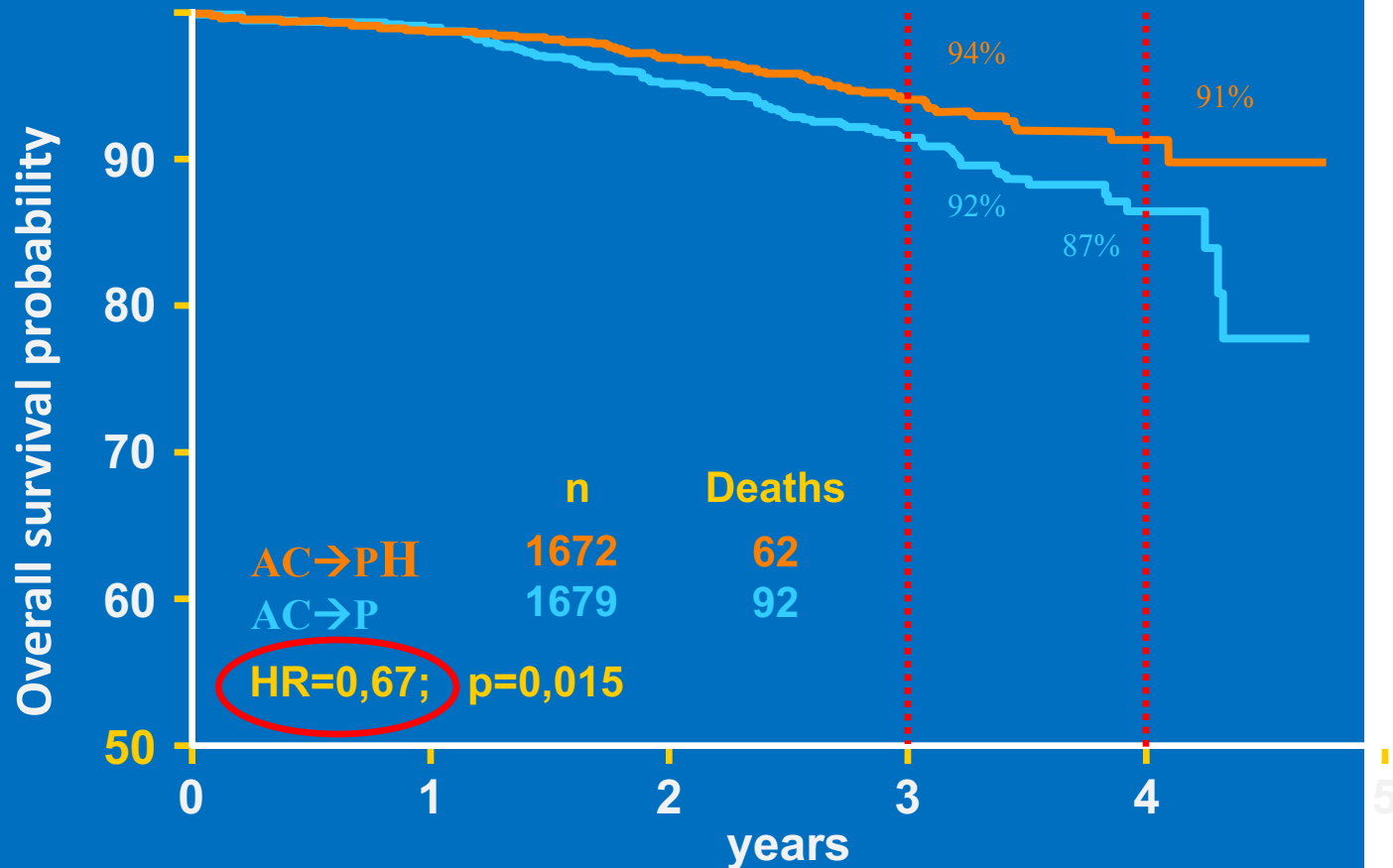
# HER2 PROGNOSTIC BIOMARKER IN BREAST CANCER PATIENTS





# HER2 – PREDICTIVE BIOMAKER OF TRASTUZUMAB (Herceptin) EFFICACY

B-31 i N9831 – combined analysis





# THE REAL EFFICACY OF TRASTUZUMAB

- IN METASTATIC BREAST CANCER (MBC), RESISTANCE TO TRASTUZUMAB MONOTHERAPY – 66-88%
- THE MAJORITY OF MBC PATIENTS PRIMARILY RESPONDING TO TRASTUZUMAB WILL DEVELOP RESISTANCE WITHIN 1 YEAR
- IN ADJUVANT TREATMENT – DISSEMINATION OF DISEASE WILL OCCUR IN ~15% OF PATIENTS



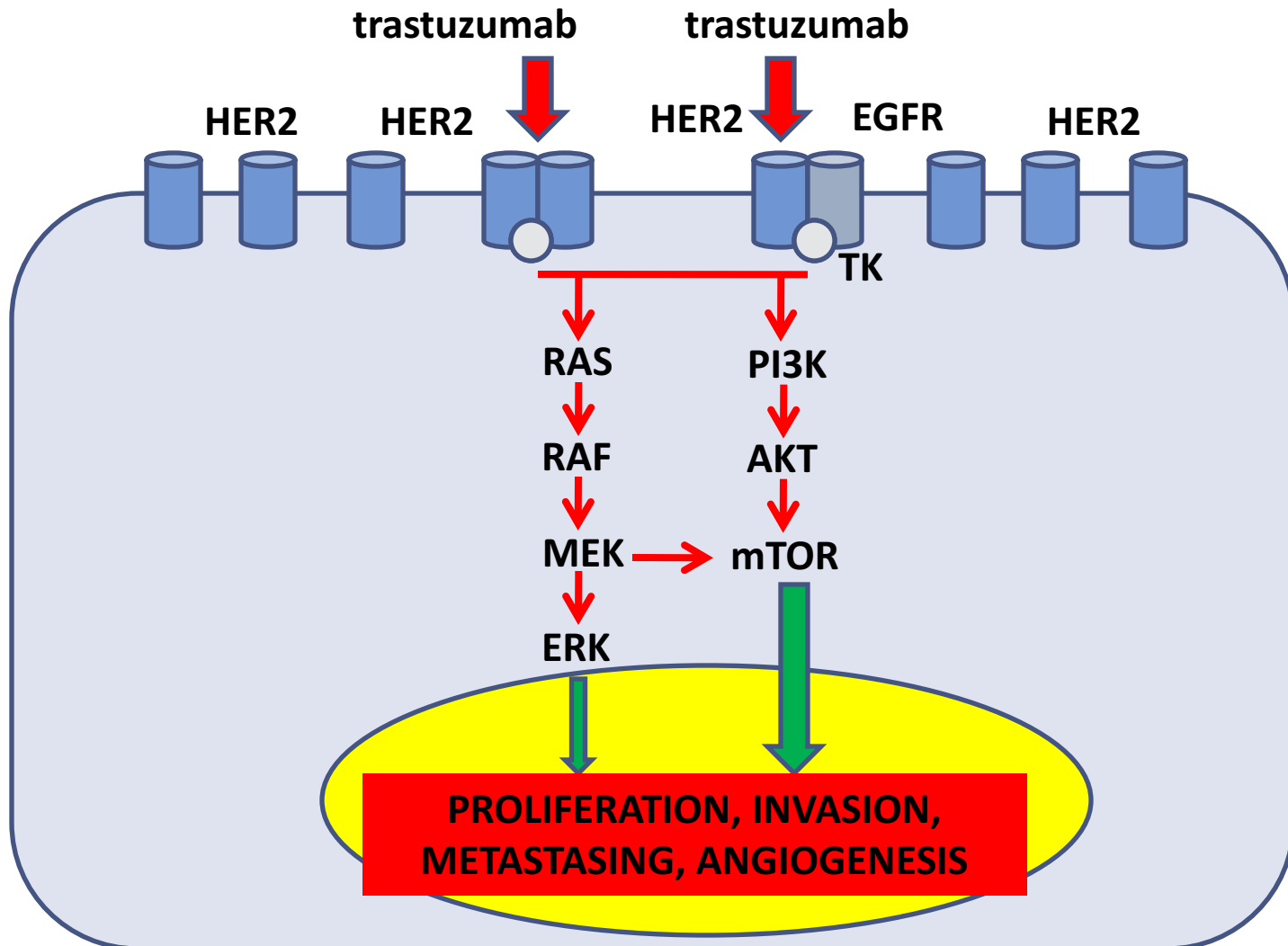
# AT THE CELL MEMBRANE

HER2 AND RESPONSE TO TRASTUZUMAB





# TRASTUZUMAB IN HER2-OVEREXPRESSING BREAST CANCER

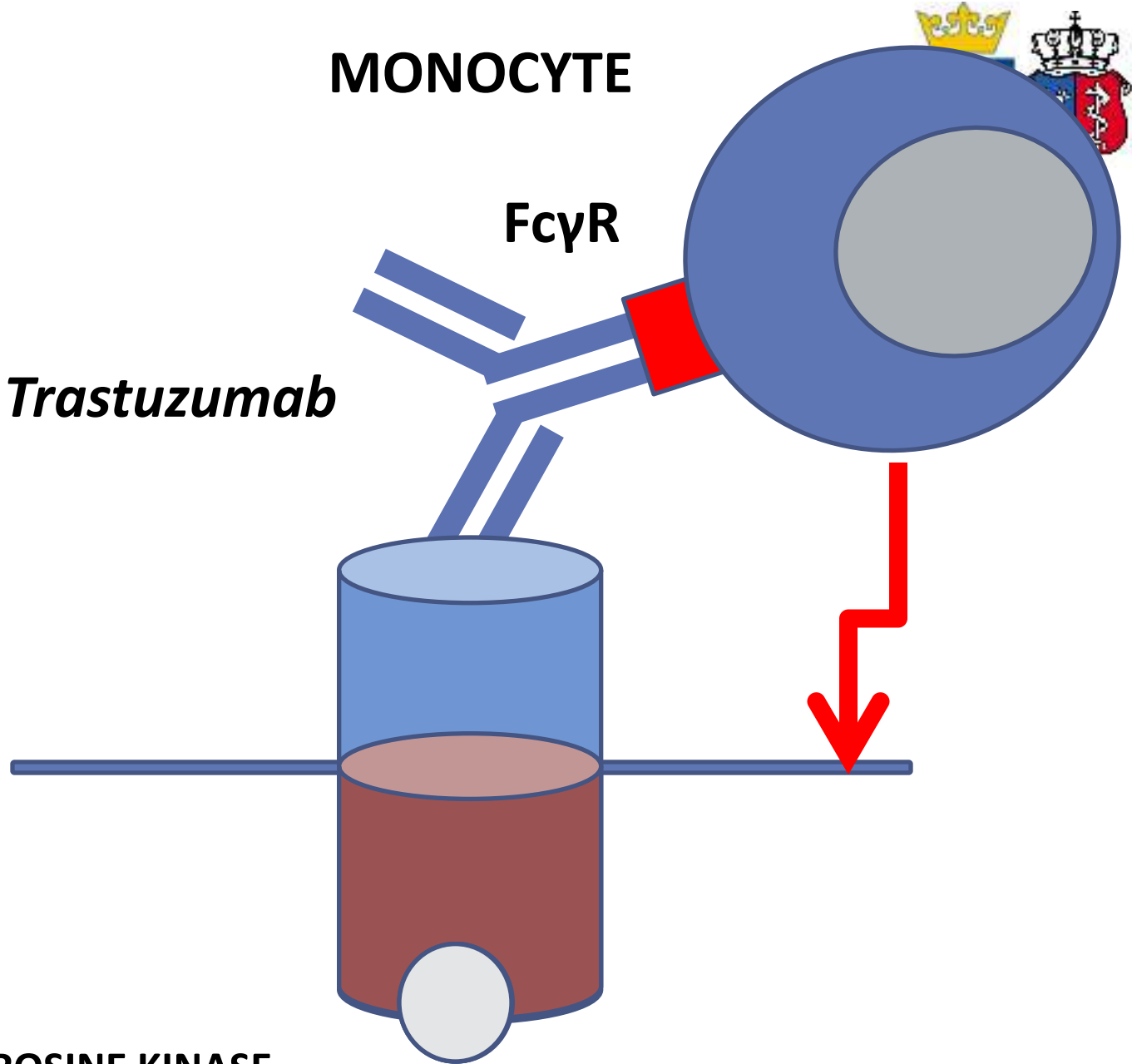


**MONOCYTE**

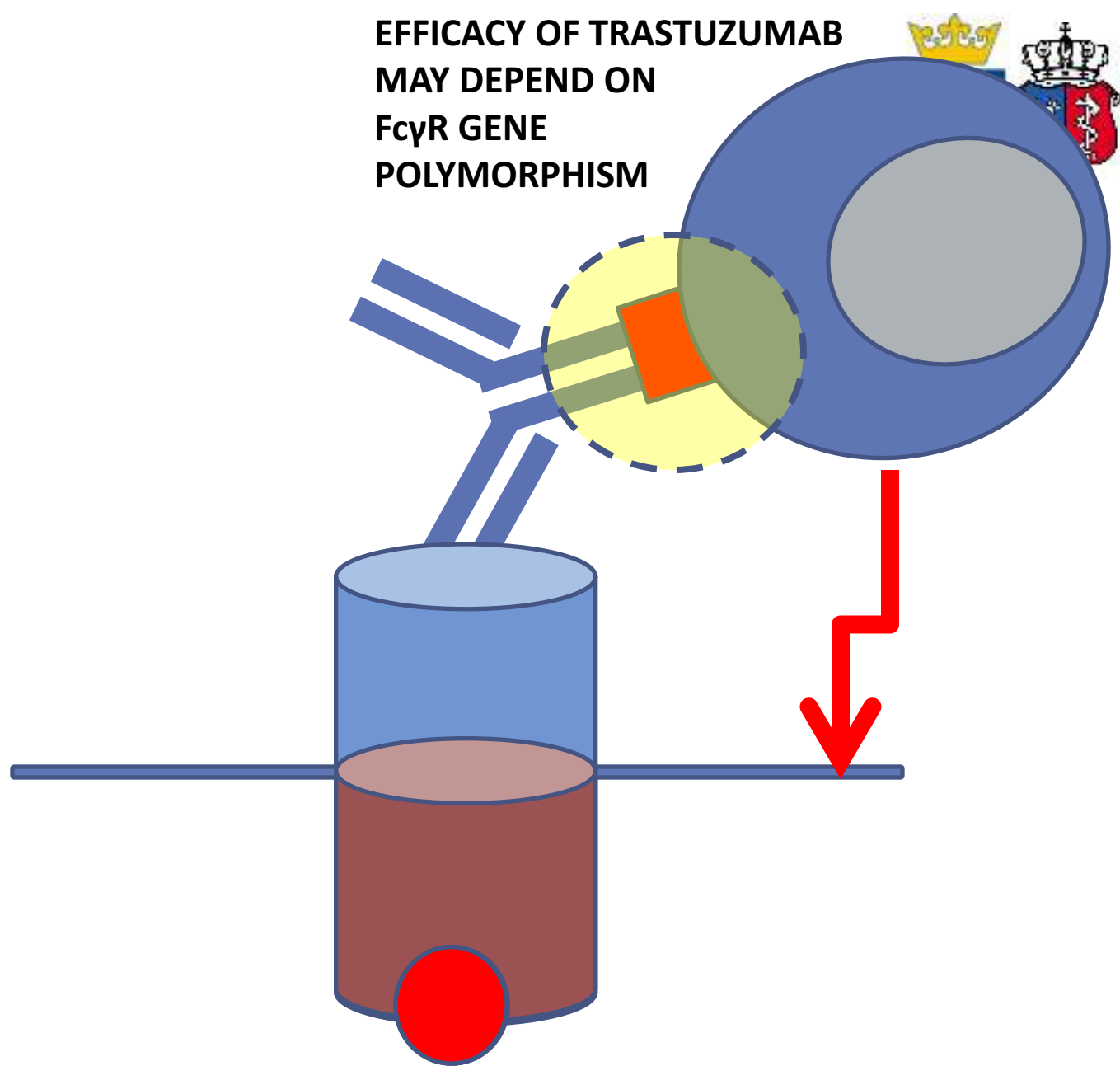
**FcγR**

*Trastuzumab*

**TYROSINE KINASE**



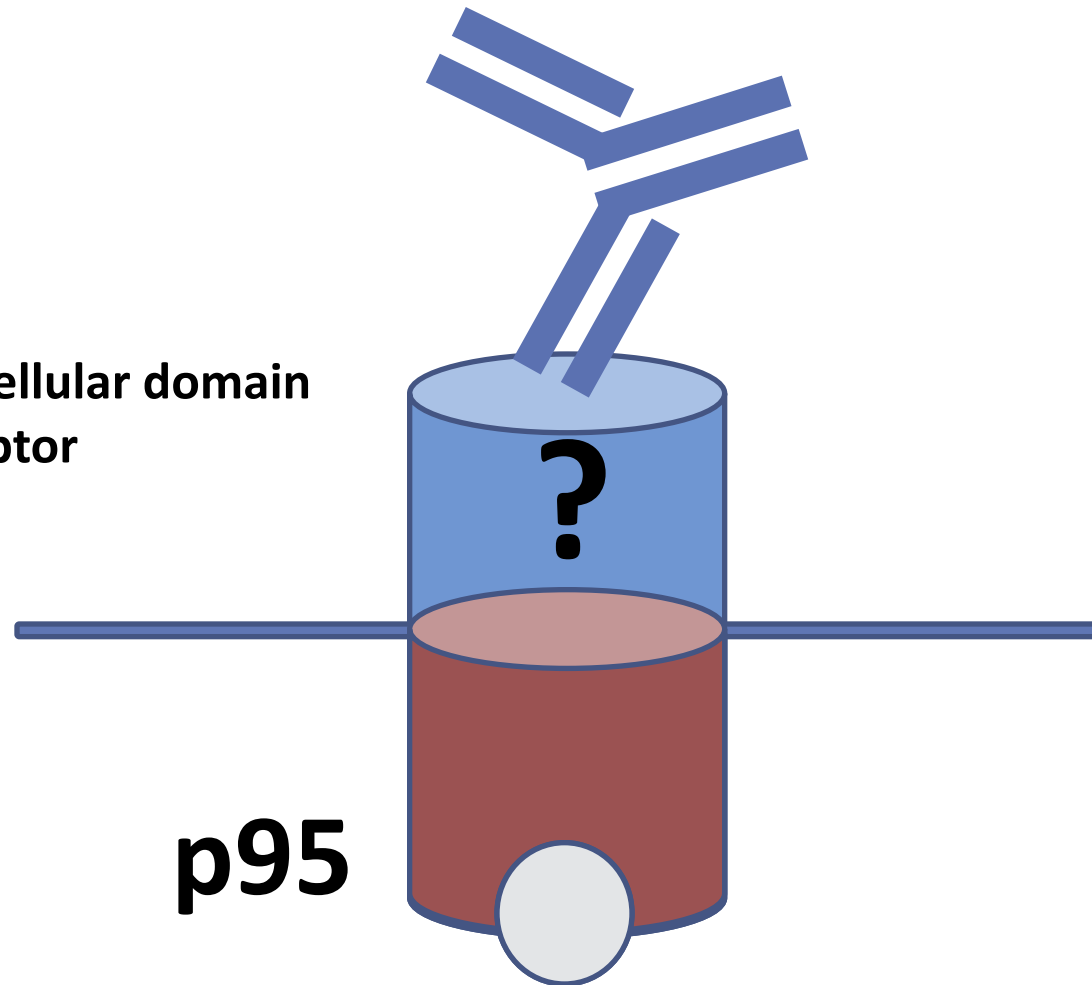
**EFFICACY OF TRASTUZUMAB  
MAY DEPEND ON  
FcγR GENE  
POLYMORPHISM**





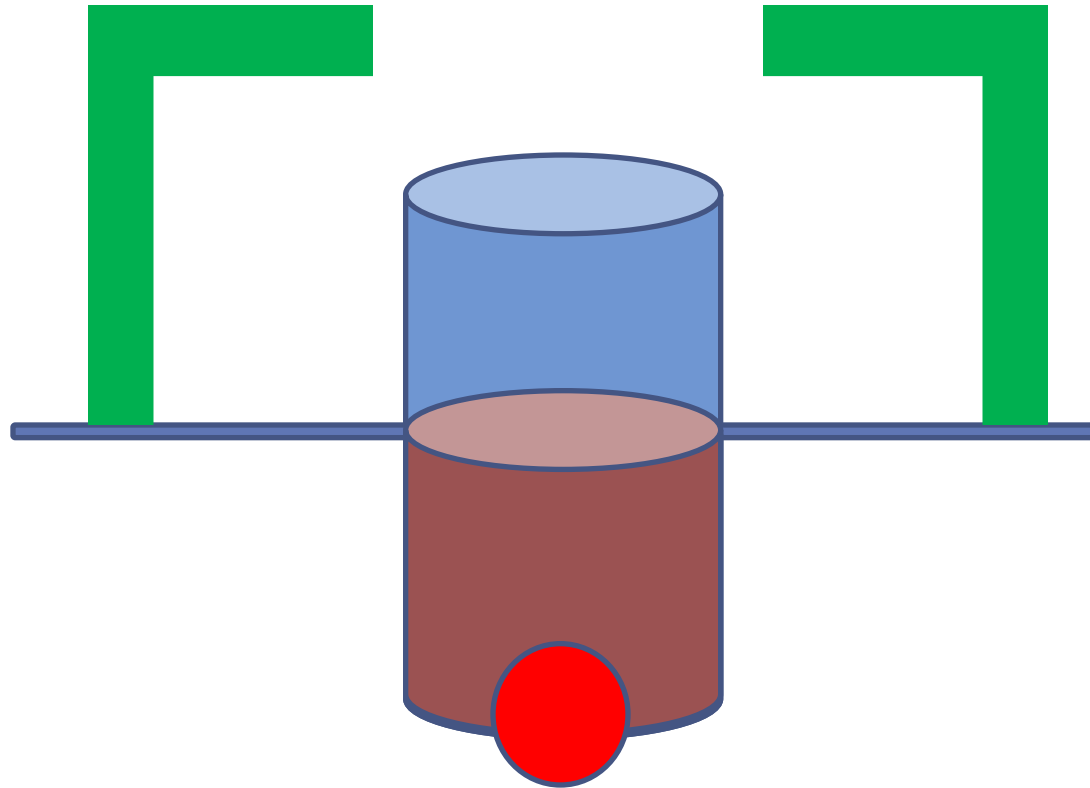
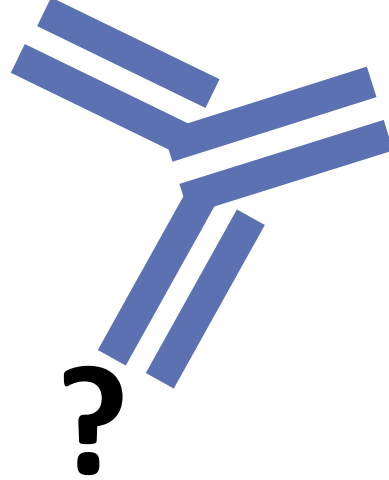


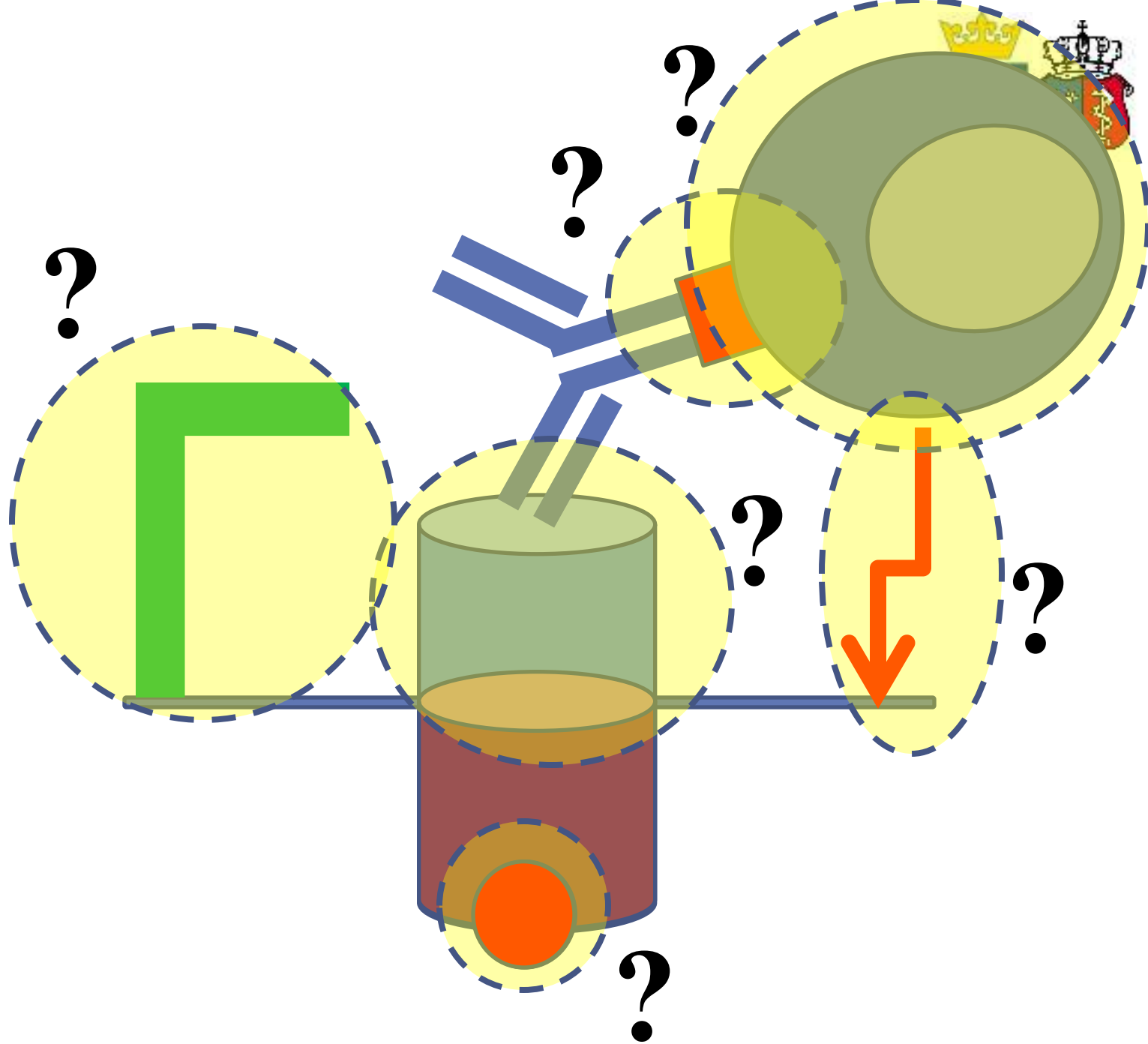
Loss of extracellular domain  
of HER2 receptor





**Overexpression of MUC4**

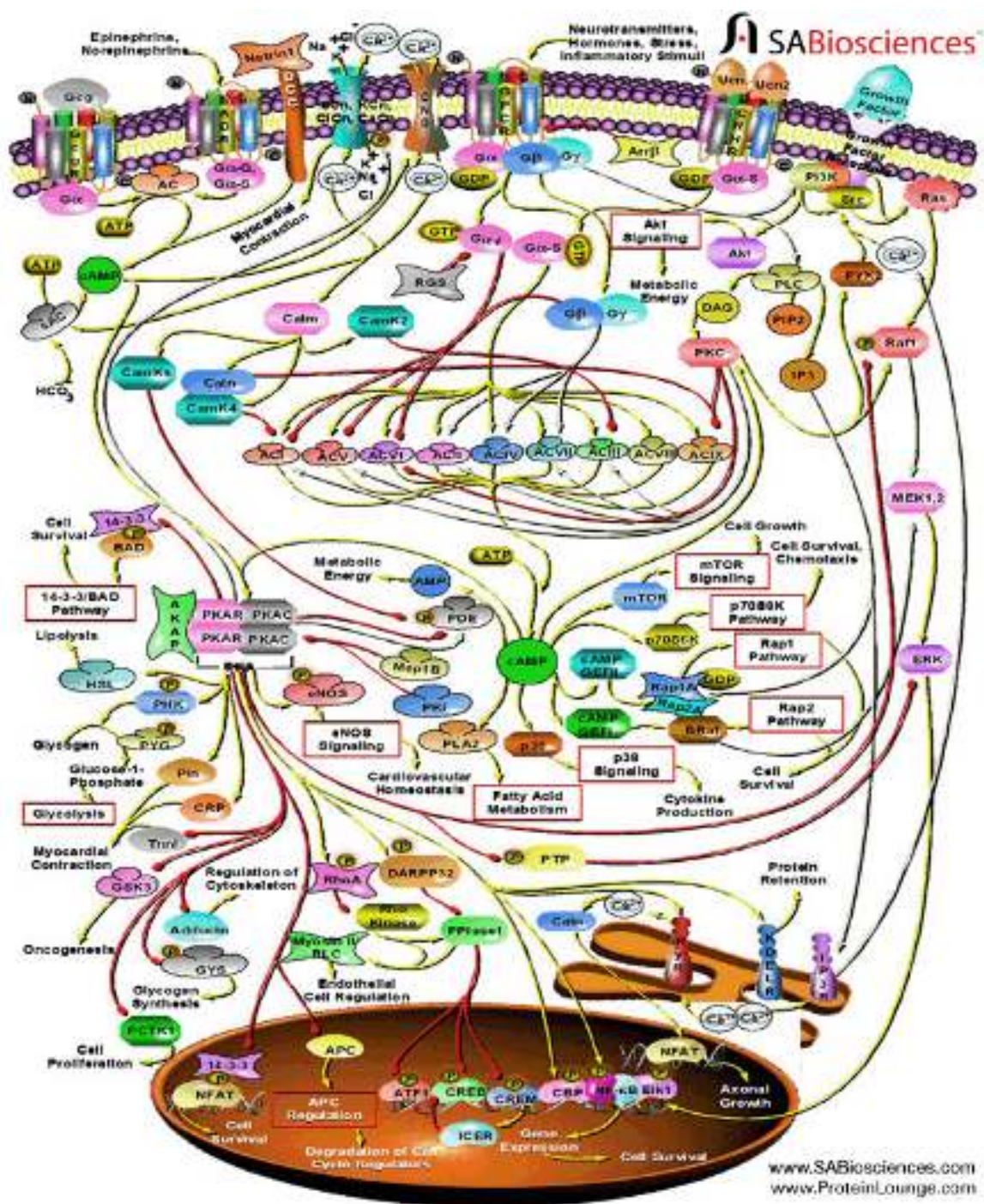






# INSIDE THE CANCER CELL

HER2 AND RESISTANCE TO SYSTEMIC TREATMENT





# EVALUATION OF RESPONSE TO TREATMENT

TARGETED THERAPIES – RESPONSE TO TREATMENT



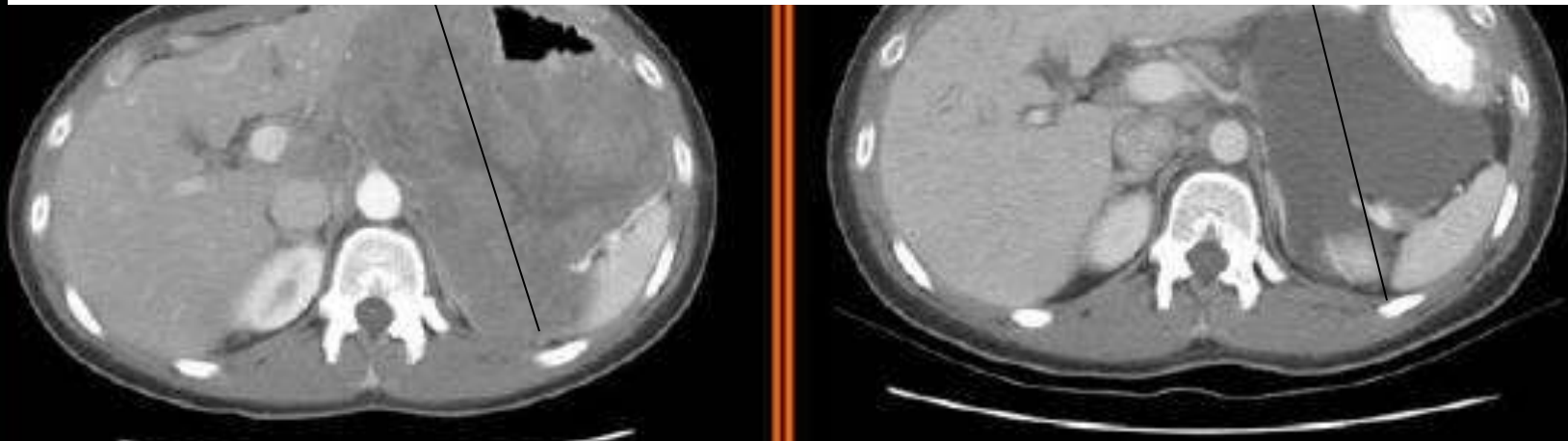
**TRASTUZUMAB – CYTOSTATIC BUT ALSO CYTOTOXIC DRUG – EVALUATION OF RESPONSE TO TREATMENT IS OBJECTIVE AND QUITE SIMPLE**



**BUT**

**IN THE CASE OF NOVEL ANTIANGIOGENIC TARGETED THERAPIES– BEVACIZUMAB, SORAFENIB, SUNITYNIB,**

**The same size of tumor following 4 months of treatment – no response?**



**ALMOST 95% OF TUMOR – NECROSIS  
- BIOMARKERS OF RESPONSE ARE EXTREMELY HELPFUL-**



# TOXICITY AND PATIENTS' SELECTION

TARGETED THERAPIES





# ADVERSE EVENTS ASSOCIATED WITH TARGETED THERAPIES

- MYELOSUPPRESSION
- HEART FAILURE
- HYPERTENSION
- HYPOTHYROIDISM
- IMMUNOSUPPRESSION
- DERMATOLOGIC DISORDERS
- AUTOIMMUNOLOGICAL DISORDERS
- ANAPHYLAXIS, ALLERGIC REACTIONS
- ELECTROLYTE IMBALANCE
- HEMORRHAGE
- THROMBOEMBOLIC EVENTS
- NEUROPATHY
- IMPOTENCE
- INTESTINAL PERFORATION
- MUSCLE CRAMPS
- PERIPHERAL OEDEMA





A CRUCIAL POINT IN CLINICAL ONCOLOGY

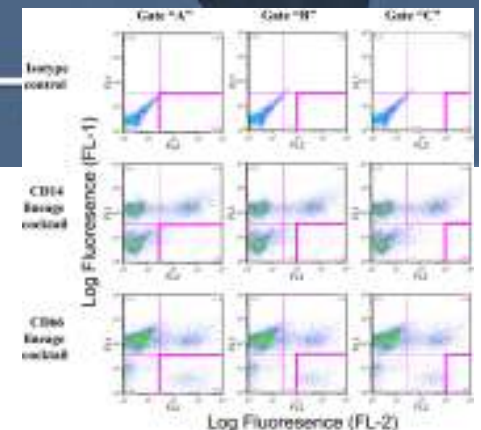
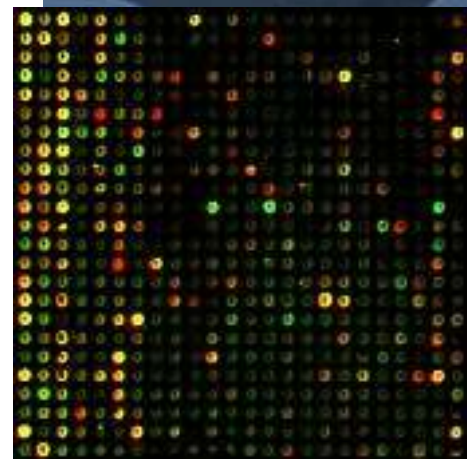
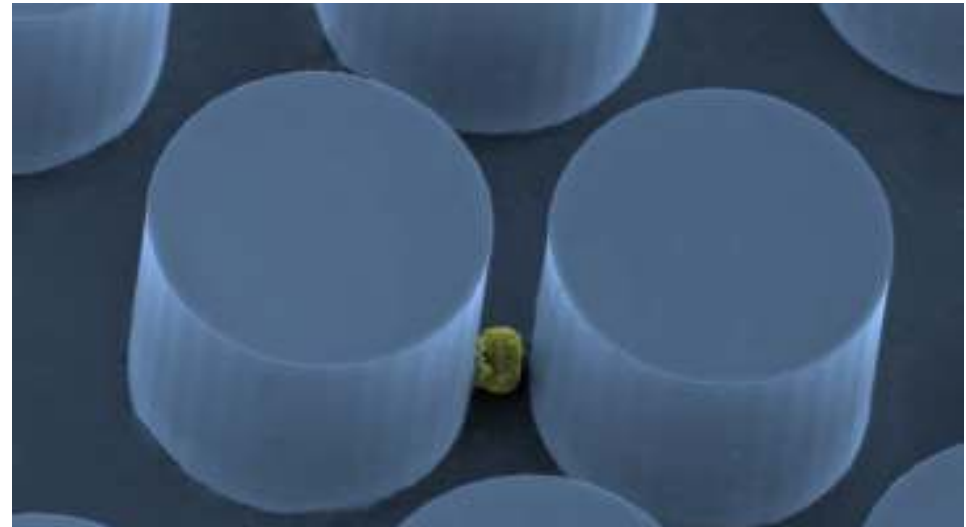
EARLY DETERMINATION OF RESISTANCE TO TREATMENT  
WHEN A PARTICULAR DRUG IS STILL ADMINISTERED

????????????????

**CIRCULATING TUMOR  
CELLS**

# GENOMIC AND PROTEOMIC ANALYSIS OF CIRCULATING TUMOR CELLS

## *-INTELLIGENCE SERVICE IN ONCOLOGY-*





# TARGETED THERAPIES – STRIKE ON A WELL-KNOWN ENEMY

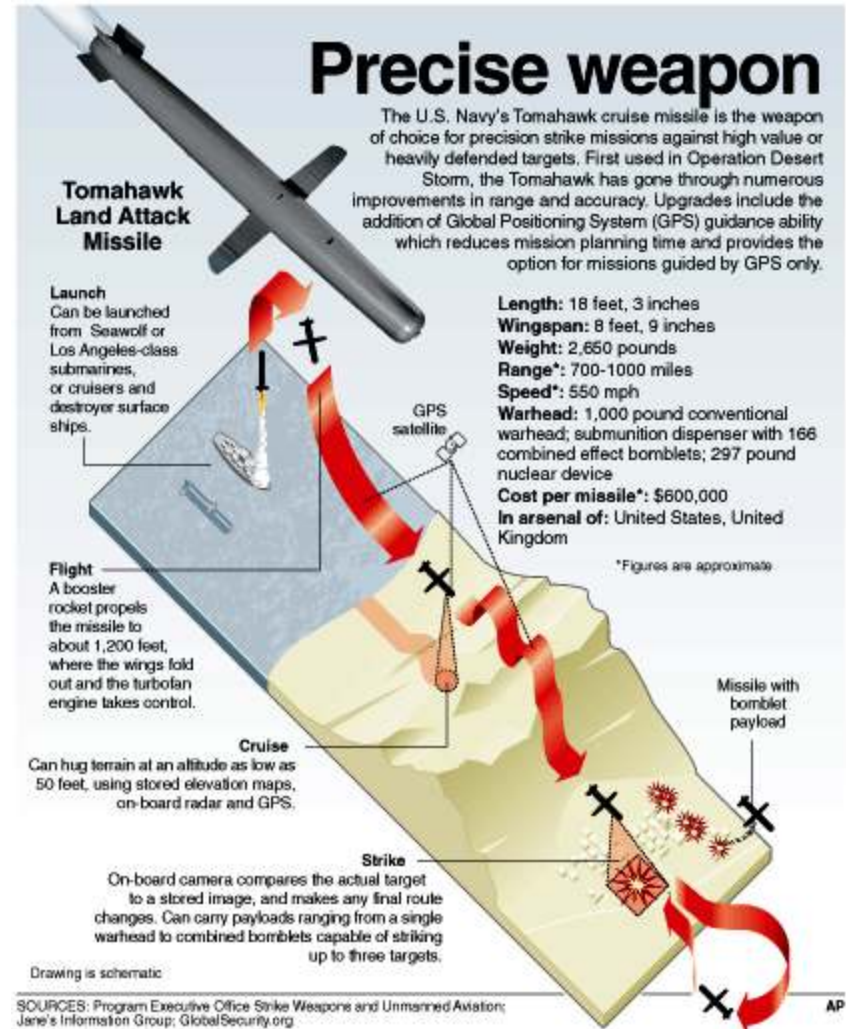
FROM A HISTORICAL POINT OF VIEW



# CHEMOTHERAPY



# TARGETED THERAPIES



BUT IN ORDER ...



TO KNOW WHERE, WHEN AND HOW  
WE CAN TARGET THE ENEMY (CANCER CELLS)

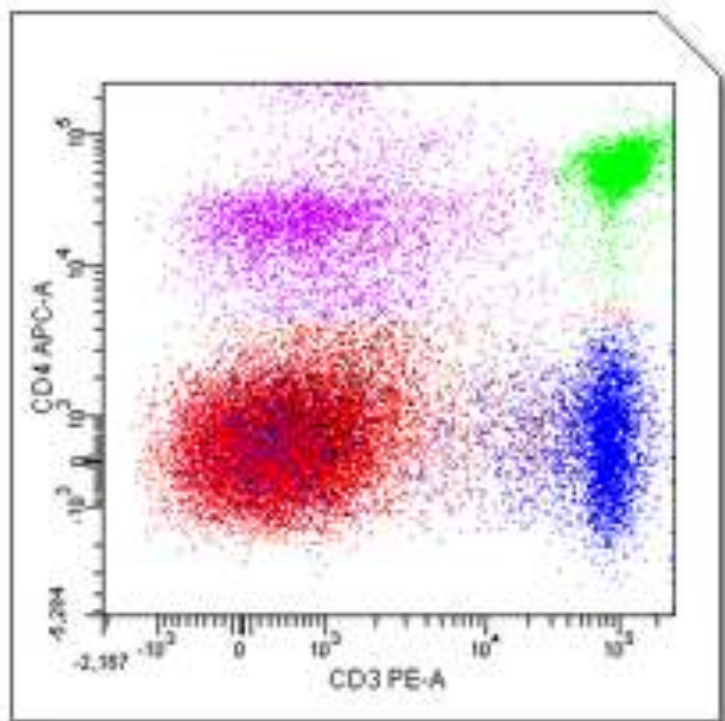
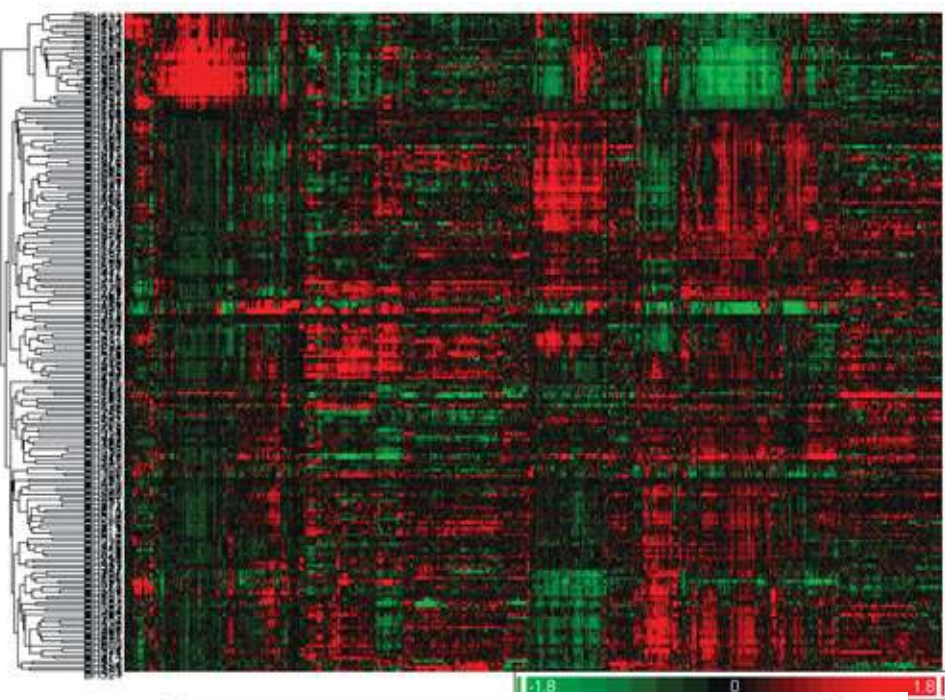
IN ORDER TO BE PREPARED ON A  
COUNTERSTRIKE

**WE NEED A LOT OF INTEL DATA!!!!**

# WE NEED A PERFECT INTELLIGENCE SERVICE









# IMMUNOTHERAPY



# BEGINNING OF IMMUNOTHERAPY



1893 – Wilam B Coley, New York –  
case report on spontaneous  
regression advanced sarcoma in a patient  
following a high fever from erisipelas infection

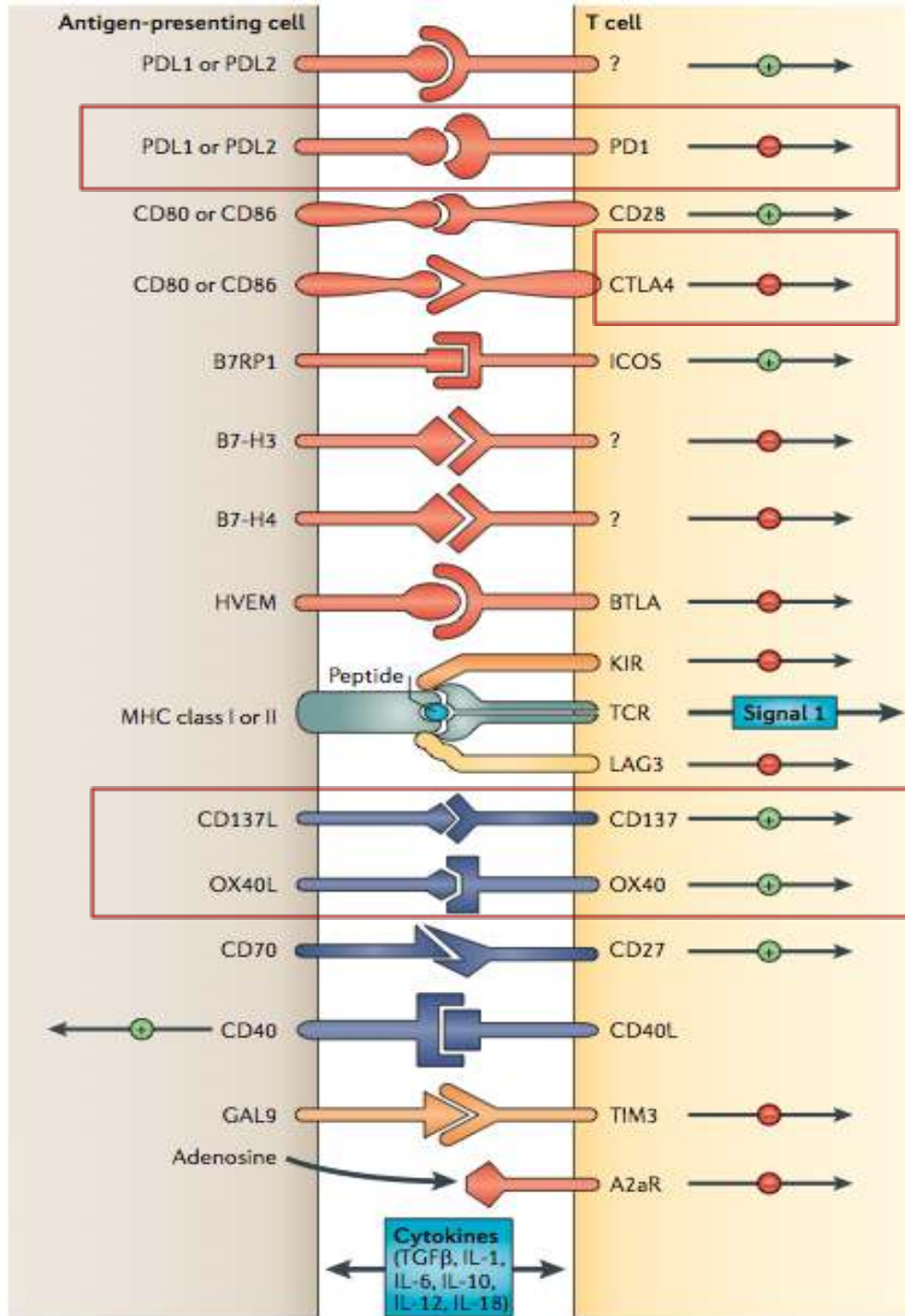


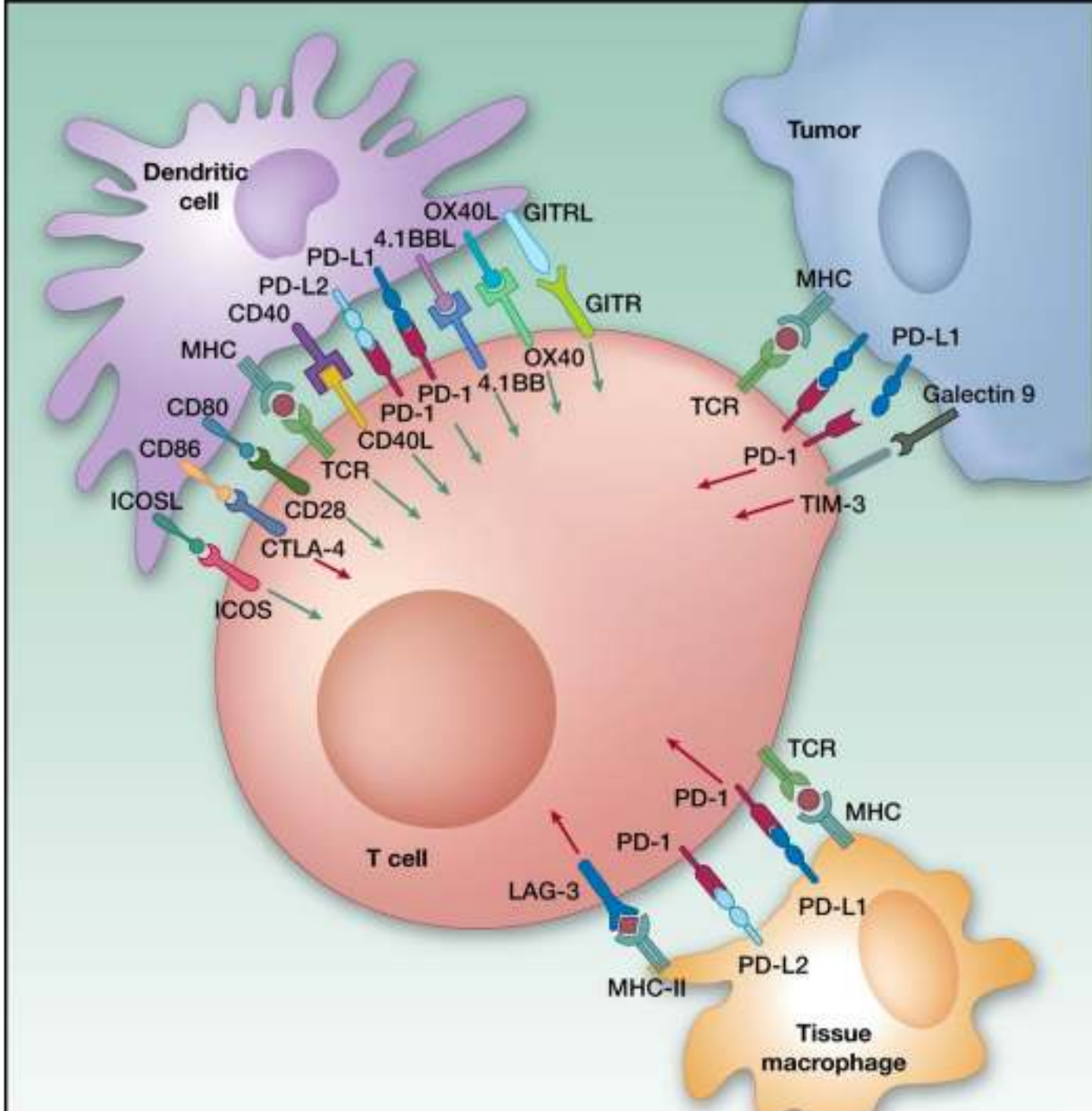
1895 – First 'trials' on immunotherapy –  
subcutaneous injection of streptococcus pyogenes to patients with advanced  
tumors to provoke immune response

MECHANISM OF ACTION – RAPID INFLAMMATORY REACTION – "CYTOKINE  
STORM" LEADING TO REACTIVATION OF SUPPRESSED IMMUNE RESPONSES.

**COLEY'S TOXIN INDUCED PRODUCTION OF TNF $\alpha$**

**PFIZER CONTINUES DEVELOPMENT OF COLEY TOXIN**





# IMMUNE HOMEOSTASIS MECHANISMS

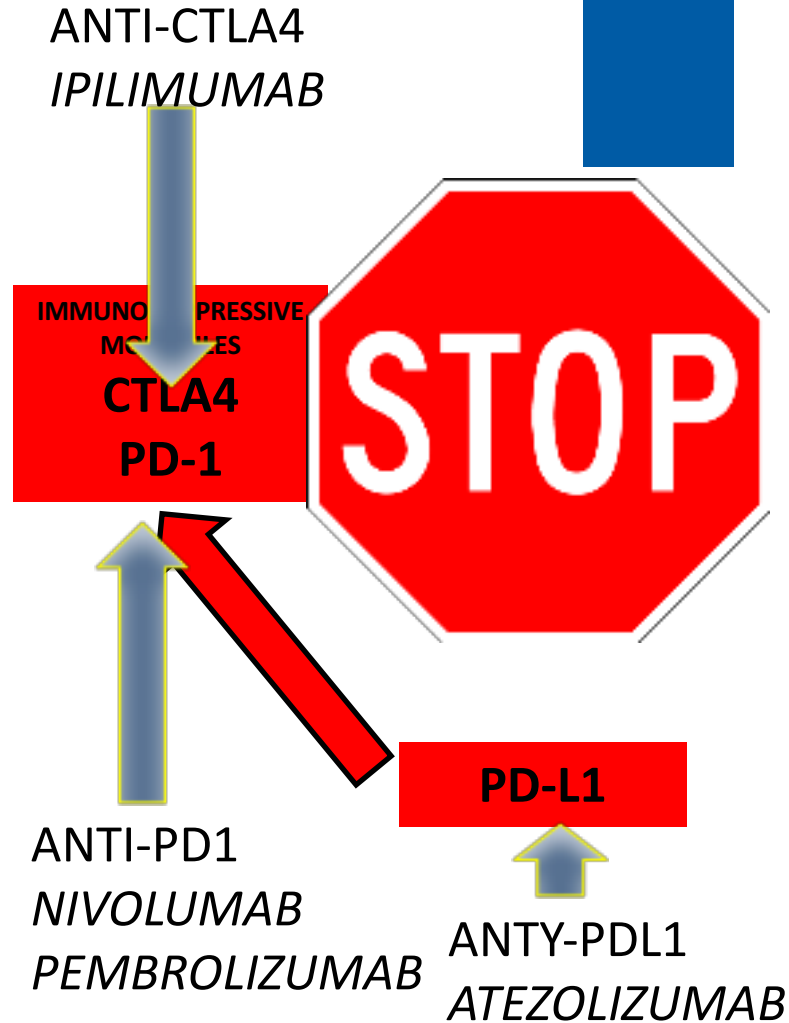
## THE KEY TO CANCER-INDUCED IMMUNOSUPPRESSION

### CHECKPOINTS



COSTIMULATORY  
RECEPTORS

- MHC I
- CD28
- IL-12R
- IL-2R





# CHECKPOINT INHIBITORS THE BREAK THROUGH IN CLINICAL ONCOLOGY





# Breakthrough of the Year 2013



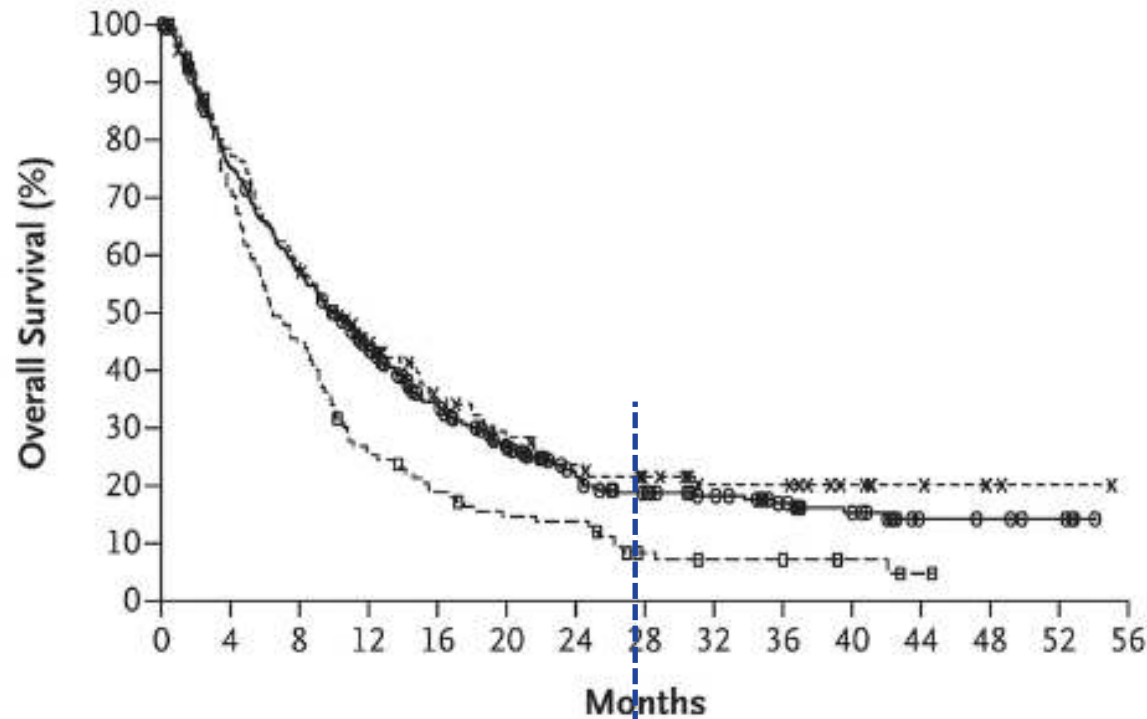
1. Cancer Immunotherapy
2. CRISPR
3. CLARITY
4. Human Stem Cells from Cloning
5. Mini-Organs
6. Cosmic Particle Accelerators
7. Perovskites Solar Cells
8. Why We Sleep
9. Our Microbes, Our Health
10. In Vaccine Design, Looks Do Matter





# IPIILIMUMAB (ANTI-CTLA4) OVERALL SURVIVAL

A Overall Survival

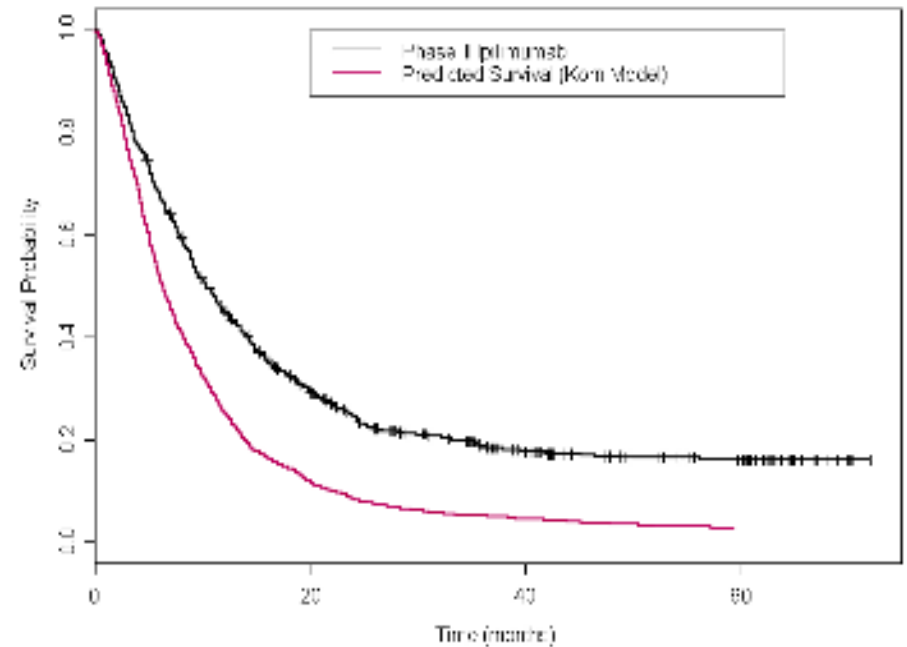
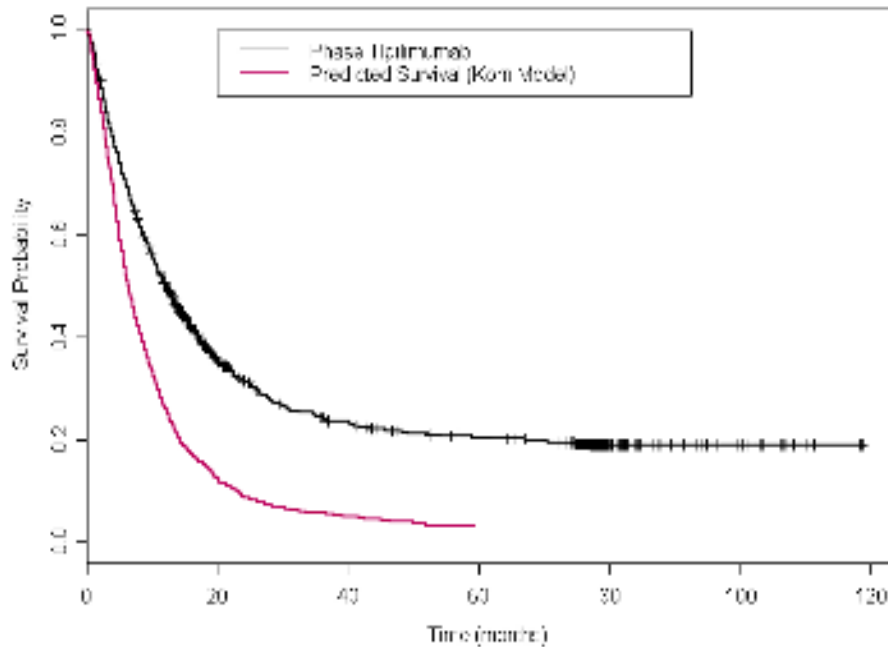


IPI – mediana follow-up (27 mies.)

**No. at Risk**

Ipi plus gp100	403	297	223	163	115	81	54	42	33	24	17	7	6	4	0
Ipi	137	106	79	56	38	30	24	18	13	13	8	5	2	1	0
gp100	136	93	58	32	23	17	16	7	5	5	3	1	0	0	0

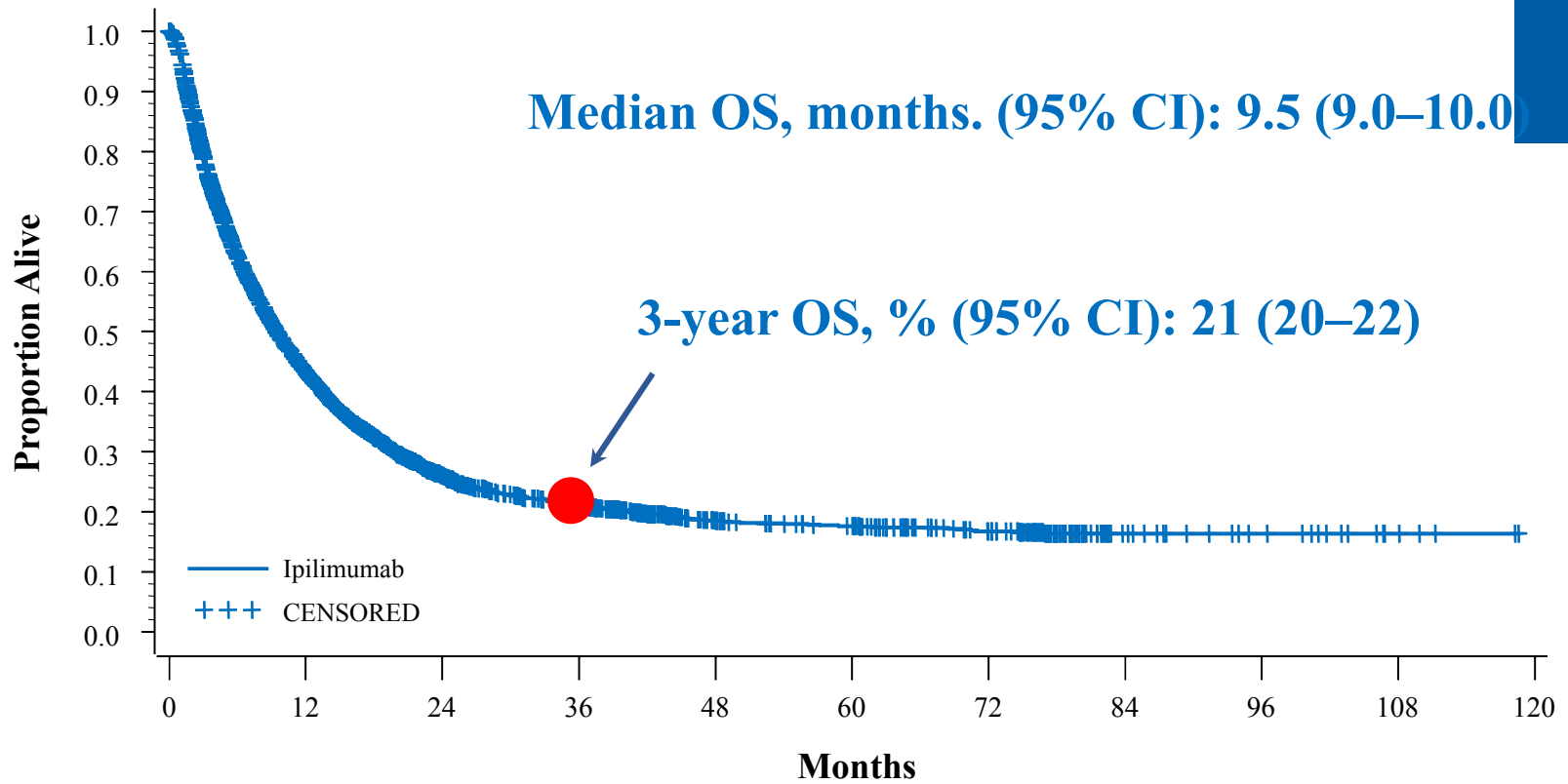
# ADVANCED MELANOMA OVERALL SURVIVAL IPIILIMUMAB vs HISTORICAL CONTROL



Korn EL i wsp. JCO 2008  
Schadendorf D i wsp. ESMO 2013



N:4846

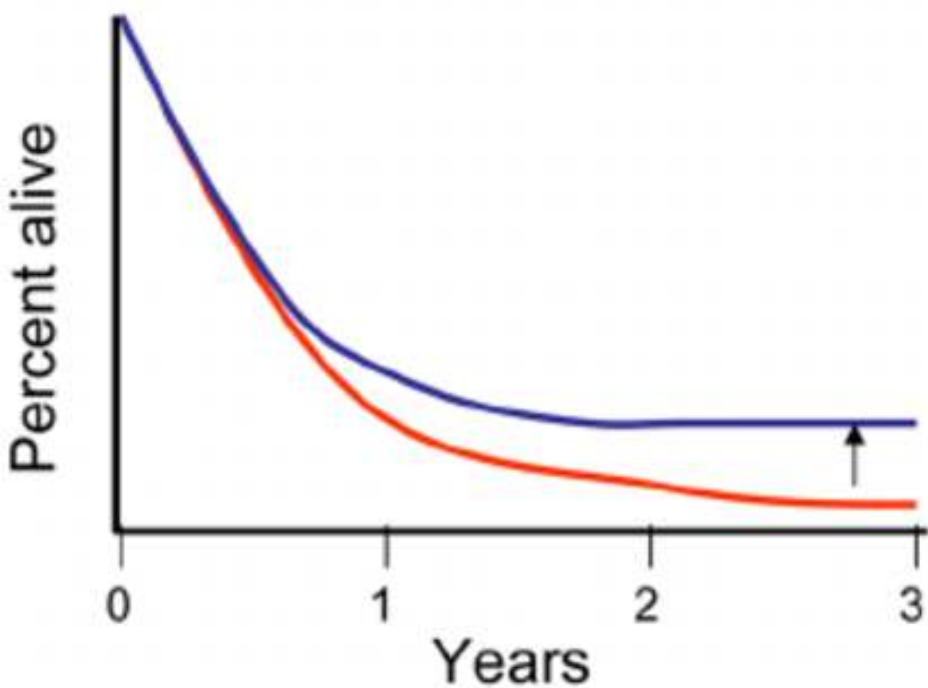


**Patients at Risk**

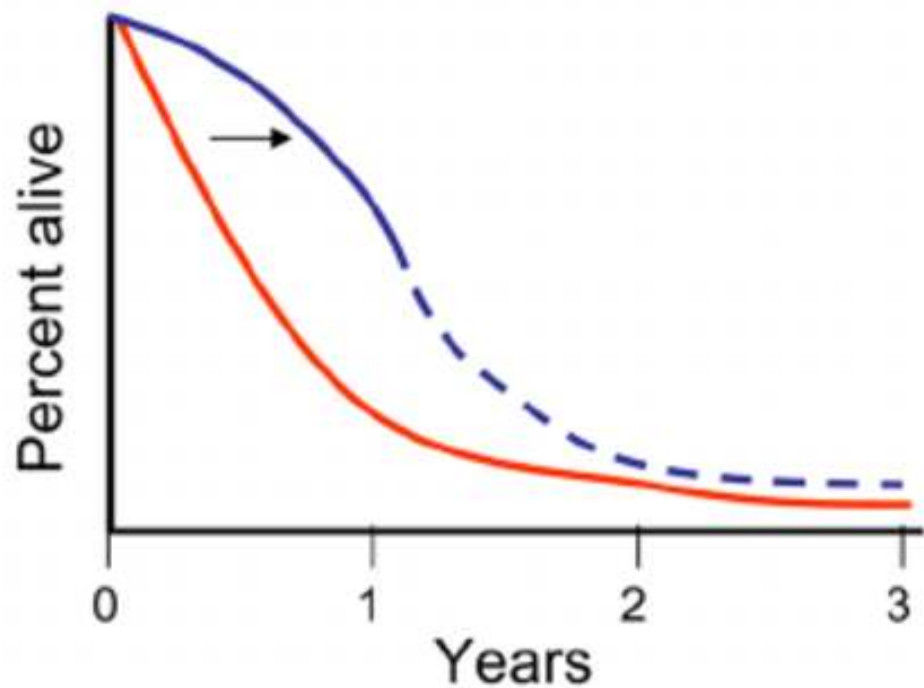
Ipilimumab	4846	1786	612	392	200	170	120	26	15	5	0
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Immunotherapy

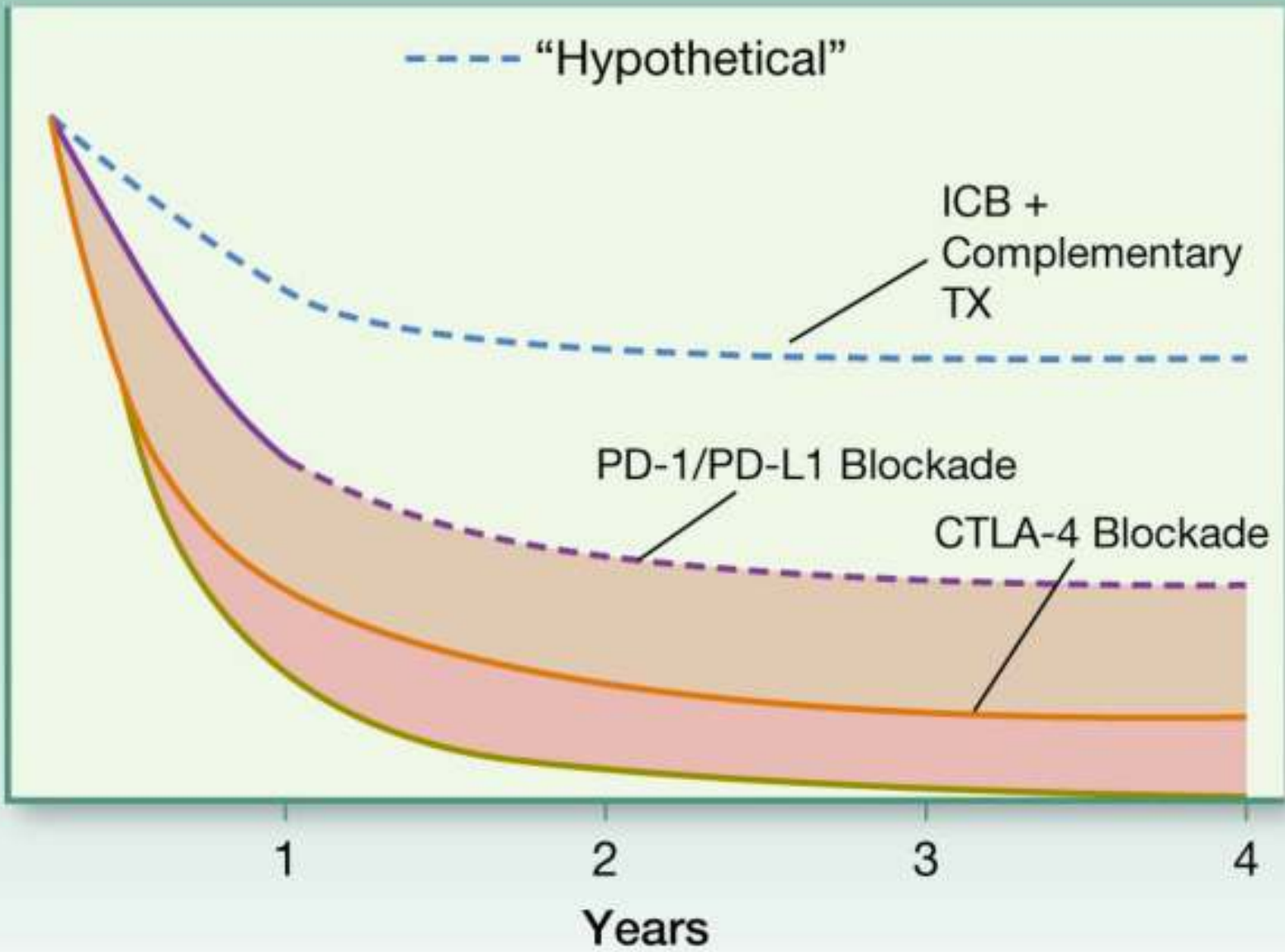


Targeted therapy

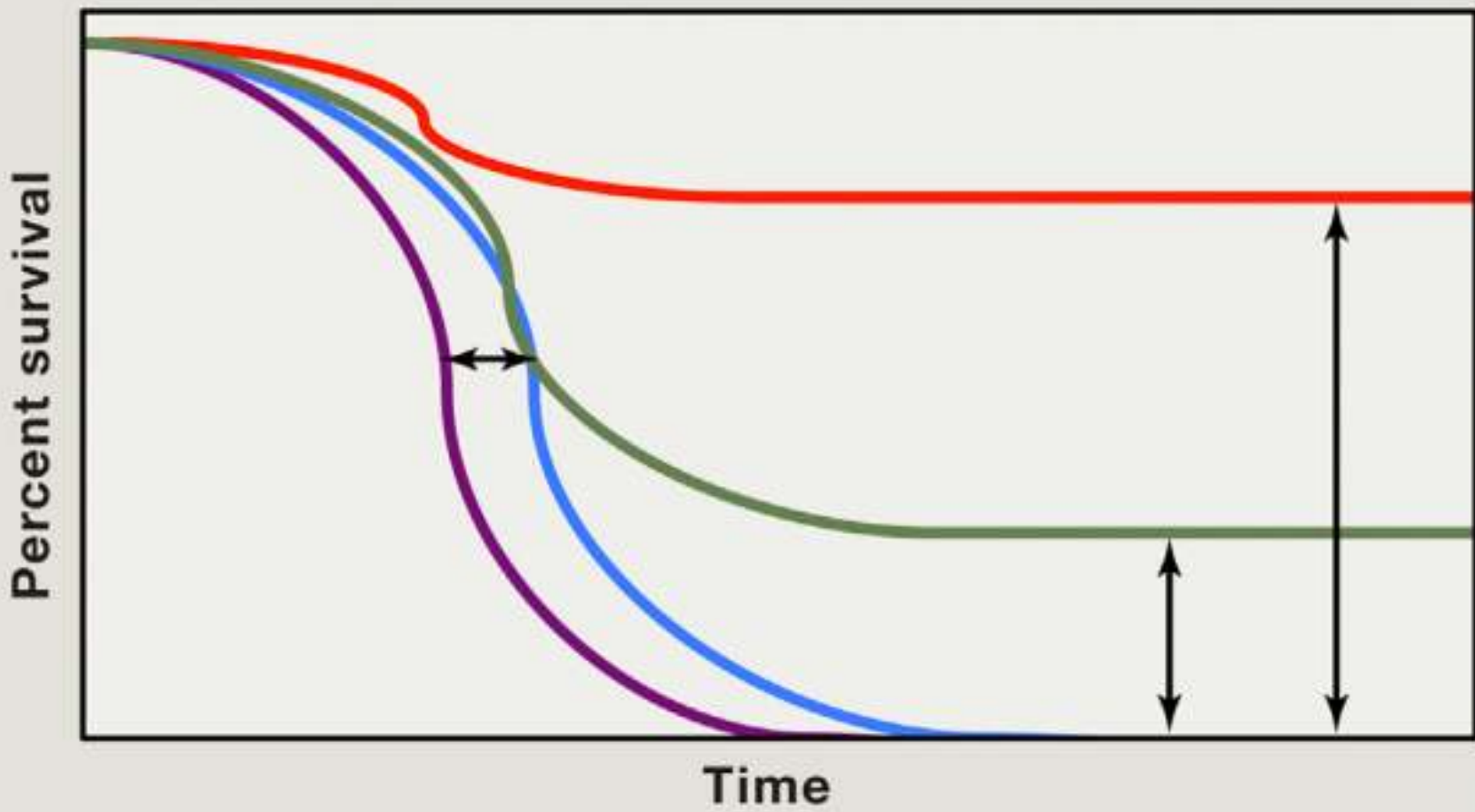




Patients alive



© 2013 American Association for Cancer Research



- |  |  |
|--|--|
|  Chemotherapy                 |  Combination with genomically targeted agent and immune checkpoint therapy |
|  Genomically targeted therapy |  |
|  Immune checkpoint therapy    |  |

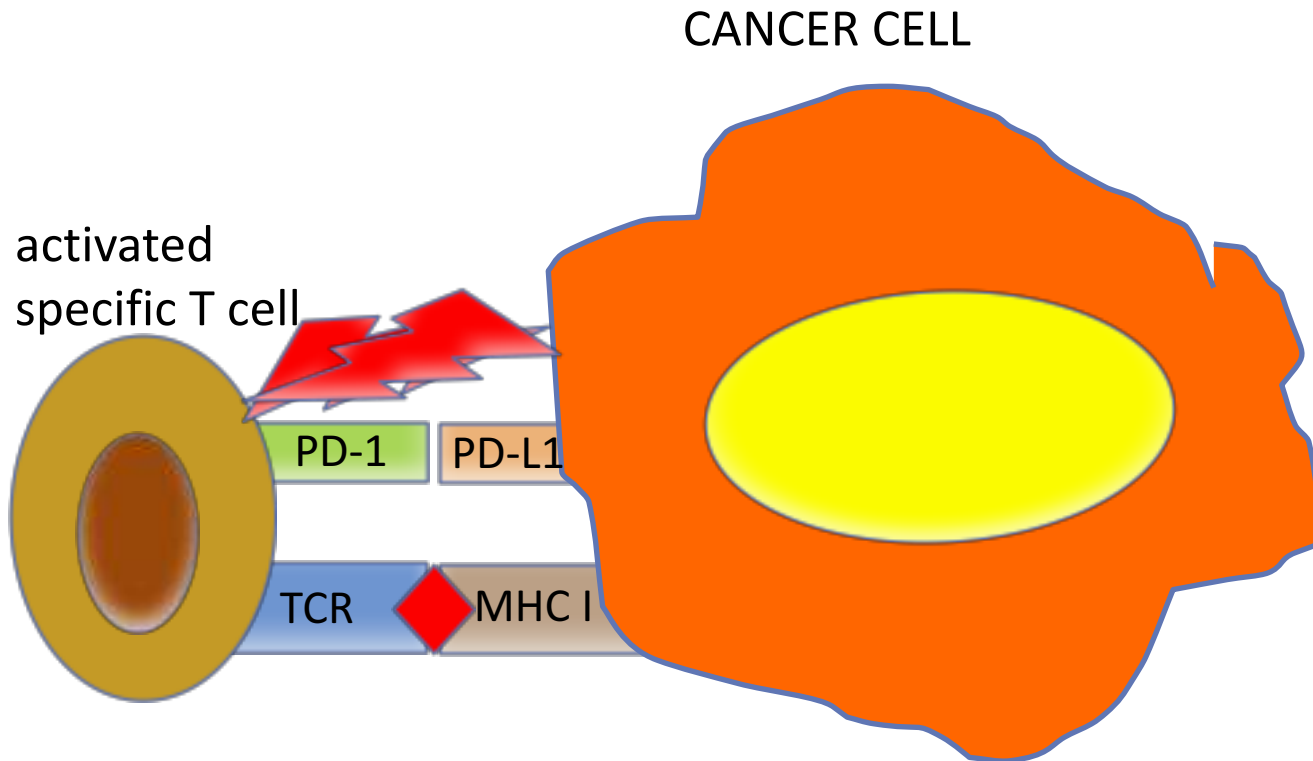


# ANTI-PD1/ANTI-PD-L1 CHECKPOINT INHIBITORS



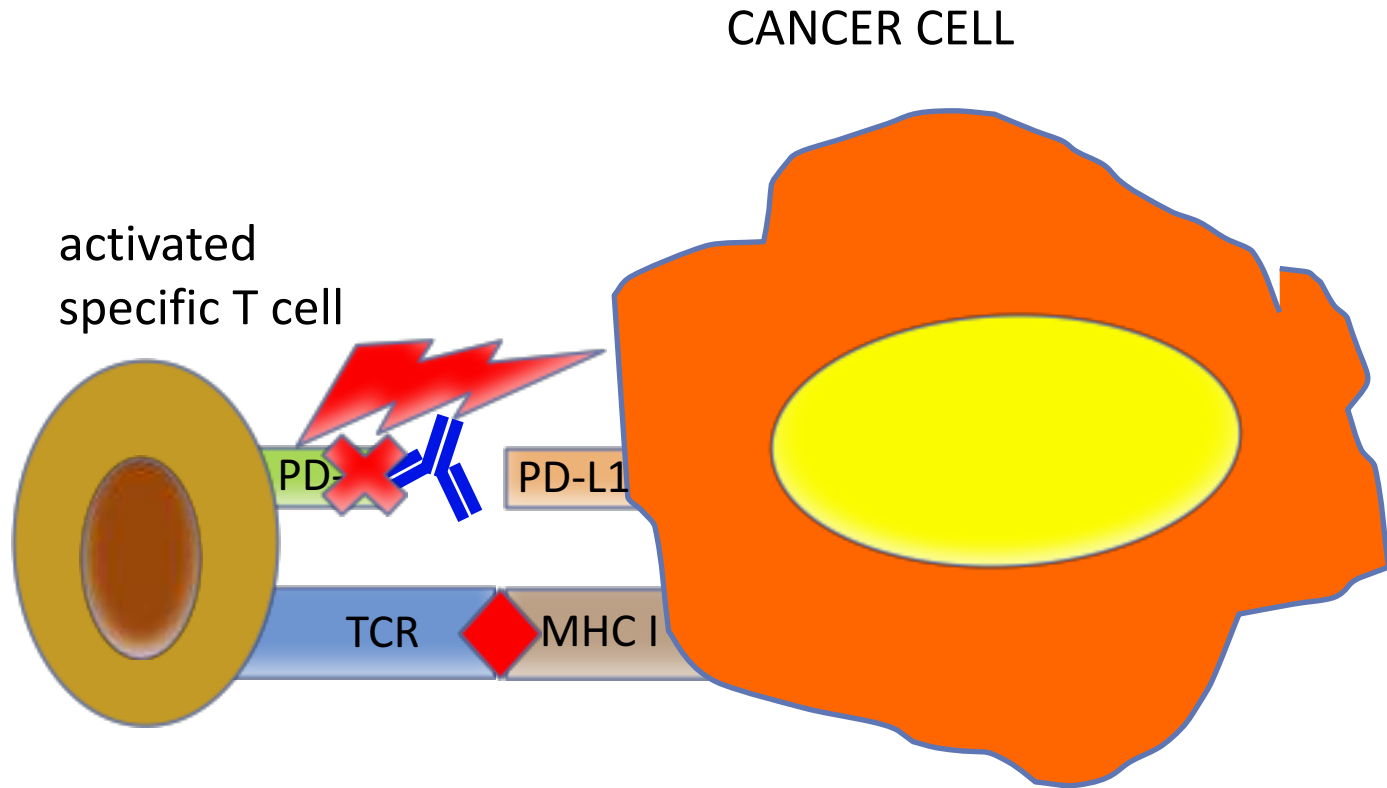


# PD-1 – PD-L1 – MECHANISM OF IMMUNOSUPPRESSION

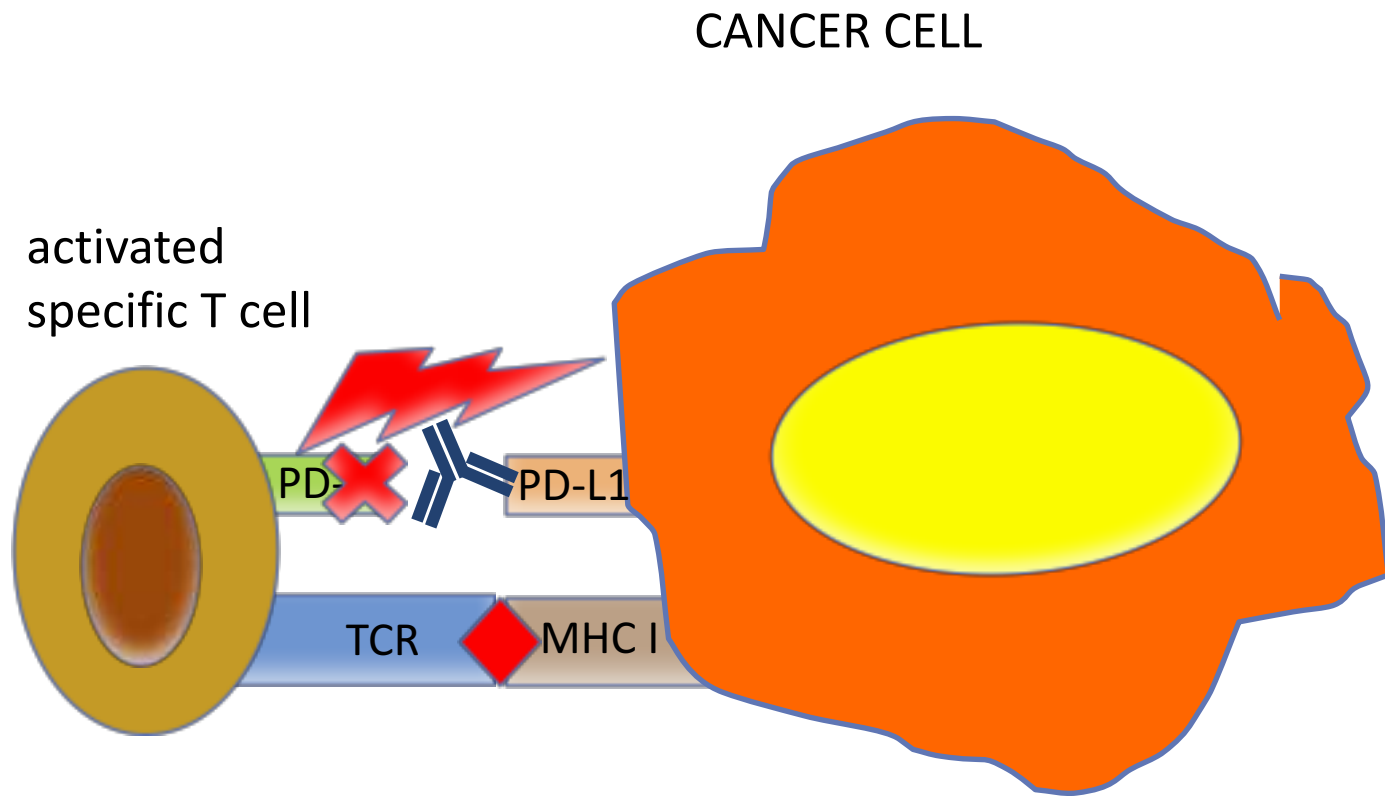




# anti-PD1 – MECHANISM OF ACTION



# ANTI-PD-L1 – MECHANISM OF ACTION



# CHECK-POINT INHIBITORS APPROVED 2014-2016



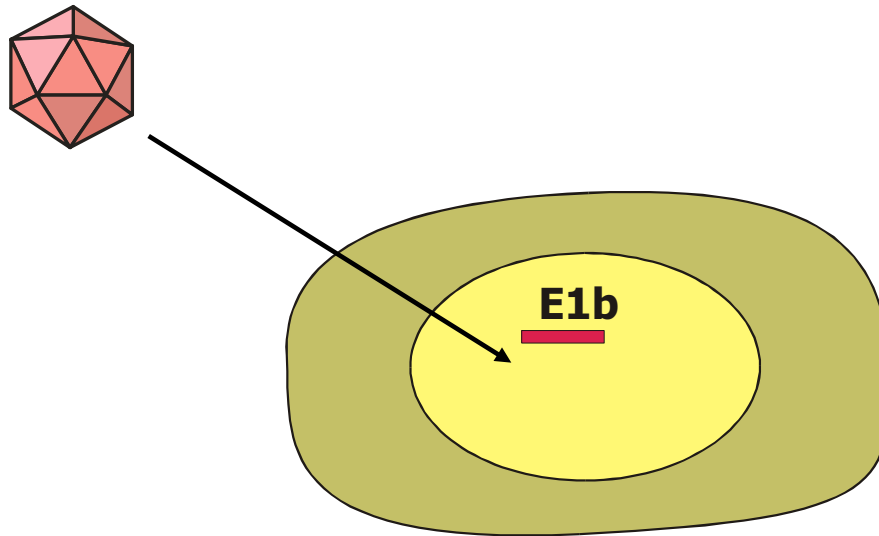
- ANTI-PD1
  - MELANOMA
  - SQUAMOUS NON-SMALL CELL LUNG CANCER
  - NON-SQUAMOUS NON-SMALL CELL LUNG CANCER
  - RENAL CELL CANCER
  - HODGKIN LYMPHOMA
  
- ANTI-PDL1
  - BLADDER CANCER

EXPECTED APPROVAL – COLRECTAL CANCER, HEAD&NECK  
CANCER, BLADDER CANCER, BREAST CANCER,

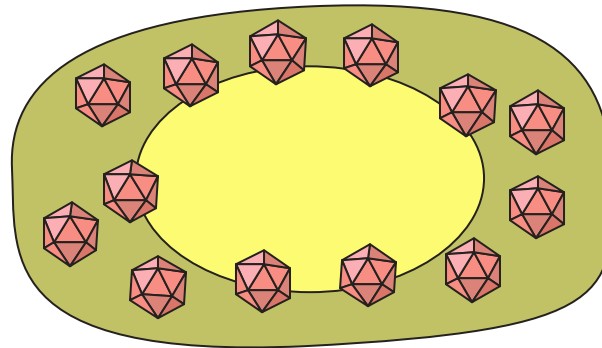


# ONCOLYTIC VIRUSES

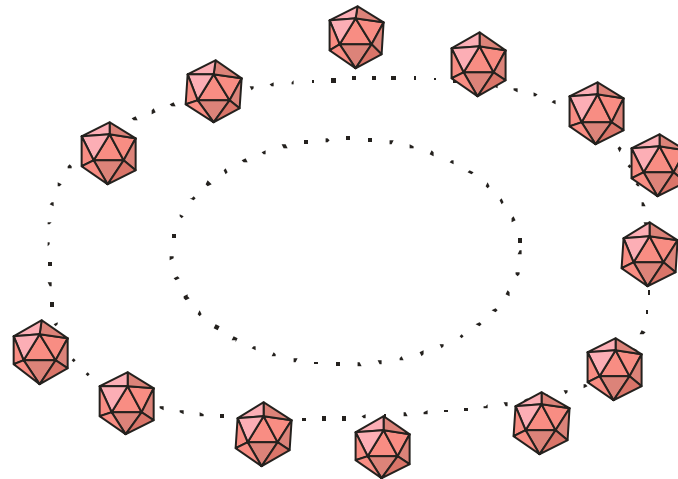




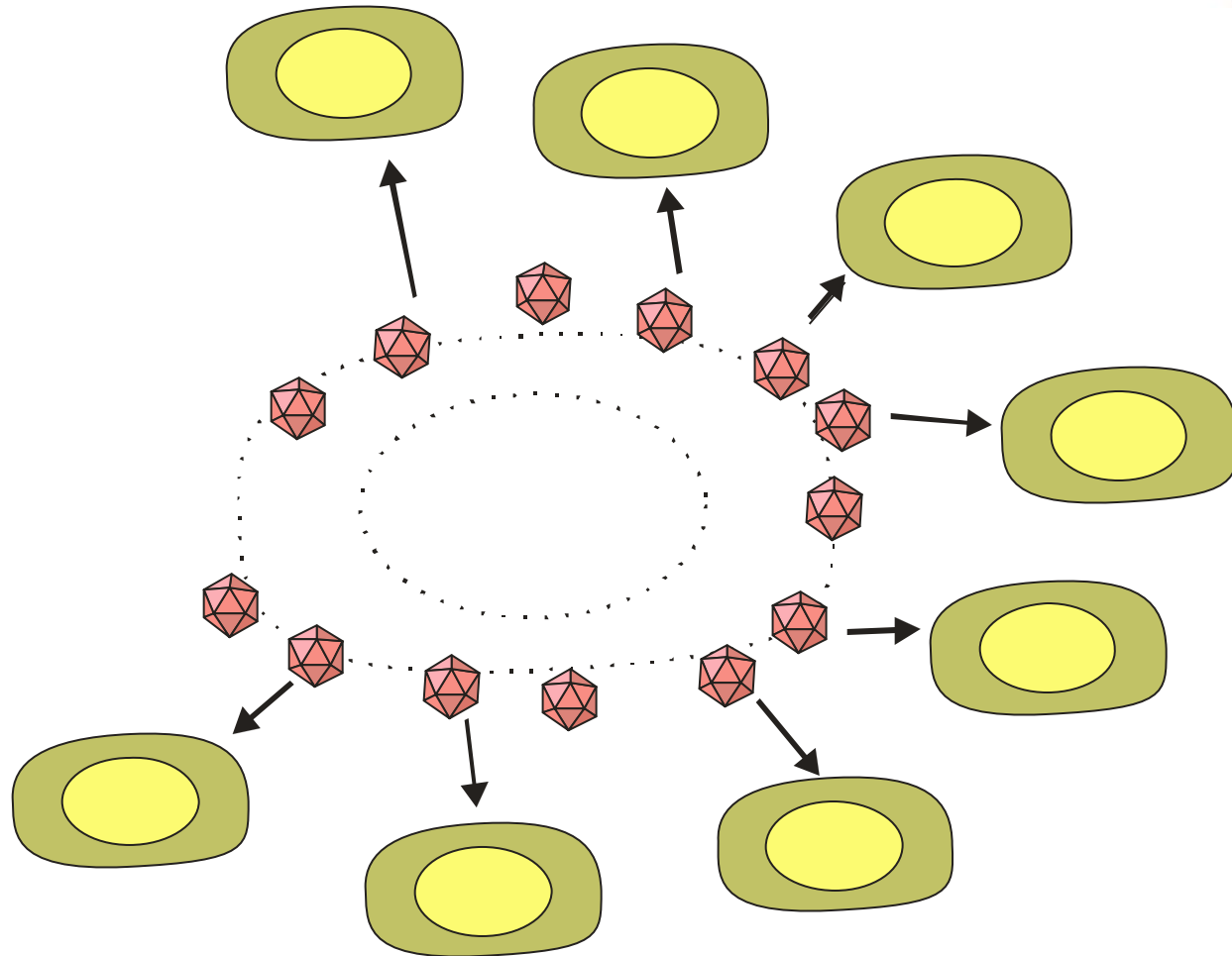
E.G. „WILD” ADENOVIRUS INFECTS A TARGET CELL  
PRODUCT OF THE E1 VIRAL GENE  
PREVENTS TP53-MEDIATED APOPTOSIS OF INFECTED CELL



ADENOVIRAL REPLICATION IN THE INFECTED CELL



LYSIS OF THE INFECTED CELL AND RELEASE  
OF VIRAL PARTICLES AND TUMOR ANTIGENS



REPLICATED VIRUSES INFECT ADJACENT CELLS



# T-VEC – NOVEL IMMUNOTHERAPY BASED ON ONCOLYTIC HSV – APPROVED IN MELANOMA



Selective viral replication in tumor tissue

Tumor cells rupture for an oncolytic effect

Systemic tumor-specific immune response

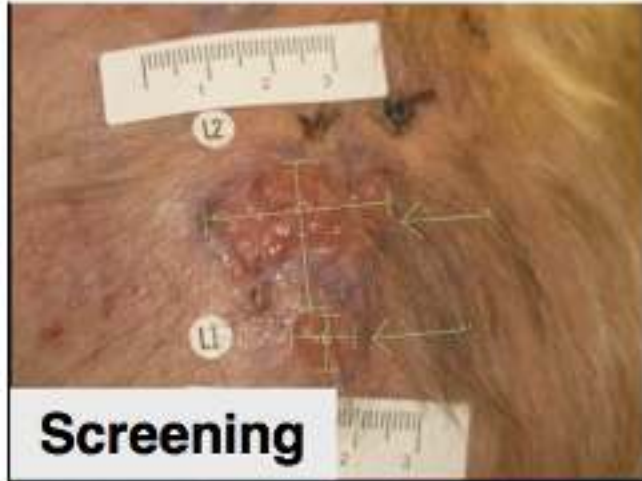
Death of distant cancer cells



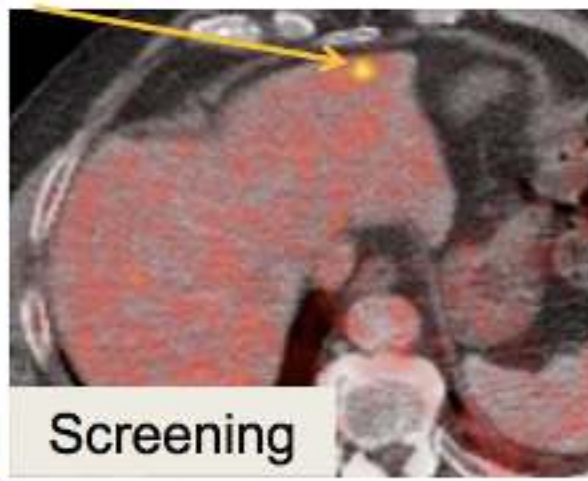
Local Effect:  
Tumor Cell Lysis

Systemic Effect:  
Tumor-Specific Immune Response

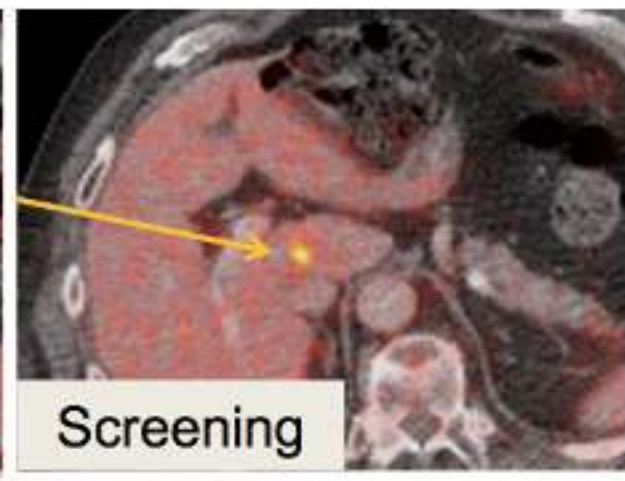
# T-VEC



Screening



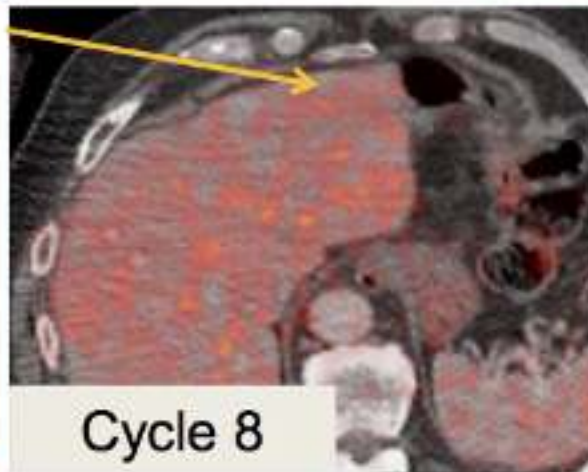
Screening



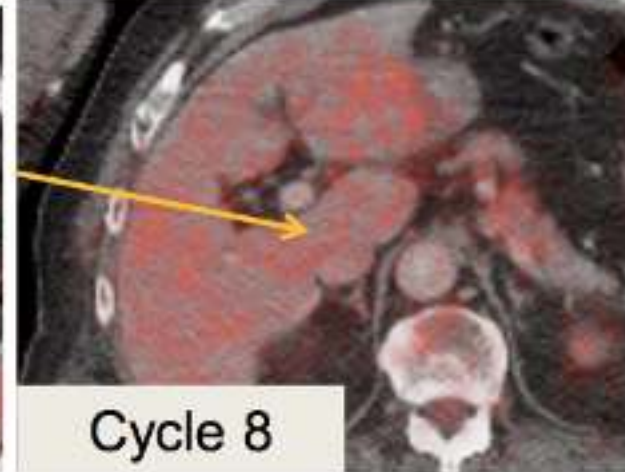
Screening



Cycle 3



Cycle 8



Cycle 8