

Cancer Therapies

**From Standard of Care
to Targeted Therapies**

Standard of Care

- **Surgical Resection**
 - Remove the tumor surgically
- **Chemotherapy**
 - Chemical agents which kill rapidly dividing cells
- **Radiation Therapy**
 - Beams of intense energy which can kill cancer cells (x-rays, protons)

Chemotherapy

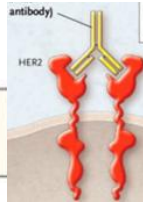
- World War II: observed that nitrogen mustard caused suppression of lymphoid and myeloid cells.
- Later discovered that nitrogen alkylates DNA
- 1950s: cancer cells divide at a higher rate than healthy cells
- Led to the development of a new class of chemical drugs that interfere with mitosis → more toxic to rapidly dividing cells
- Chemotherapeutics → weaken the patient's immune system (immune cells are rapidly dividing).

Classes of Chemotherapy Agents

“Targeted”

Ex: Trastuzumab
(Herceptin)

Monoclonal antibodies



Ex: Tamoxifen

Hormone inhibitors

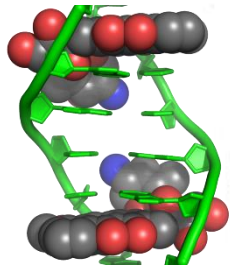


Ex: Adriamycin

Topoisomerase inhibitors

Antibiotics

Anthracyclines



Centrioles

Microtubule inhibitors

Vinca alkaloids
Taxanes

Plant-deived anti-microtubule agents
Ex: docetaxel, vincristine

Ex: Methotrexate, 5-fluorouracil

Antimetabolites

Folate
Purine
Pyrimidine analogs

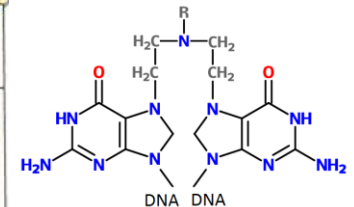
“Non-specific”

Transcription

Alkylating agents

Mustards
Nitrosoureas
Platinum compounds

Ex: Cyclophosphamide



N7 interstrand crosslinked DNA

Cancer Treatment:

Paul Ehrlich's Magic Bullet Concept

- A magic bullet = a drug that is specific for its intended cell structural target
- Root = Ehrlich's studies of cellular stains, which bind to specific cellular structures.
- Bridged the fields of chemistry, biology and medicine
- In 1908 Ehrlich received the Nobel Prize for Physiology or Medicine for his work.

Better Targeted Therapies

- 1970s and 1980s: oncogenes and tumor suppressor genes were discovered.
- Understanding of the signal pathways involved in the function of these genes led to the discovery of:
 - **Small molecule** inhibitors of specific mutations involved in the development of cancer.
 - Example – **Imatinib (Gleevec)** - Inhibits BCR-ABL
 - **Antibody** (large protein) inhibitors of specific growth factors involved in the development of cancer.
 - Example – **Trastuzumab (Herceptin)** – Inhibits HER2

Patients in this Curriculum: Breast Cancer Drivers and Current Treatments

- *BRCA1* Mutation → Chemotherapy
- HER2 Amplification → Herceptin (Antibody)
- Over-Expression of Estrogen Receptor → Tamoxifen (Small Molecule)

Characteristics of Breast Tumors: Growth Factor Receptors

HER2 Positive Tumors (HER2+)

- Human Epidermal growth factor Receptor (HER)2 is found in normal breast tissue
- Sometimes the gene overexpresses or duplicates
 - more HER2 protein
 - more cell growth
- 15-20% of breast cancers are HER2 +

Blocking Growth Factor Receptors

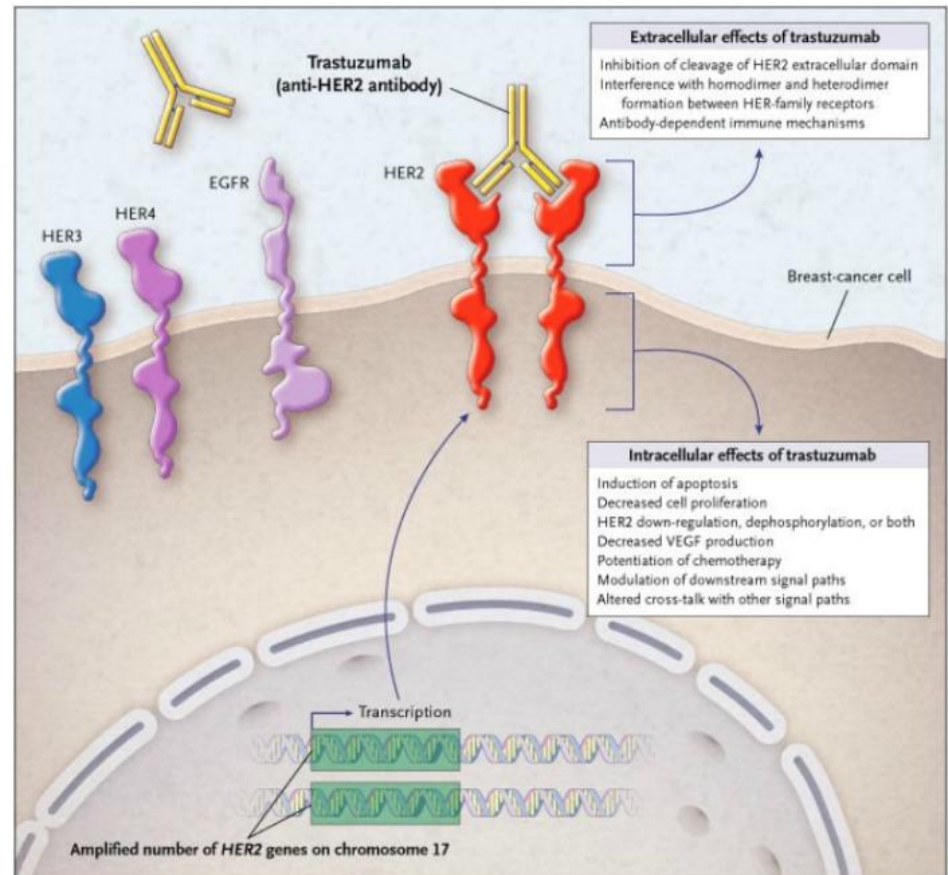
2005: 12% increase in disease-free survival and **33% reduction in risk of death**

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

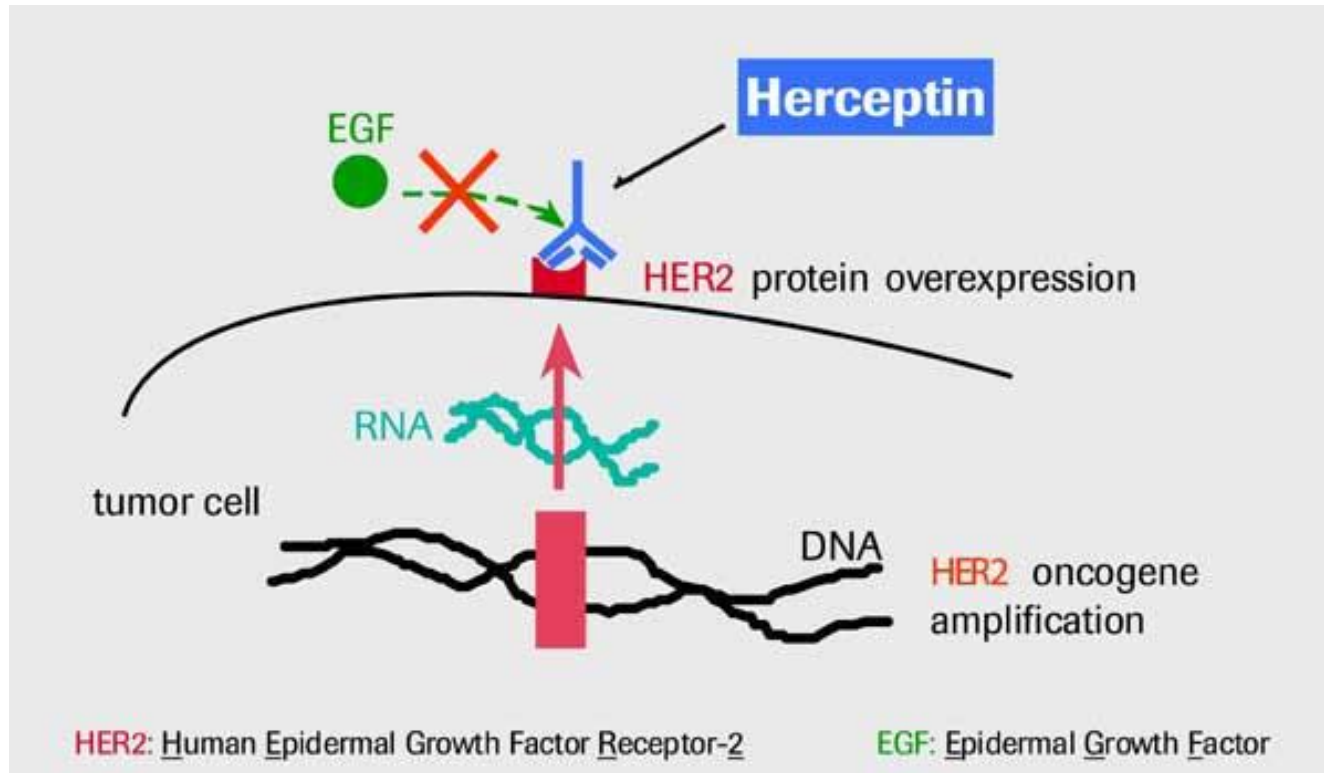
Trastuzumab plus Adjuvant Chemotherapy for Operable HER2-Positive Breast Cancer

Edward H. Romond, M.D., Edith A. Perez, M.D., John Bryant, Ph.D., Vera J. Suman, Ph.D., Charles E. Geyer, Jr., M.D., Nancy E. Davidson, M.D., Elizabeth Tan-Chiu, M.D., Silvana Martino, D.O., Soonmyung Paik, M.D., Peter A. Kaufman, M.D., Sandra M. Swain, M.D., Thomas M. Pisansky, M.D., Louis Fehrenbacher, M.D., Leila A. Kutteh, M.D., Victor G. Vogel, M.D., Daniel W. Visscher, M.D., Greg Yothers, Ph.D., Robert B. Jenkins, M.D., Ph.D., Ann M. Brown, Sc.D., Shaker R. Dakhil, M.D., Eleftherios P. Mamounas, M.D., M.P.H., Wilma L. Lingle, Ph.D., Pamela M. Klein, M.D., James N. Ingle, M.D., and Norman Wolmark, M.D.



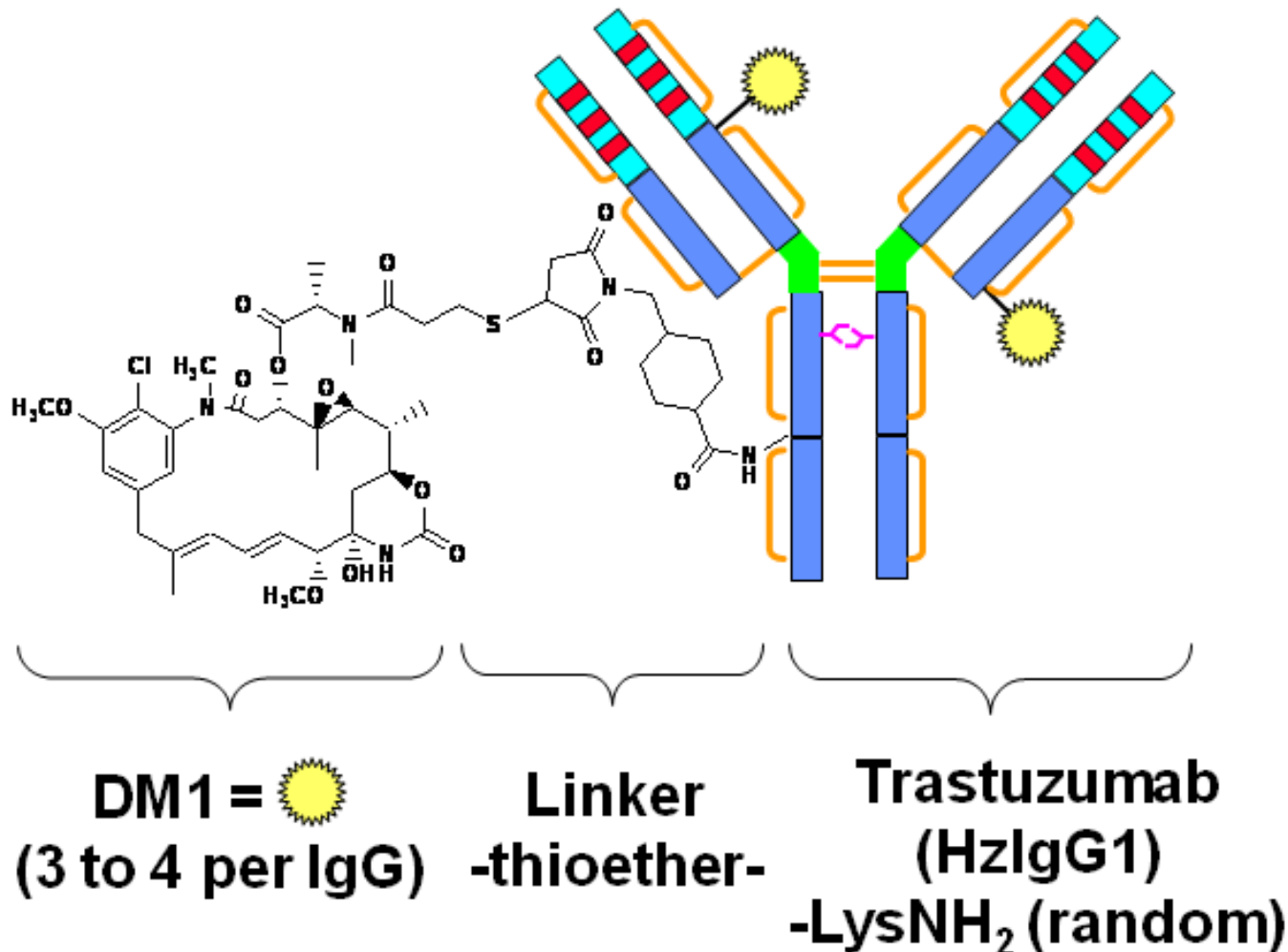
HER2 & Trastuzumab (Herceptin)

- 1980s: Monoclonal antibody technology developed
- Example – **Trastuzumab (Herceptin)**
- Inhibits HER2 (Human Epidermal growth factor receptor)

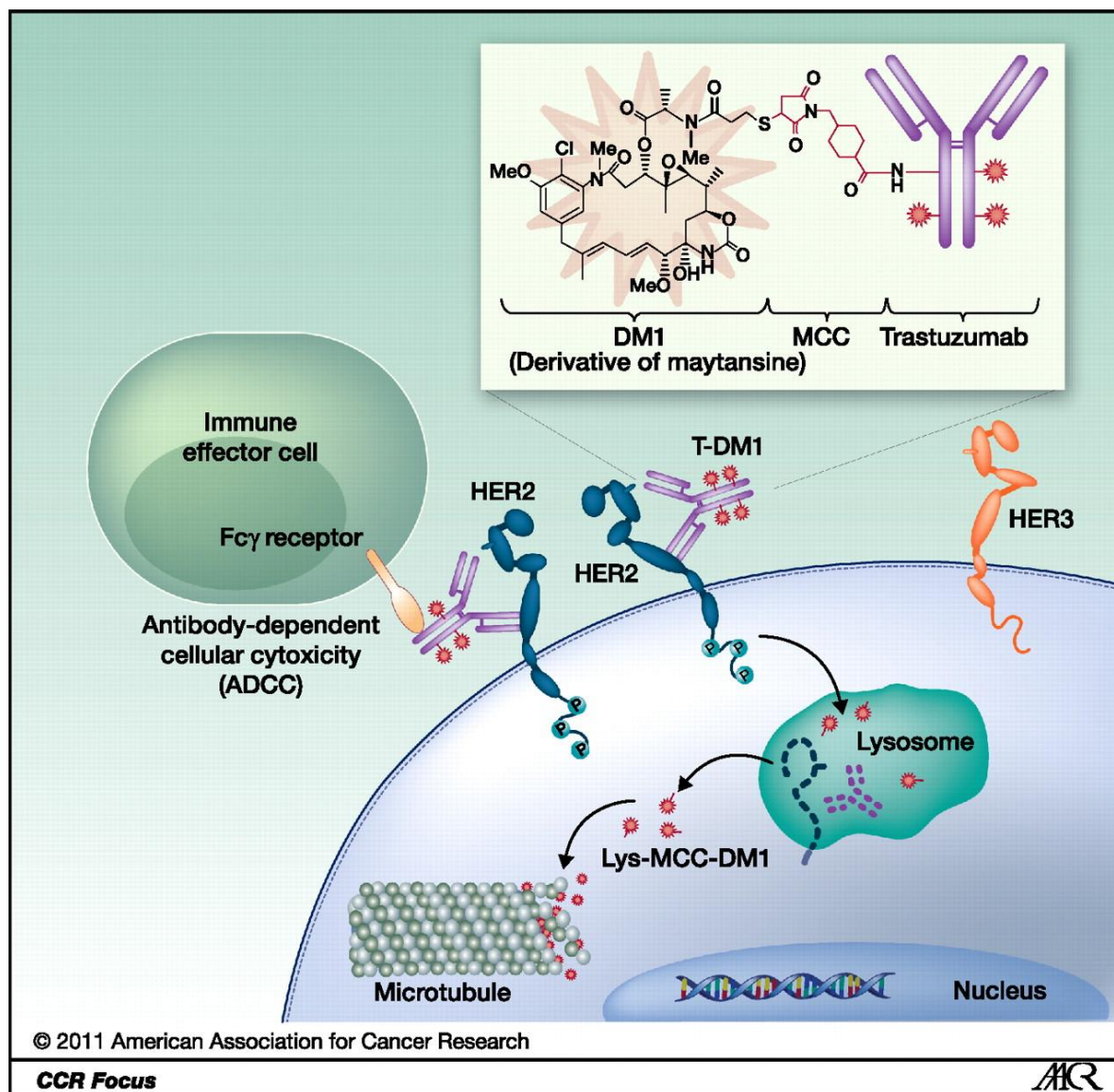


Trialx.com

HER2 & Trastuzumab Emtansine (Kadcyla)



HER2 & Trastuzumab Emtansine



Characteristics of Breast Tumors: Hormone Receptors

14th Century, breast cancer is known as “nuns’ disease”

The New England Journal of Medicine

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Volume 332

JUNE 15, 1995

Number 24

THE USE OF ESTROGENS AND PROGESTINS AND THE RISK OF BREAST CANCER IN POSTMENOPAUSAL WOMEN

GRAHAM A. GOLDITZ, M.B., B.S., SUSAN E. HANKINSON, S.G.D., DAVID J. HUNTER, M.B., B.S.,
WALTER C. WILLETT, M.D., JOANN E. MANSON, M.D., MEIR J. STAMPFER, M.D.,
CHARLES HENNEKENS, M.D., BERNARD ROSNER, PH.D., AND FRANK E. SPEIZER, M.D.

ORIGINAL CONTRIBUTION

JAMA-EXPRESS

Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women

Principal Results From the Women's Health Initiative
Randomized Controlled Trial

Writing Group for the
Women's Health Initiative
Investigators

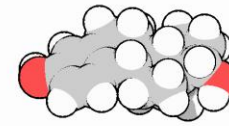
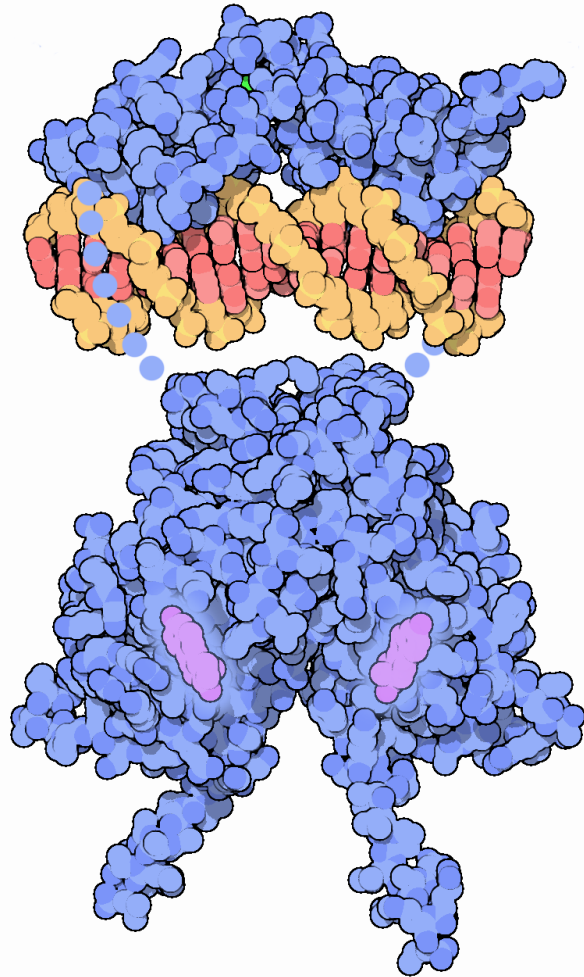
Context Despite decades of accumulated observational evidence, the balance of risks and benefits for hormone use in healthy postmenopausal women remains uncertain.

Objective To assess the major health benefits and risks of the most commonly used

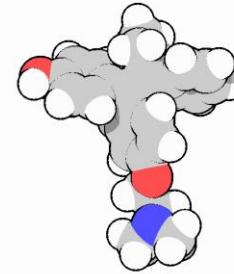
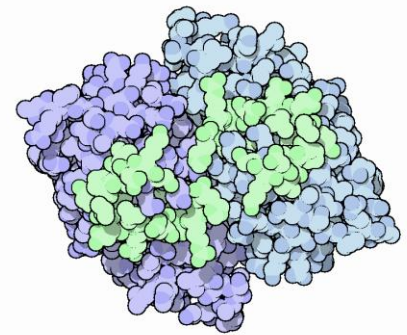
Hormone Receptor-Positive Tumors (ER+ / PR+)

- Normal breast tissue responds to the hormones via Estrogen Receptor (ER) & Progesterone Receptor (PR) → growth signal
- Cancerous cells make more ER & PR, and grow more
- About 75% of breast cancers are hormone-receptor positive

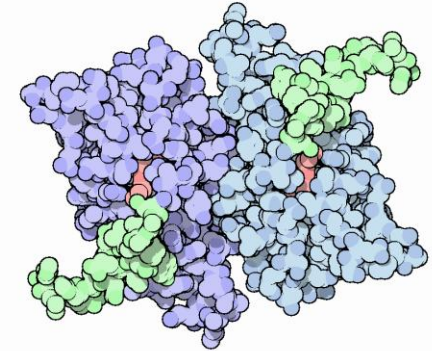
Blocking ER Receptors



estradiol



tamoxifen



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The Lancet, [Volume 351, Issue 9114](#), Pages 1451 - 1467, 16 May 1998
doi:10.1016/S0140-6736(97)11423-4 [Cite or Link Using DOI](#)

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Tamoxifen for early breast cancer: an overview of the randomised trials

Early Breast Cancer Trialists' Collaborative Group

Collaborators listed at end of paper

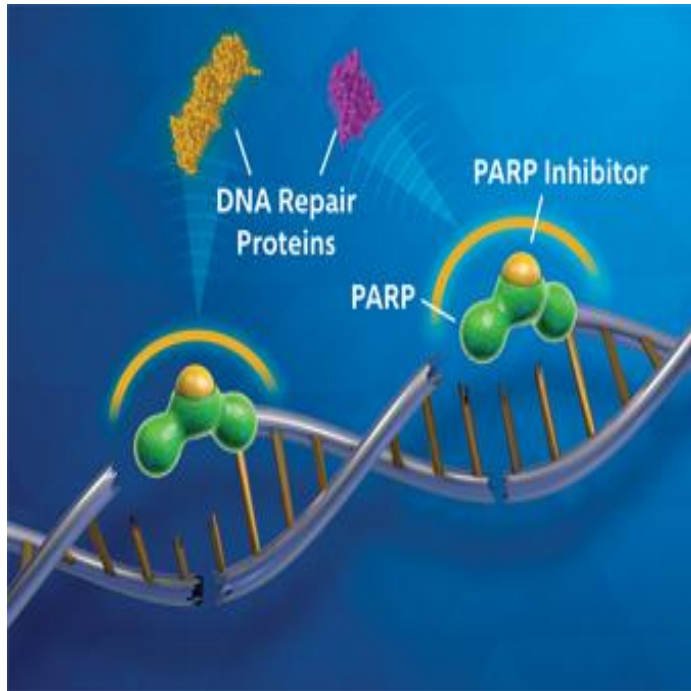
1998 Meta-analysis of clinical trials:
reduced mortality 12-26%

Left, top: PDB ID 1hcg. bottom: PDB ID 1a52
Right, top: PDB ID 1qku. bottom: PDB ID 3ert
<http://www.rcsb.org/pdb/101/motm.do?momID=45>

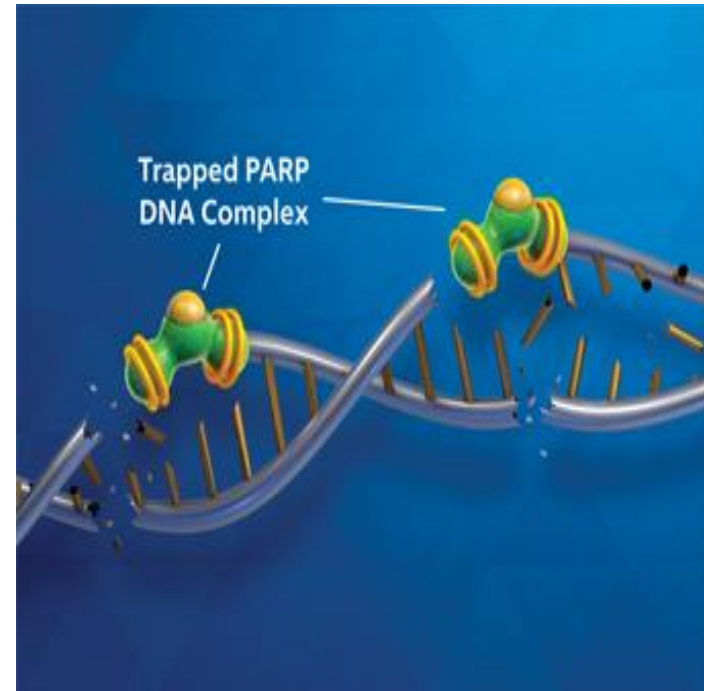
Treatment of Cancers with BRCA1 Mutations

Talazoparib and Olaparib - PARP Inhibitors

The enzyme poly ADP ribose polymerase (PARP) is involved in DNA damage repair.

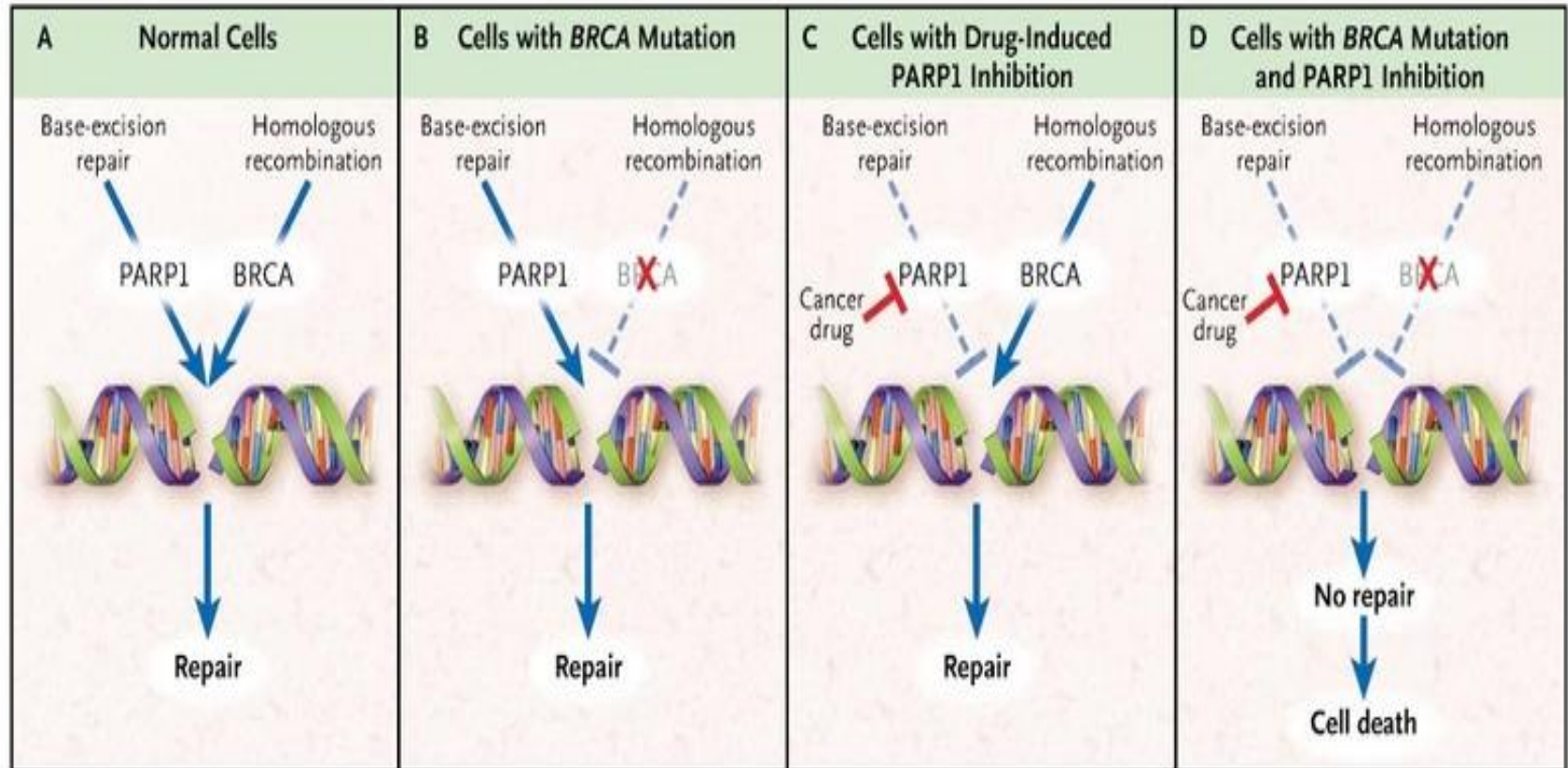


PARP inhibitors block PARP enzymatic activity and the subsequent recruitment of DNA repair proteins



PARP inhibitors cause formation of PARP-DNA complexes, trapping PARP on the DNA, which interferes with damage repair and leads to cell death

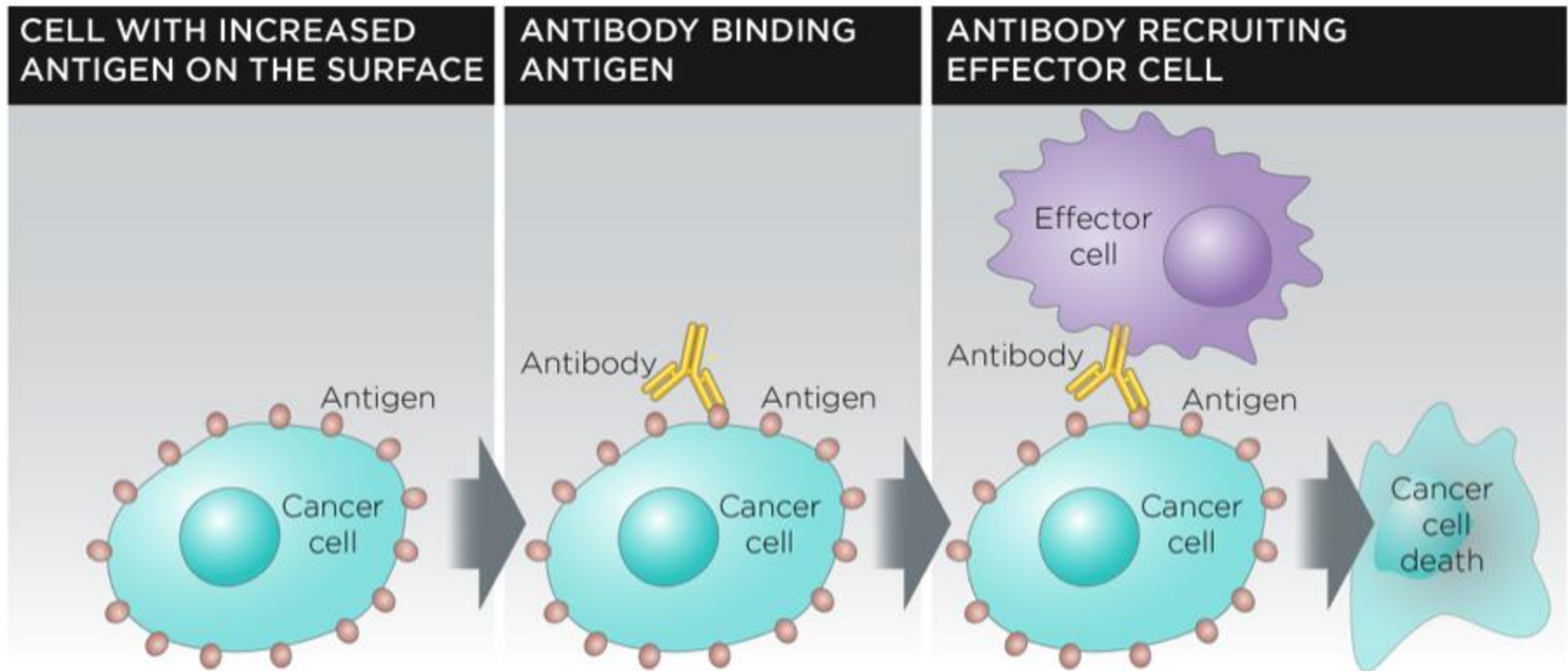
PARP Inhibitor Mechanism of Action



Cancer Immunotherapy

- Refers to a diverse set of therapeutic strategies to induce the patient's own immune system to fight the tumor
- **Examples:**
 - Monoclonal Antibodies: Stimulate immune cells to attack cancer cells
 - Therapeutic Vaccines: Injection of proteins and/or cells to stimulate the immune system to attack cancer cells
 - Adoptive Cell Transfer : Include engineered T cells (CAR-T)
- These “personalized” treatments program a patient's own immune system and must be prepared specifically for each patient.

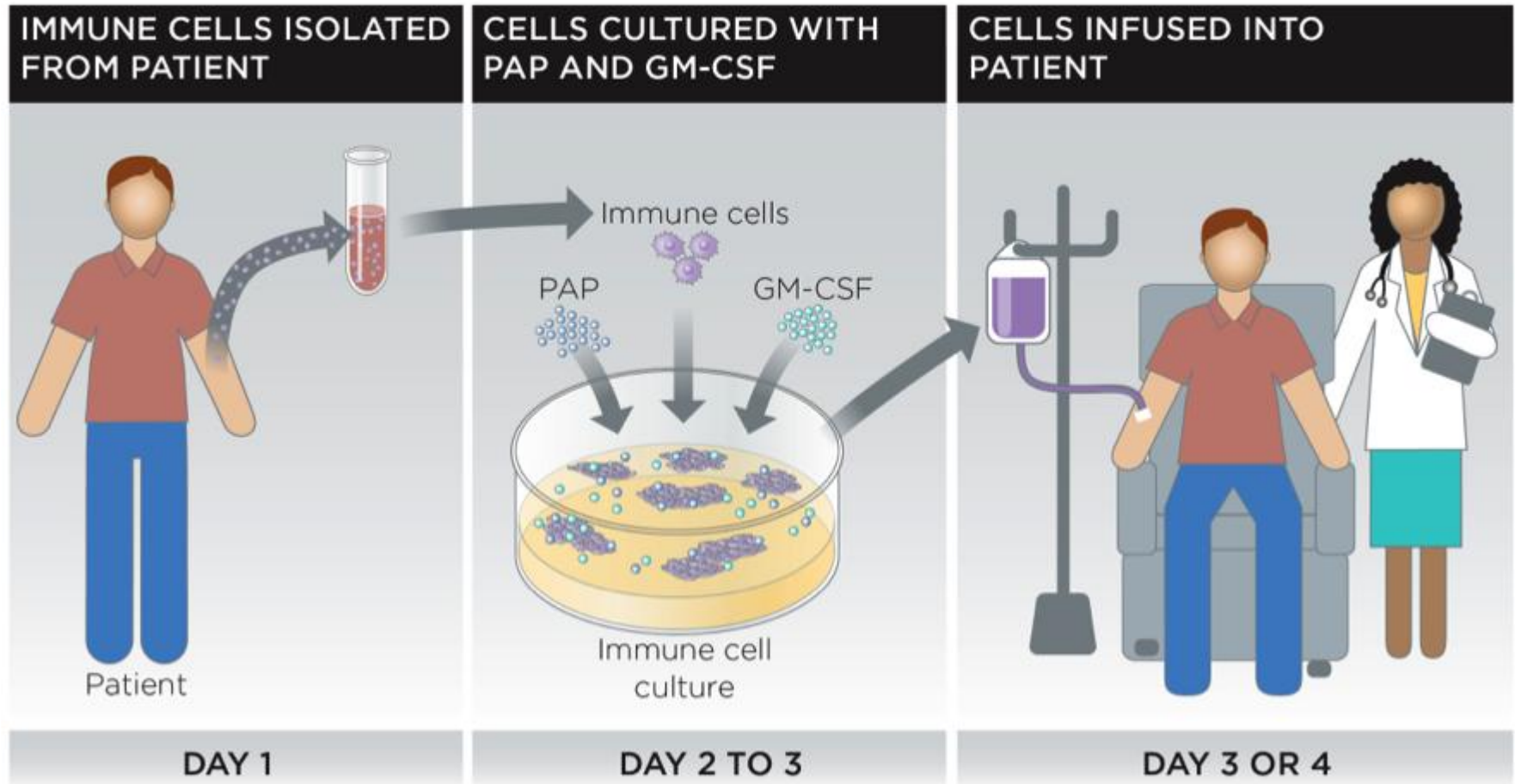
Monoclonal Antibody-Mediated Immunotherapy



Antibodies attract killer cells. Ex: Rituxan (anti-CD20) for treatment of non-Hodgkin lymphoma.
Aegiscreative.com

<https://www.youtube.com/watch?v=UtNelmBmQCM>

Therapeutic Cancer Vaccine: Provenge



Aegiscreative.com

<http://www.provenge.com/how-provenge-works.aspx>

Chimeric Antigen Receptor T Cells (CAR-T Cells)

REVIEW

CAR T cell immunotherapy for human cancer

Carl H. June,^{1,2,3*} Roddy S. O'Connor,^{1,2} Omkar U. Kawalekar,¹
Saba Ghassemi,^{1,2} Michael C. Milone^{1,3}

Science (2018) 359: 1361-1365

Antibody variable region –
Specific for a tumor target protein

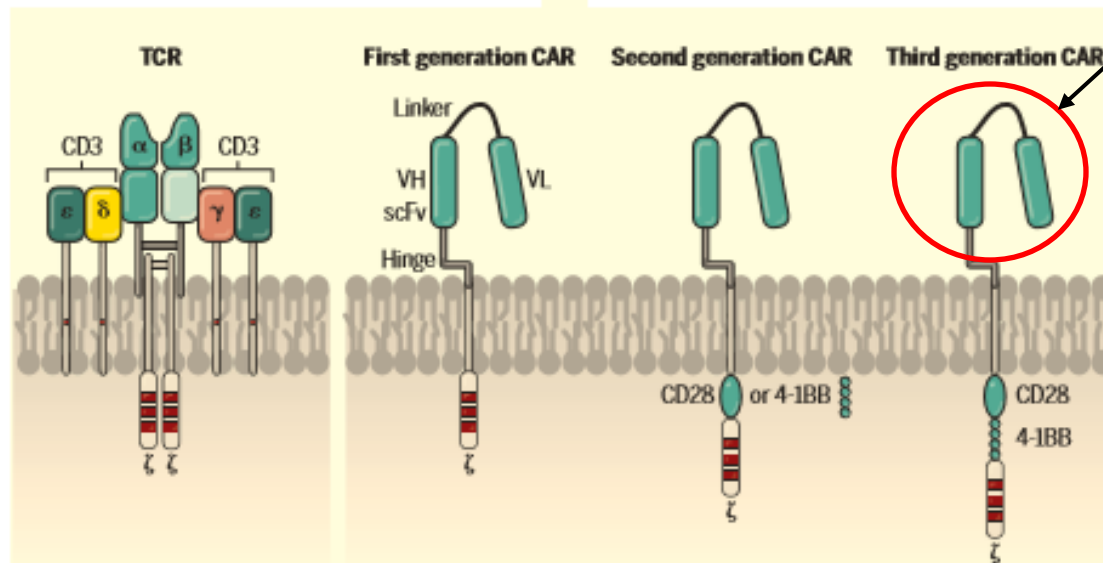


Fig. 1. Engineered T cells: design of TCR versus CAR T cells. T cells can be redirected to have specificity for tumors by the introduction of (left) transgenic TCRs (T cell receptors) or (right) CAR (chimeric antigen receptor) proteins. CARs are fusion proteins composed of an extracellular portion that is usually derived from an antibody and intracellular signaling modules derived from T cell signaling proteins. First-generation CARs contain CD3 ζ , whereas second-generation CARs possess a costimulatory endodomain (e.g., CD28 or 4-1BB) fused to CD3 ζ . Third-generation CARs consist of two costimulatory domains linked to CD3 ζ . scFv, single-chain variable fragment; VH, variable heavy chain; VL, variable light chain.

The Future of Cancer Therapeutics: Combination Therapy

Combination therapy aims to treat patients with drugs to multiple cancer targets and decrease the likelihood that a cancer will become resistant to treatment.

Cancer Drug Targets

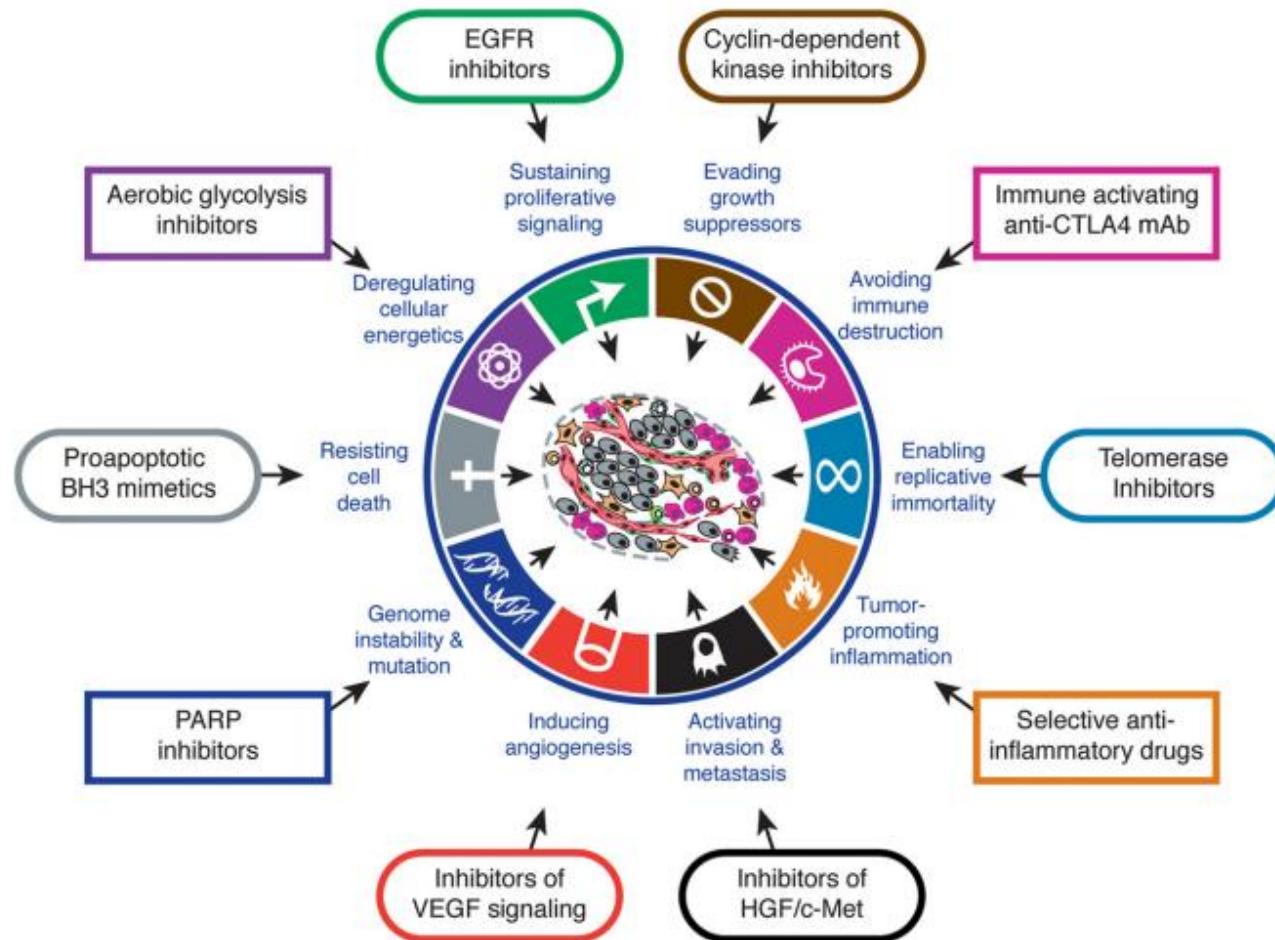
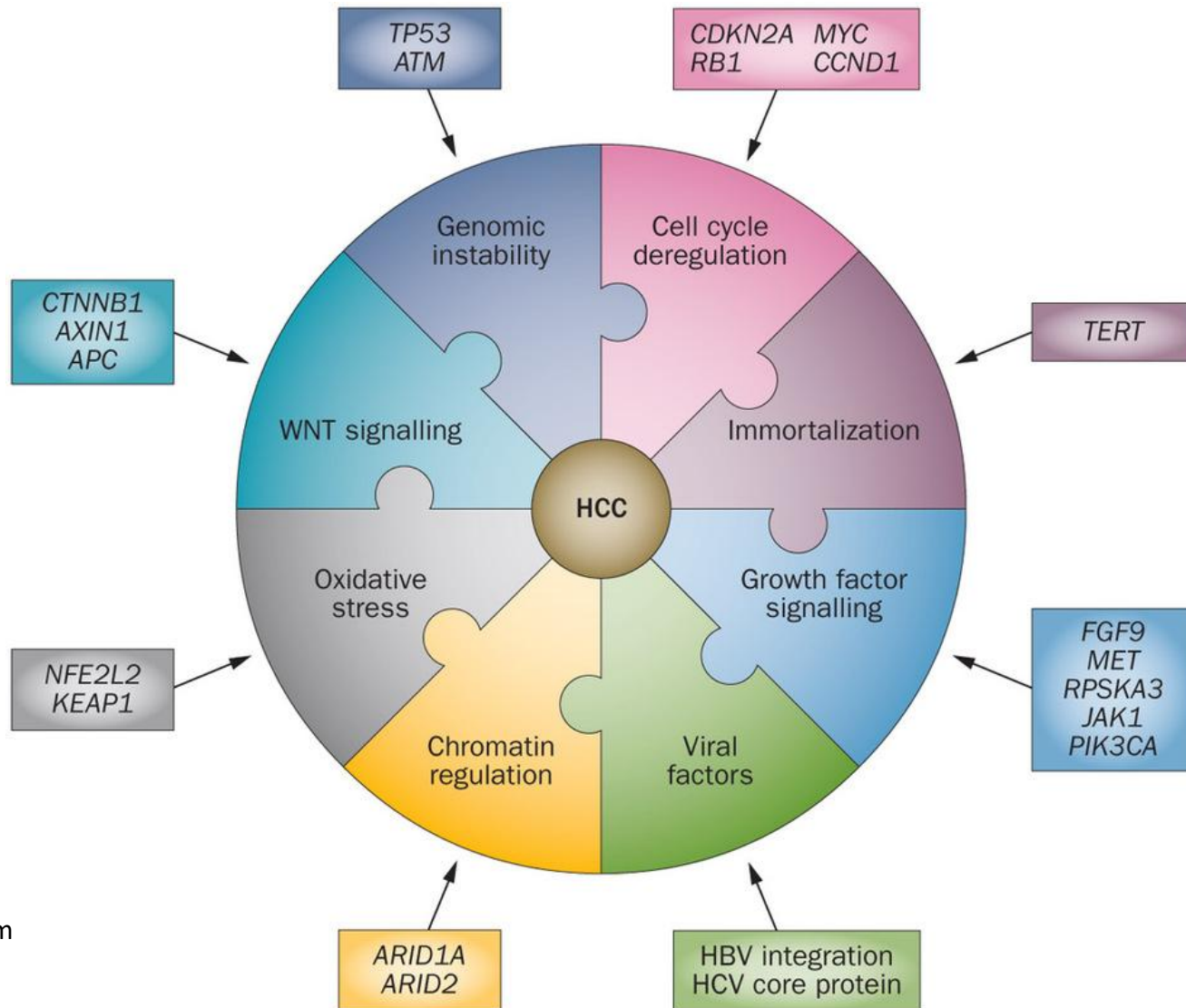


Figure 6. Therapeutic Targeting of the Hallmarks of Cancer

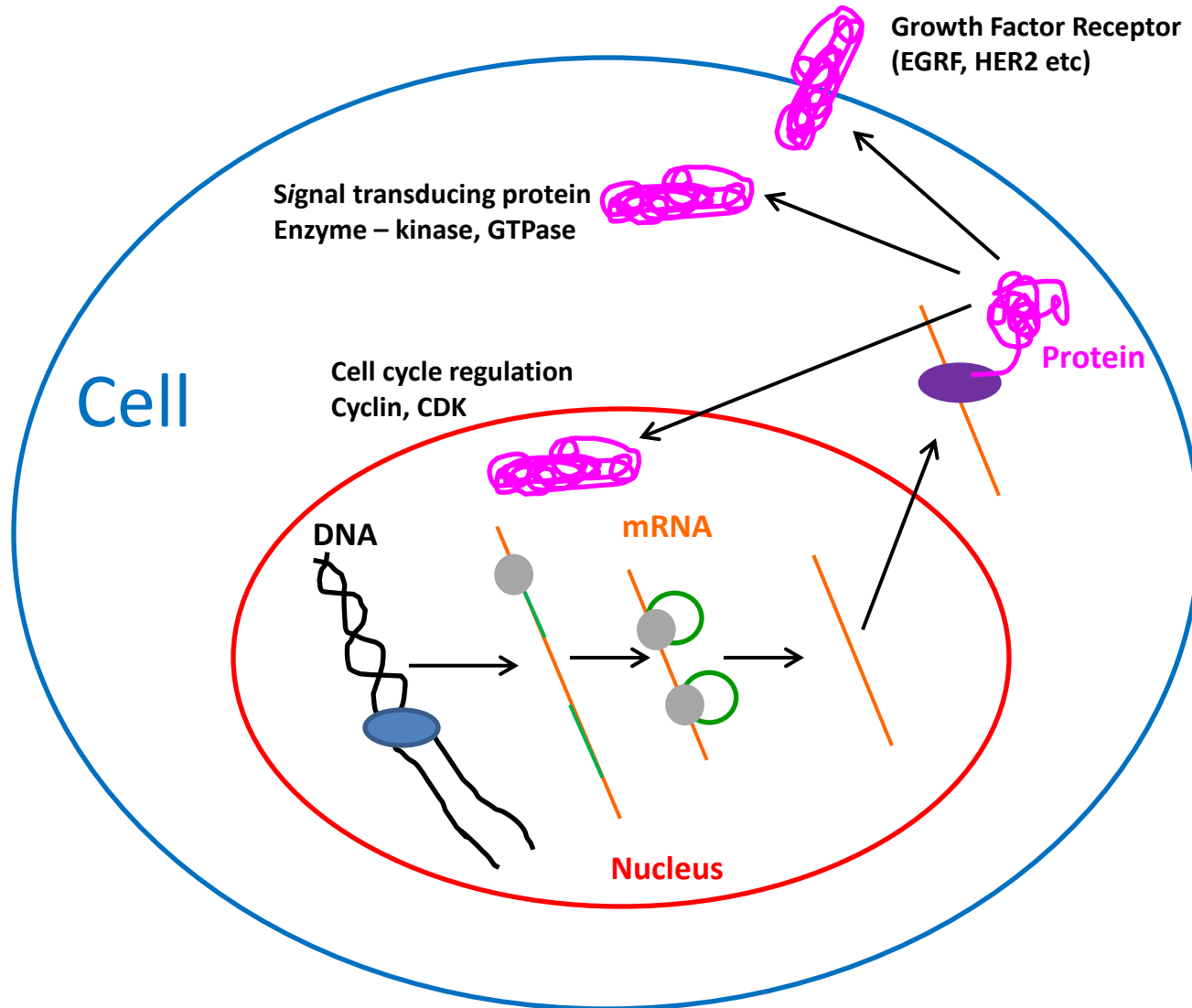
Drugs that interfere with each of the acquired capabilities necessary for tumor growth and progression have been developed and are in clinical trials or in some cases approved for clinical use in treating certain forms of human cancer. Additionally, the investigational drugs are being developed to target each of the enabling characteristics and emerging hallmarks depicted in Figure 3, which also hold promise as cancer therapeutics. The drugs listed are but illustrative examples; there is a deep pipeline of candidate drugs with different molecular targets and modes of action in development for most of these hallmarks.

Extra slides

Gene Groups Which Can Cause Liver Cancer When Mutated

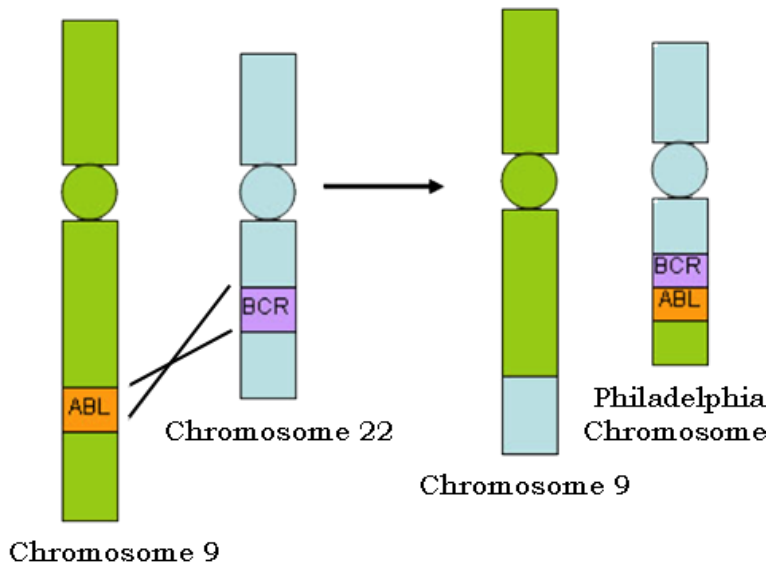


Potential Cancer Targets

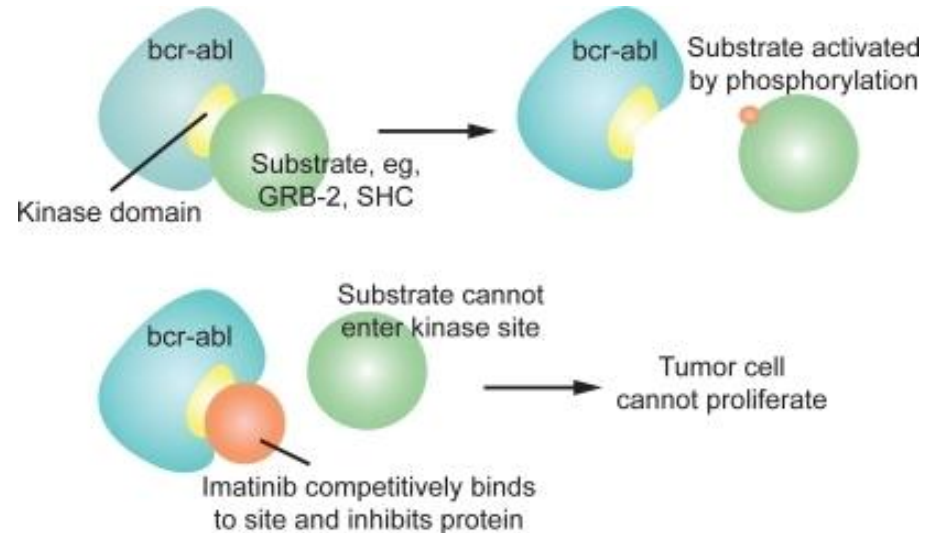


Other Examples of Small Molecule Inhibitors & Antibody Inhibitors

BCR-ABL: Imatinib (Gleevec)



www.khanacademy.org



Gallery4share.com

<https://www.youtube.com/watch?v=7ZMVQ1Vbb7Y>

95% of people with Chronic Myelogenous Leukemia (CML) have this translocation.

EGFR:

Panitumumab (Vectibix) & Cetuximab (Erbix)

- 1980s: Monoclonal antibody technology can block specific growth factor receptors.
- Examples: **Panitumumab (Vectibix) & Cetuximab (Erbix)**
- Inhibit EGFR

