

Overview of Cancer Therapeutics

Foundations of Cancer Therapeutics

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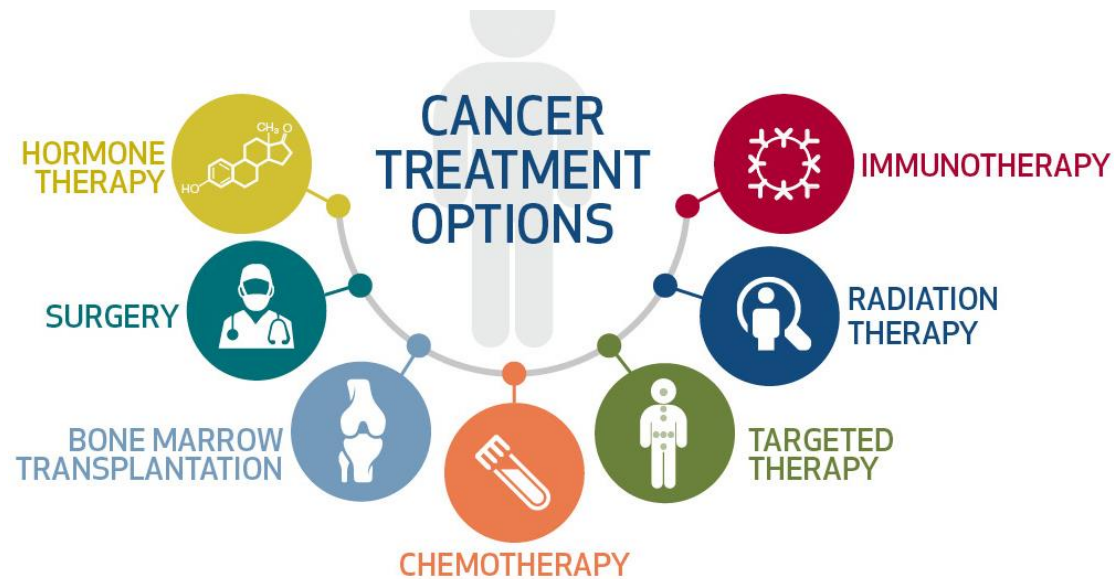
Approaches to Cancer Drug Discovery

A Question of Perspectives

Scientific and the Clinical Perspectives

Scientific Perspective – Translational Biomedical Research – Bench – to- Bedside
Clinical Perspective - Integrated Management of a Complex Disease

Clinical Perspective – Multiple Therapeutic Options



Multi-modal therapies whose application depends on a variety of factors

- Type (and sub-type) of cancer
- Anatomic Location
- Primary versus metastatic disease
- Prior therapies – primary vs recurrent disease ; acquired resistance
- Patient – based factors – tolerability, side-effect profile
- Therapeutic goal – Eradication versus containment

Approaches to Cancer Drug Discovery

Factors to consider before launching program to develop a new therapy

Clear understanding of anticipated clinical context

- Degree need – Standard-of-care vs unmet needs
- Feasibility of clinical testing –
- Likely application
 - Duration of therapy
 - Monotherapy versus combination therapies,
 - Adjuvant and Neo-adjuvant use
 - Specialized applications
- Side effect profile

Unmet Needs in Cancer Therapeutics

- 1) Cancers with poor long-term survival
Lung, Pancreas, Brain and Esophageal cancers
- 2) Rare Cancers (20% of US cancers)
Salivary gland, Small bowel, Rare hematologic cancers
- 3) Pediatric Cancers

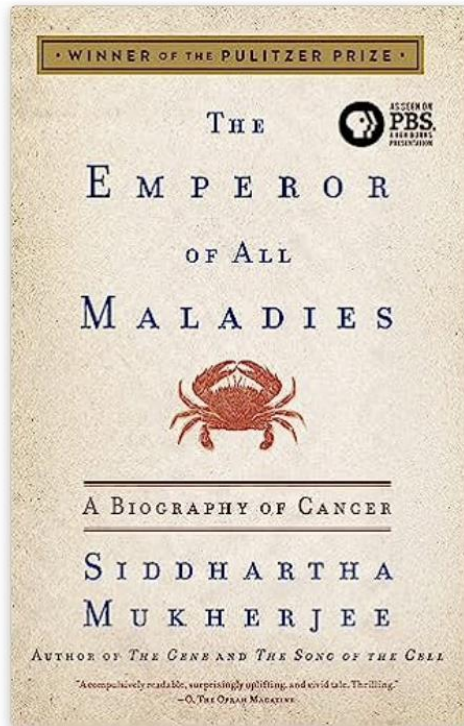
5-year relative survival rates for breast cancer

SEER Stage	5-year Relative Survival Rate
Localized	99%
Regional	86%
Distant	27%

5-year relative survival rates for pancreatic cancer

SEER Stage	5-year Relative Survival Rate
Localized	37%
Regional	12%
Distant	3%

Cancer Chemotherapy



3 Major Classes of Cancer Chemotherapies

- **Cytotoxic Chemotherapy** – Drugs that kill cancer cells based on their increased proliferative activity compared to their normal counterparts
- **Hormone Ablation Therapy** – Drugs that suppress or kill hormone-dependent cancer cells
- **Targeted therapies** – Drugs that suppress or kill cancer cells by targeting the activity of mutant proteins responsible for cancer cell survival.

Cancer Chemotherapy – Cytotoxic Chemotherapy

Mainstay for standard-of-care, front-line therapy for many cancers

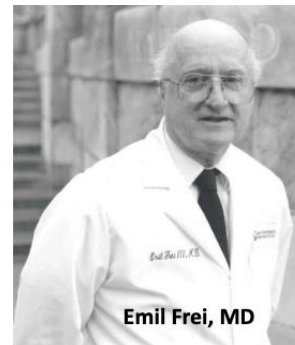
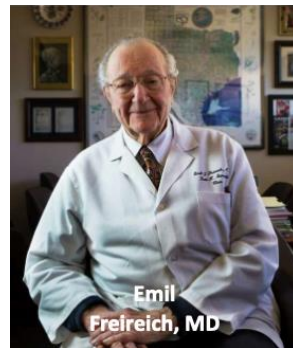
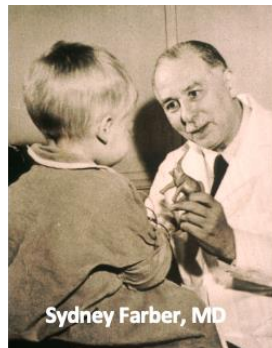
Rationale: Vulnerability based on Proliferative Activity

Background

- 1914 - 1918: Myelosuppression observed in soldiers exposed to mustard gas in WWI; triggered research in using nitrogen mustards as for therapy of leukemias
- 1940s and 1950s treatment of leukemia was based on single agent chemotherapy – nitrogen mustards and anti-folates
- 1960's Combination cytotoxic chemotherapies for leukemias and lymphomas. Chemotherapy with addition of radiation
- 1950s-1980s Development of many cytotoxic chemotherapy drugs for treatment of both leukemias and solid tumors

Classes of Cytotoxic Chemotherapies

- DNA-damaging drugs, alkylating agents etc
- Cytotoxic antibiotics and alkaloids – intercalating agents
- Ant-mitotics – mitotic spindle inhibitors
- Anti-metabolites, purine / pyrimidine biosynthesis
- Topoisomerase inhibitors
- Anti-proliferative Hormones – steroids



Cancer Chemotherapy – Hormone Ablation Therapy

Hormone-dependent Breast Cancer

- 1896 – Beatson reported that ovariectomy could treat some forms of breast cancer
- Led to the recognition of hormone – dependent cancers and hormone ablation therapy
- Today Estrogen Receptor Antagonists and Aromatase Inhibitors are mainstays in treatment of ER - positive breast cancer

Prostate Cancer

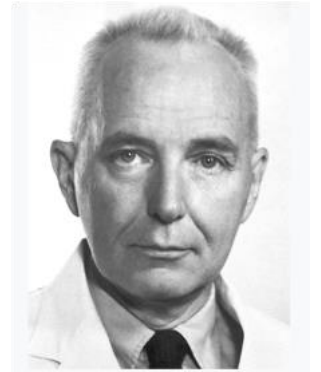
- 1940's Huggins reported that orchiectomy used to treat prostate cancer
- Identified Prostate Cancer as a hormone-dependent cancer
- Led to development of a range of Androgen Depletion Therapies, mainstays in therapy of prostate cancer today

Foundation for concept of Targeted Therapies that exploit specific molecular vulnerabilities to treat specific types of cancer

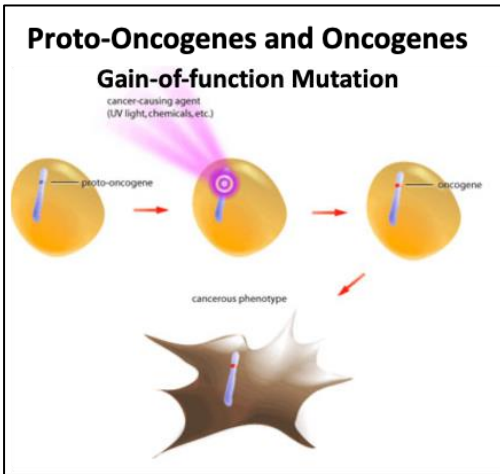
George Beatson, MD



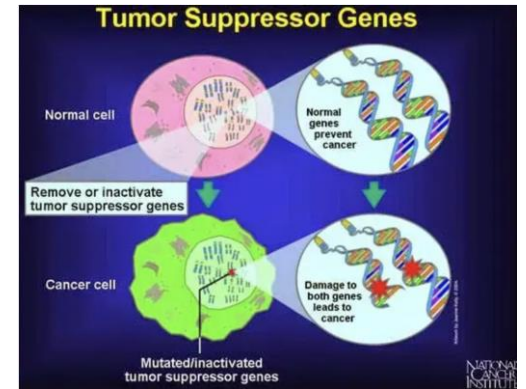
Charles Huggins, MD



Cancer Chemotherapy – Targeted Therapies



- **First report of a tumor suppressor gene 1971**
- **First report of an oncogene 1977**
- **Identification of mutations that occur in most types of cancer (1977 to the present day)**



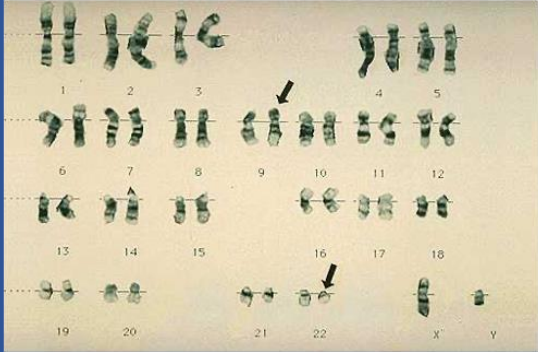
‘Targeted Therapy’:
Treat cancer by targeting the genes that are either activated or inactivated in cancer cells

1st Example - Targeted Therapy

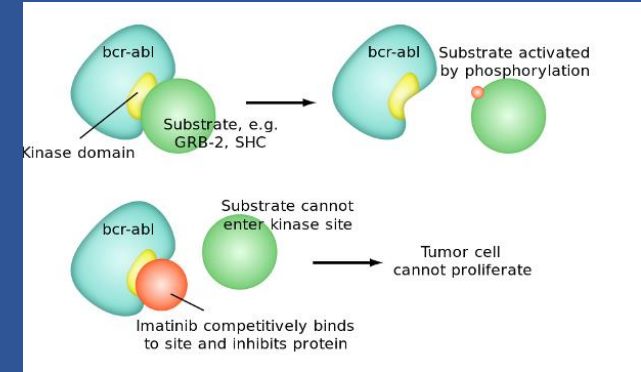
The Philadelphia Chromosome Story

Chronic Myelogenous Leukemia (CML)

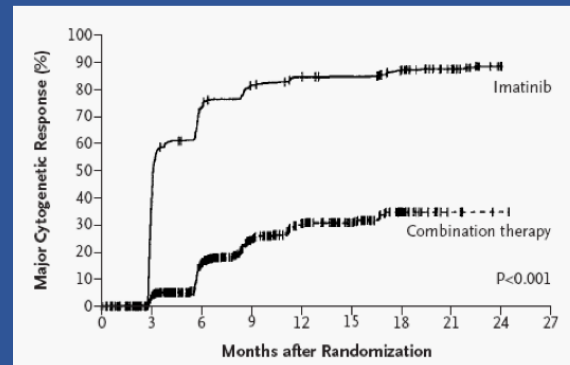
Philadelphia Chromosome t(9;22)



- 1960s Philadelphia chromosome
- 1970s Breakpoint identified
- 1980s BCR/ABL fusion protein
- 1990s Imatinib: inhibits BCR/ABL
- 2003 Imatinib: 1st-line therapy



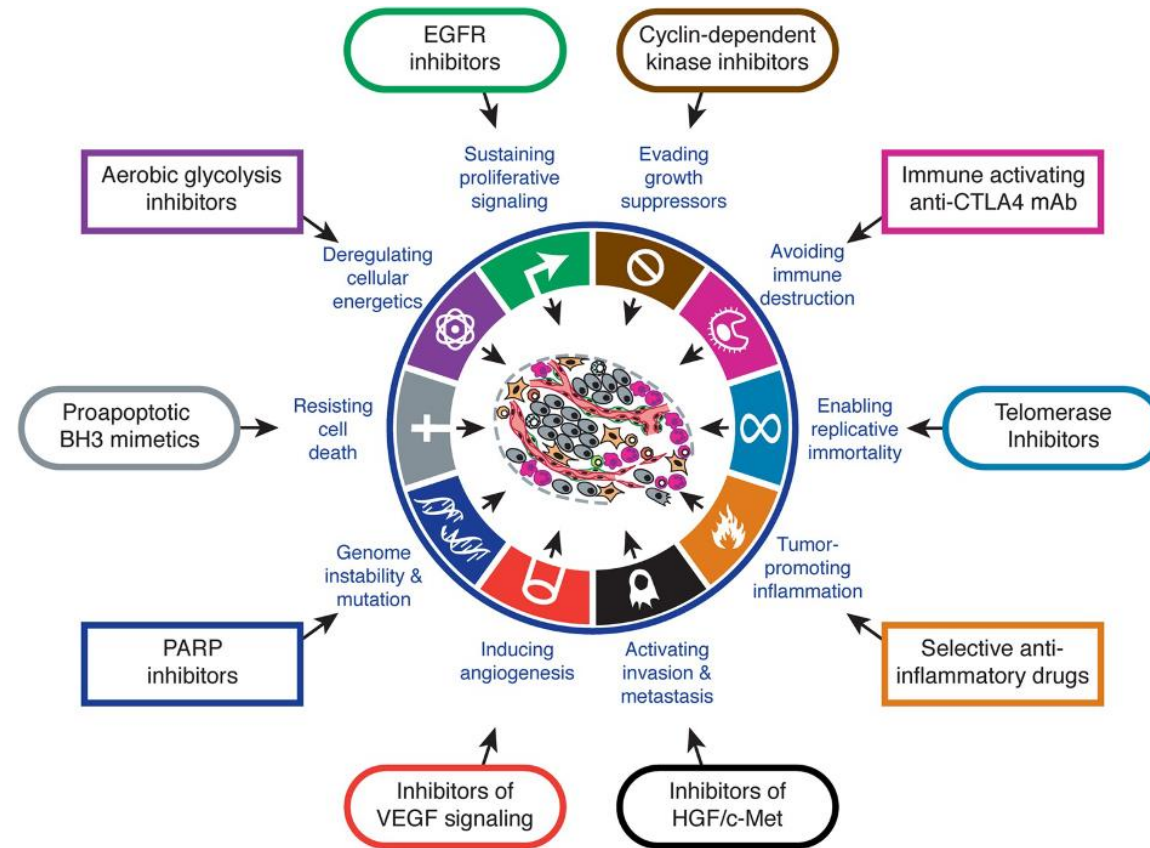
Imatinib (Gleevec) for CML



O'Brien NEJM 348: 994, 2003

Disease with a Universal & Targetable Genetic Event

Cancer Chemotherapy – Targeted Therapies Exploiting Vulnerabilities of Cancer Cells

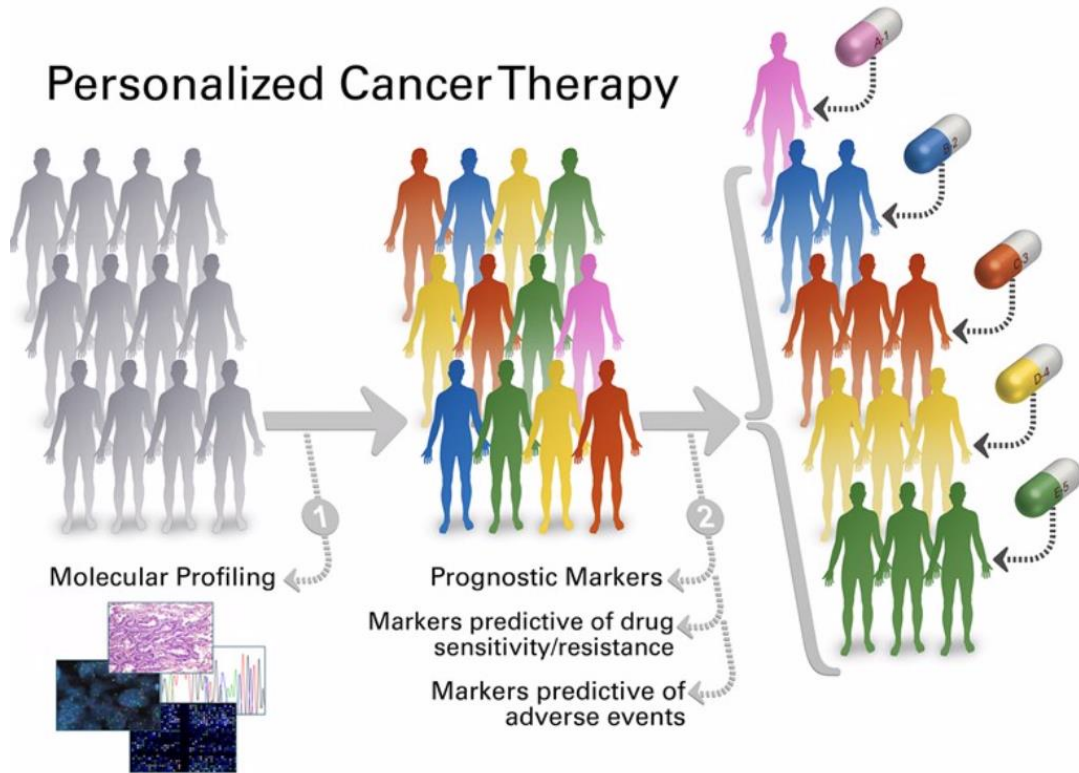


Hallmarks of Cancer

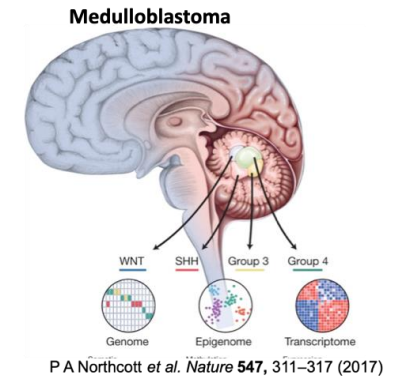
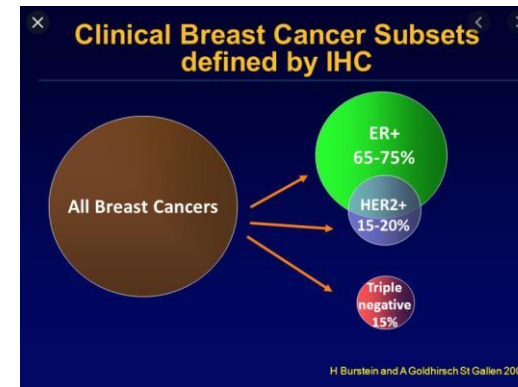
Hanahan, D., & Weinberg, R. A. (2011).

Cancer Chemotherapy – Precision Medicine

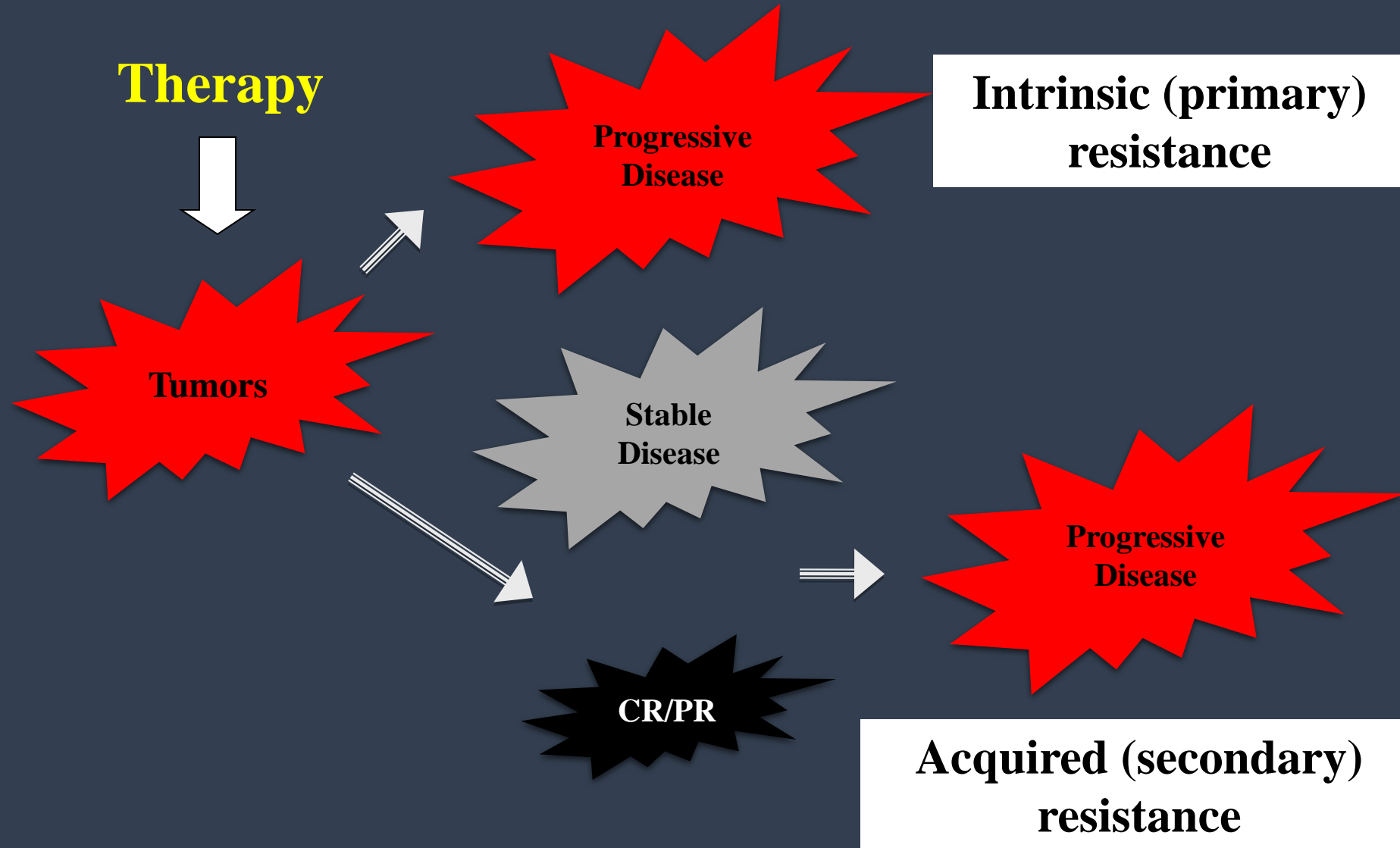
Personalized Cancer Therapies



Tumor types and Sub-types



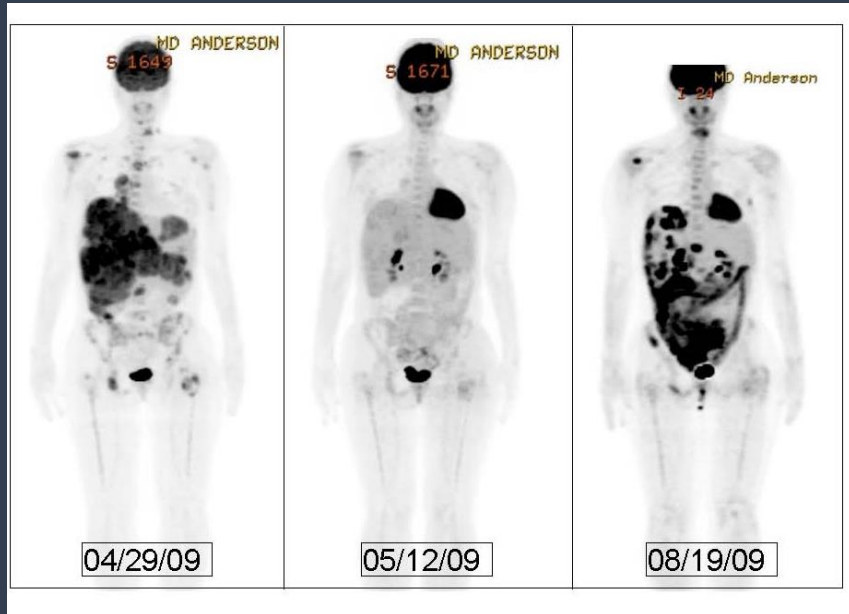
Therapeutic Resistance



Types of Resistance - Secondary Resistance

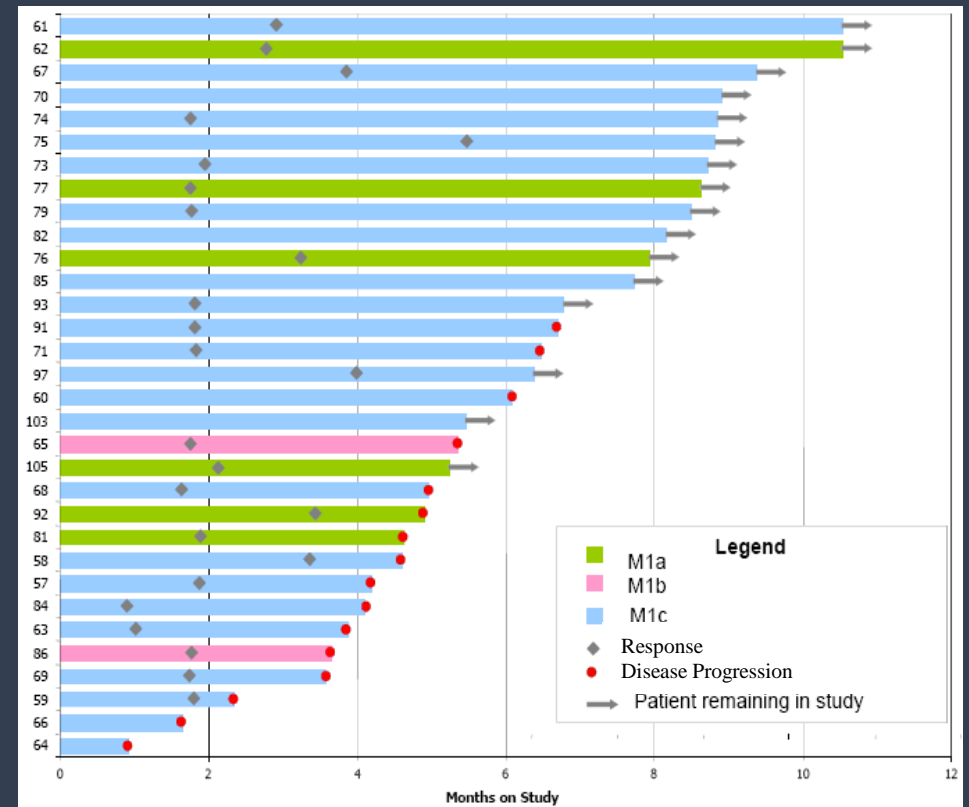
Changes that develop after the start of treatment that prevent/reverse tumor growth inhibition

Baseline Response Progression



Images courtesy of Dr. P Hwu and Dr. R. Joseph, MDACC

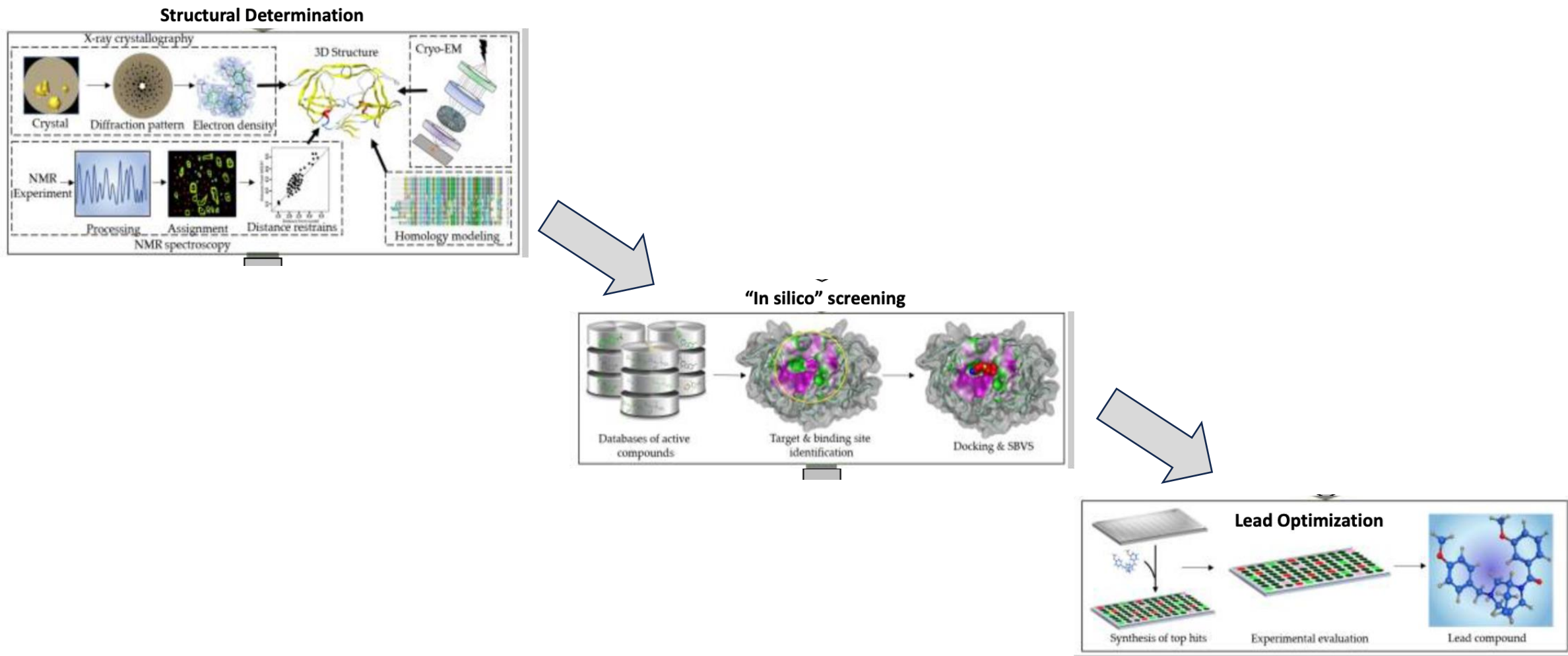
Vemurafenib Phase I: Response Duration



Flaherty, *NEJM*, 2010

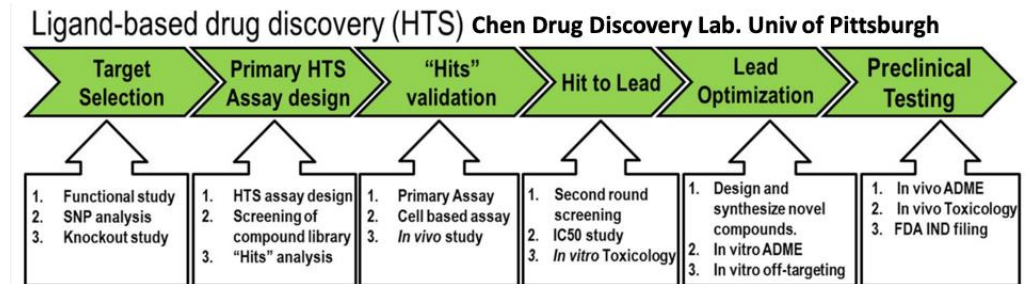
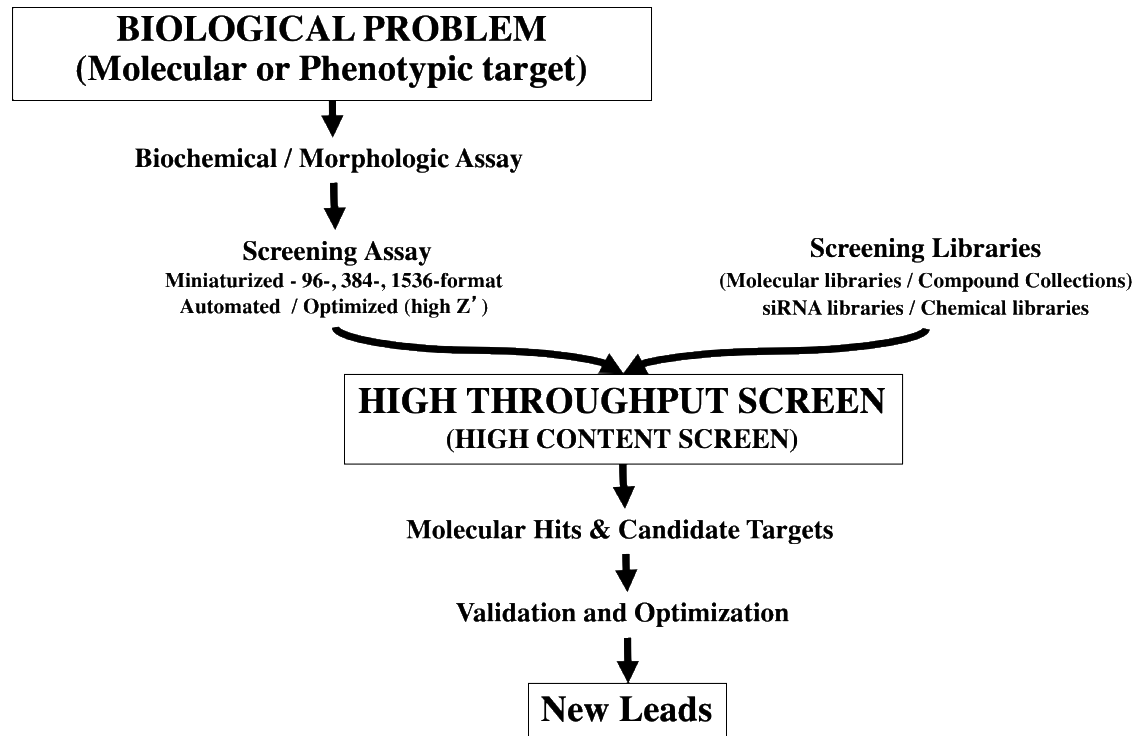
Cancer Chemotherapy – Small Molecule Targeted Therapeutics

Structure-Based Drug Discovery

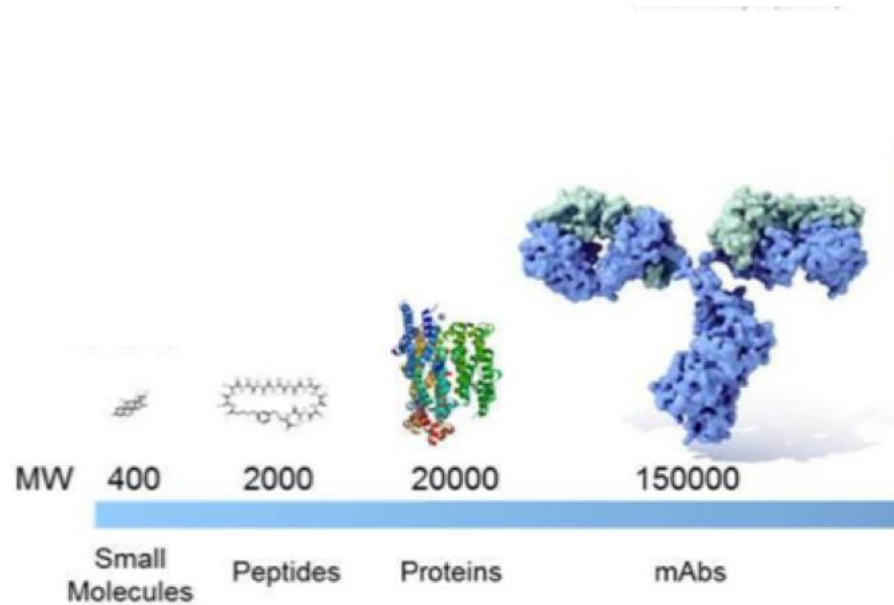


Cancer Chemotherapy – Small Molecule Targeted Therapeutics

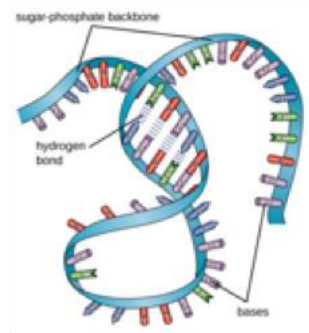
Screening Based Drug Discovery



Cancer Chemotherapy –Targeted Therapeutics

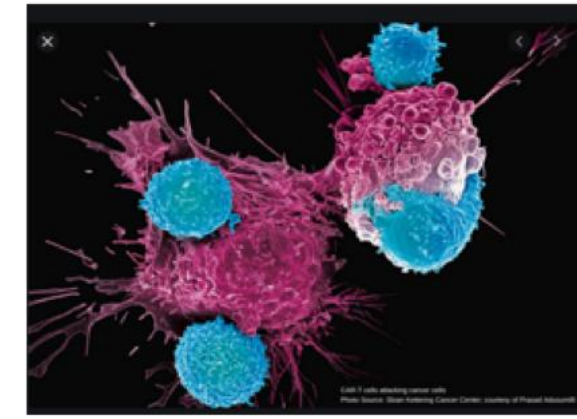


Nucleic Acid Vaccines



RNA

Adoptive T-cell Therapies



CAR-T cells

Small Molecule Therapeutics

Advantages:

- “Drug-like” Properties
- Intra- and Extracellular Targets
- Blood-brain barrier
- Orally active
- Cost

Disadvantages

- On- vs off-target activities
- Metabolism
- Clefts and pockets
- Resistance

Therapeutic Antibodies

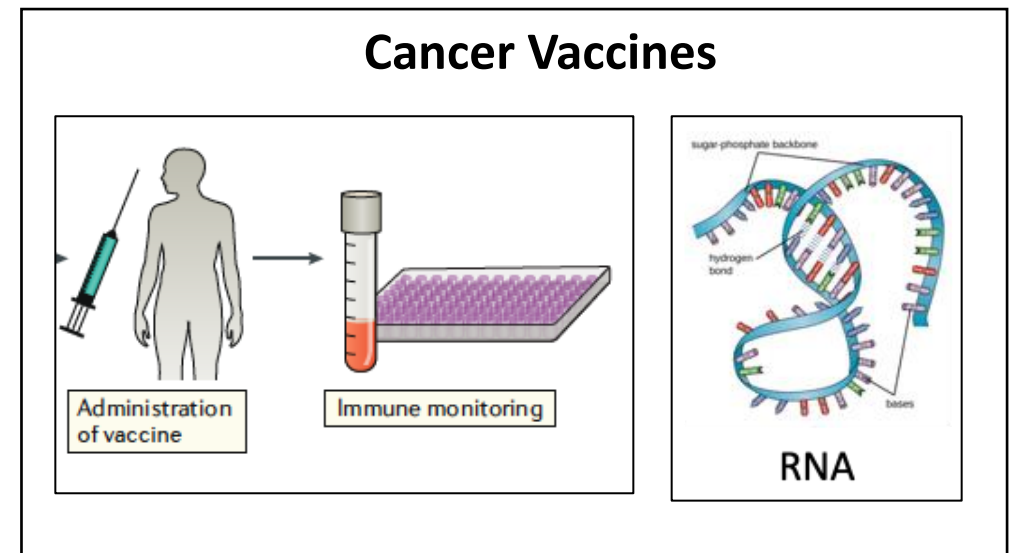
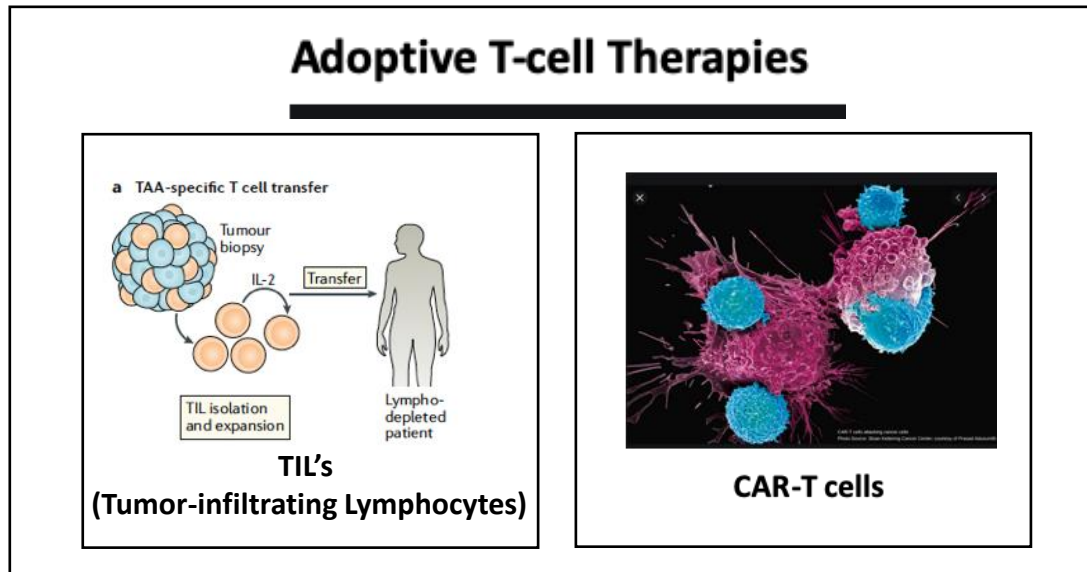
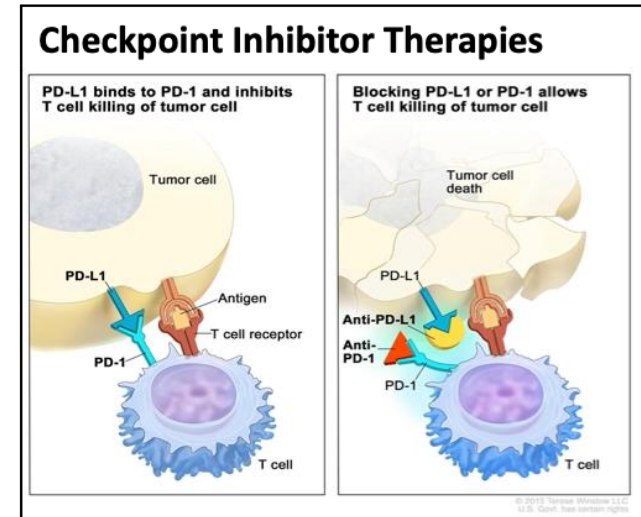
Advantages

- Circulating or Cell Surface targets
- Specificity
- Engineered Properties
- Ease of generation

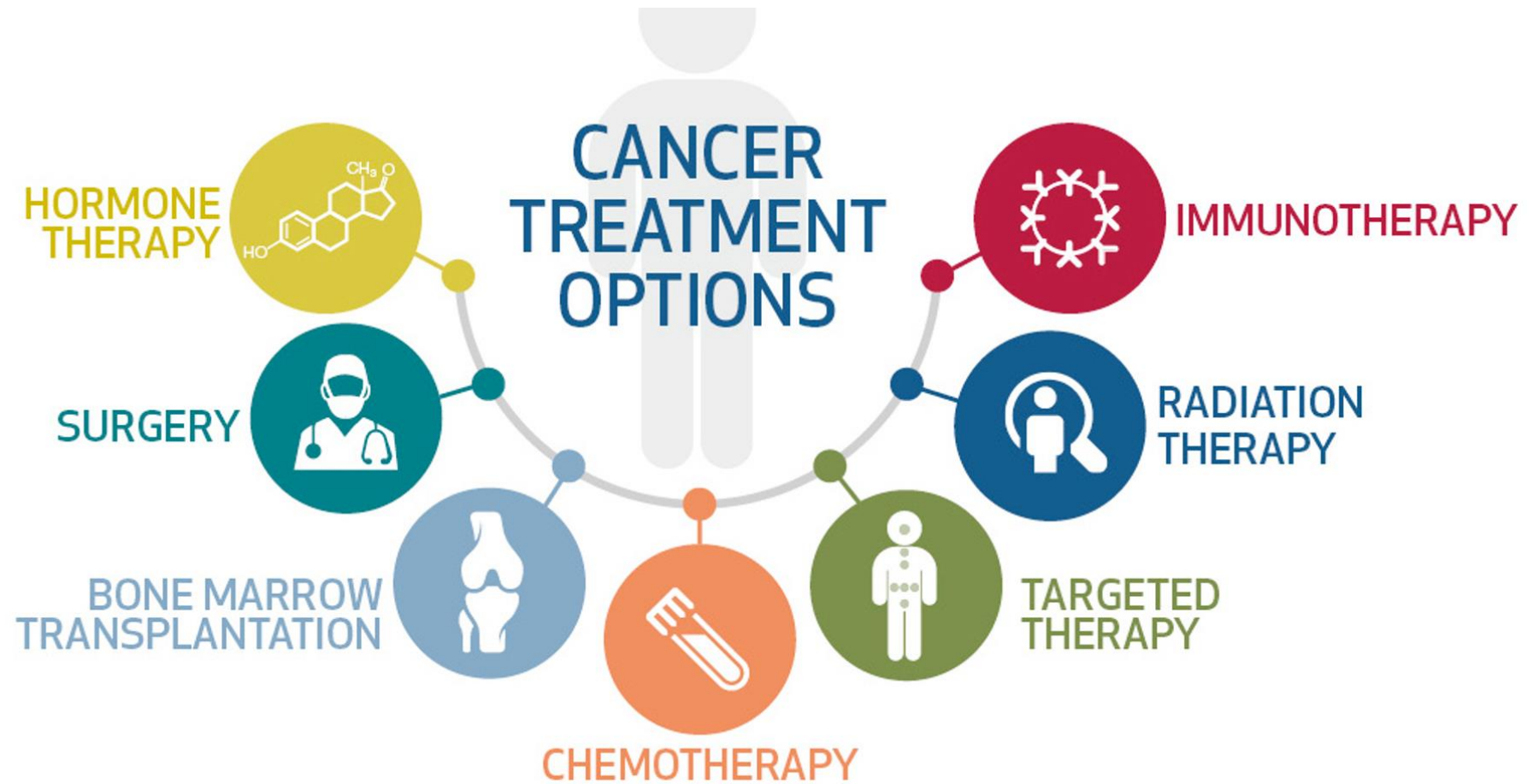
Disadvantages

- Intracellular targets
- Blood-brain barrier
- Routes of Administration
- Cost

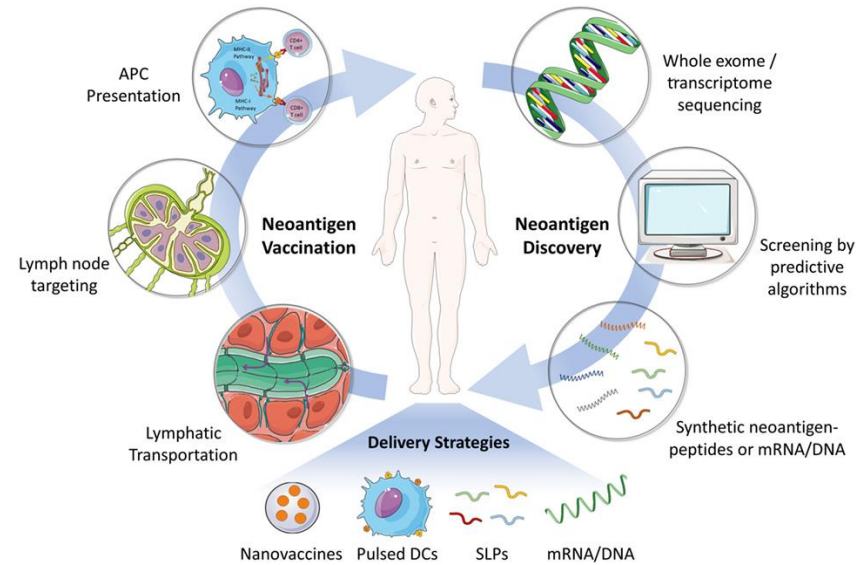
Cancer Chemotherapy – Immunotherapies



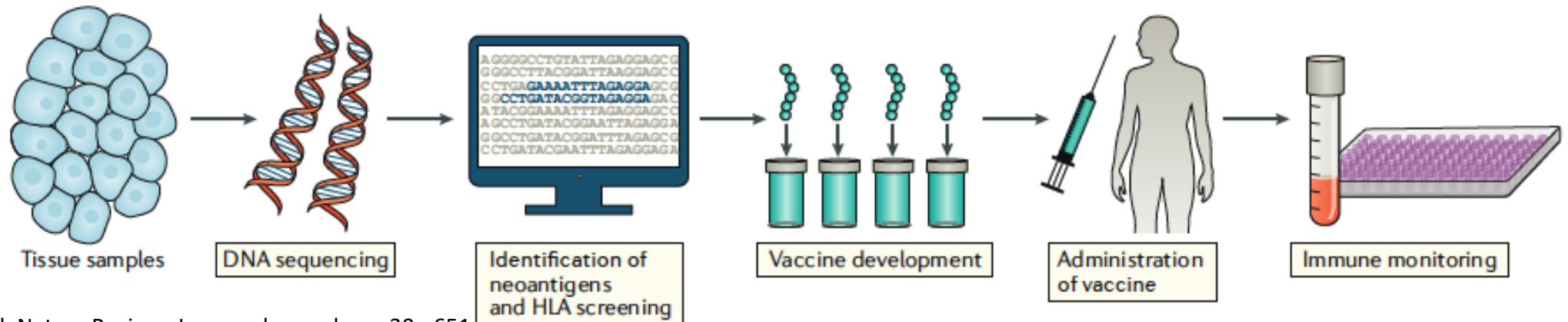
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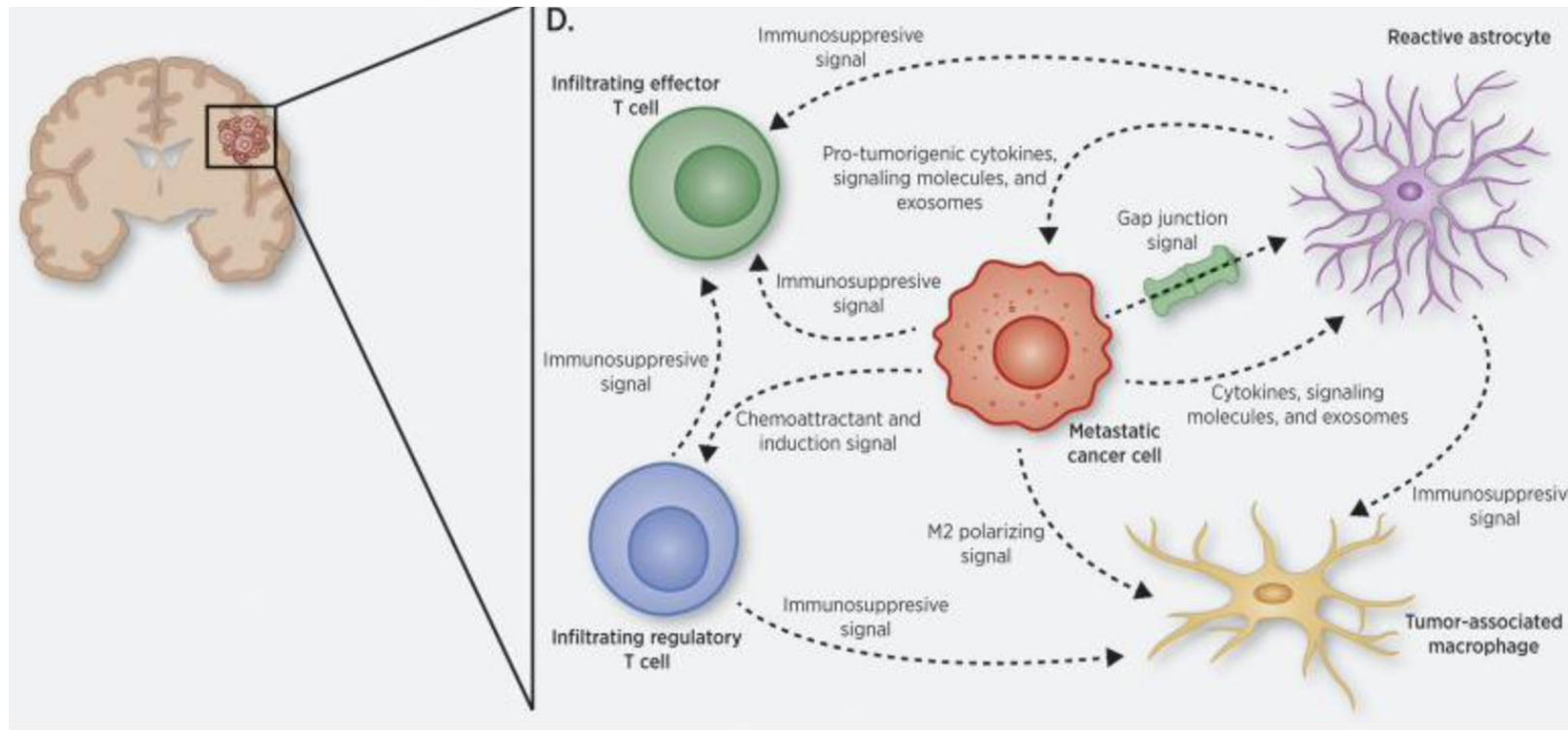
Cancer Chemotherapy – RNA Vaccines



Guo et al. *Frontiers in Immunology* 9, p1499 2018



Waldman et al, *Nature Reviews Immunology* volume 20 p651



Srinivasan ES, Tan AC, Anders CK, Pendergast AM, Sipkins DA, Ashley DM, Fecci PE, Khasraw M. Salting the Soil: Targeting the Microenvironment of Brain Metastases. *Mol Cancer Ther.* 2021 Mar;20(3):455-466. doi: 10.1158/1535-7163.MCT-20-0579. Epub 2021 Jan 5. PMID: 33402399; PMCID: PMC8041238.