OVERVIEW OF CANCER PATHOPHYSIOLOGY

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A Few Definitions to Get Us Started…

Physiology
- A science that deals with the ways that living things function
- The ways that living things or any of their parts function
- A branch of biology that deals with functions & activities of life or of living matter (as organs, tissues, or cells) & of physical / chemical phenomena
- Organic processes & phenomena of an organism or any of its parts or of a particular bodily process

Pathophysiology
- The physiology of abnormal states; specifically: the functional changes that accompany a particular syndrome or disease

Cancer
- Northern zodiacal constellation between Gemini & Leo: 4th zodiac sign in astrology. From Latin, crab, cancer
- Malignant tumor of potentially unlimited growth: expands locally by invasion and systemically by metastasis; abnormal body state marked by such tumors
- Evil / malignant thing spreads destructively e.g. cancer of hidden resentment
Definition: Cancer

- A large group of diseases characterized by
  - Cells growing out of control
  - Spreading throughout the body
  - Malignant cell have been altered genetically to look and function differently than normal cells

- Disease of the cell and involves
  - Mutations/changes in genetic makeup or DNA of the cell


Defining Targeted Molecular Therapy

- Targeted molecular therapy uses drugs or substances to interfere with specific molecules so can block tumor growth and proliferation

- These drugs or substances work by disrupting or blocking cell communication signals 1 of 2 locations:
  - From the outside of the cell to the inside of the cell
  - Inside the cell so that signals do not reach the nucleus to instruct the cell to divide, or make proteins

- Can categorize targeted therapies according to effects on cancer hallmarks. Are divided into 2 broad categories: small molecule (suffix “ib” or “tinib”) & monoclonal antibodies (suffix “mab”)

Setting the Stage: Why is Cancer Pathophysiology / Biology Important?

- Aids clinicians in planning a patient's treatment
- Provides prognostic information
- Evaluates the results of treatment
- Facilitates the exchange of information between treatment centers
- Contributing to and advancing research on cancer

Classification of Cancer Biomarkers by Function

<table>
<thead>
<tr>
<th>Function</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening</td>
<td>Most tumor markers are not useful for screening; only one tumor marker (prostate-specific antigen (PSA)) is used for screening, and its value in detecting prostate cancer has been heavily debated.</td>
</tr>
<tr>
<td>Diagnostic aid</td>
<td>Tumor markers can add to the information about the molecular features of a tumor, helping to define its molecular subtype.</td>
</tr>
<tr>
<td>Determine prognosis</td>
<td>Some tumor markers are factors considered when determining prognosis, or a prediction of the outcome.</td>
</tr>
<tr>
<td>Guide treatment</td>
<td>Some tumor markers can provide information about what types of treatment are more or less likely to be effective.</td>
</tr>
<tr>
<td>Monitor response to treatment</td>
<td>Tumor markers can monitor the effectiveness of treatment, especially for advanced cancers.</td>
</tr>
<tr>
<td>Detect recurrence or progression</td>
<td>Some tumor markers can indicate that cancer has recurred or progressed; if the level of a tumor marker is elevated before treatment, is low after treatment, and then begins to increase after treatment, it is likely that cancer is recurring or progressing.</td>
</tr>
</tbody>
</table>
Personalized Medicine: Genetic Biomarkers

- Advanced tests analyze tumor samples, other tissue for abnormal gene feature (allow cancer to develop or spread)

- May look at single gene OR entire chromosome. With tests, look for genetic mutations / alterations in some tumors to help guide treatment decisions, e.g. seek a genetic profile or fingerprint.

- Limited to breast and colorectal cancer. Tests improve care as the right person is matched to the right treatment plan

- OncotypeDX – calculates recurrence score. Measures activity 16 cancer genes, 5 control genes

- Precision Medicine – Mutations in Mismatch repair gene

Personalized Medicine: Protein Biomarker

- Include substances that are either produced by cancer cells themselves or by other cells in response to cancer.

- Most protein biomarkers related to cancer are used to monitor response and/or detect recurrence or progression during follow-up after treatment.

- Some biomarkers used to predict outcome or prognosis
ASCO Names Immunotherapy 2.0 Advance of Year

• Growing numbers of patients with cancer benefit from research advances in immunotherapy. In 2017, ASCO cited immunotherapy as the Advance of the Year for 2nd consecutive year. National Institutes of Health and National Cancer Institute call for federal funding to drive progress against cancer.

• Clinical Cancer Advances 2017: ASCO’s Annual Report on Progress Against Cancer highlights the expanding role of immunotherapy. Evolving research findings provide new insights on how to get optimal results from these relatively new treatments.

• “In less than a decade, immunotherapy has gone from being considered a promising theoretical treatment to one that has become a standard of care that is helping extend or improve the lives of thousands of patients”, says ASCO President Daniel F. Hayes, MD, FACP, FASCO. “Today, increased knowledge about both cancer and immunology leads to more and smarter use of treatments that activate a patient’s own immune system”.

Protein Biomarkers for Cancer Types

![Protein Biomarkers Table]
Objectives. By the end of this presentation, participants will be able to:

- Describe 3 parts of a cell’s anatomy & list 3 normal functions
- Review angiogenesis in normal cell functioning
- Explain how cell signaling affects normal cell function in contrast to cell signaling influences on the cell cycle in a cancer cell.
- Describe how genetic mutations lead to malignant transformation
- Explore theories of carcinogenesis
- Identify steps in malignant angiogenesis and metastases
- Describe the common signal transduction pathways identified in the development of new therapeutic cancer agents
- Identify several therapeutic agents approved to target the signal transduction pathways commonly associated with malignancy, e.g. targeted immunotherapy agents.

Normal Cell Anatomy and Function

Cell Anatomy:
- Cell Membrane
- Receptors: Extracytoplasmic, transmembrane, intracytoplasmic
- Organelles: Mitochondria, smooth / rough endoplasmic reticulum, lysosomes, proteosomes, Golgi apparatus
- Nucleus: RNA (messenger, translation, & transcription), DNA, chromosomes, genes, nucleolus, nucleotides (base pairs)

Cell Function:
- Signaling pathways – activate or inhibit genetic signals
- Protein production unique to cell type (surfactant, insulin)
- Produce energy (ATP): aerobic (Kreb’s cycle) Anaerobic glycolosis (lactic acid)
- Cell replication / Programmed cell death (apoptosis)
Cell Schematic

DNA Packaging

Structure / Function of DNA and Chromosomes

DNA is Copied During Cell Division

- The DNA “parent” strands pull apart
- Complementary bases are added
  - (A-T, C-G)
- The result is two complete DNA molecules that are an exact copy of the original molecule
- Each cell gets a complete copy

Cell Life Cycle

Regulation of the Cell Cycle

- Cyclins D, E, A, B
- Inhibitors
- Restriction point

# Hallmarks of Cancer: Observed Differences Between Normal Cells and Cancer Cells

<table>
<thead>
<tr>
<th>Normal Cells</th>
<th>Cancer cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Controlled growth and division</td>
<td>• Uncontrolled cell division</td>
</tr>
<tr>
<td>• Contact Inhibition</td>
<td>• Lack contact inhibition</td>
</tr>
<tr>
<td>• Anchorage dependent</td>
<td>• Tend to invade other tissues</td>
</tr>
<tr>
<td>• Noninvasive</td>
<td>• Have potential to spread</td>
</tr>
<tr>
<td>• Not immortal</td>
<td>• Lack of differentiation</td>
</tr>
</tbody>
</table>

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**Hallmarks: Cancer Cell Growth & Progression / Targeted Agents Action**

Genetic Mutations

Mutated cell may:
- Die from damage or by initiating programmed cellular suicide (apoptosis)
- Recognize damage and repair itself
- Survive and pass on damage

Genetic mutations: Acquired or Hereditary?

Genes can become mutated, or abnormal, if the DNA sequence is changed. Change in gene’s DNA sequence usually causes the protein it helped to build to either not function normally or not function at all.

Result? Growth, division or survival of cells may be abnormal. Changes in DNA sequences occur often, mostly during cell division, but DNA can fix these errors (p53 tumor suppressor gene / DNA repair gene). Sometimes, repair method fails & the genetic mutation passes on to future copies of changed cell.

The most common types of mutations in cancer involve four abnormalities:
1) **AMPLIFICATION**: Increase in # copies of a specific DNA fragment DNA

2) **DELETION**: Loss of genetic material, ranging from small (a single missing DNA base pair) to large (a piece of a chromosome)

3) **INACTIVATION**: Loss of the biologic function of the gene

4) **TRANSLOCATION**: A broken chromosome reattaches to a different one

BCR-ABL inhibitors used to treat CML: Dasatinib, Imatinib, Nilotinib, Ponatinib

Genetic Mutations:
Somatic (Acquired) vs. Germline (Inherited)

- Somatic mutations
  - Multifactorial
  - Majority of cancers
- Germline mutations
  - Inherited/familial
  - Minority of cancer

Somatic Genetic Mutations

- **Proto-Oncogenes**
  - Oncogenes
  - K-Ras

- **Tumor suppressor genes**
  - P53
  - Apoptosis

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### Important Genes in Carcinogenesis

1. Apoptosis Gene (programmed cell death) shuts down / inactivated in cancer

2. DNA Repair Gene (repair abnormal copy / signal cell if can’t )

3. Proto-oncogene (signals cell to begin replicating, enter cell cycle). Mutations to gene transform it, making gene oncogenic. Continuous signals to divide

4. Tumor suppressor gene (instructs cell – stop dividing). Mutations here are like losing car brakes; cell never receives signal to stop dividing
Angiogenesis: Hallmark of Cancer

- Normally only present if require wound healing or during pregnancy when gene is activated

- Recruit elements to build new vasculature, capillaries:
  - Endothelial cells
  - Fibroblasts
  - Epidermal cells

- Respond to messages / signaling of vascular endothelial growth factor (VEG-F), fibroblast growth factor (FBG-F), & epidermal growth factor

- Malignant angiogenesis: tumor makes VEG-F, FBG-F in conditions of hypoxia, need for nutrients, waste disposal, promote metastases

- Therapeutic Anti-angiogenic agents: Thaladomide (Thaladomid®, Cetuximab (Erbitux®) – Blocks VEG-R receptor on endothelial cell)
  - Bevacizamab (Avastin®) – Binds with VEG ligand prior to VEGF-R
Angiogenesis

- Growth of new blood vessels
- Normal in embryo
- Quiet in adults in most tissues

Steps in Angiogenesis

- Modulated by a number of factors:
  - Vascular Endothelial Growth Factor (VEGF)
  - Fibroblast Growth Factor
  - Epidermal Growth Factor

So What Causes Cancer?

- Age
- Hereditary factors
- Lifestyle choices (tobacco/alcohol use and diet)
- Occupational hazards (asbestos, chemicals, metals)
- Environmental exposure (radiation, sun and viruses)
- Combination of factors


Carcinogenesis

- The process by which cancer arises
  - Initiation
    - Carcinogens damage DNA
    - Irreversible change in DNA
  - Promotion
    - Further carcinogen exposure
    - May be reversible
  - Progression
    - Detectable symptomatic disease - 1 cm mass

New Research: Stress & Inflammation Combine to Fuel Cancer Growth

Definitions

- **Stress**: Experience of significant or negative life event or an event without effective coping. Psychological / physiologic response to body perceives as a threat.

- **Inflammation**: Cellular manifestation stress. “Acute”, i.e. innate immunity activates immune system to ward off infection or “Chronic”, i.e. lingering inflammation can predispose individuals to illness such as cancer.

- **Stress & inflammation**: Probably mediate cancer development & progressions. 25% of cancers are associated with chronic inflammation of broad origin.

New Research: Stress & Inflammation Combine to Fuel Cancer Growth

- Many cancer-related deaths caused by treatment resistant-metastases. Stress & inflammation drive metastatic process.

- Body produces pro-inflammatory markers, e.g. cytokines in response to stress. Cytokines regulate immune responses and inflammation. Two pro-inflammatory cytokines are interleukins & tumor necrosis factor; these turn on various transcription factors.

- Inflammation changes tissue homeostasis; leads to chronic response promotes tumor growth, angiogenesis, invasion and metastasis by activating surrounding stromal cells & recruiting inflammatory cells (e.g. mast & NK, neutrophils & leukocytes).

- Inflammatory cells create reactive O2 & Nitrogen species, turn on oncogenes, and silence tumor suppressor genes


Psycho-Oncology Interventions for Managing Stress and Inflammation in Cancer

- Mind-body techniques
  - Yoga
  - Cognitive / Behavioral therapy
  - Energy-Based Techniques
  - Acupuncture
  - Meridian tapping
  - Vitamins and minerals
  - Fish Oils
  - Exercise
  - Swimming / Hiking
  - Zumba / Dance Fitness

Theories of Cancer Development

- Multistep
- Mutagenesis
- Epigenetics
- Oncogene hypothesis
- Tumor suppressor gen
- Knudson's "two hit"
- Cancer stem cell hypothesis
- Immunosurveillance


Knudson 2 Hit Theory of Cancer Development

Cancer Stem Cell Theory


Cancer Etiology: Bad Luck Random Mutations
(Source: Science 1-2-15)

- Cancer often strikes individuals without any type of known risk factors; new research says many cancer types due to “bad luck”

- With statistical model measuring proportion of cancer incidence across 31 tissue types, Johns Hopkins Univ. School of Medicine researchers found that 22 cancers, (2/3’s of the total reviewed), could be largely explained by "bad luck" or random mutations during DNA replication in normal, non-cancerous stem cells.

- The remaining 9 cancer types were more attributable to environmental, lifestyle, and hereditary factors.

- Focus on stem cell division—the more divisions taking place e.g. stem cell turn-over, the more prone tissue is to develop cancer
The Metastatic Process

Overall most common sites of metastases
- Bone
- Brain
- Liver
- Lungs
- Lymph nodes
TUMOR LIST

Different body tissues types give rise to different tumors, both benign and malignant. The following tables show the different kinds of tumors each of the following tissue types are vulnerable to:

- Connective Tissue
- Endothelium and Mesothelium
- Blood and Lymphoid Cells
- Muscle
- Neural
- LIP (Lymphoid Organ), and Endocrine System
- Other Tissues

### Connective Tissue

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Benign Tumors</th>
<th>Malignant Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adipose Tissue</td>
<td>Fibroma</td>
<td>Fibrosarcoma</td>
</tr>
<tr>
<td>Connective Connective Tissue</td>
<td>Osteoma</td>
<td>Osteosarcoma</td>
</tr>
<tr>
<td>Fat</td>
<td>Lipoma</td>
<td>Liposarcoma</td>
</tr>
<tr>
<td>Cartilage</td>
<td>Chondroma</td>
<td>Chondrosarcoma</td>
</tr>
<tr>
<td>Bone</td>
<td>Chondroma</td>
<td>Chondrosarcoma</td>
</tr>
<tr>
<td>Adipose Tissue</td>
<td>—</td>
<td>Chondrosarcoma</td>
</tr>
</tbody>
</table>

### Endothelium and Mesothelium

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Benign Tumors</th>
<th>Malignant Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood vessel</td>
<td>Hemangiona</td>
<td>Hemangiosarcoma</td>
</tr>
<tr>
<td>Mesothelium</td>
<td></td>
<td>Mesothelioma</td>
</tr>
</tbody>
</table>

### Blood and Lymphoid Cells

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Benign Tumors</th>
<th>Malignant Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mononuclear Cell</td>
<td>Macrophage</td>
<td>Macrophage</td>
</tr>
<tr>
<td>Lymphocyte</td>
<td>Lymphoma</td>
<td>Lymphosarcoma</td>
</tr>
</tbody>
</table>

### Muscle

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Benign Tumors</th>
<th>Malignant Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle</td>
<td>Myosarcoma</td>
<td>Myosarcoma</td>
</tr>
</tbody>
</table>

### Neural

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Benign Tumors</th>
<th>Malignant Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nerve</td>
<td>Neurofibroma</td>
<td>Neurofibrosarcoma</td>
</tr>
<tr>
<td>Neuron</td>
<td>—</td>
<td>Neuronoma</td>
</tr>
</tbody>
</table>
Pathologic Diagnosis of Cancer

- Pathologist key to determining extent of cancer
  - Identifies and grades biopsy
  - Examine sentinel lymph nodes
  - Examine regional lymph nodes
  - Examine tissue from distant sites

Table L: Some important parts of a pathology report

<table>
<thead>
<tr>
<th>Determinant</th>
<th>Macroscopic changes</th>
<th>Histologic changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical diagnosis</td>
<td>First and foremost no reliable data in the primary tumor, needle biopsy is available for correlation.</td>
<td>The microscopic changes are in accordance with the clinical diagnosis, but need to be confirmed.</td>
</tr>
<tr>
<td>Pathology</td>
<td>No single feature is present in the primary tumor, needle biopsy is available for correlation.</td>
<td>The microscopic changes are in accordance with the clinical diagnosis, but need to be confirmed.</td>
</tr>
<tr>
<td>Location</td>
<td>No single feature is present in the primary tumor, needle biopsy is available for correlation.</td>
<td>The microscopic changes are in accordance with the clinical diagnosis, but need to be confirmed.</td>
</tr>
<tr>
<td>Vascular invasion</td>
<td>No single feature is present in the primary tumor, needle biopsy is available for correlation.</td>
<td>The microscopic changes are in accordance with the clinical diagnosis, but need to be confirmed.</td>
</tr>
<tr>
<td>Metastatic spread</td>
<td>No single feature is present in the primary tumor, needle biopsy is available for correlation.</td>
<td>The microscopic changes are in accordance with the clinical diagnosis, but need to be confirmed.</td>
</tr>
<tr>
<td>Surgical margins</td>
<td>The microscopic changes are in accordance with the clinical diagnosis, but need to be confirmed.</td>
<td>The microscopic changes are in accordance with the clinical diagnosis, but need to be confirmed.</td>
</tr>
</tbody>
</table>
Pathologic Diagnosis of Cancer

- Mitotic activity
  - Presence of dividing cells
- Pleomorphism
  - Variation in size and shape of cells
- Hyperchromatism
  - Nucleoli that stain darker than normal
- Abnormal chromosome arrangements
  - Aneuploidy

Grading and Differentiation

**Grade:** Degree to which tumor cells resemble parent tissue

- **GX** Grade can not be assessed
- **G1** Well-differentiated (Low grade)
- **G2** Moderately-differentiated
- **G3** Poorly-differentiated
- **G4** Undifferentiated (High grade)
Tumor Grade

- Internationally developed grading systems
  - Gleason
  - Scarff-Bloom-Richardson (Nottingham)
- Uses more specific and objective criteria based on
  - Nuclear grade may be assigned
  - Mitotic count

TMN Staging

- T = TUMOR Local involvement, invasion e.g. extent of primary tumor
- N = NODES Lymph node involvement, e.g. presence / absence of regional lymph node metastases
- M = METASTASIS Distant location(s), e.g. presence or absence of distant metastases
**The International TNM Staging System**

**Stage 1**
Early disease: tumor confined to the breast (node-negative).

**Stage 2**
Early disease: tumor spread to in movable ipsilateral axillary nodes (node-positive).

**Stage 3**
Locally advanced disease: tumor spread to the superficial structures of the chest wall; involvement of ipsilateral internal mammary lymph nodes.

**Stage 4**
Advanced (or metastatic) disease: metastases present at distant sites, such as bone, liver, lungs, and brain and including supraclavicular lymph node involvement.

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**TMN Staging for Lung Cancer**

**LUNG STAGING FORM**

| Clinical | Stage Category Definitions | Pathologic | Clinical 
<table>
<thead>
<tr>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Location and Distance of Disease Spread</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **T1**: Primary tumor cannot be assessed for evidence of primary tumor.
- **T2**: Tumor spread to contralateral pleura.
- **T3**: Tumor spread to ipsilateral pleura or to ipsilateral hilar or mediastinal lymph nodes.
- **T4**: Tumor spread to contralateral hilar or mediastinal lymph nodes.

<table>
<thead>
<tr>
<th>Pathologic</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Location and Distance of Disease Spread</td>
<td>Pathologic</td>
<td>Clinical</td>
</tr>
</tbody>
</table>

- **T1a**: Tumor confined to the bronchus or bronchi.
- **T1b**: Tumor extends beyond bronchus or bronchi but not involving the main bronchus.
- **T2a**: Tumor extends beyond the bronchus or bronchi but not involving the main bronchus (T1b).
- **T2b**: Tumor extends beyond the bronchus or bronchi but not involving the main bronchus (T1b).
- **T3**: Tumor extends beyond the bronchus or bronchi but not involving the main bronchus (T1b).
- **T4**: Tumor extends beyond the bronchus or bronchi but not involving the main bronchus (T1b).
TMN Staging for Lung Cancer

Regional Lymph Nodes (N):
- N0: No regional lymph nodes metastases
- N1: Metastases in ipsilateral peripheral or hilar lymph nodes
- N2: Metastases in contralateral mediastinal, hilar, or subcarinal lymph nodes
- N3: Metastases in contralateral mediastinal, hilar, subcarinal, or supraventricular lymph nodes

Distant Metastases (M):
- M0: No distant metastases
- M1: Distant metastases

These elements and clinical judgement dictate that the effusion is not related to the tumor; the effusion should be excluded as a staging element and the patient should be classified as M0.
Advances in Cancer Therapy

- Oncogenes, when mutated or expressed aberrantly, disrupt normal signaling pathways to allow cells to divide continuously and invade adjacent tissues & metastasize to distant body organs.

- Thriving cancer cells must continually divide, evade tumor suppressors & immune system, an environment conducive to growth, an adequate blood supply, avoid programmed cell death, & use cellular energy (glycolysis).

- Newer trial designs such as “umbrella” or “basket” trials are being used to speed evaluation of targeted therapies.

- Molecular targeted therapy blocks signals that stimulate cancer cells to grow and proliferate, to invade, and to metastasize.


Types of targeted molecular therapy:

- **Angiogenesis inhibitors**
- **BCR-ABL inhibitors**
- **BRAF and MEK inhibitors**
- **BTK inhibitors**
- **EGFR inhibitors**
- **HDAC inhibitors**
- **Multikinase inhibitors**
- **PARP inhibitors**
- **PI3K inhibitors**
- **Proteasome inhibitors**
- **Cyclin-dependent kinase inhibitors**
- **Hedgehog pathway inhibitors**

Mammalian target of rapamycin (mTOR) inhibitors

Hallmarks: Cancer Cell Growth & Progression / Targeted Agents Action

<table>
<thead>
<tr>
<th>Hallmarks</th>
<th>Action of Targeted Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sustained proliferative signaling instructing cells to divide</td>
<td>Stop autophagy (e.g., mTOR inhibitors, rapamycin)</td>
</tr>
<tr>
<td>Evoke cell growth suppression</td>
<td>Stop cell division by targeting cell cycle checkpoints (e.g., cyclin-dependent kinases)</td>
</tr>
<tr>
<td>Evasion of immune destruction</td>
<td>Block mechanisms that downregulate immune response (e.g., anti-CTLA-4 antibodies)</td>
</tr>
<tr>
<td>Enable cells to evade apoptosis (non-autonomous)</td>
<td>Block cells undergoing programmed cell death (e.g., by blocking TNF receptor)</td>
</tr>
<tr>
<td>Induction of genetic instability</td>
<td>Induce mutations in cancer cells (e.g., by inhibiting DNA repair)</td>
</tr>
<tr>
<td>Maximize replicative capacity</td>
<td>Maximize replicative capacity (e.g., by inhibiting telomerase)</td>
</tr>
</tbody>
</table>

Cytoplasmic Signal Inhibition: Small molecule inhibitors, mTOR Inhibitors, PARP inhibitors & Proteasome Inhibitors
Communication

**Identifying the Target**
- Cells are instructed by messages from outside the cell, which pass through cell surface receptors (cell signaling).
- These messages, and other messages from inside the cell are delivered to the cell nucleus by a process called *signal transduction*.
- Receptor tyrosine kinases and non-receptor tyrosine kinases are proteins that carry the message.

**Signal Transduction**
- A receptor tyrosine kinase (RTK) is made of extracellular (outside cell), transmembrane (across membrane) & cytoplasmic parts.
- When a ligand attaches to a receptor, dimerization occurs; this activates phosphorylation & sends message through the cell membrane to activate the cytoplasmic tyrosine kinase.
- Cell's energy moves message “downstream” towards cell nucleus.
- Communication from outside cell to nucleus is signal *transduction*.

Cellular Communication

**Nonreceptor Tyrosine Kinases**
- nRTKs regulate differentiation, growth, division, adhesion, and survival.
- Mutation of nRTK genes can alter the transmission of messages to the cell nucleus allowing uncontrolled and continuous growth and proliferation.
- Therapeutic targets include mTOR, and within the MAPK pathway, RAS, RAF, MEK, ERK and c-Kit.

**Cancer and Signal Transduction**
- In cancer cells, components of signal transduction pathways are often mutated (eg, RAS, BRAF), enabling cell nucleus to receive continuous signals to proliferate, grow & not respond to programmed cell death.
- Continual genetic mutation within tumor cells can lead to the development of alternate pathways and subsequent drug resistance.

Figure 1: Where’s the target?

It has taken scientists more than a century to learn how to harness the immune system to fight cancer.

A number of strategies to achieve this have been tried, but one approach—blocking immune checkpoints—has been particularly effective against a range of different cancers.

Immune checkpoints are specialized proteins that act as brakes on the immune system, ensuring that immune defenses are engaged only when they are needed and for as long as they are needed.

They prevent the immune system from becoming overactive, which can lead to excessive inflammation or autoimmune disease.

**Blocking Immune Checkpoints**

*Fig. 2: When a cancer cell encounters a T cell (a type of immune cell), the interaction between the major histocompatibility complex (MHC) and the T-cell receptor (TCR) molecules activates the T cell. But when the PD-L1 checkpoint protein on the cancer cell attaches to the PD-1 checkpoint receptor on the T cell, the T cell is deactivated.*
New drugs act at PD-1 receptors; are monoclonal antibodies
1) First drug – Ipilimumab (Yervoy™) approved in 2011
2) Second drug - Pembrolizumab (Ketruda™) approved in 2014
3) Third drug – Nivolumab (Opdivo™) approved in 2014

- Immune system uses feedback loop to regulate self; at check-points, receives signals telling it to slow down or turn off. Goal: to prevent over-activation or attack of body’s own cells. Tumors express such signals with the end result the body’s natural cancer defenses are limited.

- Checkpoint inhibitor drugs block the tumor’s signals: thus, immune system is up-regulated & body’s natural defense against cancer cells is enhanced.
### Table 3. Some genetic alterations used as biomarkers in radiotherapy

<table>
<thead>
<tr>
<th>Type of Genetic Alteration</th>
<th>Radical Alternation</th>
<th>Name</th>
<th>Type of Treatment</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRAD</td>
<td>Radiation sensitivity</td>
<td>Radiation Resistance</td>
<td>Increase in drug sensitivity</td>
<td>Increase in drug resistance</td>
</tr>
<tr>
<td>HER</td>
<td>HER2</td>
<td>Hercepton</td>
<td>Increase in HER2 expression</td>
<td>Increase in HER2 expression</td>
</tr>
<tr>
<td>DUSL-ALK</td>
<td>Non-small cell lung cancer</td>
<td>ALK</td>
<td>Increase in ALK expression</td>
<td>Increase in ALK expression</td>
</tr>
<tr>
<td>H&amp;E</td>
<td>Tumor necrosis</td>
<td>Necrosis</td>
<td>Increase in tumor necrosis</td>
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<td>E-CC</td>
<td>Radiation sensitivity</td>
<td>Radiation Resistance</td>
<td>Increase in drug sensitivity</td>
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<tr>
<td>SNP</td>
<td>SNPs</td>
<td>SNPs</td>
<td>Increase in SNPs expression</td>
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Questions?