Course Introduction Part I
Cancer: Importance

Affects 20% of the U.S. population

- Older adults: epithelial cancers (carcinomas) of the lung, breast, colon/rectum, prostate, pancreas, other sites; cancers of the lymphoid system (lymphomas)

- Children and young adults: bone marrow (leukemias), brain, soft tissues (sarcomas), kidney (Wilms), testis

Genetic aberrations in cancer cells point to fundamental biological processes: cancer research subsumes research into basic biology
Cancer: Acquired Characteristics

• Relentless cell proliferation
• Failure of cellular differentiation
• Resistance to cell death
• Angiogenic capacity
• Metastatic potential

Molecular Safeguards
= Tumor Suppressor Genes
Carcinogens; Radiation; Viruses

Normal cell

DNA damage

Epigenetic changes

Mutations

Proto-oncogenes

Apoptosis genes

Tumor suppressor genes

Malignant neoplasm

Deficiencies in DNA repair
- **Course overview**
- **Tumor pathology**
- **Cancer Cytogenetics**
  - Oncogenes 1, 2
  - Carcinogens/DNA repair
  - Cell cycle/Rb
  - Tumor suppressors 1
  - p53
  - Tumor suppressors 2
  - Pancreatic cancer
  - Apoptosis
  - Viral carcinogenesis
  - Invasion/Metastasis
  - Metabolic pathways
  - Angiogenesis
  - Lymphoma, leukemia genetics
  - Targeted anti-cancer Rx
Carcinogens; Radiation; Viruses

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Proto-oncogenes Apoptosis genes

Tumor suppressor genes

Benign tumor

Deficiencies in DNA repair

Malignant tumor

Carcinogens; Radiation; Viruses

Epigenetic changes

Proto-oncogenes Apoptosis genes

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Benign tumor

Deficiencies in DNA repair

Malignant tumor
Cancers classified by histological criteria; histology often predicts biological behavior.

Importance of using a precise nomenclature

Cancer is a multi-stage disease. Changes in histology reflect molecular progression: benign → malignant.

Histology is the current “gold standard” for treatment and prognosis; but molecular analysis is an increasingly important adjunct...

cancer research is driven by the interplay between tumor pathology and molecular biology
Tumor Pathology

Figure 2.1a  The Biology of Cancer (© Garland Science 2007)
Diagnostic chromosomal translocations in cancers – some examples:

- **Follicular lymphoma**
  - t(14;18) chromosomal translocation: BCL2 gene activation, resistance to apoptosis

- **Chronic myelogenous leukemia**
  - t(9;22) translocation: creates the BCR-ABL fusion gene, an oncogenic tyrosine kinase

- **Ewings’s sarcoma**
  - t(11;22) translocation: creates the EWS-FLI fusion gene, oncogenic transcription factor
Proto-oncogene Activation by Chromosomal Translocation: CML

Targeted drug: Imatinib
Molecular Pathology: CML Diagnosis

FISH of interphase nuclei in CML

• BCR-ABL fusion, Ph+ chromosome
Mol. Pathology: chromosome painting

Normal cell

Breast cancer cell

Figure 1.11b The Biology of Cancer (© Garland Science 2007)
Molecular Pathology: Prognosis

N-myc gene amplification predicts survival

Percent survival

N-myc = 1

N-myc > 1

Months after diagnosis of neuroblastoma
Molecular Pathology: Microarray Data
Molecular Pathology: Tumor Progression

Cancer evolves through a progression of histological stages; each with characteristic molecular changes

- Normal Epithelium
- Dysplastic
- Early Adenoma
- Intermed. Adenoma
- Late Adenoma
- Carcinoma
- Metastasis

APC loss → K-RAS* loss → Chrom. 18 loss → p53 loss → Other changes

progression of human colon cancer
Adenomatous Polyposis Coli

**APC loss** (initiating event)

- Normal Epithelium
- Dysplastic
- **Early Adenoma**
- Intermed. Adenoma
- Late Adenoma
- Carcinoma
- Metastasis

**Chrom. 18** loss

- K-RAS*
- p53 loss
- Other changes
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**Baer**
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Weinstein
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Gelmann
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Apoptosis genes

Tumor suppressor genes

Malignant neoplasm

Deficiencies in DNA repair
Dominant Oncogenes

**Acutely transforming retroviruses**
- animal models; discovery of viral oncogenes in the 1970’s (prototype: v-src)

**Cellular ancestors of v-onc genes: “proto-oncogenes”**
- transformation assays by transfection of cultured cells; mutated HRAS gene discovered in the early 1980’s

**Multiple mechanisms of oncogene activation**
- Point mutation, chromosomal translocation, gene amplification

**Role of proto-oncogene activation in human cancers**
- N-myc gene amplification: neuroblastoma
- K-ras/B-raf mutations: colon and pancreatic CA; melanoma
- Beta-catenin activating mutations: diverse cancers
- Various oncogenes activated by chromosomal translocations: leukemias, sarcomas; some carcinomas
Discovery of Oncogenes

Figure 3.7a *The Biology of Cancer* (© Garland Science 2007)
Functions of Proto-Oncogenes

- Growth factors (tyrosine kinases) and their receptors
  - PDGFb, FGFs, IGF1 and IGF2
  - EGF receptors (erb-B family: HER2/Neu)
  - Ret proto-oncogene

- Cytoplasmic signal transduction proteins
  - Ras, Abl

- Transcription factors
  - C-Myc, N-Myc (amplification and translocations)
  - Chimeric transcription factors from fusion genes (translocations)

- Cell cycle regulators
  - Cyclin D, CDK4

- Anti-apoptotic proteins
  - Bcl-2
Proto-oncogenes and TK Signaling

Normal pathway shown here; constitutively activated by gain-of-function mutations in Ras/Raf genes and tyrosine kinase genes in cancer.
Normal fibroblasts: Ras* is not sufficient to create transformed cells; but...

Ras* + Myc (overexpressed) → transformation

Cancer is a multi-stage process
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  - Troy
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• Mouse models
  - Ludwig
• Angiogenesis
  - Kitajewski
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  - Pasqualucio, Ferrando
• Prostate cancer
  - Abate-Shen
• Targeted anti-cancer Rx
  - Gelmann
Carcinogens; Radiation; Viruses

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Proto-oncogenes  Apoptosis genes  Tumor suppressor genes

Genetic instability

Malignant neoplasm

Deficiencies in DNA repair
Carcinogens and DNA Damage

Preventable causes of the common adult cancers

• Tobacco smoking (lung, oral cavity)
• Dietary fat (colon, breast)
• Sunlight/UV (skin)
• Occupational carcinogens (asbestos: mesothelioma)

Mechanisms of DNA damage

• Carcinogen activation
• Carcinogen targets (DNA adducts; mutations)
• Spontaneous DNA strand breakage
DNA damage in S-phase

Bidirectional Replication

Repaired by homologous recombination

Rothstein et al., G&D 2000
Topics in DNA repair

- Repair of mutations: nucleotide excision repair, mismatch repair
- Repair of DNA strand breaks: homologous recombination, non-homologous end-joining
- Genetic susceptibility to cancer based on deficient DNA repair
- Genetic instability in cancer cells
DNA Damage Sensors are Tumor Suppressors

DNA damage

- p53
  - p21
    - Cyclin/cdk
      - Rb
      - E2F1
- ATM/ATR
- MRN
- Chk1,2
  - cdc25
  - cyclinB/cdk1

G1 → S → G2 → M
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• **Cell cycle/Rb**

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Cell Cycle

Malignant neoplasm

Deficiencies in DNA repair
Tumor Suppressors/Oncogenes at the G1-S Transition

- Rb (active suppressor)
- Rb~P (inactive)
- CyclinD-Cdk

G1-S transition

Cell proliferation

G1 → S → G2 → M

G0
S-phase genes activated (Cyclin-E)

S-phase genes repressed

CyclinD/Cdk4, 6

p16

Rb~P

DP1

Rb

E2F

DP1

E2F
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Pasqualuci, Ferrando
Gelmann
TS Gene Loss: “Two-hit” Model

Familial form
inherited/multifocal

Sporadic form
not inherited/unifocal

1-hit; rate: $10^{-5}$

2-hits; overall rate: $10^{-12}$

Cells of child
(Chr. 13)

Retinal cells

Retinoblastoma(s)
## Functional Diversity of TS Genes

<table>
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<tr>
<th>Gene/Protein</th>
<th>Function</th>
<th>Somatic Mutations</th>
<th>Germline Mutations</th>
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<tr>
<td>E-cadherin</td>
<td>Cell adhesion</td>
<td>Gastric CA</td>
<td>Familial gastric CA</td>
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<tr>
<td>NF-1</td>
<td>Ras signaling</td>
<td>Schwannoma</td>
<td>Neurofibromatosis 1</td>
</tr>
<tr>
<td>NF-2</td>
<td>Cytoskeletal</td>
<td>Meningioma, schwannoma</td>
<td>Neurofibromatosis 2</td>
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<tr>
<td>PTEN</td>
<td>Phosphatase</td>
<td>Various cancers</td>
<td>Cowden syndrome</td>
</tr>
<tr>
<td>APC</td>
<td>Wnt signaling</td>
<td>Colon CA, others</td>
<td>Adenomatous polyposis coli</td>
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<tr>
<td>Rb</td>
<td>Cell cycle</td>
<td>RB, breast CA, other</td>
<td>Familial retinoblastoma</td>
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<tr>
<td>p53</td>
<td>Cell cycle/apoptosis</td>
<td>Many; high-grade cancers</td>
<td>Li-Fraumeni syndrome</td>
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<tr>
<td>WT1</td>
<td>Transcription</td>
<td>rare</td>
<td>WAGR, Deny-Drash (Wilms tumor)</td>
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<tr>
<td>BRCA1, 2</td>
<td>DNA repair</td>
<td>rare</td>
<td>Familial breast/ovarian CA</td>
</tr>
<tr>
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The PTEN gene encodes a phosphatase that plays a crucial role in regulating cell growth and survival. Somatic mutations in PTEN can occur in various cancers, while germline mutations are associated with Cowden syndrome. The diagram illustrates the interaction of PI3K, PIP3, and Akt/PKB, which are affected by PTEN mutations.
Central TS Proteins: Rb and p53

- **Rb**
  - Restrains cell proliferation in normal tissues
    - Rb protein suppresses transcription of S-phase genes
    - Promotes cell differentiation

- **p53**
  - Activates a “checkpoint” in cells that have undergone DNA damage, pathological proliferation, or hypoxic stress
    - p53 activates transcription of specific target genes after binding directly to DNA
    - Leads to growth-arrest or apoptosis
Normal cell

DNA damage

Cell with p53 mutation/loss

p53 activates downstream targets

Growth arrest

Successful damage repair

Normal cell

Unsuccessful repair

Apoptosis (cell death)

Accumulation of mutations; Tumor progression

No response

Apoertotic pathway disabled; persistent DNA damage; genomic instability
Central Interactions: p53 and Rb

- **p14Arf**
- **MDM2**
- **E2F-1**
- **p53**
- **CyclinD/Cdk4, 6**
- **p16**

- **Rb**
  - phosphorylation

- **transcriptional activation**

- **ubiquitin-mediated proteolysis**
Developmental Regulators can be Tumor Suppressors

- TGFβ
- HH
- WNT
DNA Repair Genes Are TS Genes

DNA mismatch repair defective in hereditary non-polyposis colon cancer (HNPCC)

• *MLH1, MSH2* genes

DNA nucleotide excision repair defective in xeroderma pigmentosum (XP): skin cancers

• at least seven different XP genes

DNA damage sensing defective in ataxia telangiectasia (AT): leukemias

• *ATM* gene

• *BRCA1* and *BRCA2* also fit into this category of TS genes; role in homologous recombination
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Deficiencies in DNA repair
Control of Apoptosis

- **Bcl-2 family proteins**
  - modulators of the apoptosis set-point
  - control mitochondrial integrity; cytochrome C release

- **Caspases**
  - effectors of cell death; activated in a protease cascade

- **IAP-related proteins**
  - endogenous caspase inhibitors

- **Input from signaling pathways**
  - TNF receptor family
  - p53 tumor suppressor
Pro-survival vs. Pro-apoptotic Bcl2-family (BH3-domain) proteins
Examples: BCL-2 versus BAX

**BCL2**: anti-apoptotic gene product activated by the t(14;18) chromosomal translocation in low-grade B-cell lymphoma
- founding member of a family of proteins, some anti-apoptotic and others pro-apoptotic
- control mitochondrial membrane permeability

**BAX**: pro-apoptotic member of the BCL-2 family
- forms pores in mitochondrial outer membranes
- transcriptional target (direct and indirect) for activation by p53 in some cell types: p53 activation kills cells by inducing apoptosis
Role of mitochondrial permeability in apoptotic pathways
TP53: apoptotic sentinel system

- DNA damage
- p53
- ARF
- Bax
- AKT
- Bcl2/Bcl-X_L
- Cytochrome C
- CASPASES
- Apoptosis

Myc
Ras*

Trophic growth factors (IGF’s; PDGF)
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Tumor viruses

Normal cell

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Viral carcinogenesis

- **Retroviruses**: important in animal models

- **DNA tumor viruses**: induce several specific human cancers
  - Burkitt lymphoma -- EBV
  - Adult T-cell leukemia – HTLV (RNA virus)
  - Kaposi’s sarcoma – KSHV/HHV8
  - Cervical carcinoma – HPV (subtypes)
  - Hepatocellular carcinoma -- HBV, HCV

- **Mechanisms -- viral subversion of oncogene/tumor suppressor pathways**
  - HPV-E7, HPV-E6 and their interaction with RB and p53
  - KSHV/HHV8 genome -- multiple oncogenic proteins
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Cancer Invasion
Cancer Metastasis
Ability of tumor cells to breach basement membranes, to travel in the bloodstream or lymphatics to distant sites, and to colonize these sites to form metastatic tumors.

Multiple genetic events required for the metastatic phenotype

- Loss of cell-cell adhesion (loss of cadherins, integrins)
- Secretion of proteases (MMP-2/collagenase)
- Increased cell motility (hepatocyte growth factor); epithelial → mesenchymal transition (EMT)
- Other as yet unknown genetic events
Steps in Invasion and Metastasis

- primary tumor formation
- localized invasion
- intravasation (interaction with platelets, lymphocytes, and other blood components)
- transport through circulation
- arrest in microvessels of various organs
- extravasation
- formation of a micrometastasis
- colonization – formation of a macrometastasis

Figure 14.4 The Biology of Cancer (© Garland Science 2007)
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Gelman
Tumor angiogenesis

Essential for growth of neoplasms beyond 2 mm in diameter

Ischemic central area:
Hypoxia $\rightarrow$ p53 activation
$\rightarrow$ apoptosis $\rightarrow$ selection

Angiogenesis

Vascularized tumor with outgrowth of p53-null cells
Tumor angiogenesis: promotion and inhibition

Angiogenic peptides

• VEGF, bFGF, PDGF others: secreted by tumor cells

• Induced by over-expression of proto-oncogenes (i.e. c-Myc, Ras*)

Anti-angiogenic Rx

• Peptides: angiostatin, endostatin

• VEGF inhibitors: Avastin/Bevacizumab antibody prolongs survival in colon CA
Unique aspects of tumor vs. normal angiogenesis
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**Pancreatic cancer**
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• Viral carcinogenesis
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**Lymphoma, leukemia**
• Targeted anti-cancer Rx

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B-cell Lymphoma: Comprehensive Analysis of a Human Cancer

Lymphoma pathogenesis: integrating histopathology and molecular biology

- **Burkitt lymphoma**: t(8;14) C-Myc dysregulation
- **Follicular lymphoma**: t(14;18) Bcl-2 dysregulation
- **Large cell lymphoma**: t(3;various) Bcl-6 dysregulation

Basic principals of cancer biology can be formulated, but each type of cancer has a specific molecular profile, related to the stage of development of its precursor cells
Pancreatic Cancer

Pathogenesis
- K-ras gain-of-function mutations
- p53 loss-of-function mutations
- Additional tumor suppressor losses (*p16, DPC4/SMAD4*)

Special issues in therapy
- Highly drug-resistant
- Stroma-rich (cancer-associated fibroblasts; macrophages)
- Imaging for dx and screening?
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**Targeted anti-cancer Rx**

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Gelmann
Need for better targeted anti-cancer therapies
Early example: ATRA for treating acute promyelocytic leukemia

Figure 16.6a The Biology of Cancer (© Garland Science 2007)
Targeted Therapies: examples in Lymphoma/Leukemia

- **Monoclonal Antibodies**
  - *Rituximab* (anti-CD20)
    - Now standard Rx for B-cell lymphoma

- **Tyrosine Kinase Inhibitors**
  - *Imatinib* (Bcr-Abl kinase inhibitor)
    - Now standard Rx for CML
    - New kinase inhibitors for salvage Rx in patients whose leukemias become resistant