

**RADIATION BIOLOGY SYLLABUS**  
**2007-2008**

**Time:** Wednesday, 8:00-9:00 am

**Place:** Cancer Center Conference Room: G-3111

**Instructors:** Peter Keng, Ph.D. 5-6332 peter\_keng@urmc.rochester.edu  
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<b>Date</b>	<b>Instructor</b>	<b>Topics</b>
9/12/07	Bruce Fenton	Interaction of Radiation with Biological Systems Definition of ionizing radiation Types of ionizing and non-ionizing radiation Definition of LET and quality of ionizing radiation Generation of free radicals Direct and indirect action of ionizing radiation
9/19/07	Peter Keng	Molecular Mechanisms of DNA Damage Assays for DNA damage neutral and alkaline elution, pulsed field electrophoresis, comet, plasmid-based assay Types of DNA lesions and numbers per cell/Gy Multiply damaged sites Single lethal hits and accumulated damage (inter- and intra-track) Role of oxygen in the generation of damage Role of LET and radiation quality
9/26/07	Peter Keng	Molecular Mechanisms of DNA Repair Different types of DNA repair mechanisms Mechanisms involved in repair of base damage and DNA single strand breaks Mechanisms involved in repair of double strand breaks Homologous recombination Non-homologous end joining

10/3/07 Peter Keng

### Chromosome and Chromatid Damage

#### Assays

Conventional smears, banding, comparative genomic hybridization (CGH) and FISH

#### Dose response relationships

Use of peripheral blood lymphocytes in in vivo dosimetry

Stable and unstable chromatid and chromosome aberrations

Human genetic diseases that affect DNA repair, fragility, and radiosensitivity

10/10/07 Jackie Williams

### Mechanisms of Cell Death

#### Apoptotic death

Developmental and stress induced

Morphological and biochemical features of apoptosis

Molecular pathways leading to apoptosis

Radiation-induced apoptosis in normal tissues and tumors

#### Necrotic death

Morphological, pathological, and biochemical features of necrosis

#### Mitotic death following irradiation

Types of mitotic death - mitotic catastrophe vs. apoptosis

Cell division post-radiation and time to clonogenic cell death

#### Radiation-induced senescence

10/17/07 Bruce Fenton

### Cell and Tissue Survival Assays

#### In vitro clonogenic assays

Calculation of plating efficiency and surviving fraction

#### In vivo clonogenic assays

Bone marrow stem cell assays, jejunal crypt stem cell assay, skin clones, kidney tubules

#### Functional endpoints

10/24/07	Bruce Fenton	<p>Models of Cell Survival</p> <ul style="list-style-type: none"> <li>Random nature of cell killing and Poisson statistics</li> <li>Doses for inactivation of viruses, bacteria, and eukaryotic cells after irradiation</li> <li>Single hit, multi-target models of cell survival</li> <li>Two component models</li> <li>Linear quadratic model</li> <li>Calculations of cell survival with dose</li> <li>Effects of dose, dose rate, cell type</li> </ul>
10/31/07	ASTRO meeting	No class
11/07/07	Bruce Fenton	<p>Modifiers of Cell Survival: Linear Energy Transfer</p> <ul style="list-style-type: none"> <li>Definition of RBE</li> <li>RBE as a function of LET</li> <li>Effect of LET on cell survival</li> <li>Endpoint dependence of RBE</li> <li>Effects of dose, dose rate, cell type</li> </ul>
11/14/07	Bruce Fenton	<p>Modifiers of Cell Survival: Oxygen Effect</p> <ul style="list-style-type: none"> <li>Definition of OER</li> <li>Effect of dose, dose rate, cell type</li> <li>OER as a function of LET</li> <li>Impact of O<sub>2</sub> concentration</li> <li>Time scale of oxygen effect</li> <li>Mechanisms of oxygen effect</li> </ul>
11/21/07		Thanksgiving Holiday
11/28/07	Jackie Williams	<p>Modifiers of Cell Survival: Repair</p> <ul style="list-style-type: none"> <li>Sub-lethal damage repair</li> <li>Potentially lethal damage repair</li> <li>Half-time of repair</li> <li>Effects of dose, dose rate, and cell type</li> <li>Effect of dose fractionation</li> <li>Effect of LET</li> </ul>

Effects of oxygen/hypoxia

12/5/07	Bruce Fenton	Solid Tumor Assay Systems TD50 limiting dilution assay Tumor regrowth assay TCD50 tumor control assay Lung colony assay In vitro/in vivo assay Monolayers vs. 3-D spheroid cultures
12/12/07	Bruce Fenton	Tumor Hypoxia and Therapeutic Resistance Tumor vasculature Hypoxia in tumors Measurement of hypoxia Transient and chronic hypoxia Reoxygenation following irradiation Relevance of hypoxia in radiation therapy Hypoxia as a factor in tumor progression Cellular composition of tumors
12/19/07	Bruce Fenton	Angiogenesis and Antiangiogenic Strategies Angiogenesis Hypoxia-induced signal transduction
12/26/0		Christmas/New Year Holiday
		2008
01/09/06	Peter Keng	Cell and Tissue Kinetics Cell cycle Measurement of cell cycle parameters by 3H-thymidine Measurement by flow cytometry, DNA staining and BrdU Cell cycle synchronization techniques and uses

- Effect of cell cycle phase on radiosensitivity
- Cell cycle arrest and redistribution following irradiation
- Cell cycle checkpoints, cyclins, cyclin dependent kinase inhibitors
- Tissue kinetics
  - Stem, progenitor, differentiated cells
  - Growth fraction
  - Cell loss factor
  - Volume doubling times
  - Tpot
- Growth kinetics of clinical and experimental tumors

01/16/08 Peter Keng

- Molecular Signaling
  - Receptor/ligand interactions
  - Phosphorylation/dephosphorylation reactions
  - Transcriptional activation
  - Radiation-induced gene expression
    - Gene expression profiling
    - Proteomics
  - Radiation-induced signals
    - DNA damage response
    - Non-DNA damage responses
  - Cell survival and death pathways

01/23/08 Peter Keng

- Cancer
  - Cancer as a Genetic Disease
  - Oncogenes
  - Tumor suppressor genes
  - Telomeric changes in cancer
  - Epigenetic changes in cancer
    - e.g hypermethylation
  - Multi-step nature of carcinogenesis
  - Repair genes in carcinogenesis
  - The metastatic process
  - Molecular profiling and staging of cancer
    - Gene expression profiling
    - Proteomics
  - Signaling abnormalities in cancer
  - Effects of signaling abnormalities on radiation responses

Prognostic significance of tumor characteristics  
Therapeutic targets and strategies for intervention  
Monoclonals, small molecule inhibitors, gene  
therapy

01/30/08 Jackie Williams

Total Body Irradiation  
Prodromal radiation syndrome  
Cerebrovascular syndrome  
Gastrointestinal syndrome  
Hematopoietic syndrome  
Mean lethal dose and dose/time responses  
Immunological effects  
Assessment and treatment of radiation accidents or  
terrorism  
Bone marrow transplantation

02/06/08 Jackie Williams

Clinically Relevant Normal Tissue Responses to Radiation  
Responses in skin, oral mucosa, oropharyngeal and  
esophageal mucous membranes, salivary glands, bone  
marrow, lymphoid tissues, bone and cartilage, lung,  
kidney, testis, ovary, eye, central and peripheral  
nervous tissues  
Scoring systems for tissue injury  
LENT and SOMA

02/13/06 Jackie Williams

Mechanisms of Normal Tissue Radiation Responses (I)  
Differences between slowly and rapidly proliferating  
tissues  
Molecular and cellular responses in slowly and rapidly  
proliferating tissues  
Cytokines and growth factors  
Regeneration  
Remembered dose  
Functional subunits

02/20/08 Jackie Williams

Mechanisms of Normal Tissue Radiation Responses (II)  
Mechanisms underlying clinical symptoms  
Latency

Inflammatory changes  
Cell killing  
Radiation fibrosis  
Vascular damage  
Volume effects  
Pharmacological modification of normal tissue responses

02/27/08 Jackie Williams

Therapeutic Ratio

Tumor control probability (TCP) curves  
Calculation of TCP  
Factors affecting shape and slope of TCP curves  
Influence of tumor repopulation/regeneration on TCP  
Normal tissue complication probability (NTCP) curves  
Influence of normal tissue regeneration on responses  
Response of subclinical disease  
Causes of treatment failure  
Factors determining tissue tolerance  
Normal tissue volume effects  
Dose-volume histogram analysis  
Effect of adjuvant or combined treatments on therapeutic ratio

03/05/08 Jackie Williams

Time, Dose, Fractionation (1)

The 4 R's of fractionation  
The radiobiological rationale behind dose fractionation  
The effect of tissue type on the response to dose fractionation

03/12/08 Jackie Williams

Time, Dose, Fractionation (2)

Effect of tissue/tumor types on a/b ratios  
Quantitation of multifraction survival curves  
BED and isoeffect dose calculations

03/19/08 Jackie Williams

Brachytherapy

- Dose rate effects (HDR and LDR)
- Choice of isotopes
- Interstitial and intracavitary use
- Radiolabeled antibodies
- BED and Isoeffective dose calculations

03/26/08\*     Bruce Fenton     \*If it is removed, one of my lectures will replace it.  
Radiobiological aspects of alternative dose delivery systems  
Protons, high LET sources, BNCT  
Stereotactic radiosurgery/radiotherapy, IMRT,  
IORT  
Dose distributions and dose heterogeneity

04/02/08     Jackie Williams  
Chemotherapeutic agents and radiation therapy  
Classes of agents  
Mechanisms of action  
The oxygen effect in chemotherapy  
Multiple drug resistance  
Interactions of chemotherapeutic agents with radiation  
therapy (chemoradiation therapy)  
Photodynamic therapy

04/9/08     Jackie Williams  
Radiosensitizers, Bioreductive drugs, Radioprotectors  
Tumor radiosensitization  
Halogenated pyrimidines, nitroimidazoles  
Hypoxic cell cytotoxins  
tirapazamine  
Normal tissue radioprotection  
Mechanisms of action, sulfhydryl compounds,  
WR series, dose reduction factor (DRF)  
Biological response modifiers

04/16/08     Peter Keng  
Hyperthermia  
Delivery modalities  
Cellular response to heat  
Heat shock proteins  
Thermotolerance  
Response of tumors and normal tissues to heat

## Combination with radiation therapy

04/23/08	Peter Keng	<p>Radiation Carcinogenesis</p> <ul style="list-style-type: none"><li>Initiation, promotion, progression</li><li>Dose response for radiation-induced cancers</li><li>Importance of age at exposure and time since exposure</li><li>Malignancies in prenatally exposed children</li><li>Second tumors in radiation therapy patients</li><li>Effects of chemotherapy on incidence</li><li>Risk estimates in humans</li><li>Calculations based on risk estimates</li></ul>
04/30/08	Peter Keng	<p>Heritable Effects of Radiation</p> <ul style="list-style-type: none"><li>Single gene mutation</li><li>Chromosome aberrations</li><li>Relative vs. absolute mutation risk</li><li>Doubling dose</li><li>Heritable effects in humans</li><li>Risk estimates for hereditary effects</li></ul>
05/07/08	Peter Keng	<p>Radiation Effects in the Developing Embryo</p> <ul style="list-style-type: none"><li>Intrauterine death</li><li>Congenital abnormalities and neonatal death</li><li>Microcephaly, mental retardation</li><li>Growth retardation</li><li>Dose, dose rate, and stage in gestation</li><li>Human experience of pregnant women exposed to therapeutic dose</li></ul>
05/14/08	Peter Keng	<p>Radiation Protection</p> <ul style="list-style-type: none"><li>General philosophy</li><li>Stochastic and deterministic effects</li><li>Effective dose - relative weighting factors</li><li>Equivalent dose – tissue weighting factor</li><li>Committed dose</li><li>Collective exposure dose</li><li>Dose limits for occupational and public exposure</li></ul>

## ICRP and NCRP

05/21/06	Peter Keng	Review
05/28/08	Peter Keng	Review
06/04/08	Peter Keng	Review
06/11/08	Peter Keng	Internal Examinations