

**RADIATION-CANCER BIOLOGY SYLLABUS  
2009-2010**

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

**Place:** G-0712, Cooper Conference Room, J. P. Wilmot Cancer Center

**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>
09/09/09	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
09/16/09	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  Role of LET and radiation quality
09/23/09	Bruce Fenton	Models of Cell Survival Random nature of cell killing and Poisson statistics Doses for inactivation of viruses, bacteria, and eukaryotic cells after irradiation Single hit, multi-target models of cell survival Two component models Linear quadratic model Calculations of cell survival with dose Effects of dose, dose rate, cell type
09/30/09	Bruce Fenton	Modifiers of Cell Survival: Linear Energy Transfer Definition of RBE RBE as a function of LET

Effect of LET on cell survival  
Endpoint dependence of RBE  
Effects of dose, dose rate, cell type

10/07/09 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

10/14/09 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

10/21/09 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

10/28/09	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
11/04/09	ASTRO meeting	No class
11/11/09	Jackie Williams	Modifiers of Cell Survival: Repair Sub-lethal damage repair Potentially lethal damage repair Half-time of repair Effects of dose, dose rate, and cell type Effect of dose fractionation Effect of LET Effects of oxygen/hypoxia
11/18/09	Bruce Fenton	Modifiers of Cell Survival: Oxygen Effect Definition of OER Effect of dose, dose rate, cell type OER as a function of LET Impact of O <sub>2</sub> concentration Time scale of oxygen effect Mechanisms of oxygen effect 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
11/25/09	Thanksgiving Holiday	
12/02/09	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
12/09/09	Bruce Fenton	Angiogenesis and Antiangiogenic Strategies Angiogenesis Hypoxia-induced signal transduction
12/16/09	Peter Keng	Cell Cycle 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
12/23/09		Christmas/New Year Holiday
12/30/09		Christmas/New Year Holiday
Year 2010		
01/13/10	Peter Keng	Tissue Kinetics Stem, progenitor, differentiated cells Growth fraction Cell loss factor Volume doubling times Tpot Growth kinetics of clinical and experimental tumors
01/20/10	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
01/27/10	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

02/03/10

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

02/10/10

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

02/17/10

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

- 02/24/10 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
- 03/03/10 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
- 03/10/10 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
- 03/17/10 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
- 03/24/10 Jackie Williams (Joy Anderson/Alan Katz)  
Brachytherapy  
Dose rate effects (HDR and LDR)  
Choice of isotopes  
Interstitial and intracavitary use

Radiolabeled antibodies  
BED and Isoeffective dose calculations

- 03/31/10 Jackie Williams (Mike Milano)  
Radiobiological aspects of alternative dose delivery systems  
Protons, high LET sources, BNCT  
Stereotactic radiosurgery/radiotherapy, IMRT, IORT  
Dose distributions and dose heterogeneity
- 04/07/10 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
- 04/14/10 Jackie Williams  
Radiosensitizers, Bioreductive drugs, Radioprotectors  
Tumor radiosensitization  
Halogenated pyrimidines, nitroimidazoles  
Hypoxic cell cytotoxins, e.g. tirapazamine  
Normal tissue radioprotection  
Mechanisms of action, sulfhydryl compounds, WR  
series, dose reduction factor (DRF)  
Biological response modifiers
- 04/21/10 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
- 04/28/10 Peter Keng  
Radiation Carcinogenesis  
Initiation, promotion, progression  
Dose response for radiation-induced cancers  
Importance of age at exposure and time since exposure  
Malignancies in prenatally exposed children  
Second tumors in radiation therapy patients  
Effects of chemotherapy on incidence

Risk estimates in humans  
Calculations based on risk estimates

05/05/10	Peter Keng	Heritable Effects of Radiation Single gene mutation Chromosome aberrations Relative vs. absolute mutation risk Doubling dose Heritable effects in humans Risk estimates for hereditary effects
05/12/10	Peter Keng	Radiation Effects in the Developing Embryo Intrauterine death Congenital abnormalities and neonatal death Microcephaly, mental retardation Growth retardation Dose, dose rate, and stage in gestation Human experience of pregnant women exposed to therapeutic dose
05/19/10	Peter Keng	Radiation Protection General philosophy Stochastic and deterministic effects Effective dose - relative weighting factors Equivalent dose - tissue weighting factor Committed dose Collective exposure dose Dose limits for occupational and public exposure ICRP and NCRP
05/26/10	Peter Keng	Review
06/02/10	Peter Keng	Review
06/09/10	Peter Keng	Review
06/16/10	Peter Keng	Internal Examinations