2024 Radiation and Cancer Biology Lecture Series for Radiation Oncology Residents

Molecular and Cellular Radiation and Cancer Biology:

Lecture 01. Introduction to Radiation and Cancer Biology
Includes: Recommended Biology Textbooks and Review Articles
Current ABR Content Outline and Topic Weightings
Lecture 02. Radiation Chemistry
Lecture 03. DNA Damage Response and DNA Repair
Lecture 04. Genetic, Mutagenic, Cytogenetic and Epigenetic Effects
Lecture 05. Mechanisms of Cell Death
Lecture 06. Cell Survival and Tissue Dose Response Curves
Lecture 07. Sublethal and Potentially Lethal Damage Recovery
Lecture 08. Cell Cycle Regulation and Radiation Effects
Lecture 09. RBE and LET Effects; High LET Radiotherapy
Lecture 10. Radiation Carcinogenesis, Risk Assessment and Safety

Clinical/Translational Radiation and Cancer Biology:

Lecture 11. The Oxygen Effect and Tumor Hypoxia
Lecture 12. Radiosensitizers, Radioprotectors and Bioreductive Drugs
Lecture 13. Tumor Angiogenesis and Metastasis
Lecture 14. Immuno-Oncology
Lecture 15. Mechanisms of Drug Resistance
Lecture 16. Normal and Tumor Cell Kinetics
Lecture 17. Early and Late Effects in Normal Tissues
Lecture 18. Normal Tissue Tolerance
Lecture 19. The Four R's of Radiotherapy
Lecture 20. The Linear-Quadratic Isoeffect Model

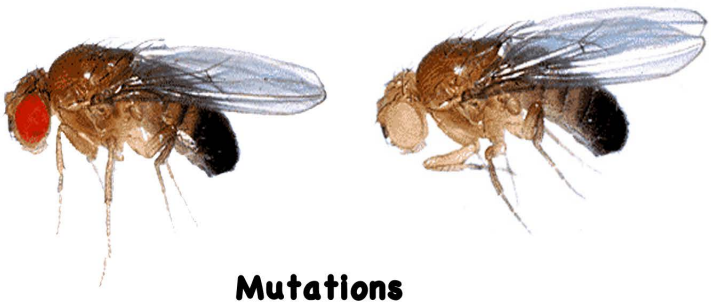
Note: New email address for Dr. Zeman = madam_curie@mac.com

WHAT IS RADIOBIOLOGY?

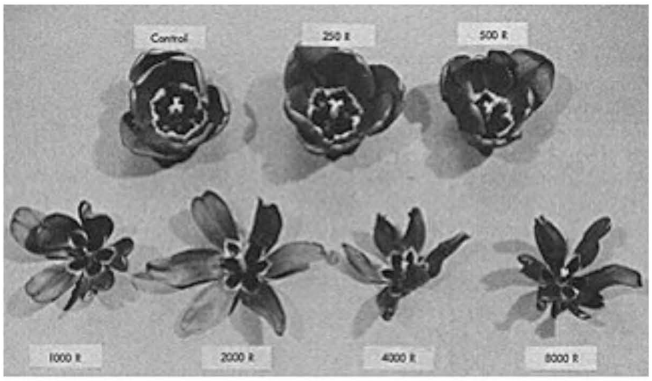
"THE STUDY OF THE EFFECTS OF ELECTROMAGNETIC RADIATION ON BIOLOGICAL SYSTEMS."

EFFECTS

Red Eye (Wild Type) White Eye (Mutant)

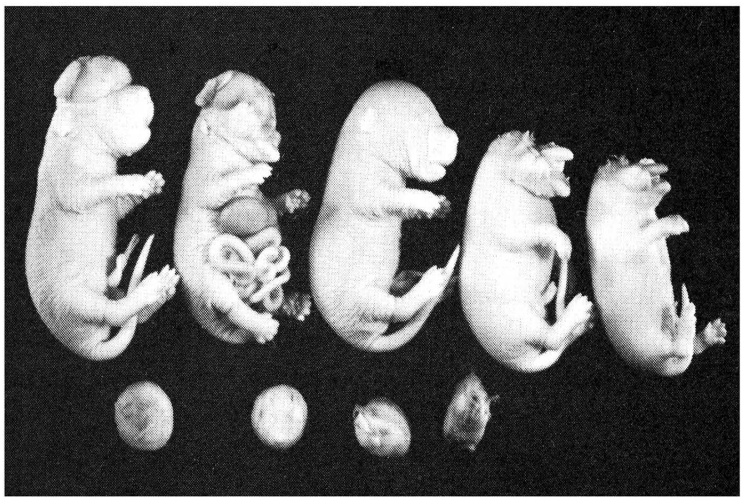


Mutations

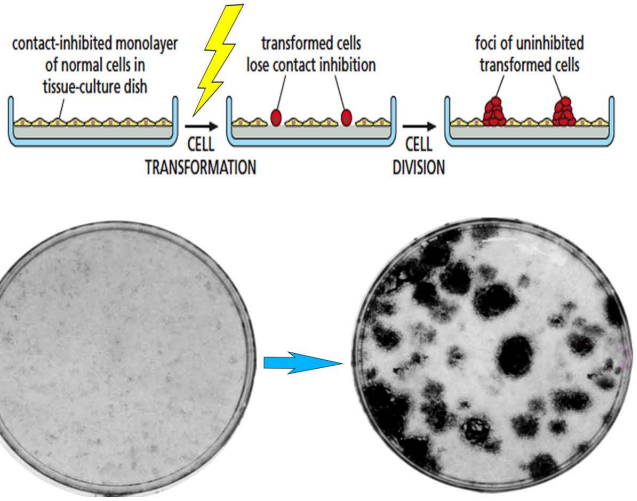


Growth Delay/Disturbance

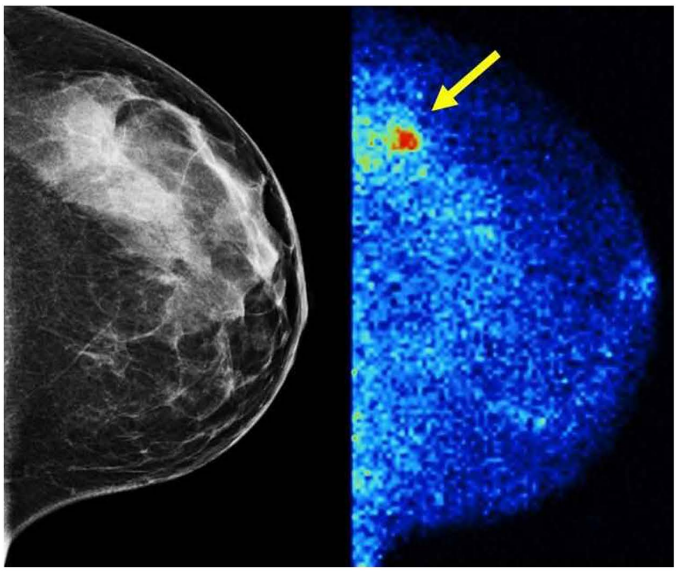
Whole-Body Radiation Syndromes



Teratogenesis

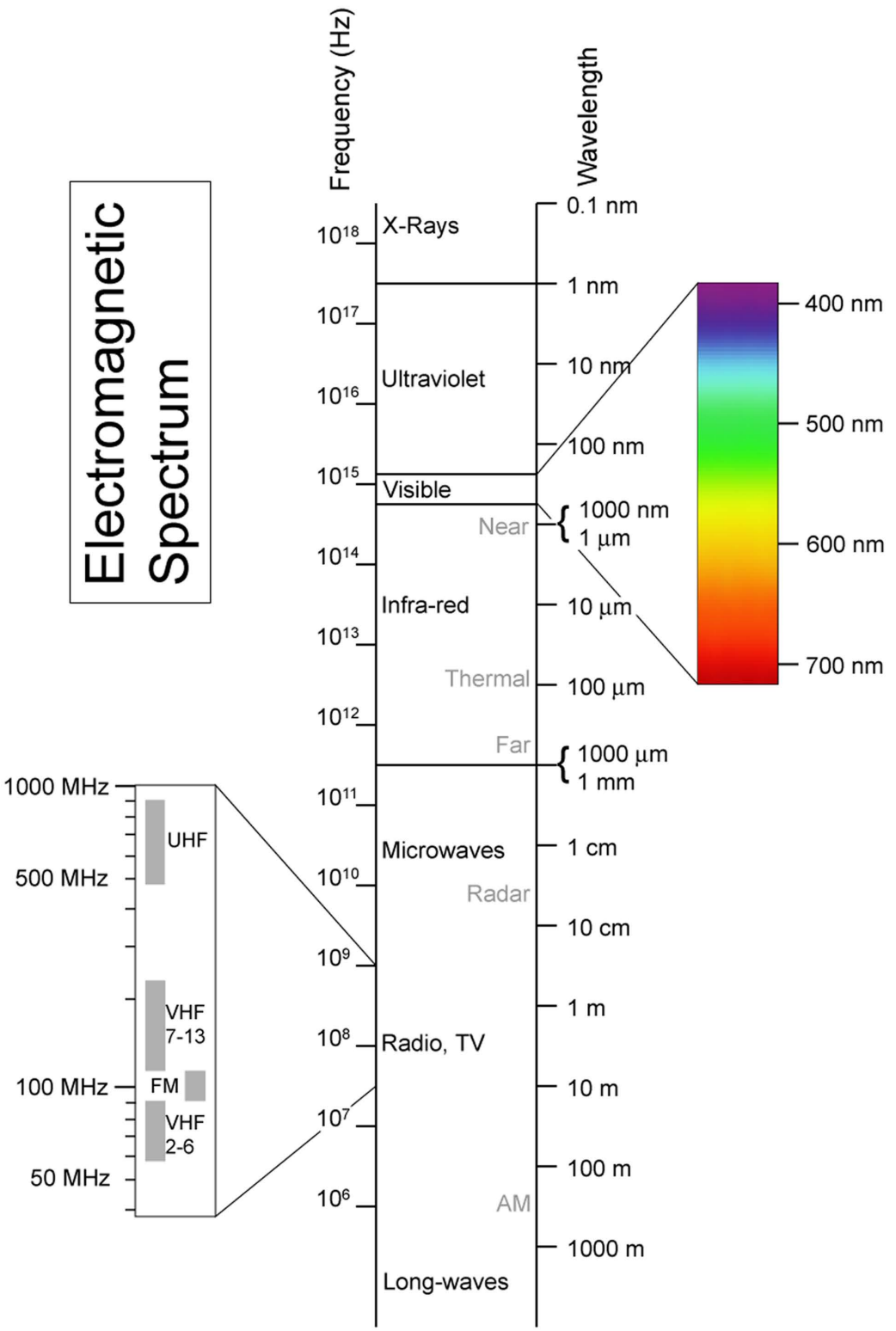


Neoplastic Transformation

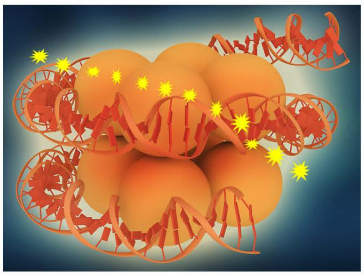


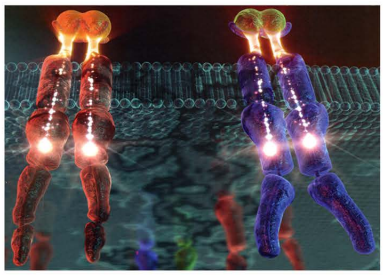
Carcinogenesis

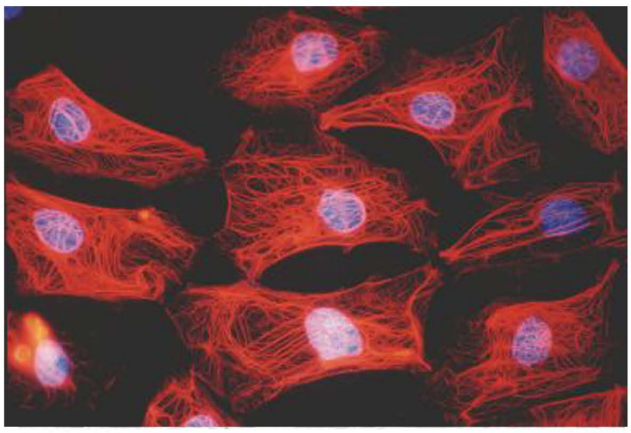
ELECTROMAGNETIC RADIATION



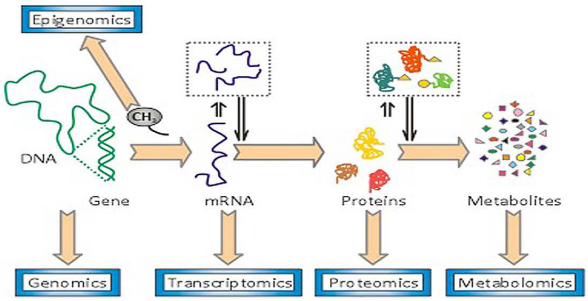
BIOLOGICAL SYSTEMS







Cells in Culture



Subcellular
(e.g., DNA damage and repair, signal transduction, 'omics, etc.)

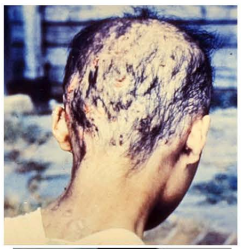
Laboratory Rodents

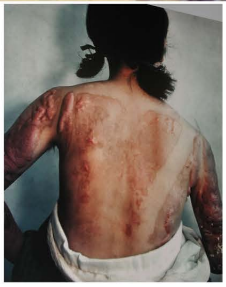
C. elegans

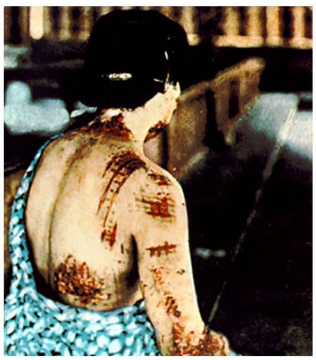
Fruit Fly

Zebrafish

Arabidopsis



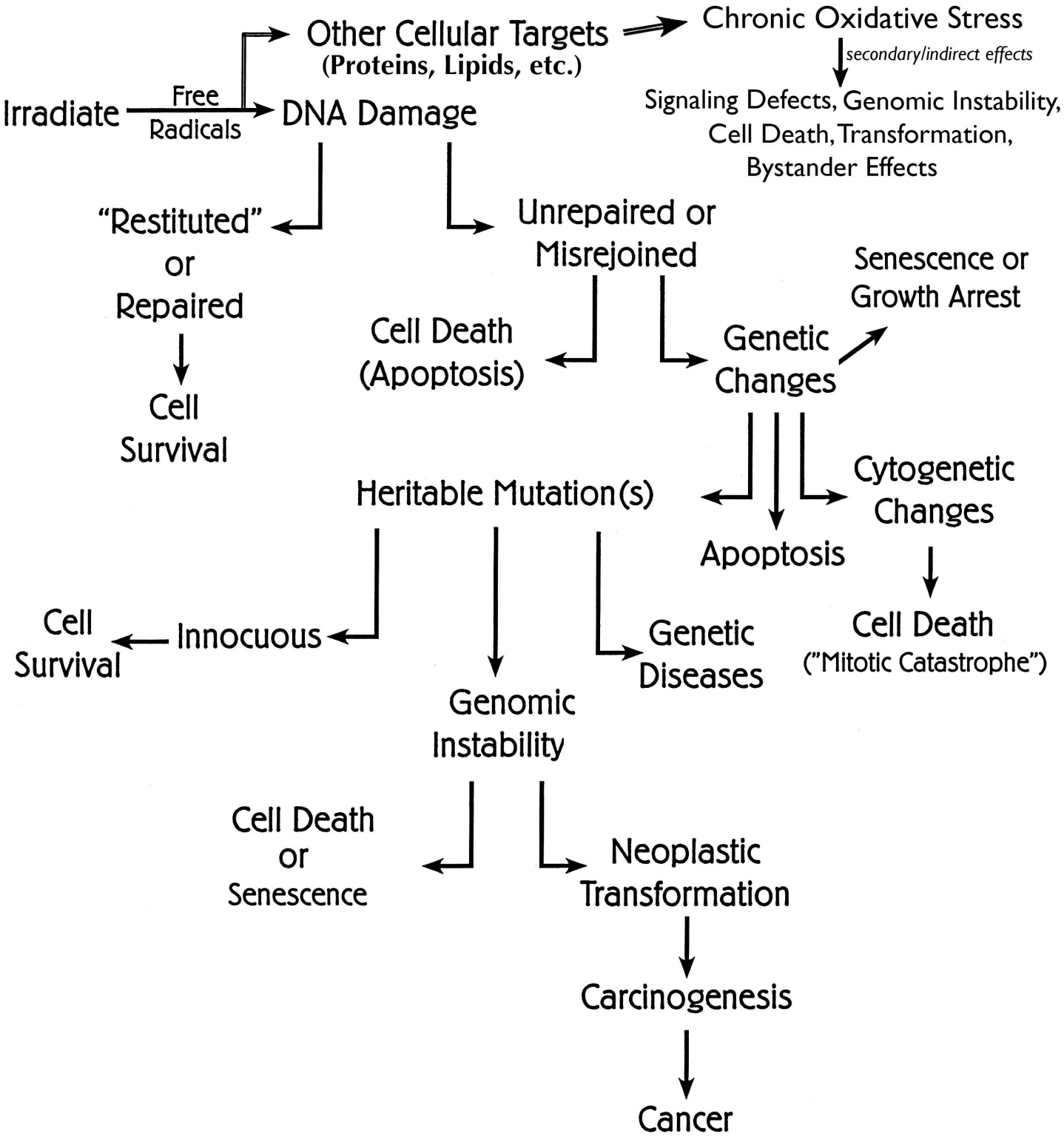




Us
(Japanese A-Bomb Survivors)

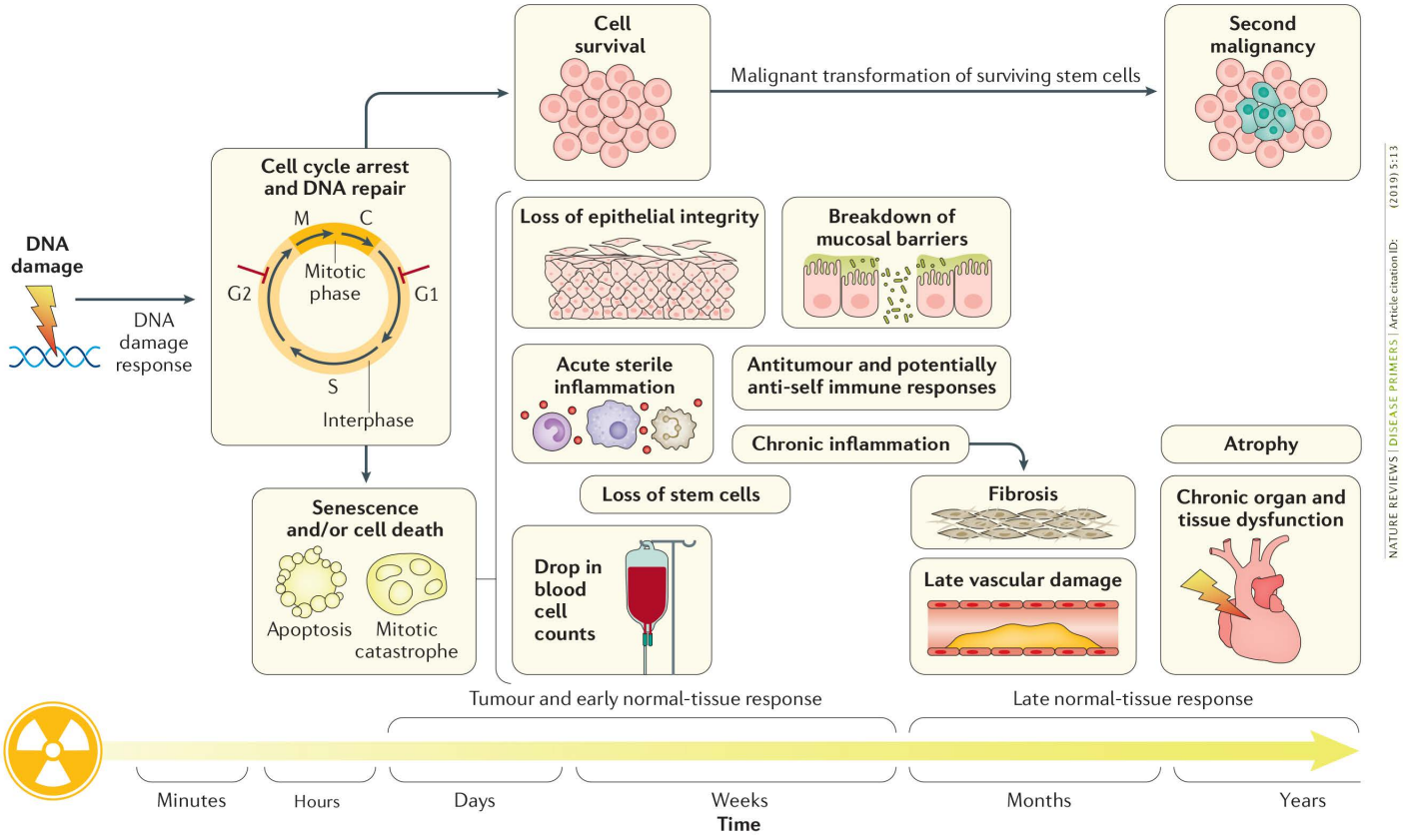
Ecosystems
(Bikini Islands)

The Flow Chart of Radiobiology



The Flow Chart of Radiobiology Part II

The flow chart of radiobiology only considers *cellular* responses, but what happens at the tissue and organ levels once cells are damaged or killed?



The loss of cells precipitates repeat cycles of inflammation and the generation of reactive oxygen species which, when combined with damage to the tissue's vasculature, lead to organ dysfunction, ultimately resulting in the kinds of clinical toxicities observed during and after radiation therapy.

These tissue-level toxicities (in both tumors and normal tissues) develop over time as part of a complicated process that depends critically on interactions between different types of cells in the tissue and the tissue's microenvironment in general.

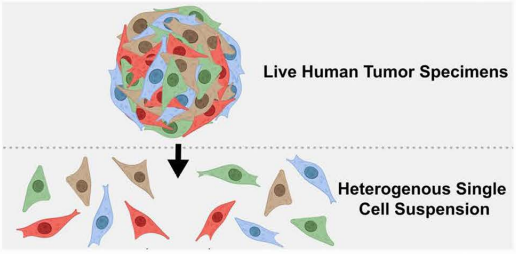
"Modifiers" of the Radiobiology Flow Chart:

Tumor Heterogeneity

Cancer is a heterogeneous and continuously evolving disease. When pathologists first looked at human cancers under the microscope, they saw that differing histologic appearances could define distinct subtypes of cancers from the same primary site of origin. These histology-based definitions of cancer subtypes have been modified and refined over time to elucidate both prognosis and prediction of response to specific treatments. Molecular data have revealed how radically different cancers from one primary site can be, and using this information, cancer classification systems have been revolutionized.

However, heterogeneity in cancer is not limited to differences between different patients, but also occurs within a single patient. This heterogeneity at the molecular, cellular and tumor levels bedevils clinical cancer care because it allows cancers to evolve and evade available therapeutics.

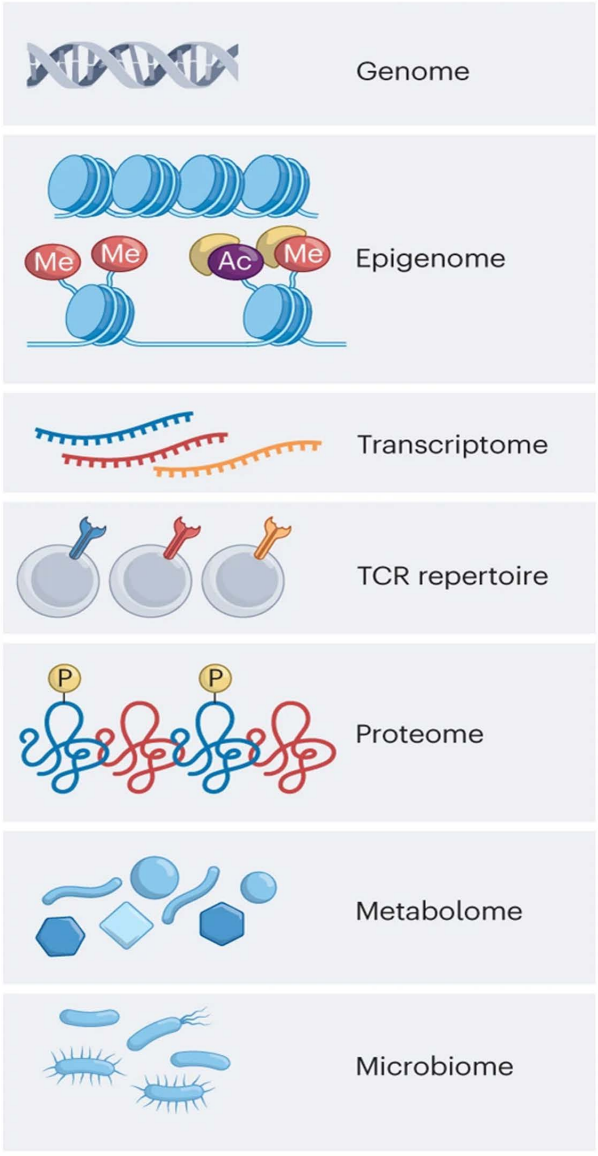
Multi-omics, the process of collecting and analyzing a combination of data that describes cells, provides a way to study tumor cell heterogeneity, and can be performed at even the single-cell level.



While tumor cells can be from the same general lineage and have some common molecular features, thanks to tumor heterogeneity, no two tumor cells are ever *exactly* alike.

Note also that tumor heterogeneity is both spatial and temporal.

It is the tools of "omics" that give us a feel for just how heterogeneous tumors can be, and armed with this information, the hope is that cancer treatment can become more and more personalized



What's the main reason we'd like to be able to "personalize" cancer treatment?

So that we don't:

- under-treat aggressive cancers

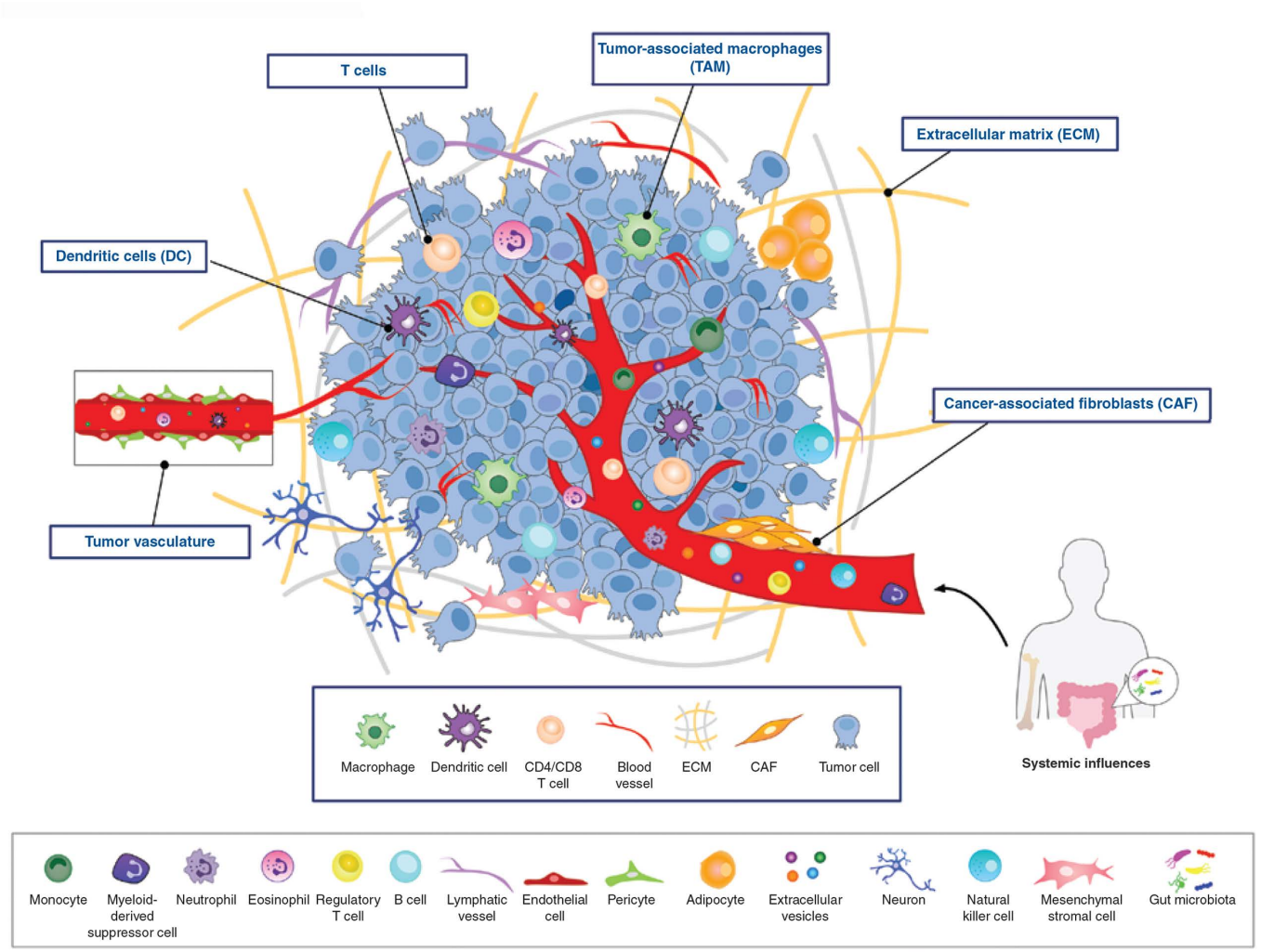
or

- over-treat indolent cancers

Sci Transl Med. 2015 July 15; *7(296)*: 296fs29
doi:10.1126/scitranslmed.aac8319

"Modifiers" of the Radiobiology Flow Chart:

The Tumor Microenvironment



Cancer Discov 2021;11:933–959

THE PRIMARY TUMOR ENVIRONMENT Cells within a tumor are supported by a complex and dynamic microenvironment composed of multiple infiltrating cell types, including endothelial cells (which line blood and lymphatic vessels), cancer-associated fibroblasts (CAFs), and a variety of bone marrow–derived cells (BMDCs). Infiltrating BMDCs mediate inflammatory responses during cancer progression and can have negative or positive consequences.

Major BMDCs within the tumor niche include tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), TIE2-expressing monocytes (TEMs), mesenchymal stem cells (MSCs), and various other cell types from lymphocyte and monocyte lineages. This tumor-associated cellular cocktail largely dictates the evolution of the surrounding environment and, ultimately, the outcome of disease.

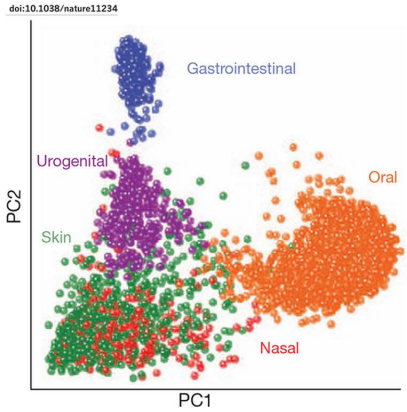
"Modifiers" of the Radiobiology Flow Chart:

The Microbiome

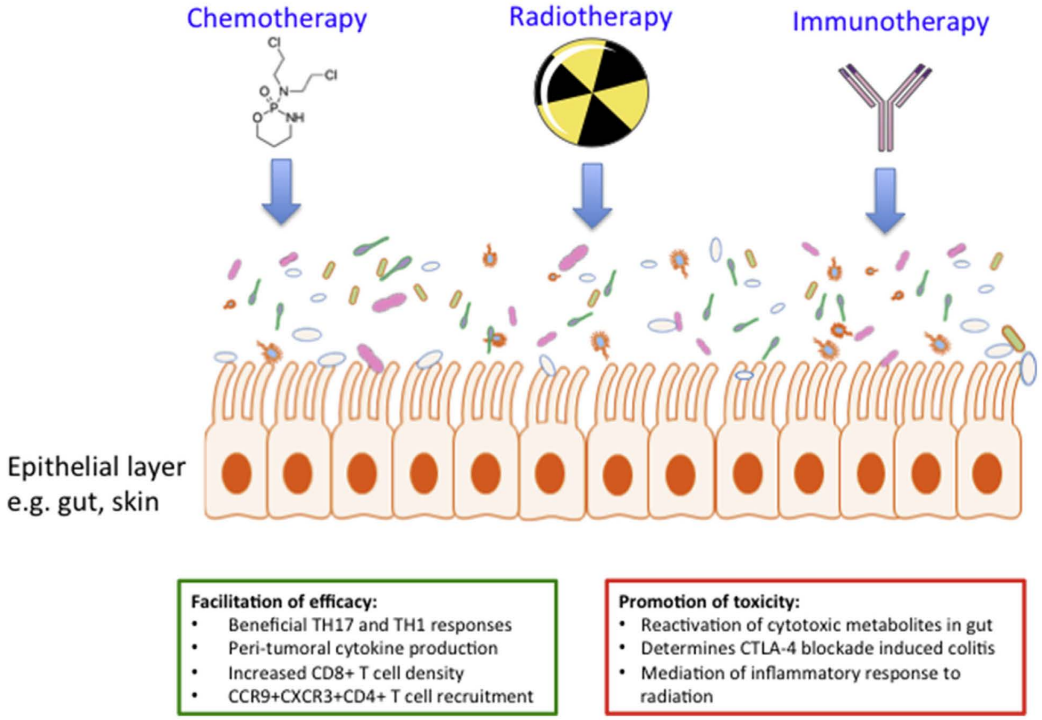
The human microbiome includes all microbiota that reside on or within human tissues and biofluids, and is categorized according to the anatomical sites in which they reside.Types of human microbiota include bacteria, archaea, fungi, protists and viruses.

Microbiota

A "principal coordinates plot" shows the clustering of families of microorganisms by body area. There is some - but not a lot - of overlap between areas.



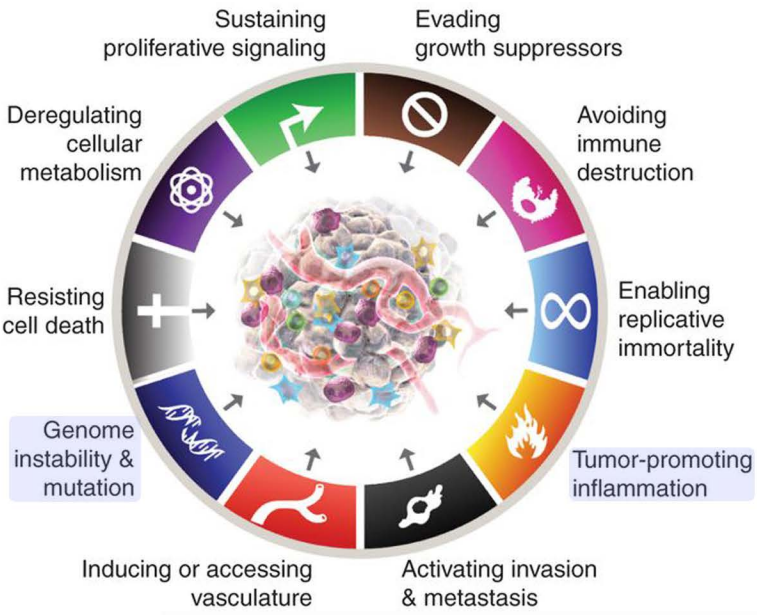
Emerging science suggests that the microbiome can not only influence the development of cancer (e.g., increasing inflammation, altering metabolism), but also affect response to cancer therapies, immunotherapies in particular. Altering the microbiome "mix" could have clinical implications – good or bad.



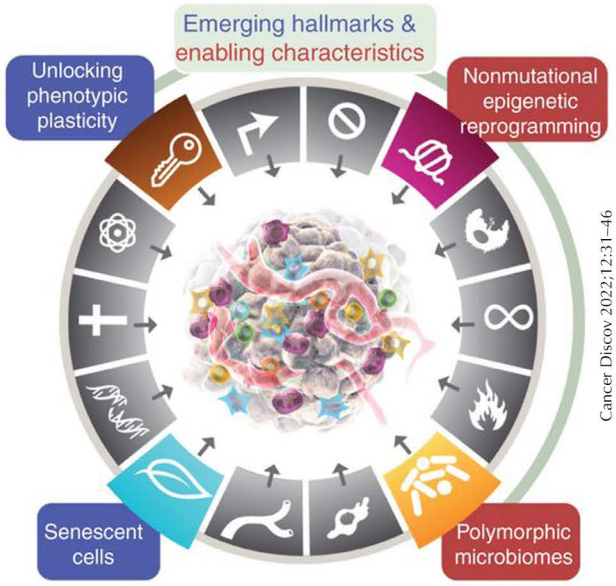
The microbiota are at the interface between cancer therapy and host responses.

Always keep in mind your "Hallmarks of Cancer"...and how they relate to both radiobiology and radiotherapy.

2011 Version



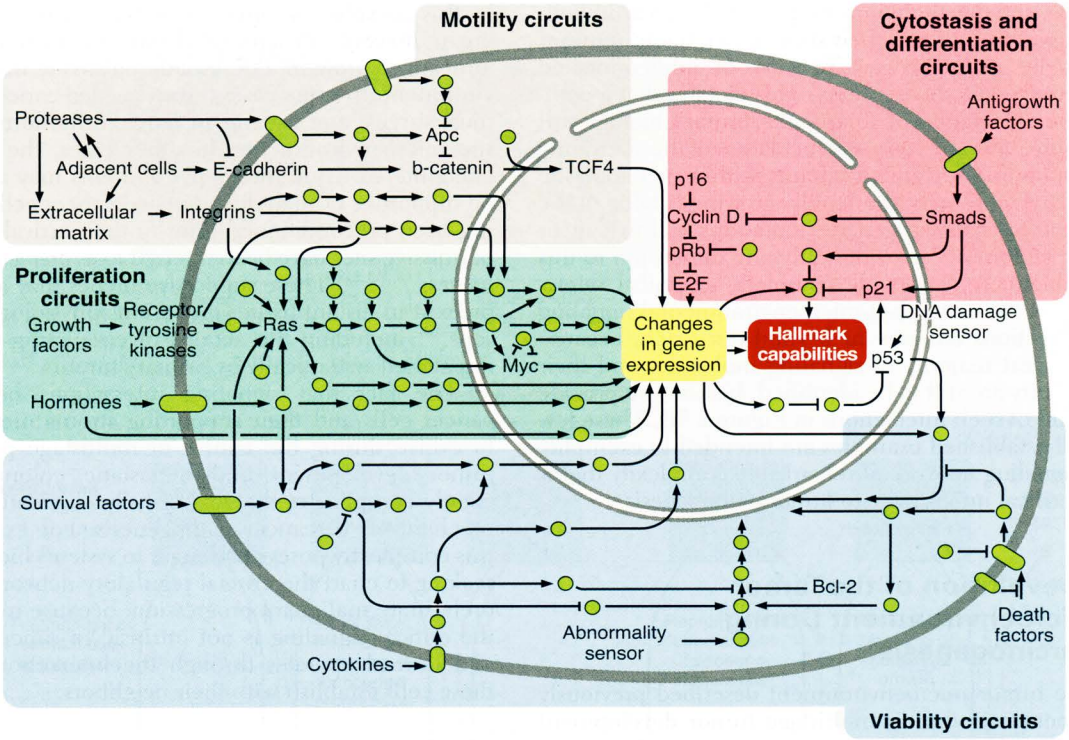
2022 Version



Cancer Discov 2022;12:31–46

Updated cancer hallmarks for 2022: "Unlocking phenotypic plasticity" = ability of tumor cells to avoid terminal differentiation (by blocking differentiation, dedifferentiating and/or transdifferentiating); "Nonmutagenic epigenetic reprogramming" = that tumor cells can change gene expression epigenetically (i.e., without needing changes to DNA itself), typically in response to cues from the tumor microenvironment; "Polymorphic microbiomes" = ability of certain tissue-resident microorganisms to exert protective or deleterious effects on carcinogenesis, tumor progression and/or response to treatment, and; "Senescent cells" = that in certain situations, the presence of sensescent cells can *enhance* rather than inhibit acquisition of the cancer hallmarks

Defects in key genetic "circuits" are responsible for cells acquiring the various hallmarks of cancer



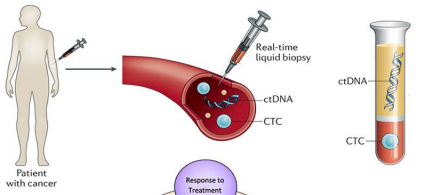
Personalized Cancer Therapy

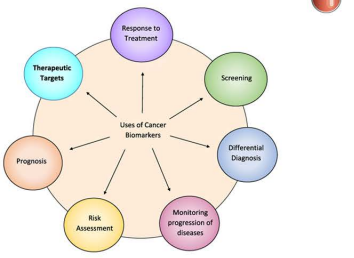
Biomarkers are cellular and molecular (including genetic and epigenetic) characteristics by which normal and/or abnormal processes can be recognized and/or monitored. They are measurable in biological materials such as tissues, cells, and/or bodily fluids.

...is the ultimate goal, given everything we've learned, and continue to learn, about cancer biology.

However, **none of this will be possible without robust biomarkers** that allow us to match patients to particular therapies, monitor their progress during treatment (and make changes, if necessary), and continue with followup looking for evidence of recurrence.

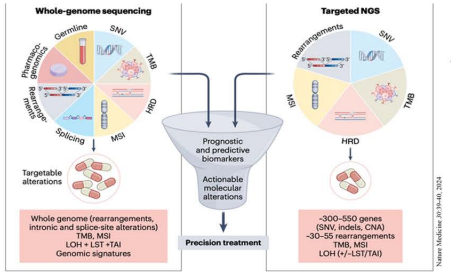
Some biomarkers are also useful in diagnosis as well as therapy.



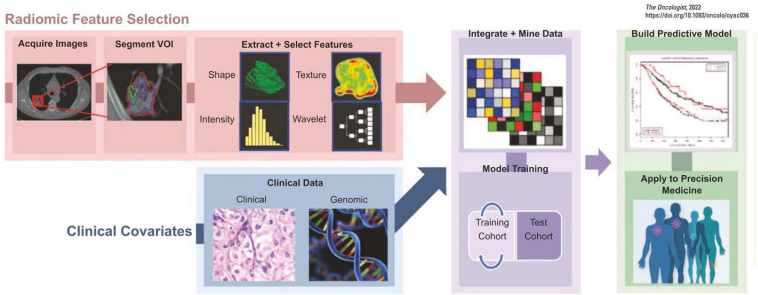


Two technologies currently being used in the quest for biomarkers include **liquid biopsy** (e.g., circulating tumor DNA or cells) and **molecular profiling** (e.g., next generation sequencing).

The newest kid on the block is **radiomics**, which involves extracting physical properties of tissues from medical images, combining this data with existing clinical and genomic data, and trying to come up with a patient-specific treatment plan or prediction of outcomes.

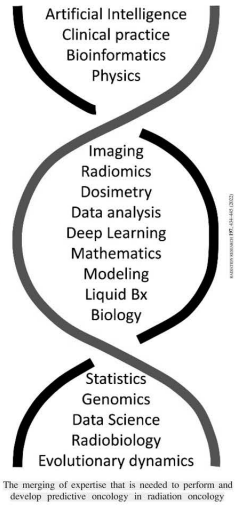


WGS versus standard-of-care targeted NGS panels. Readout and applications of WGS (left) and targeted NCS (right). +/-, with or without; CNA, copy-number alteration; IHC, immunohistochemistry; indels, insertion–deletion mutations; HRD, homologous recombination deficiency; LOH, loss of heterozygosity; LST, large-scale state transition; MSI, microsatellite instability; NGS, next-generation sequencing; SNV, single-nucleotide variant; TAI, telomeric allelic imbalance; TMB, tumor mutational burden.



The amount of "big data" generated in these studies requires a ton of computing power (and the use of AI).

In addition, any candidate biomarkers that are identified will need to be validated through functional testing in model systems.



The merging of expertise that is needed to perform and develop predictive oncology in radiation oncology

Where does "foundational" radiobiology fit into the bigger cancer biology picture?

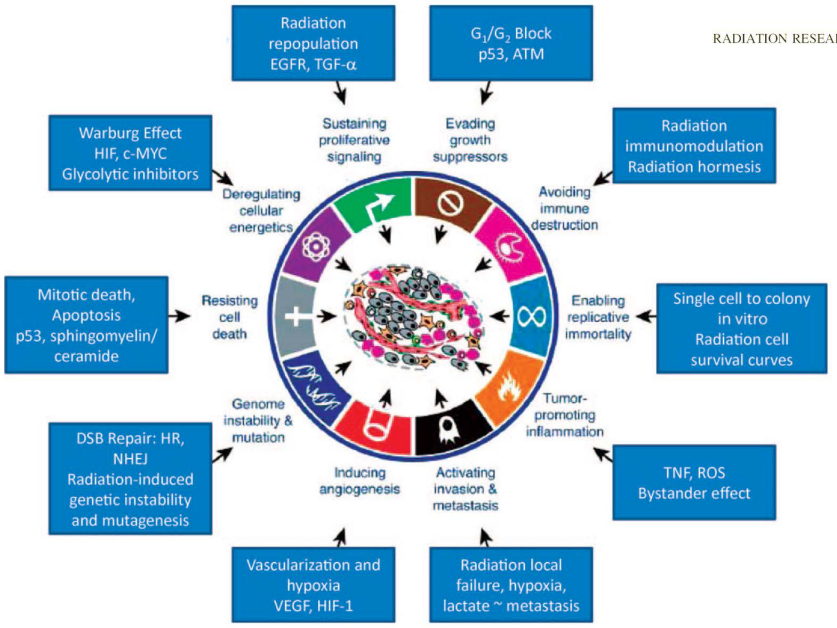
Technically, radiation biology is a sub-specialty within cancer biology, although historically, the field tended to keep to itself (to its detriment in many respects).

But, does foundational radiation biology have any hallmarks like cancer biology does?
Answer: Sort of..the so-called "Six Rs of Radiotherapy".

The challenge is to re-frame old school radiobiology concepts – elucidated, in most cases, decades before the modern era of molecular biology and biotechnology – in the context of modern cancer biology. For example:

Hallmark of radiobiology	Hallmark of cancer
Repair	Genomic instability and mutations, enabling replicative immortality
Redistribution	Sustaining proliferative signaling
Repopulation	Evading growth suppressors, sustaining proliferative signaling, tumor-promoting activation
Radiosensitivity	Resisting cell death, deregulating cellular energetics
Reoxygenation	Inducing angiogenesis
Reactivation of the immune response	Avoiding immune destruction, tumor-promoting activation, activation invasion and metastasis

Clinical Oncology (2007) 19: 561-571

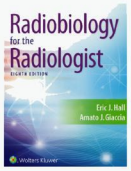


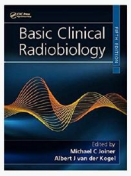
RADIATION RESEARCH **181**, 561–577 (2014)

Hallmarks of cancer with associated radiation biology concepts.

Recommended Reading for Radiation and Cancer Biology

Best two textbooks:





EJ Hall and AJ Giaccia. *Radiobiology for the Radiologist, Eighth Edition*. Wolters Kluer, Philadelphia, 2019. ISBN: 978-1496335418.

M Joiner and A van der Kogel, Editors. *Basic Clinical Radiobiology, Fifth Edition*. Taylor & Francis (CRC Press), London, 2019. ISBN: 978-1444179637.

Useful textbooks vis-à-vis radiation effects *in humans*:

FA Mettler and AC Upton. *Medical Effects of Ionizing Radiation, 3rd Edition*. Saunders-Elsevier, Philadelphia, 2008. ISBN: 978-0-7216-0200-4.

DC Shrieve and JS Loeffler. *Human Radiation Injury*. Lippincott Williams & Wilkins, Philadelphia, 2011. ISBN: 798-1-60547-011-5.

Best textbook for general cancer biology:

(Long-Awaited) New Edition! L Harrington, I Tannock, R Hill and D Cescon. *The Basic Science of Oncology, 6th Edition*. McGraw Hill / Medical, New York, 2021. ISBN: 978-1-259-86207-6.

RA Weinberg. *The Biology of Cancer, 2nd Edition*. Garland Science, Taylor & Francis Group, LLC, New York, 2014. ISBN: 0-8153-4078-8.

ABR's list of "secondary references":

Radiation-induced cell death mechanisms.
Eriksson D, Stigbrand T.
Tumour Biol. 2010 Aug;31(4):363-372. doi: 10.1007/s13277-010-0042-8. PMID: 20490962

The hallmarks of cancer and the radiation oncologist: updating the 5Rs of radiobiology.
Good JS, Harrington KJ.
Clin Oncol (R Coll Radiol). 2013 Oct;25(10):569-577. doi: 10.1016/j.clon.2013.06.009. PMID: 23850153

The tumour microenvironment after radiotherapy: mechanisms of resistance and recurrence.
Barker HE, Paget JT, Khan AA, Harrington KJ.
Nat Rev Cancer. 2015 Jul;15(7):409-425. doi: 10.1038/nrc3958. PMID: 26105538

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Bristow RG, Hill RP.
Nat Rev Cancer. 2008 Mar;8(3):180-192. doi: 10.1038/nrc2344. PMID: 18273037

Hallmarks of cancer: the next generation.
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Cell. 2011 Mar 4;144(5):646-674. doi: 10.1016/j.cell.2011.02.013. PMID: 21376230

Common markers of proliferation.
Whitfield ML, George LK, Grant GD, Perou CM.
Nat Rev Cancer. 2006 Feb;6(2):99-106. doi: 10.1038/nrc1802. PMID: 16491069

Opportunities and challenges of radiotherapy for treating cancer.
Schaue D, McBride WH.
Nat Rev Clin Oncol. 2015 Sep;12(9):527-540. doi: 10.1038/nrclinonc.2015.120. PMID: 26122185

Radiation resistance of cancer stem cells: the 4 R's of radiobiology revisited.
Pajonk F, Vlashi E, McBride WH.
Stem Cells. 2010 Apr;28(4):639-648. doi: 10.1002/stem.318. PMID: 20135685.

Cell cycle proteins as promising targets in cancer therapy.
Otto T, Sicinski P.
Nat Rev Cancer. 2017 Jan 27;17(2):93-115. doi: 10.1038/nrc.2016.138. PMID: 28127048

Molecularly targeted cancer therapy: some lessons from the past decade.
Huang M, Shen A, Ding J, Geng M.
Trends Pharmacol Sci. 2014 Jan;35(1):41-50. doi: 10.1016/j.tips.2013.11.004. PMID: 24361003

Role of local radiation therapy in cancer immunotherapy.
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JAMA Oncol. 2015 Dec;1(9):1325-1332. doi: 10.1001/jamaoncol.2015.2756. PMID: 26270858

ABR | AMERICAN BOARD OF RADIOLOGY

Radiation Oncology

Initial Certification Qualifying (Computer-based) Exam: Study Guide for Radiation and Cancer Biology

This exam tests your knowledge of the principles of radiation and cancer biology underlying the practice of radiation oncology. Included are questions on the general domains listed below. Exam performance will be reported to you based on an overall pass/fail grade, with specific information provided regarding quintile performance in the 10 individual domains. Because of the nature of scientific knowledge and subcategories, there may be some overlap of items across domains. Each exam will include items from every domain, but individual subtopics may not be included in every exam and the number of items per domain depends on the domain.

I.	Interaction of radiation with matter	1% to 4%
II.	Molecular and cellular damage and repair	13% to 17%
III.	Cellular response to radiation	7% to 10%
IV.	Linear energy transfer (LET) and oxygen effect	3% to 5%
V.	Tumor biology and microenvironment	3% to 5%
VI.	Cancer biology	19% to 23%
VII.	Radiobiology of normal tissues	9% to 12%
VIII.	Dose delivery	11% to 15%
IX.	Combined modality therapy	11% to 15%
X.	Late effects and radiation protection	6% to 9%

The ranges above are those generally in effect for the exam to be administered in 2020 and are intended only for guidance in candidate preparation. They do not necessarily represent a precise number of scorable items.

I. Interaction of radiation with matter

a. Definition of ionizing radiation, free radicals, and radical damage
b. Direct and indirect action of radiation, numbers and types of DNA lesions
c. Consequences of unrepaired DNA DSB

II. Molecular and cellular damage and repair

a. Molecular mechanisms of DNA damage
    i. Assays for measuring DNA damage and repair
    ii. Single lethal hits, accumulated damage, and multiple damaged sites
b. Molecular mechanisms of DNA repair
    i. Repair of base damage, single-strand and double-strand breaks

ii. DSB repair: Homologous recombination and non-homologous end joining
iii. Molecular mechanisms of DNA DSB damage recognition and damage signaling to initiate repair

c. Cellular recovery
i. Repair at the cellular level
ii. Sublethal damage repair
iii. Dose-rate effects and repair
iv. Dose-fractionation effects and repair

d. Chromosome and chromatid damage
i. Assays for measuring chromosome damage – Giemsa to FISH
ii. Dose-response relationships
iii. Use of peripheral blood lymphocytes in *in vivo* dosimetry
iv. Human genetic diseases that affect DNA repair, fragility, and radiosensitivity
v. Stable and unstable chromatid and chromosome aberrations

III. Cellular responses to radiation

a. Mechanisms of cell death
i. Mechanisms and major characteristics of pathways of radiation-induced apoptosis, necrosis, autophagy, and senescence
ii. Mitotic-linked cell death and chromosome aberrations
iii. Cell division post-radiation and time to clonogen death

b. Cell and tissue survival assays: measurement of response
i. In vitro clonogenic assays - effects of dose and dose rate
ii. In vivo clonogenic assays - bone marrow stem cell assays, jejunal crypt stem cell assay, skin clones, and kidney tubules

c. Models of cell survival
i. Random nature of cell killing and Poisson statistics
ii. Single hit, multitarget models of cell survival – survival curve descriptors
iii. Linear-quadratic models: definition of α/β ratio
iv. Calculations of cell survival with dose and dose rate
v. Shapes of the dose-response curves for early and late responding tissues
vi. Isoeffect curves and impact of changing fraction size and number on survival and LQ parameters

IV. Linear energy transfer (LET) and oxygen effect

a. Linear energy transfer
i. Definition of LET and quality of radiation
ii. RBE defined
iii. RBE as a function of LET in cells and tissues
iv. Effect on RBE on change in fractionation

b. Oxygen Effect
i. Definition of OER
ii. Dose or dose per fraction effects
iii. OER vs LET
iv. Impact of O_2 concentration
v. Mechanisms of oxygen effect

V. Tumor biology and microenvironment

a. Solid tumor assay systems
i. Concept of xenograft and syngeneic tumor models

ii. Assay of tumor response to treatment– growth delay
iii. TCD50 tumor control assay

b. Tumor microenvironment
i. Characteristics of tumor vasculature and microenvironment; effect of radiation on them
ii. How tumor microenvironment can regulate tumor growth and vasculature
iii. Angiogenesis and neovasculogenesis
iv. Clinical consequence and relevance of hypoxia in tumors and tumor progressions
v. Reoxygenation after irradiation
vi. Cellular and molecular responses to hypoxia and hypoxia-induced signal transduction
vii. Cellular composition of tumors
viii. Immune microenvironment and role of inflammation

VI. Cancer biology

a. Cell and tissue kinetics
i. Methods to assess cell cycle kinetics
ii. Proteins involved in cell cycle control and checkpoint initiation (e.g., CDKs, cyclins, CDK inhibitors)
iii. Phases of cell cycle and radiation sensitivity
iv. Cell cycle arrest and redistribution after irradiation

b. Molecular signaling
i. Main signaling pathways and critical proteins involved (e.g., PI3K/AKT, RAS/ERK, TGF-β, Wnt, Notch, NFkB)
a) Receptors/ligand (e.g., EGFR, VEGFR, c-MET, HER2, FGFR, ALK)
b) Kinases
1). Definition of kinases (e.g., STKs, TKs/RTKs, DSKs)
2). Common kinases in cancer (e.g., ATM, ATR, Chk1, Chk2, PI3K, MAPK) and corresponding phosphatases (e.g., PTEN)
ii. Molecular signaling pathways activated by IR
iii. Transcription factors involved in cancer regulation (e.g., MYC, TP53 and associated proteins)
iv. Cell death pathways and main associated players
a). Intrinsic vs extrinsic apoptosis (caspases)
b). *BCL-2* family member proteins (pro- vs anti-apoptotic)

c. Mechanisms of cancer development
i. Hallmarks of cancer and how they could affect 4/5 Rs of radiobiology
ii. Common oncogenes (e.g., *HER2/neu*, *Ras, Myc*) & tumor suppressors (*Rb, p16, p53, BRCA1/BRCA2, APC, NF1*)
iii. Telomeres and pathways in cancer to overcome telomere shortening (e.g., TERT promoter mutations and alternative lengthening of telomeres [ALT])
iv. Signaling abnormalities and association with treatment response
iv. Cancer as a genetic disease
v. Multistep nature of carcinogenesis
vi. Signaling abnormalities in carcinogenesis
vii. Prognostic and therapeutic significance of tumor characteristics

d. Cancer genetics/genomics
i. Types of epigenetic regulation (e.g., DNA methylation (DNMTs/TETs), histone modifications (e.g. HDACs/HATs), chromatin remodelers)
ii. Main epigenetic alterations (e.g., CpG island methylator phenotype [CIMP]) in cancer
a). *IDH1/2* mutations in glioma and AML
b). *TET2* mutations in AML

iii. Epigenetic targets in cancer (DNMTi, HDACi, IDHi, EZH2i)
iv. Omics approaches in cancer (next-gen sequencing/arrays) and newer methods (ctDNA)
v. Biomarkers in cancer (e.g., BCR-ABL, EGFR, ALK)
vi. Molecular profiling of cancer

VII. Radiobiology of normal tissues

a. Clinically relevant normal tissue responses to radiation
    i. Responses in early versus late responding tissues
    ii. Reirradiation
b. Mechanisms of normal tissue radiation responses
    i. Molecular and cellular responses in slowly and rapidly proliferating tissues
    ii. Mechanisms underlying clinical symptoms
    iii. Tissue kinetics
c. Total body irradiation
    i. Prodromal radiation syndrome
    ii. Acute radiation syndromes
    iii. Mean lethal dose and dose/time responses
    iv. Immunological effects
    v. Assessment and treatment of radiation accidents
    vi. Bone marrow transplantation

VIII. Dose delivery

a. Therapeutic ratio
    i. Tumor control probability (TCP) curves
    ii. Normal tissue complication probability (NTCP) curves
    iii. Causes of treatment failure
b. Time, dose, and fractionation
    i. The four R's of fractionation
    ii. Radiobiological rationale behind dose fractionation
    iii. Effect of tissue/tumor type on the response to dose fractionation (α/β ratios)
    iv. Quantitation of multifraction survival curves
    v. BED and isoeffect dose calculations
    vi. Hypofractionation
c. Brachytherapy
    i. Dose-rate effects (HDR and LDR)
    ii. Choice of isotopes
    iii. Radiolabeled antibodies and other ligands
d. Radiobiological aspects of different radiation modalities
    i. Protons, high LET sources
    ii. Stereotactic radiosurgery/radiotherapy, IMRT, IORT, and systemic radionuclides
    iii. Dose distributions and dose heterogeneity

IX. Combined modality therapy

a. Chemotherapeutic agents and radiation therapy
    i. Classes of chemotherapy agents
    ii. Mechanisms of action
    iii. Oxygen effect on radiation therapy and chemotherapy
    iv. Main drug resistance mechanisms (e.g., MDR genes)
    v. Interactions/synergism of chemotherapy with radiation therapy
    vi. Targeted therapeutic agents

b. Radiosensitizers, bioreductive drugs, and radioprotectors
    i. Definition of therapeutic window
    ii. Tumor radiosensitizers (e.g., oxygen) and mimics (e.g., nitromidazole)
    iii. Normal tissue radioprotectors (e.g., amifostine)
    iv. Biological response modifiers (e.g., IL-2 and IFN)
    v. DNA repair inhibitors (e.g., PARPi, ATMi, ATRi, Chk1/2i)
c. Immune therapeutics
    i. Types of immunotherapy treatments in oncology
        a) Monoclonal antibodies (MABs)
        b) Checkpoint inhibitors
        c) Cytokines
        d) Vaccines
        e) Adoptive cell transfer types (chimeric antigen receptors [CARs], tumor infiltrating lymphocytes [TILs], and T cell receptors [TCRs])
    ii. Combination of immune therapies and radiation
        a) Recently published trials (e.g., PACIFIC, KEYNOTE)
        b) Known predictors of response/biomarkers
d. Hyperthermia

X. Late effects and radiation protection

a. Radiation carcinogenesis
    i. Dose response for radiation-induced cancers
    ii. Importance of age at exposure, time since exposure, sex, and tissue
    iii. Second tumors in radiation therapypatients
    iv. Risk estimates in humans
b. Heritable effects of radiation
    i. Relative vs absolute mutation risk
    ii. Doubling dose
    iii. Heritable effects in humans
    iv. Risk estimates for hereditable effects
c. Radiation effects in the developing embryo
    i. Dependence of abnormalities and death on dose and gestational stage
    ii. Microcephaly, intellectual disabilities
d. Radiation protection
    i. Stochastic effects and tissue reactions
    ii. Tissue and radiation weighting factors
    iii. Equivalent dose, effective dose, committed dose
    iv. Dose limits for occupational and public exposure

NOTE: This study guide is subject to future revision as feedback is received on both content and clarity.