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Ion Beam Radiobiology: From the Lab to the Clinic

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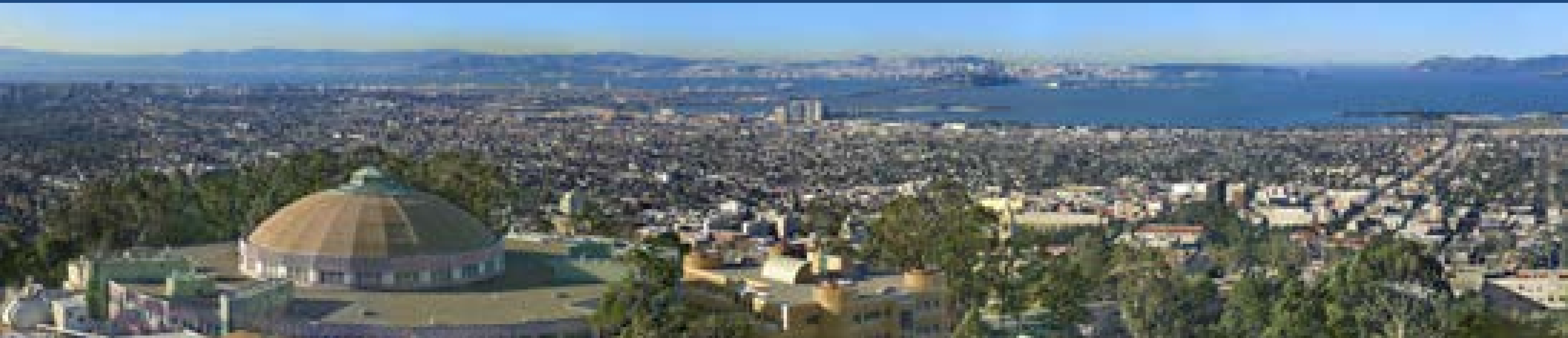


Disclosures

NONE

Objectives

- *Brief background on the role of radiobiology in ion beam radiotherapy*
- *Current status of radiobiology in treatment planning*
    - *Protons*
    - *Carbon*
- *Summary of common problems needing improvements*
- *Future Vision*

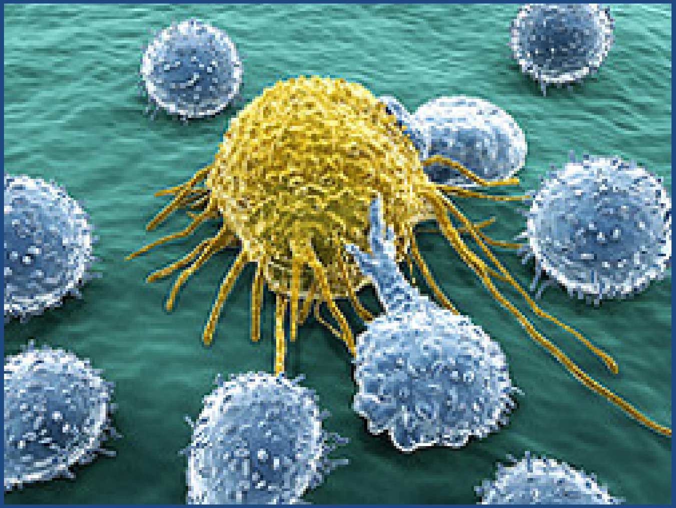
1954

- *Year that CERN was founded*

  (September 29, 1954)

- *1st clinical use of charged particles (John Lawrence used protons from a synchrocyclotron to treat breast cancer)*

CANCER



Cancer cell under attack by macrophage U. Penn

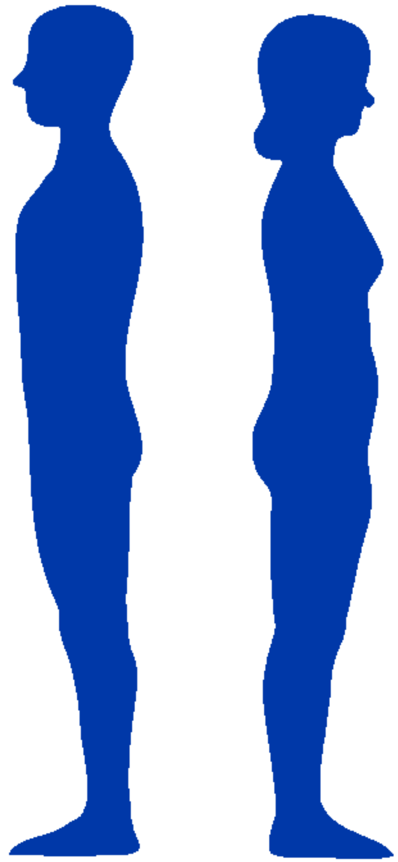
Cancer is a major public health problem worldwide and is the major cause of death for those <85 years of age (Siegel et al., 2012).

Radiotherapy alone or combined with surgery and medical treatments has been a major means of fighting cancer since the discovery of X-ray by Roentgen in 1895 (Thariat et al., 2013).

Estimated Cancer Deaths in the US in 2013

Men 306,920

Lung & bronchus	28%
Prostate	10%
Colon & rectum	9%
Pancreas	6%
Liver & intrahepatic bile duct	5%
Leukemia	4%
Esophagus	4%
Urinary bladder	4%
Non-Hodgkin lymphoma	3%
Kidney & renal pelvis	3%
All other sites	24%

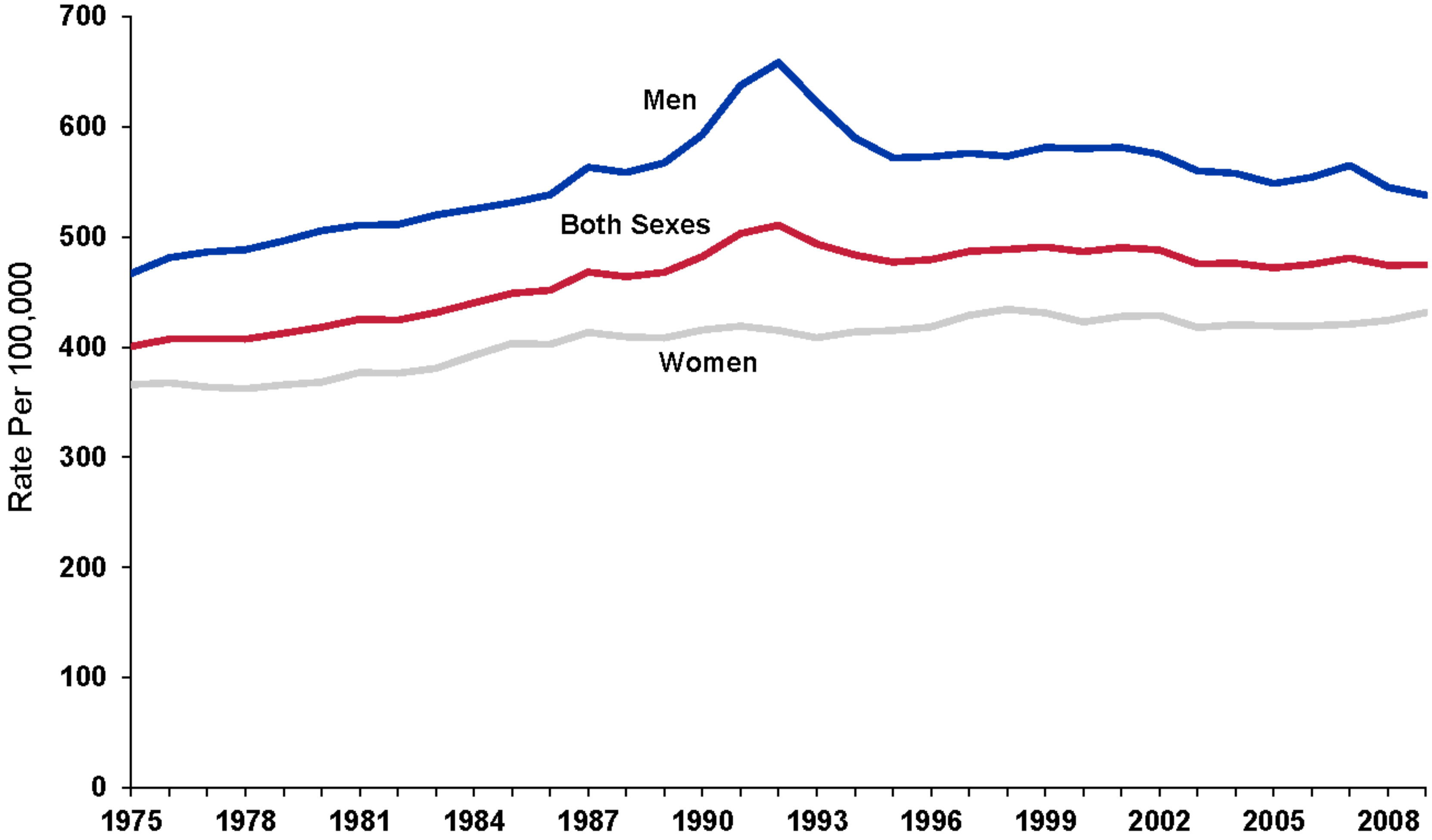


Women 273,430

26%	Lung & bronchus
14%	Breast
9%	Colon & rectum
7%	Pancreas
5%	Ovary
4%	Leukemia
3%	Non-Hodgkin lymphoma
3%	Uterine corpus
2%	Liver & intrahepatic bile duct
2%	Brain/other nervous system
25%	All other sites

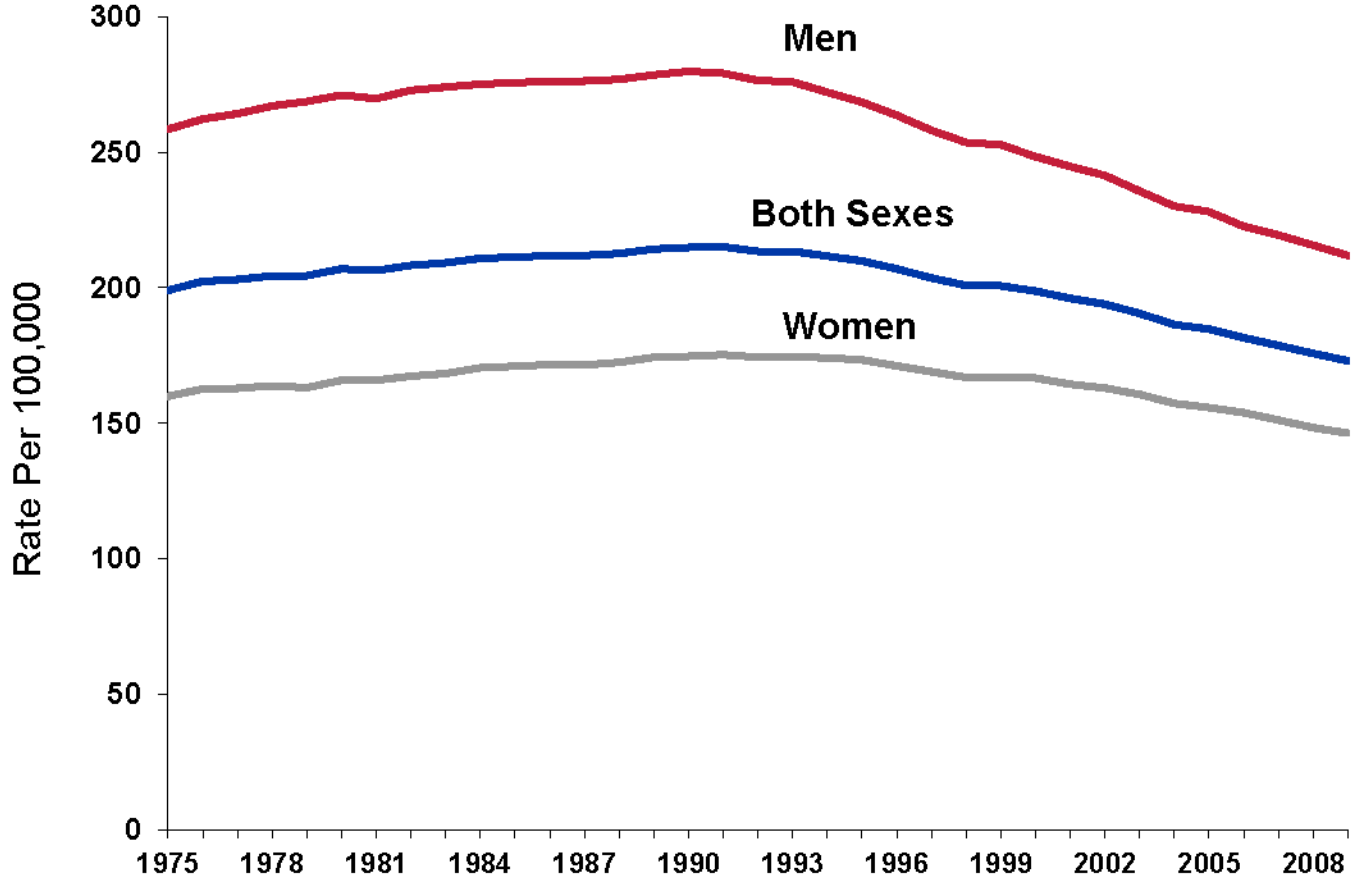
American Cancer Society, 2013

Cancer Incidence Rates* by Sex, US, 1975-2009



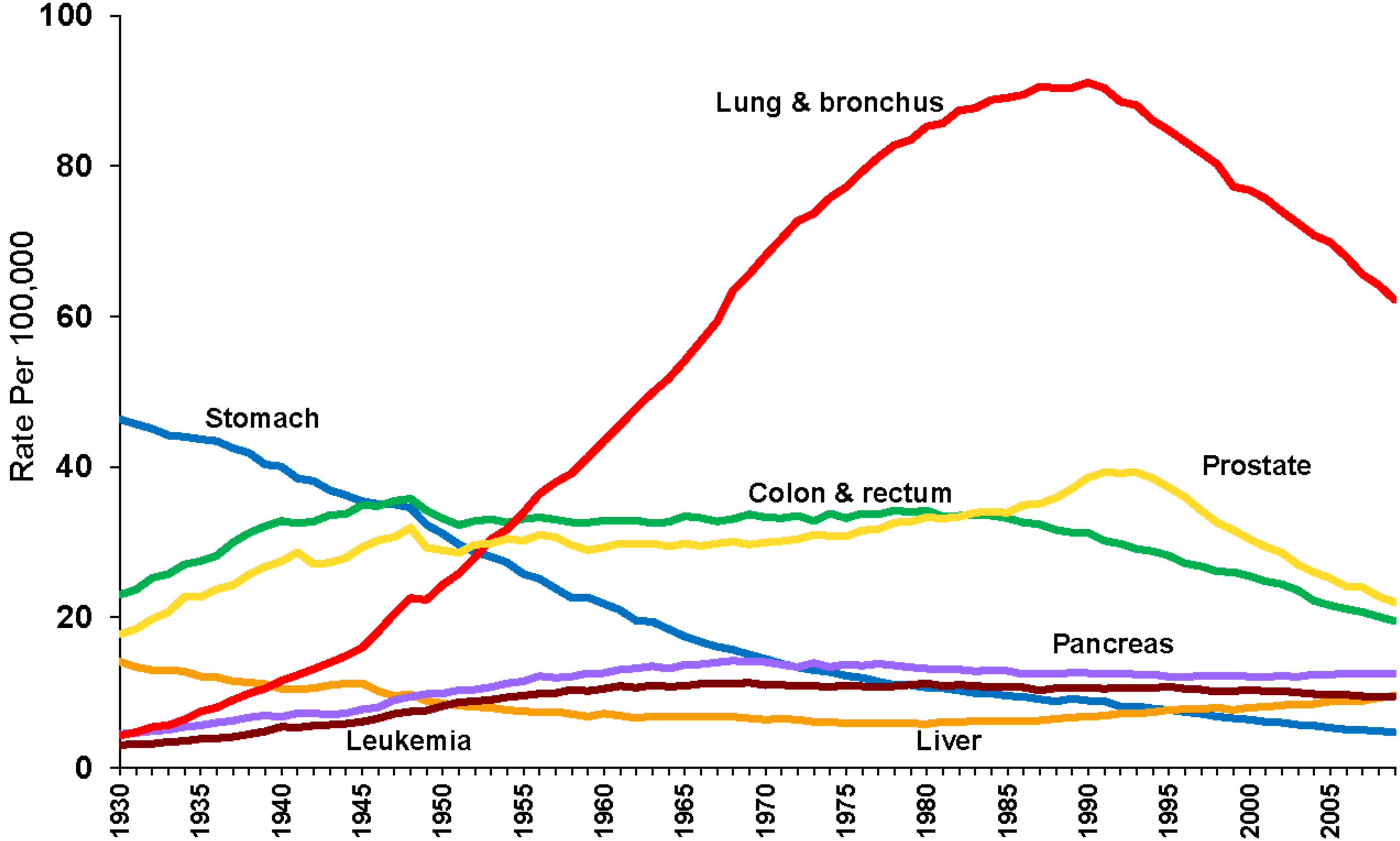
*Age-adjusted to the 2000 US standard population and adjusted for delays in reporting.
Source: Surveillance, Epidemiology, and End Results Program, Delay-adjusted Incidence database: SEER Incidence Delay-adjusted Rates, 9 Registries, 1975-2009, National Cancer Institute, 2012.

Cancer Death Rates* by Sex, US, 1975-2009



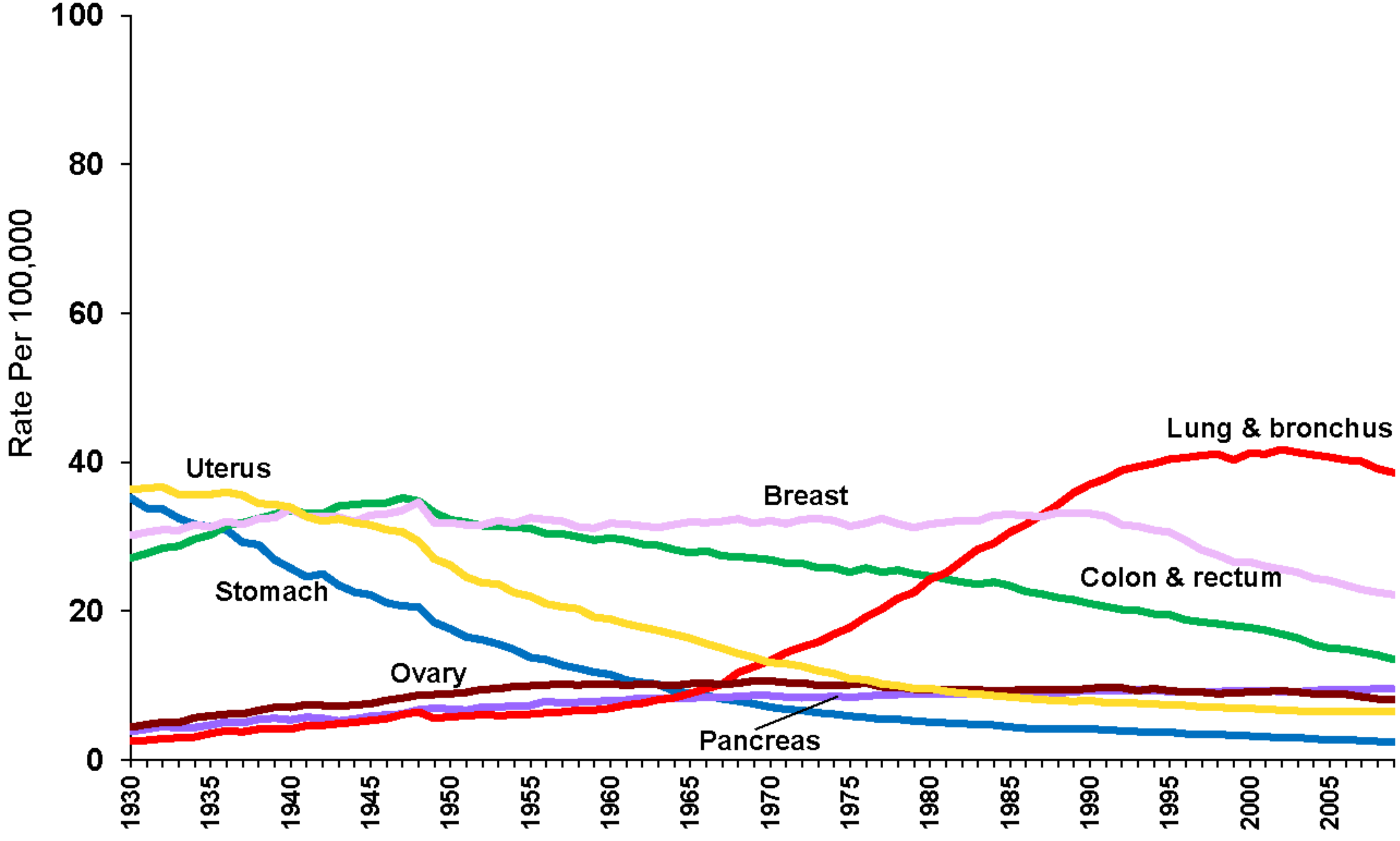
*Age-adjusted to the 2000 US standard population.
Source: US Mortality Data 1975-2009, National Center for Health Statistics, Centers for Disease Control and Prevention.

Cancer Death Rates* Among Men, US,1930-2009



*Age-adjusted to the 2000 US standard population.
Source: US Mortality Data 1960-2009, US Mortality Volumes 1930-1959,
National Center for Health Statistics, Centers for Disease Control and Prevention.

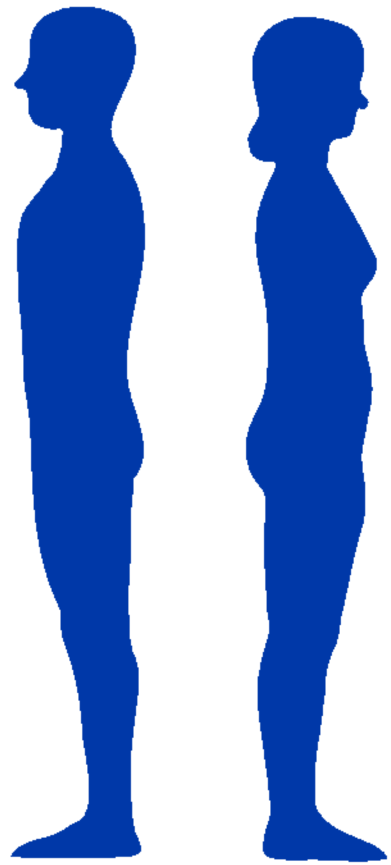
Cancer Death Rates* Among Women, US,1930-2009



*Age-adjusted to the 2000 US standard population.
Source: US Mortality Data 1960-2009, US Mortality Volumes 1930-1959, National Center for Health Statistics, Centers for Disease Control and Prevention.

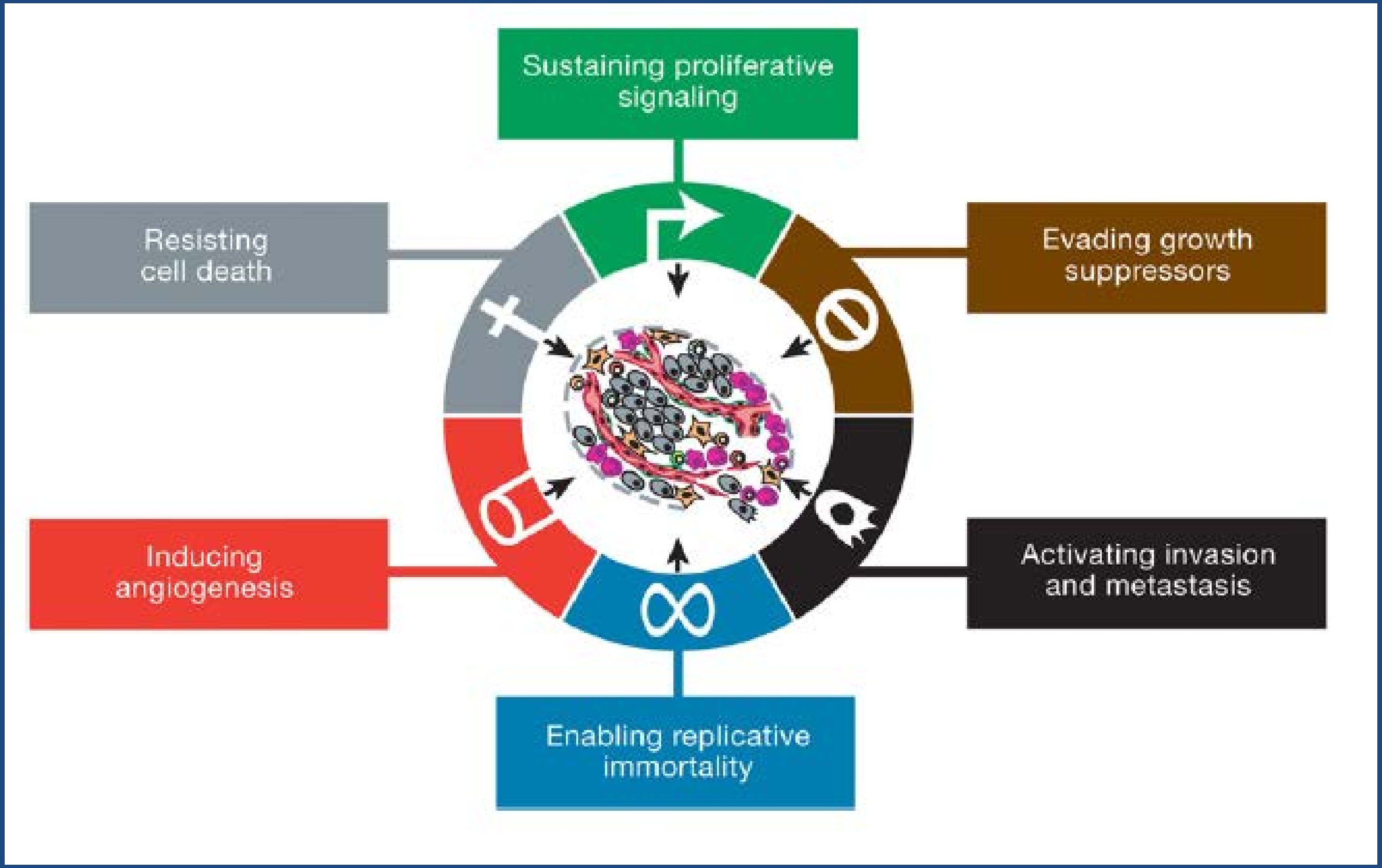
Estimated New Cancer Cases* in the US in 2013

Men 854,790		Women 805,500	
Prostate	28%	29%	Breast
Lung & bronchus	14%	14%	Lung & bronchus
Colon & rectum	9%	9%	Colon & rectum
Urinary bladder	6%	6%	Uterine corpus
Melanoma of skin	5%	6%	Thyroid
Kidney & renal pelvis	5%	4%	Non-Hodgkin lymphoma
Non-Hodgkin lymphoma	4%	4%	Melanoma of skin
Oral cavity	3%	3%	Kidney & renal pelvis
Leukemia	3%	3%	Pancreas
Pancreas	3%	3%	Ovary
All Other Sites	20%	19%	All Other Sites



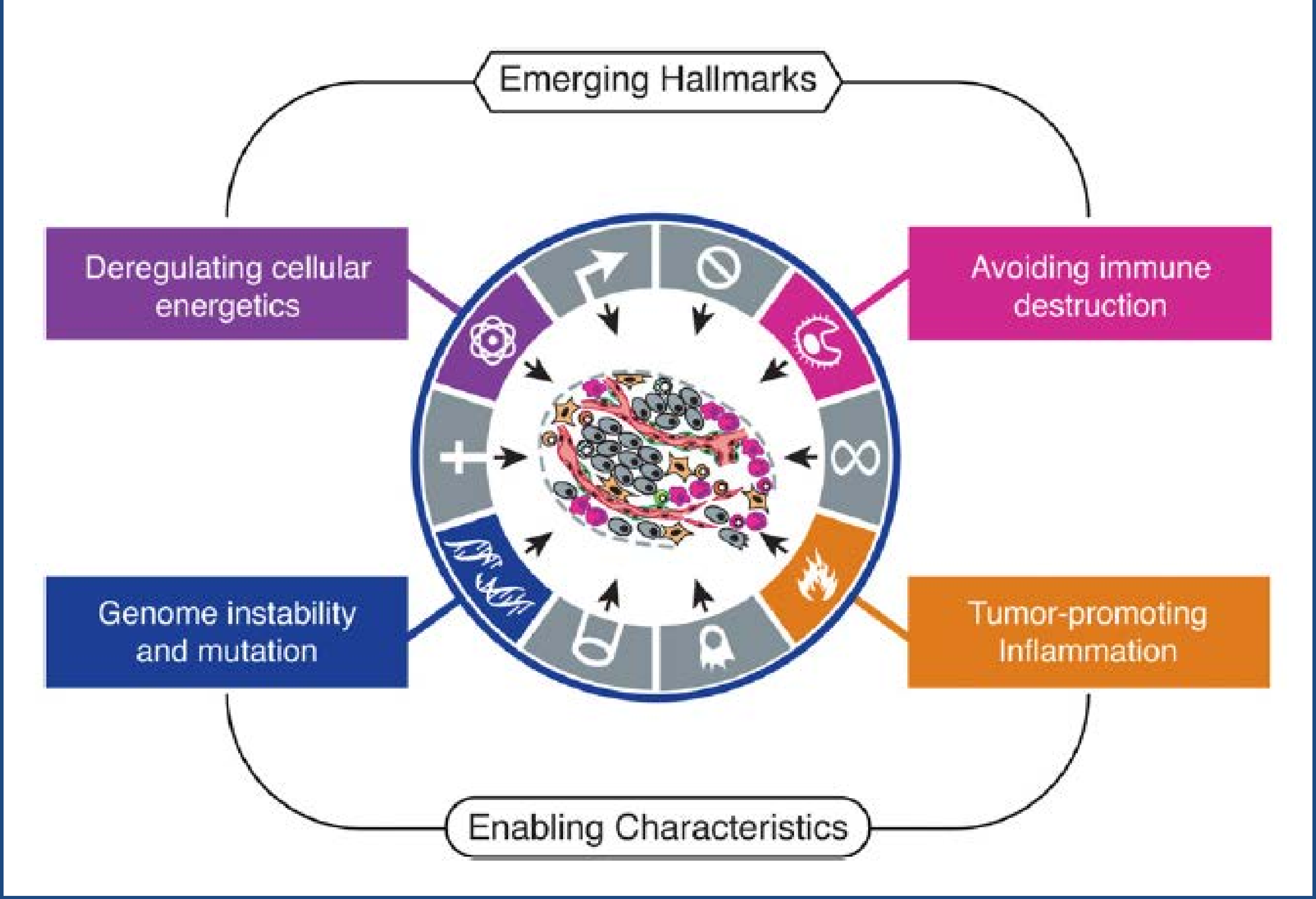
*Excludes basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder.

Original Hallmarks of Cancer



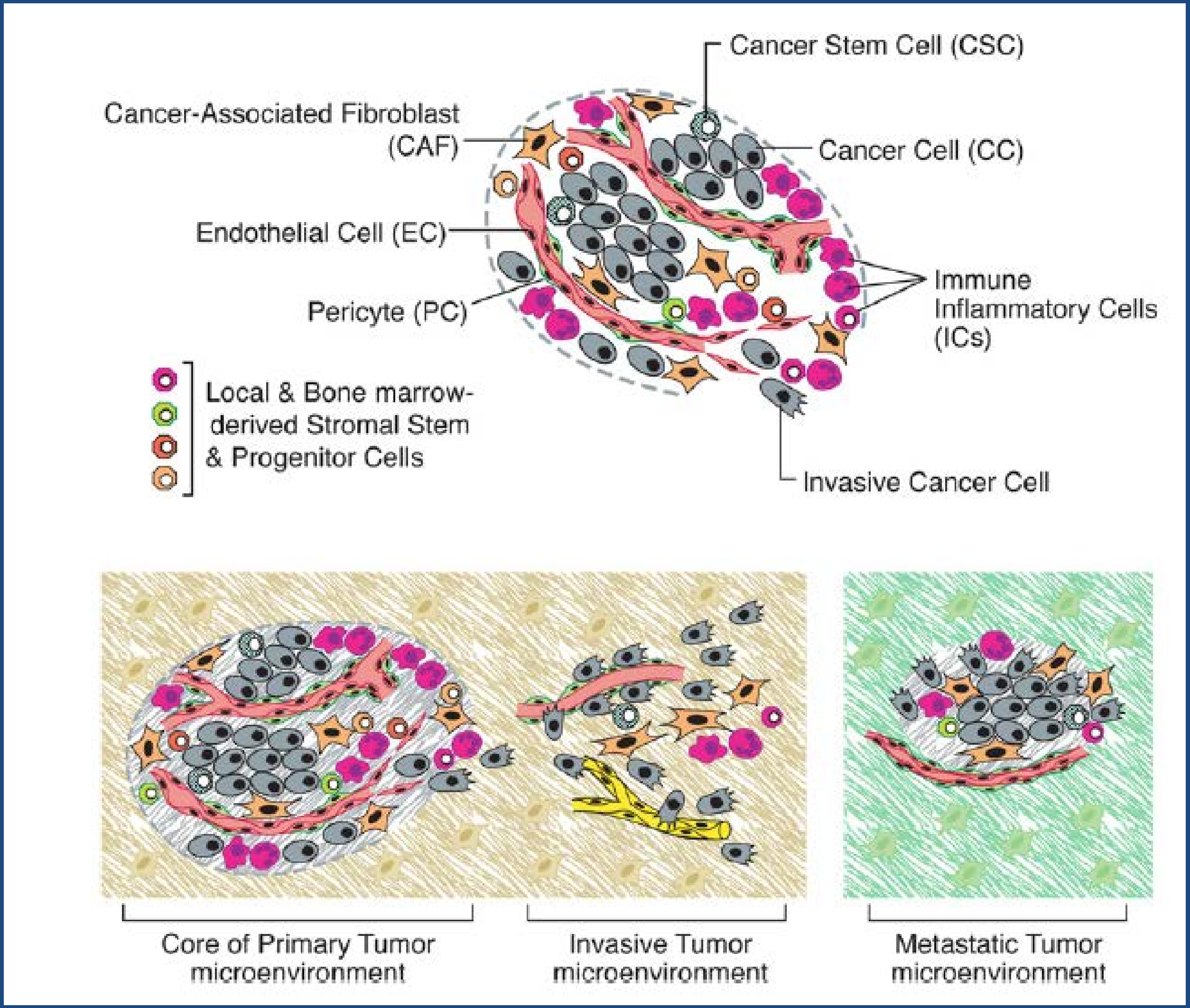
Hanahan& Weinberg, Cell 2000

Emerging Hallmarks & Enabling Characteristics



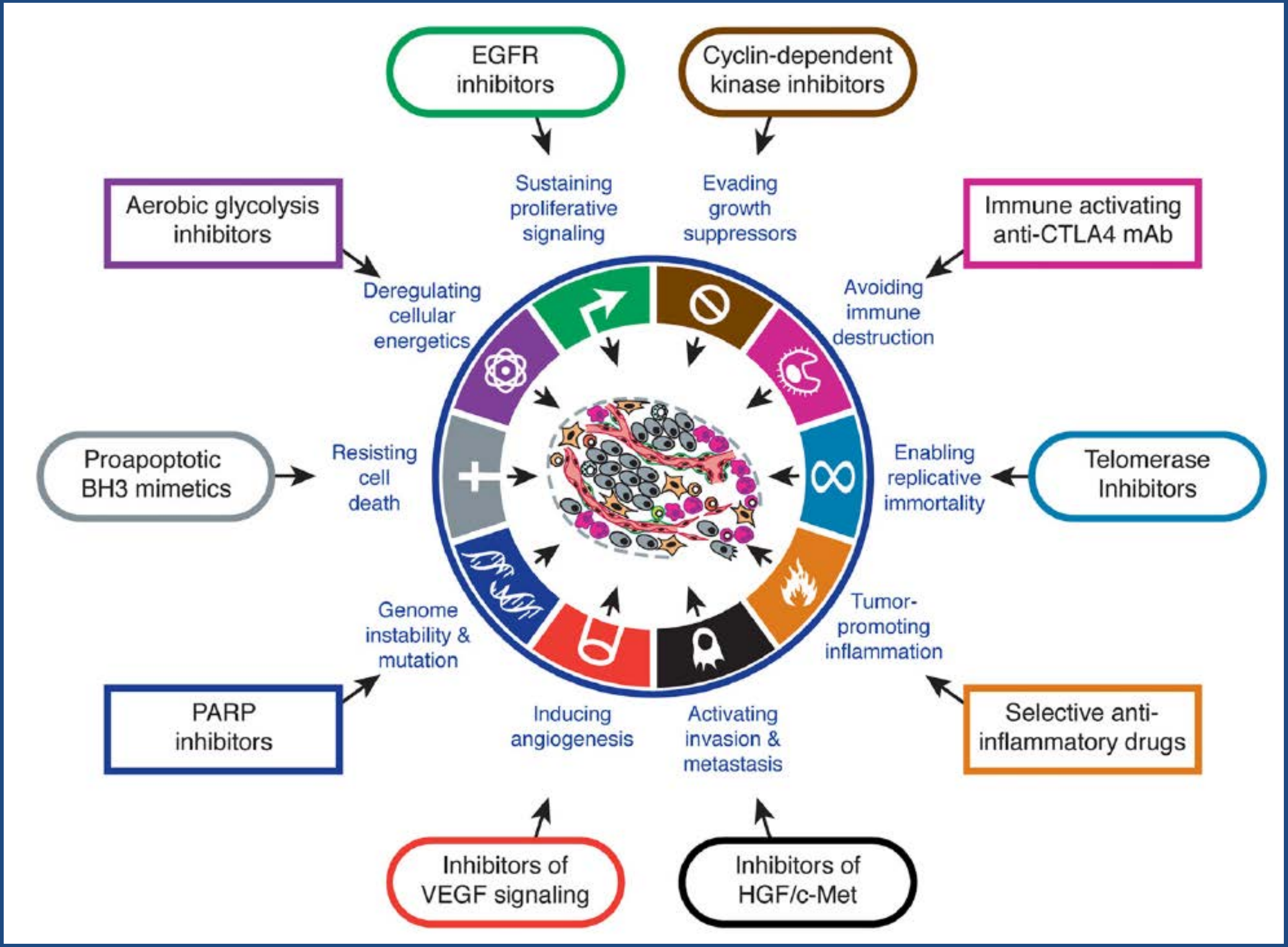
Hanahan& Weinberg, Cell 2011

Cells of the Tumor Microenvironment



Hanahan& Weinberg, Cell 2011

Therapeutic Targeting of the Hallmarks of Cancer



Hanahan& Weinberg, Cell 2011

Molecular Discoveries & Radiotherapy

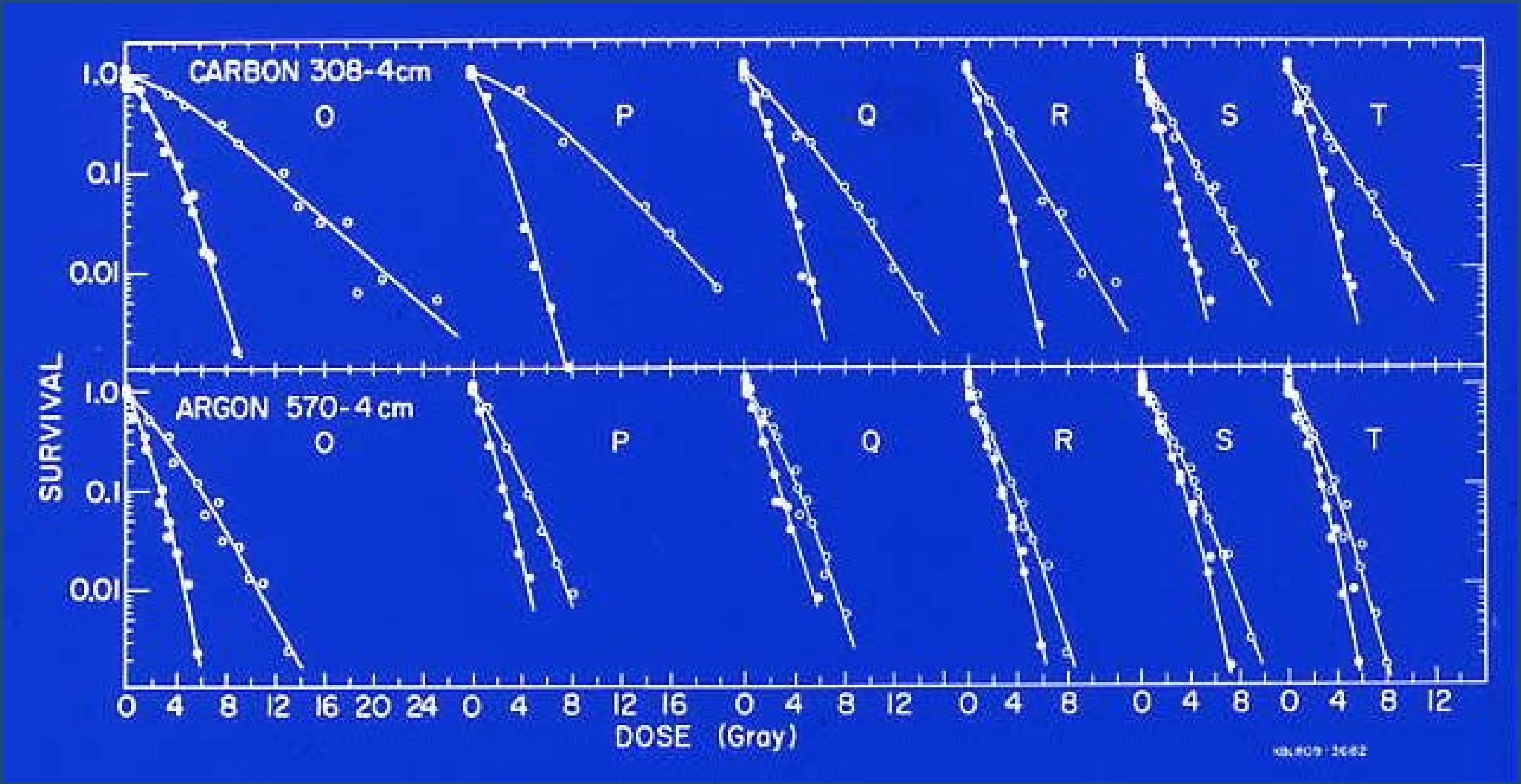
- *How do these discoveries help radiotherapy with conventional or emerging radiation modalities?*

- *The information must be validated and integrated into treatment planning.*

A Major Problem for Treatment Planning

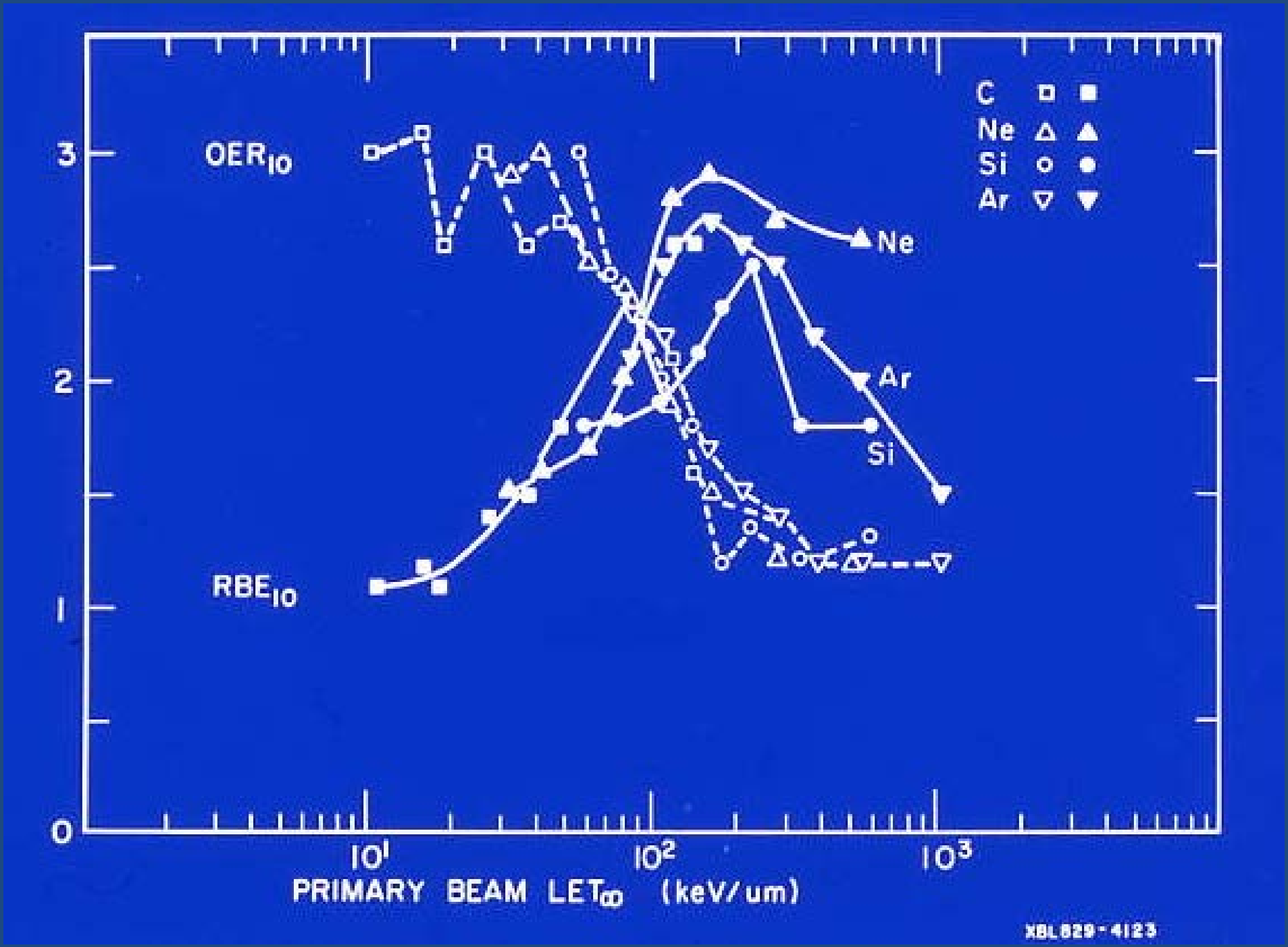
- *Physical measurements of absorbed particle radiation doses are currently inadequate to estimate biological outcome of cell- & tissue-specific effects from exposures at the stopping ranges of particle beams from stopping protons to heavier ion beams*

Aerobic & Hypoxic Cell Killing with Carbon or Argon Beams



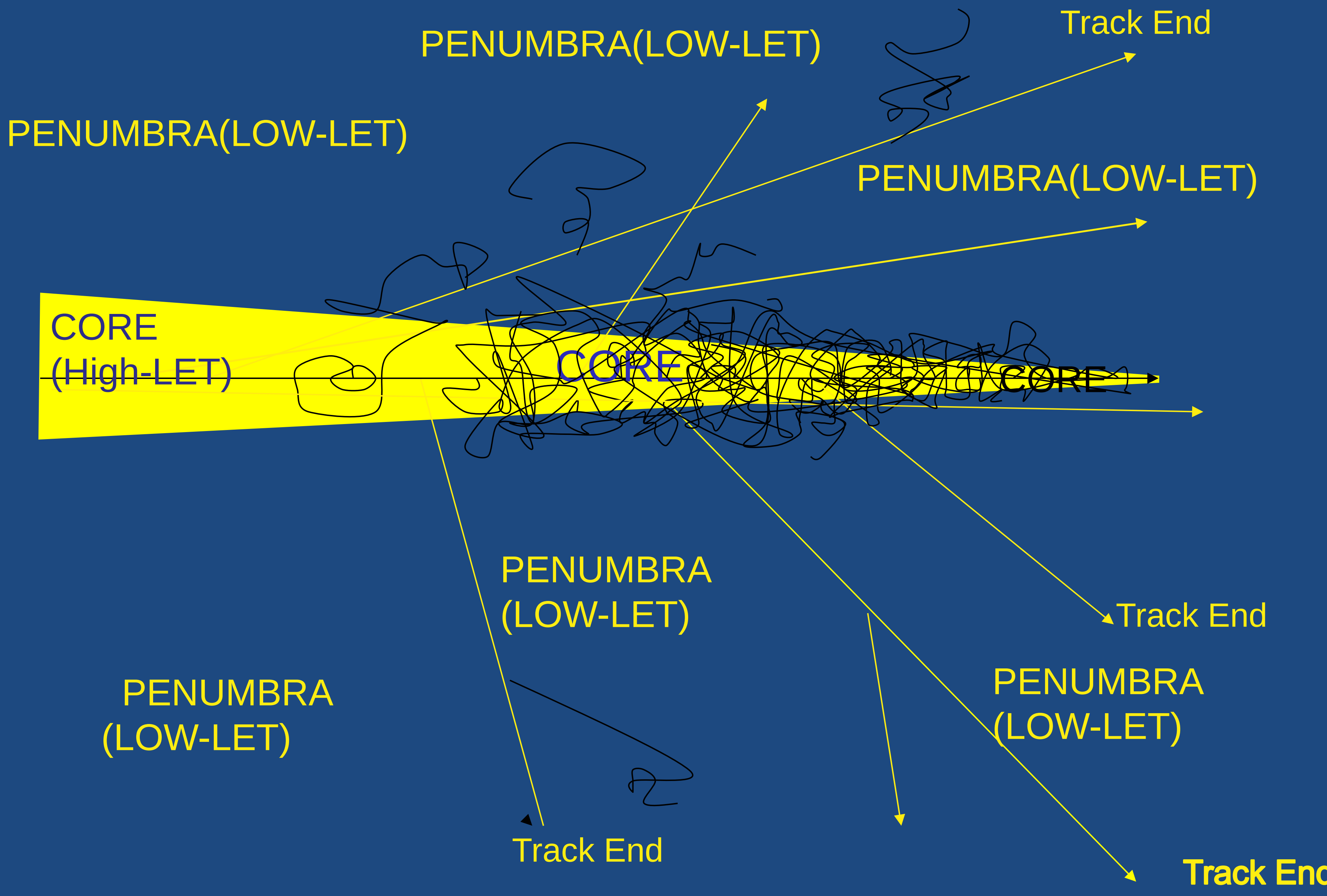
Blakely et al.

LET-Dependence of HZE RBE & OER is Maximal Near 150 keV/μm

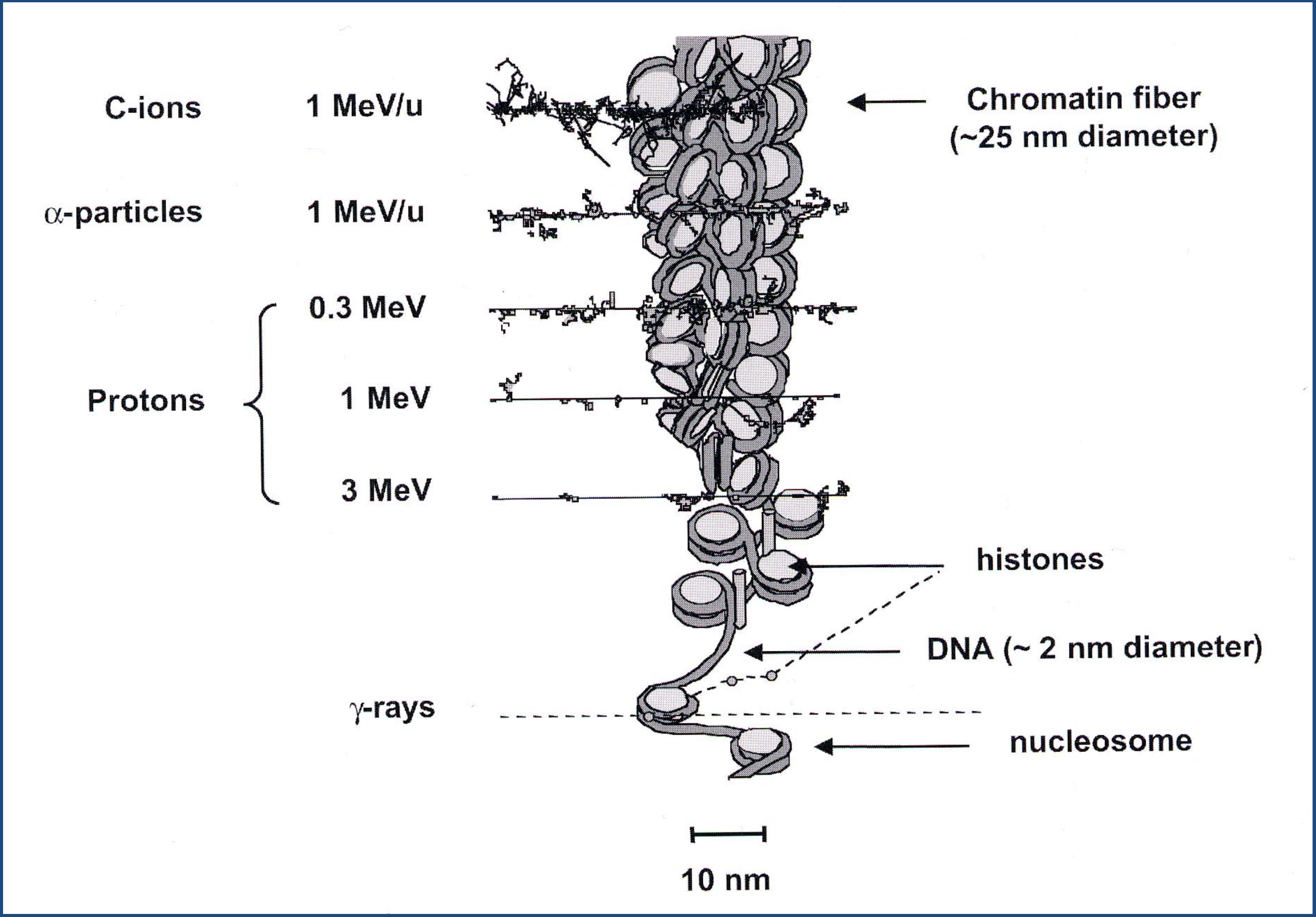


Blakely et al.

Track Structure of HZE Particles



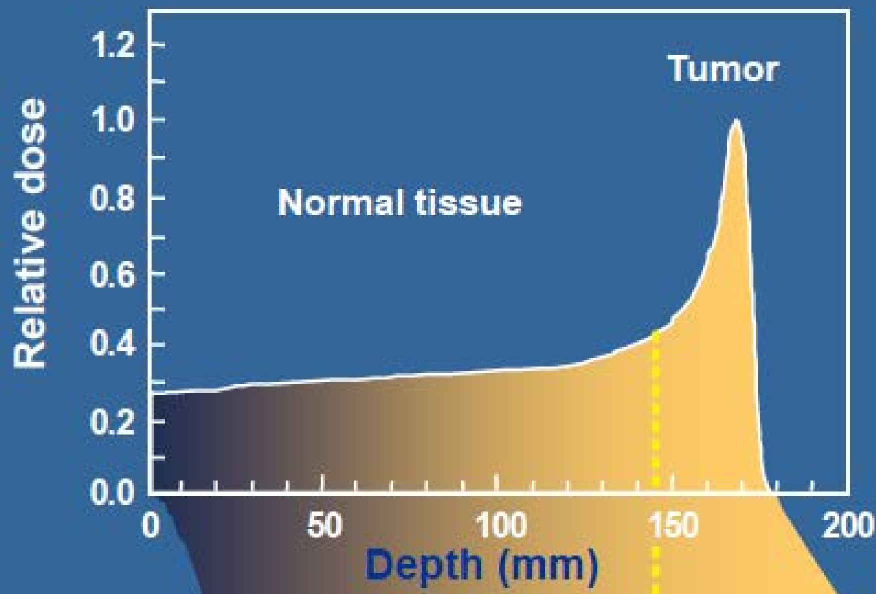
Track-Dependent DNA Targets of Particle Radiation



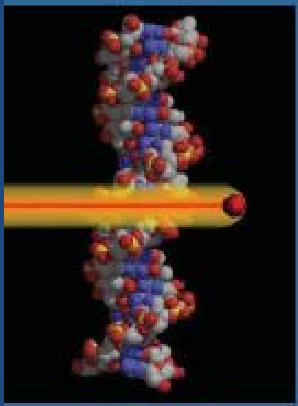
Belli et al, 2002

Durante & Loeffler,

Nature Rev Clin Oncol 2010

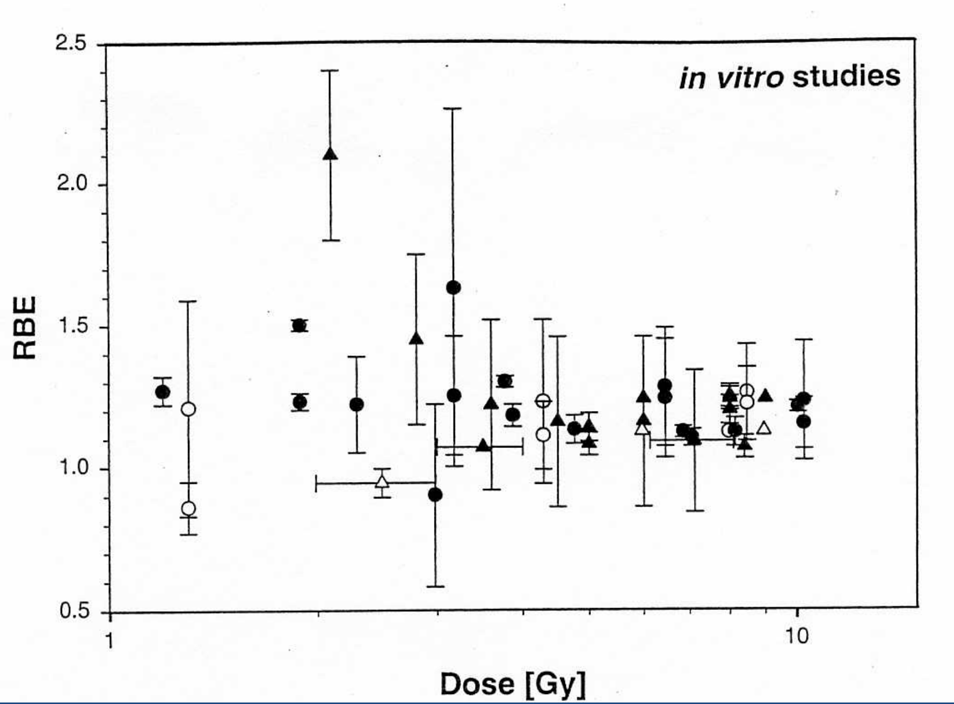


Potential advantages



Energy	high	low	
LET	low	high	
Dose	low	high	High tumor dose, normal tissue sparing
RBE	≈ 1	> 1	Effective for radioresistant tumors
OER	≈ 3	< 3	Effective against hypoxic tumor cells
Cell-cycle dependence	high	low	Increased lethality in the target because cells in radioresistant (S) phase are sensitized
Fractionation dependence	high	low	Fractionation spares normal tissue more than tumor
Angiogenesis	Increased	Decreased	Reduced angiogenesis and metastatization
Cell migration	Increased	Decreased	

Proton Radiobiology



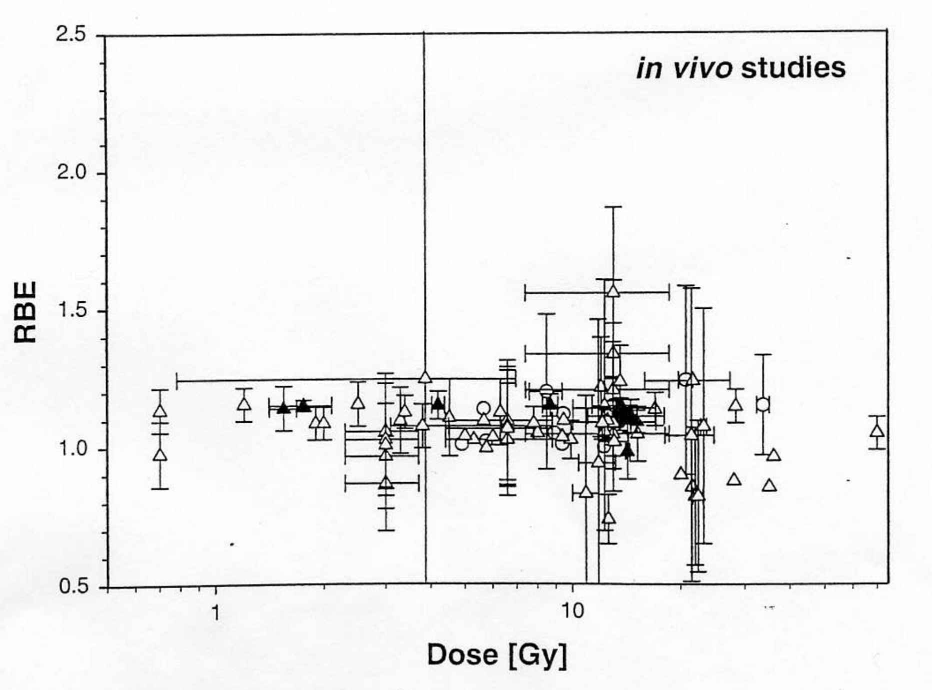
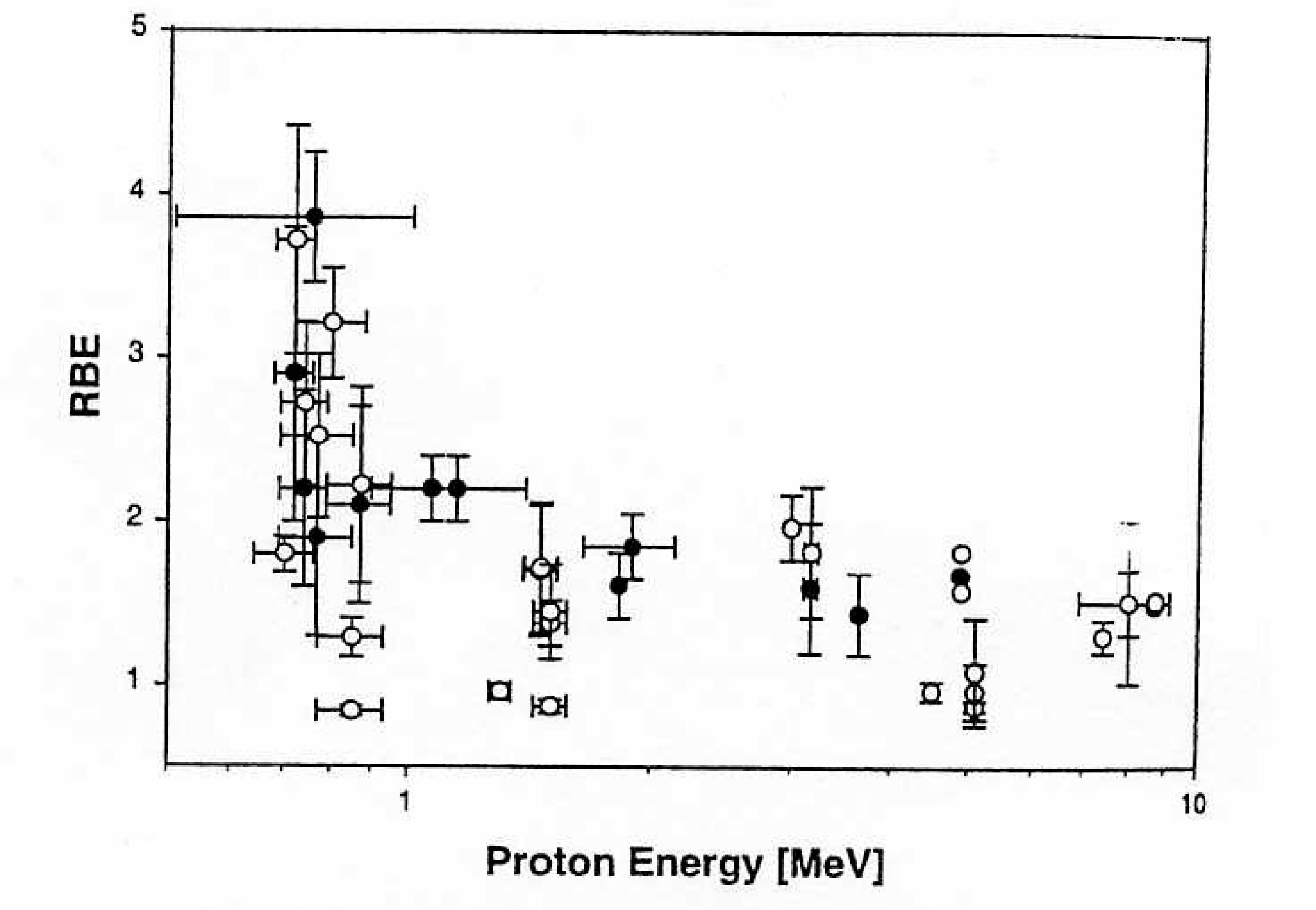


Fig. 1. Experimental proton RBE values (relative to ^{60}Co) as a function of dose/fraction for cell inactivation measured *in vitro* in the center of a SOBP. Closed symbols show measurements using Chinese Hamster cell lines; open symbols stand for other cell lines. Circles represent RBEs for <100-MeV beams and triangles for >100-MeV beams.

Fig. 2. Experimental proton RBE values (relative to ^{60}Co) as a function of dose/fraction measured *in vivo* in the center of a SOBP. Closed symbols show RBE values for jejunal crypt cells, open symbols stand for RBEs for all other tissues. Circles represent RBEs for <100-MeV beams and triangles for >100-MeV beams.

Paganetti et al. 2002

Proton RBE as a Function of Energy



Paganetti et al. 2002

For IMPT beams dose deposition, LET and RBE per voxel are highly heterogeneous

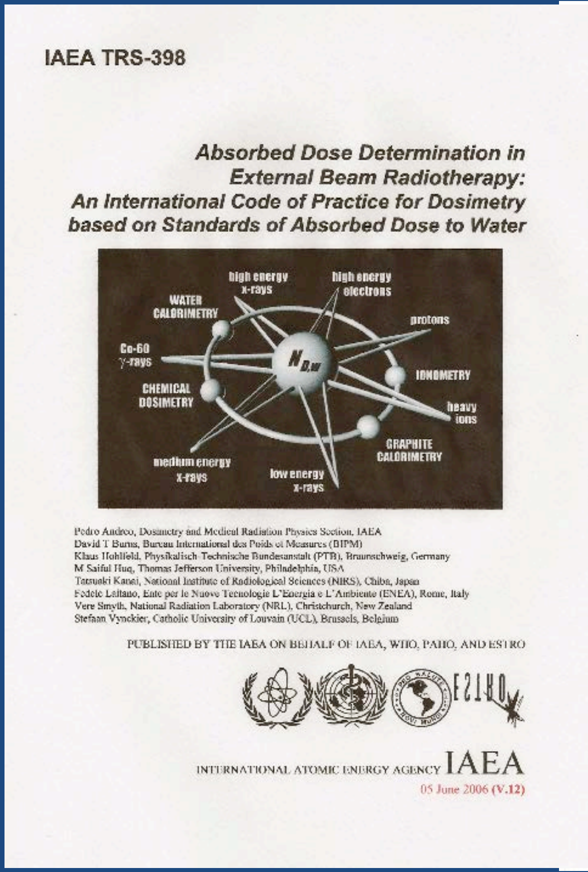
RBE of 1.1 For Protons
Becomes Even More Questionable

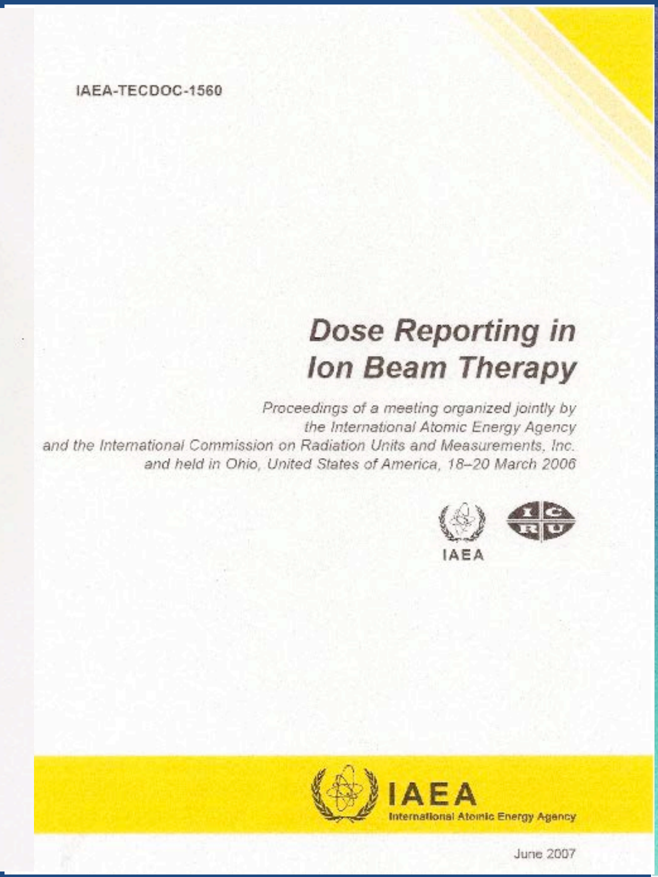
Radhe Mohan, 2013

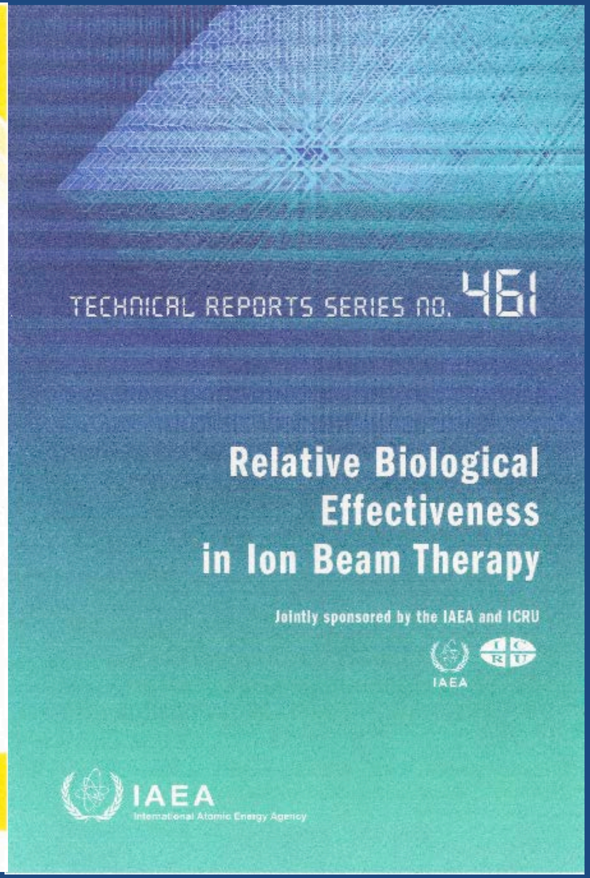
Carbon Dose Specifications by Institute

- *Specification of Carbon-Ion Doses at the NIRS (Matsufui et al., 2007)*
- *Specifying Carbon Ion Doses for Radiotherapy: The Heidelberg Approach (Jakel et al., 2007)*
- *Biological intercomparison using gut crypt survivals for proton & carbon ion beams (Uzawa et al., 2007)*

Recent IAEA Reports on Ion Beam Therapy







IAEA TRS-398
2000, ver 12 2006

IAEA-TECDOC-1560
2007

IAEA TRS-461
2008

Open Questions

Optimal Particle Species

Differential Effects:Tissue Dependence

Hypofractionation

Volume Effects

Secondary Cancer Induction

Individual Sensitivity

Role of Reduced OER

Combined Radio-Chemotherapy

Modelling

Scholz, 2013

What makes particle radiation so effective?

Track structure

Clustered damage

Production of short DNA fragments

Slower repair

Evidence of misrepair

Genomic instabilities

Microenvironmental changes

LET-dependent gene responses

Why is it important to identify molecular pathways of action?

- *We have the tools to understand the molecular pathology of cancer and how to use this information to treat individual cancers.* (Harris & McCormick, Nature Reviews Clinical Oncol, 2010; Riedel et al., Mol Cancer Ther, 2008)
- *Unique gene expression pathways are being reported in the literature for human tumors irradiated with radiations of different radiation qualities (Maalouf et al., IJROBP, 2009; Hamada et al., Radiotherapy Oncology, 2008; Higo et al., IJROBP, 2006)*

New Era for Charged Particle Radiobiology

- *Human genome mapped & being mined for tumor and normal tissue data on radioresponse*
- *Powerful new genomic & proteomic tools available*
- *Focus on individualized medicine*
- *Networks of gene & protein pathways identified*
- *Gene expression profiles change in a dose- and time-dependent fashion after exposure to particles of variable LET*
- *Tailored 3-D image-guided & intensity modulated physics*
- *Theoretical biophysical modeling is guiding treatment optimization, but more work is needed to understand microdosimetric energy deposition effects*

FULL POTENTIAL OF HADRON THERAPY IS HINDERED BY:

- Underfunding of ion beam radiobiology in most locations worldwide, despite evidence for transforming breakthrough applications
- Inadequate radiobiological funding to provide access to beams to resolve technical differences in current hadron treatment planning worldwide

Acknowledgments

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