ENLIGHT for SEEIIST in South-East Europe

Berkeley, Where It All Started

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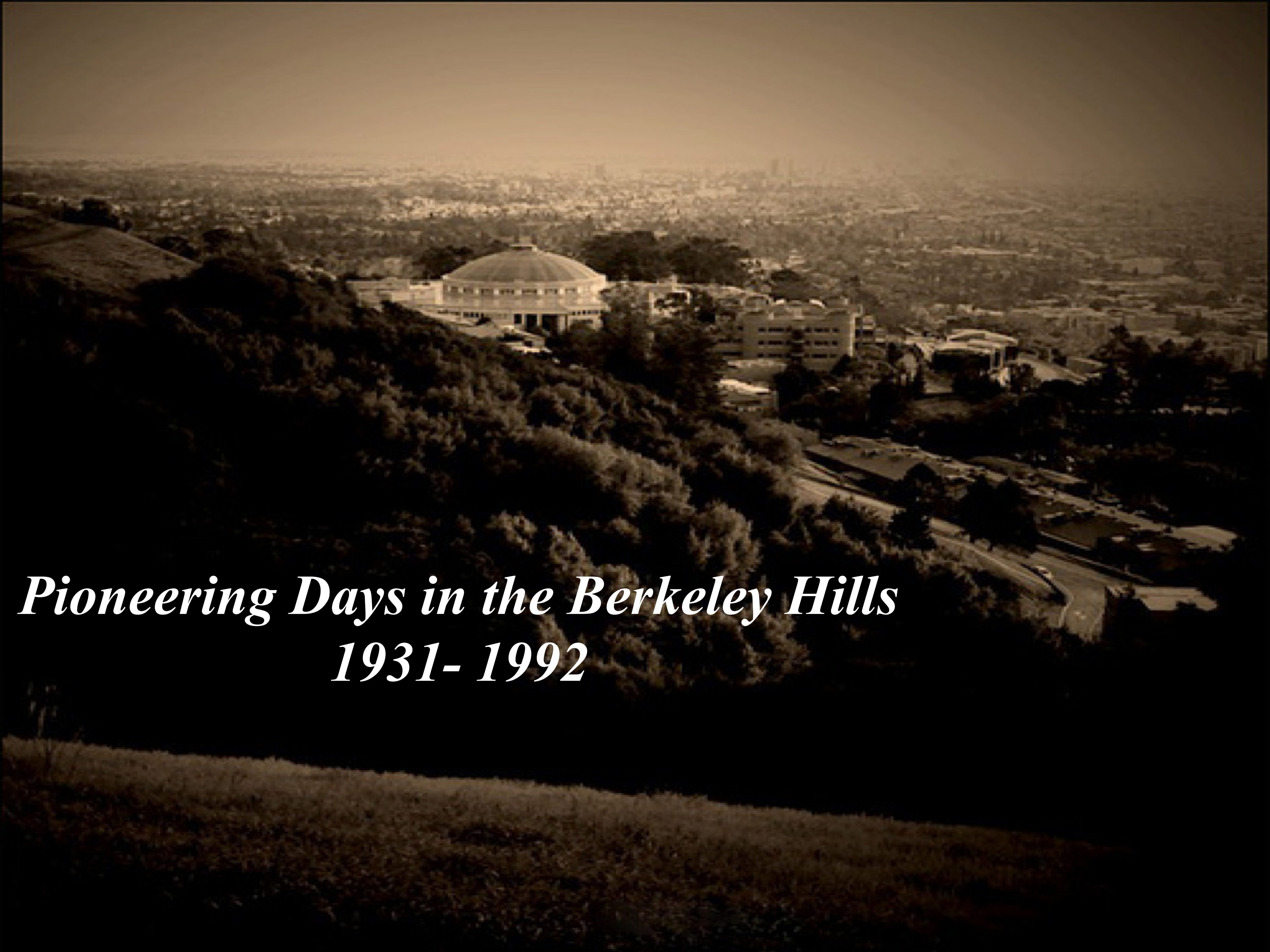
Goal of Presentation

- *To provide an historical perspective on the early Phase I/II trials using charged particle beams for the treatment of cancer in Berkeley, California 1940-1993*


Pioneering Days in the Berkeley Hills
1931- 1992

Ernest Orlando Lawrence
Physicist, UC Berkeley

The Radiation Laboratory, 1933

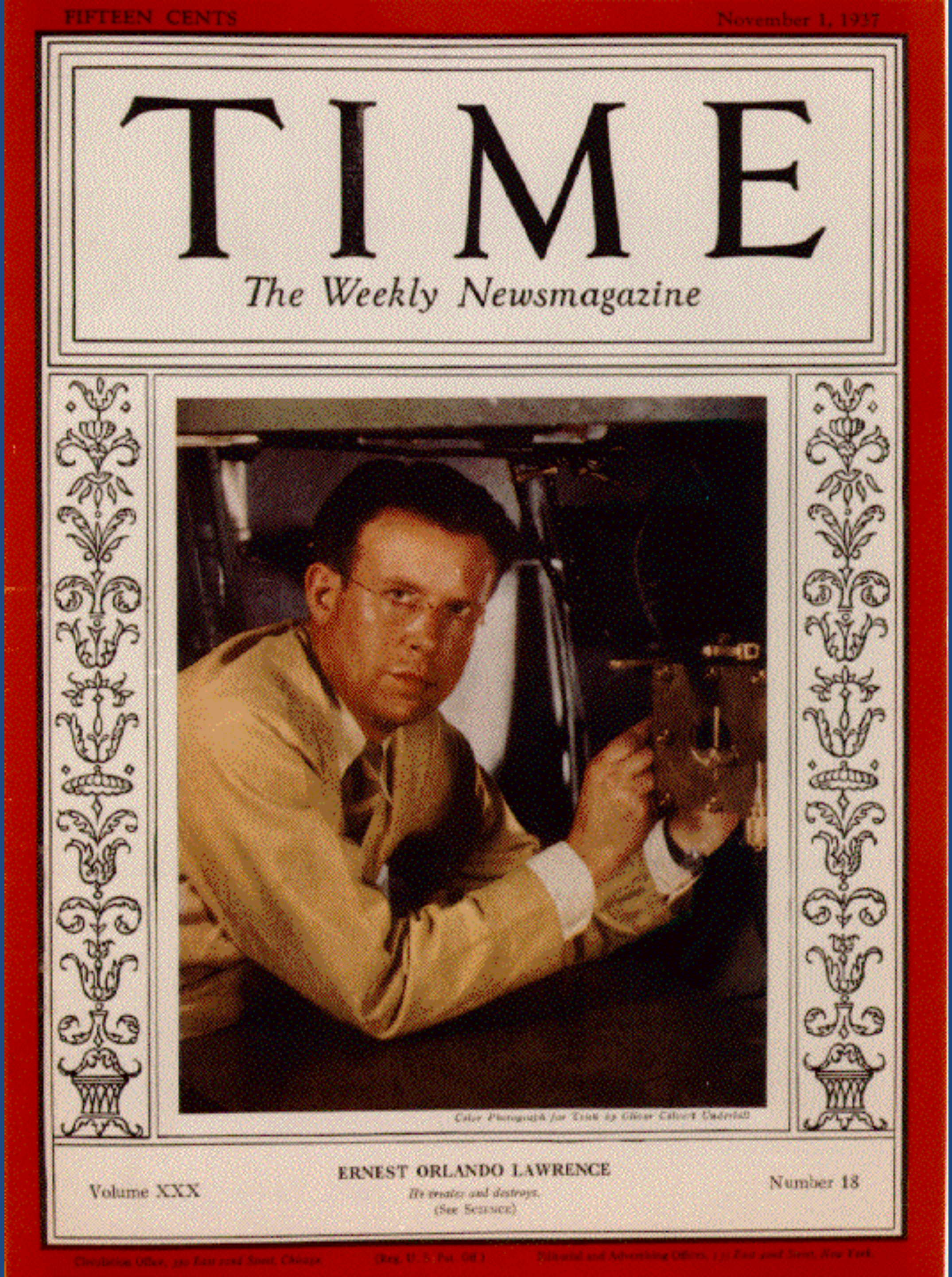
The Rad Lab was established within the UC Berkeley Physics Department with Ernest O. Lawrence as Director. Eventually the Rad Lab became the EO Lawrence Berkeley National Laboratory.

Invention of the Cyclotron

Ernest Orlando Lawrence
1931- Invented the cyclotron
1939-Nobel Prize in Physics

Prof. E. O. Lawrence and M. Stanley Livingston of UC Berkeley, constructed a 13-cm diameter cyclotron, which accelerated protons to 80,000 volts using less than 1,000 volts.

EO Lawrence and MS Livingstone, Phys. Rev 37: 1707 (1931); and MS Livingston, The Production of High-Velocity Hydrogen Ions Without the Use of High Voltages, PhD thesis, University of California, Berkeley (1931).

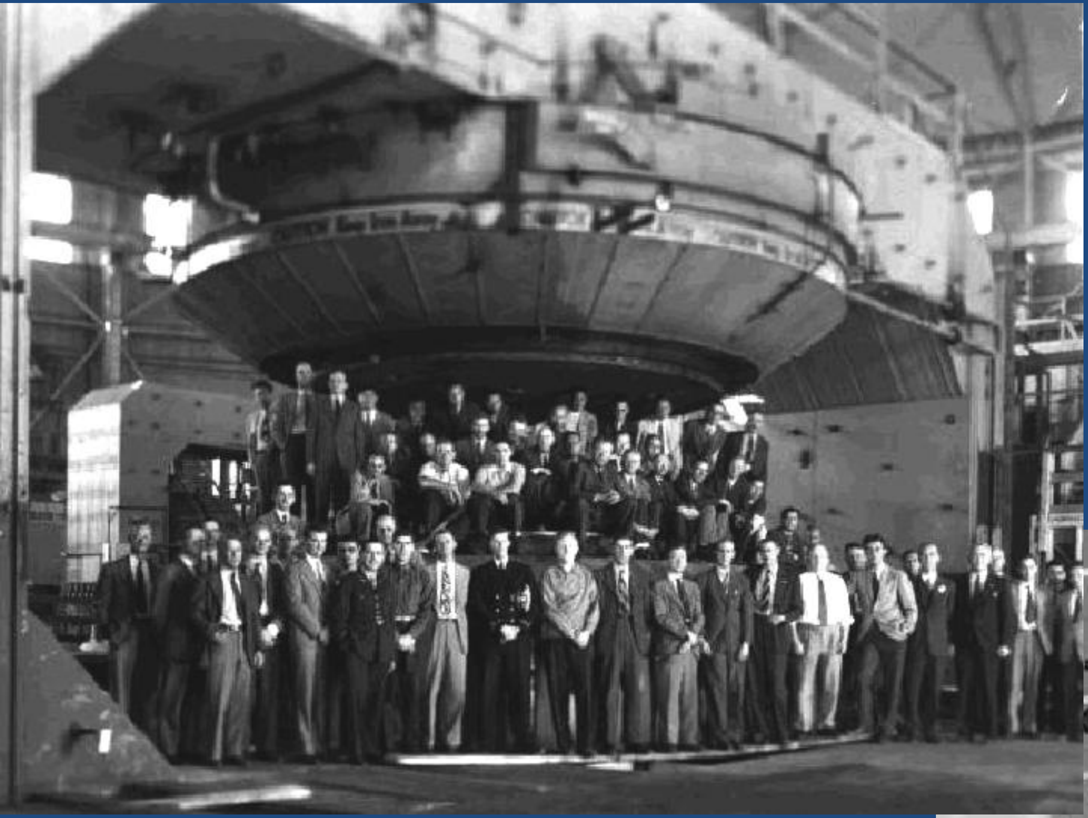


1931
Nobel Prize in Physics

Before the 184" Cyclotron was Built in Berkeley


Outside

184-Inch Cyclotron (1947)

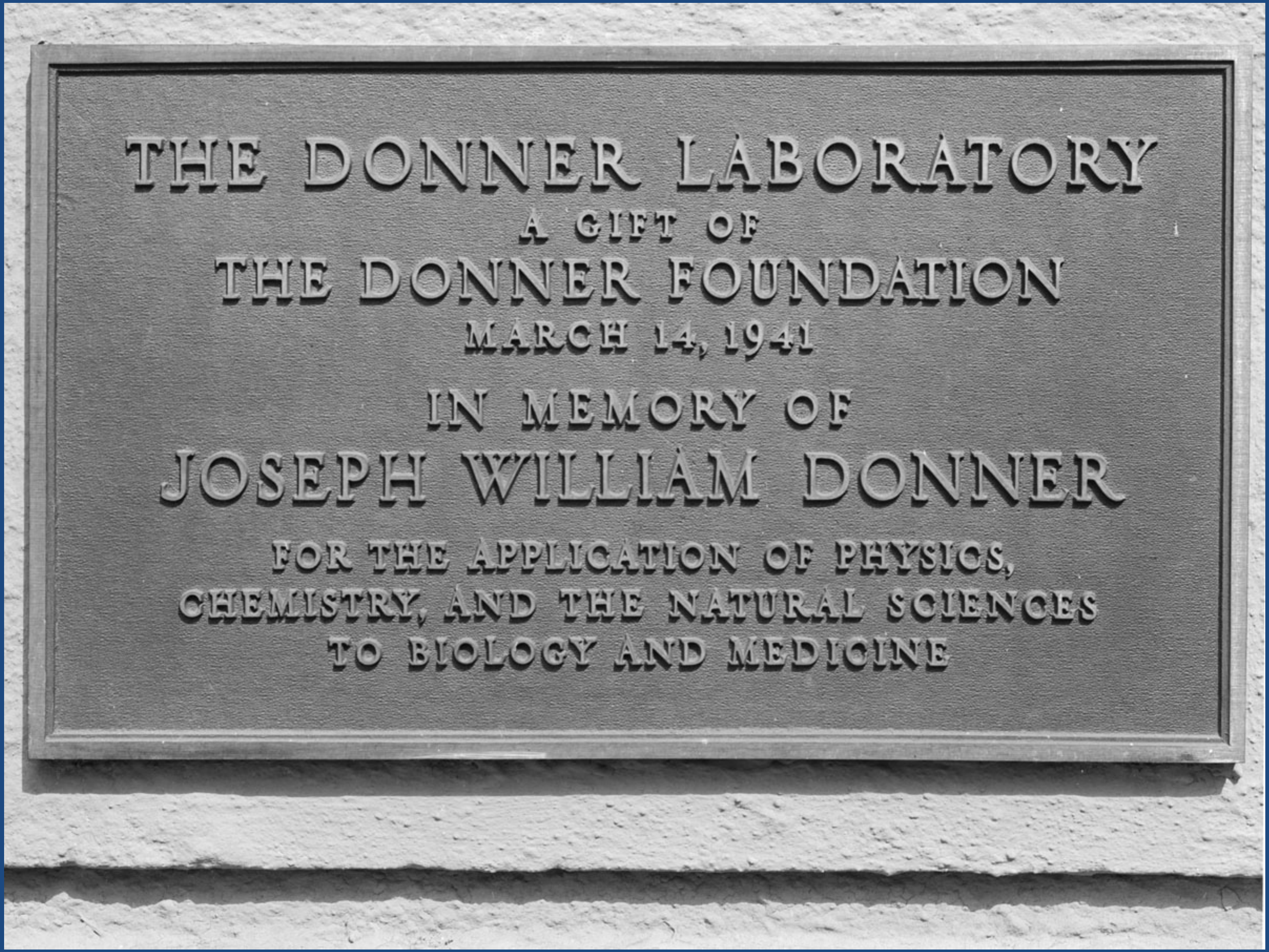


The first beam, Nov 1, 1947


CAUTION Keep Iron Away

Ernest and John Lawrence who started Donner Biomedical Laboratory at Berkeley Lab that is now known as the Biosciences Area of LBNL

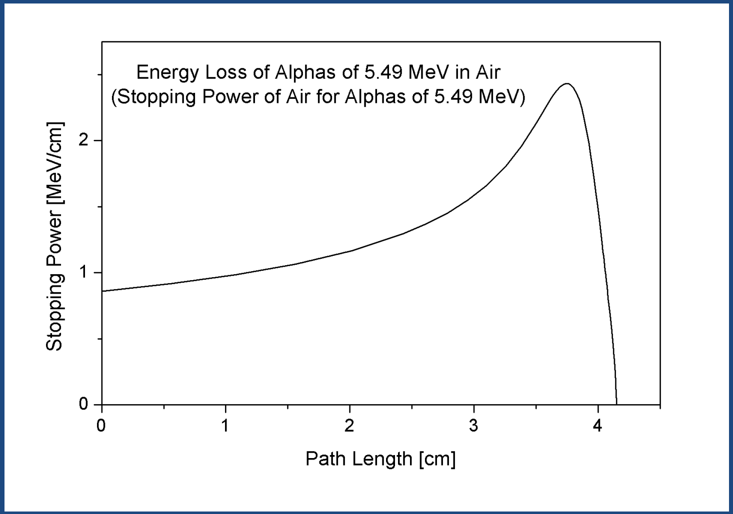
Donner Laboratory Dedication 14 March 1941

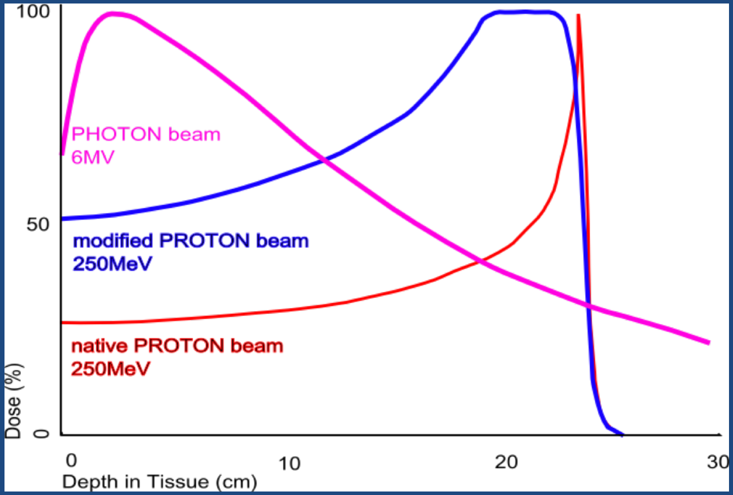


Hadron Therapy

- *First begun in 1938 when neutron beams were used in cancer therapy.*
- *Charged hadron beams (protons & carbon ions) have more favorable depth-dose interaction which is maximal at the end of their range.*
- *Initially in Europe "hadron" therapy meant proton therapy, but "charged particles" includes protons, carbon or any charged ion beam.*
- *Both macroscopic & microscopic differences exist in the physical properties of various charged ion beams.*

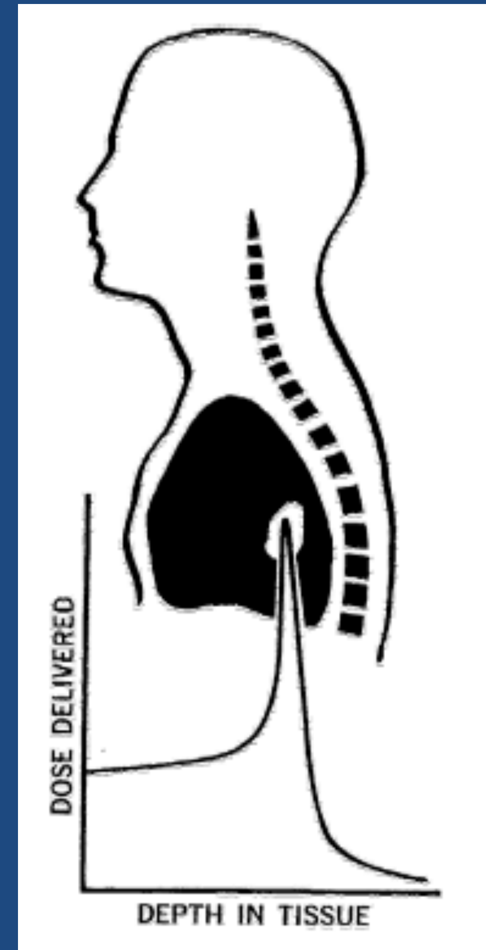
Sir William Henry Bragg first reported "Bragg Curve" 1903





R.R. Wilson and Rationale for Bragg Peak Therapy

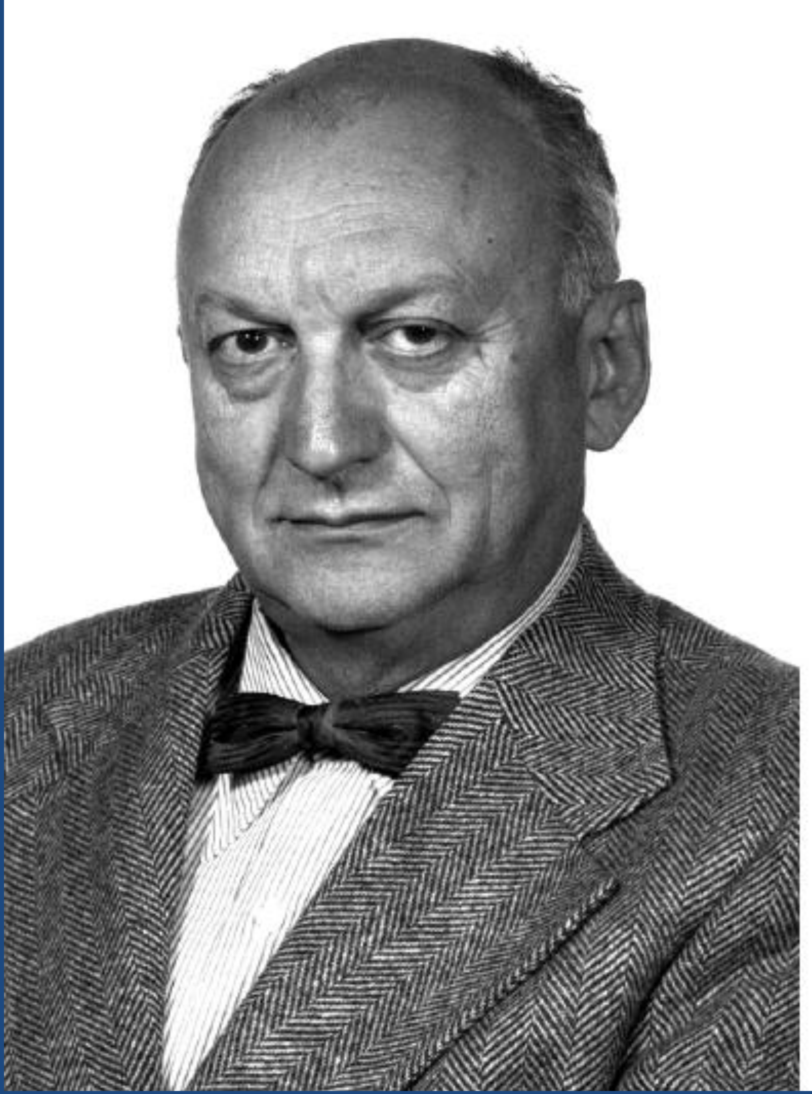
In 1946, Prof. Robert Wilson proposed the use of the Bragg Peak for radiation therapy
R.R. Wilson, "Radiological use of fast protons," Radiology. 1946; 47: 487-491. *



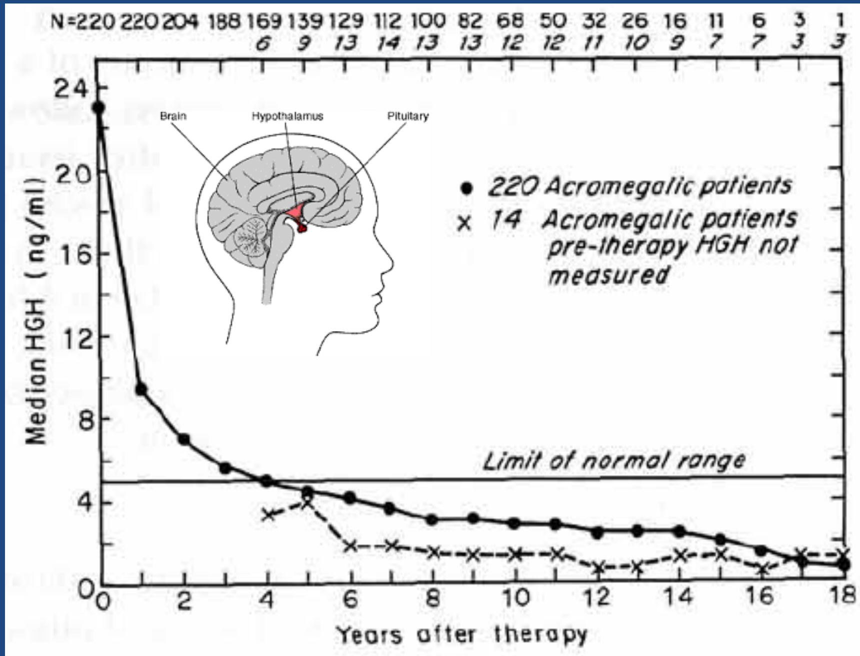
- Dose localization
- Lower entrance dose
- No or low exit dose

FIRST PROTON THERAPY PATIENT TREATED
September 1954

- ***1948: Biology experiments using protons***
- ***1952: Human exposure to deuteron & helium ion beams.***
- ***1954: Human exposure to accelerated protons.***
- ***1956-1986: Clinical Trials– 1500 patients***



Prof. Cornelius A. Tobias

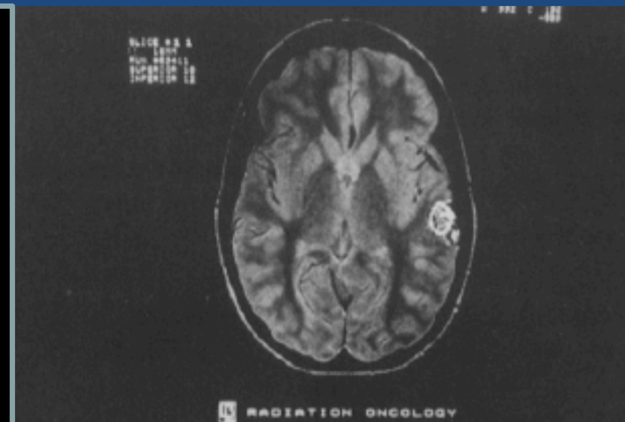


Heavy-Charged Particle Radiosurgery of the Pituitary Gland: Clinical Results of 840 Patients

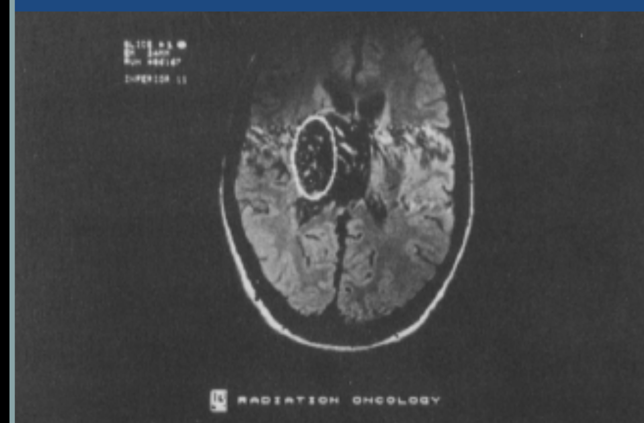
- Initial 30 Pts. Treated with Protons
- Subsequent 820 were treated with He plateau, 30-36 Gy in 3-4 Fx over 5 days.
- Marked and sustained biochemical & clinical improvement observed in majority of the Pts.
- Focal necrosis/nerve injury in only 1%

Levy, Fabrikant, Frankel, Phillips, Lyman, Lawrence, Tobias, Stereotact Funct Neurosurg, 1991

Intracranial Arteriovenous Malformations (AVMs)



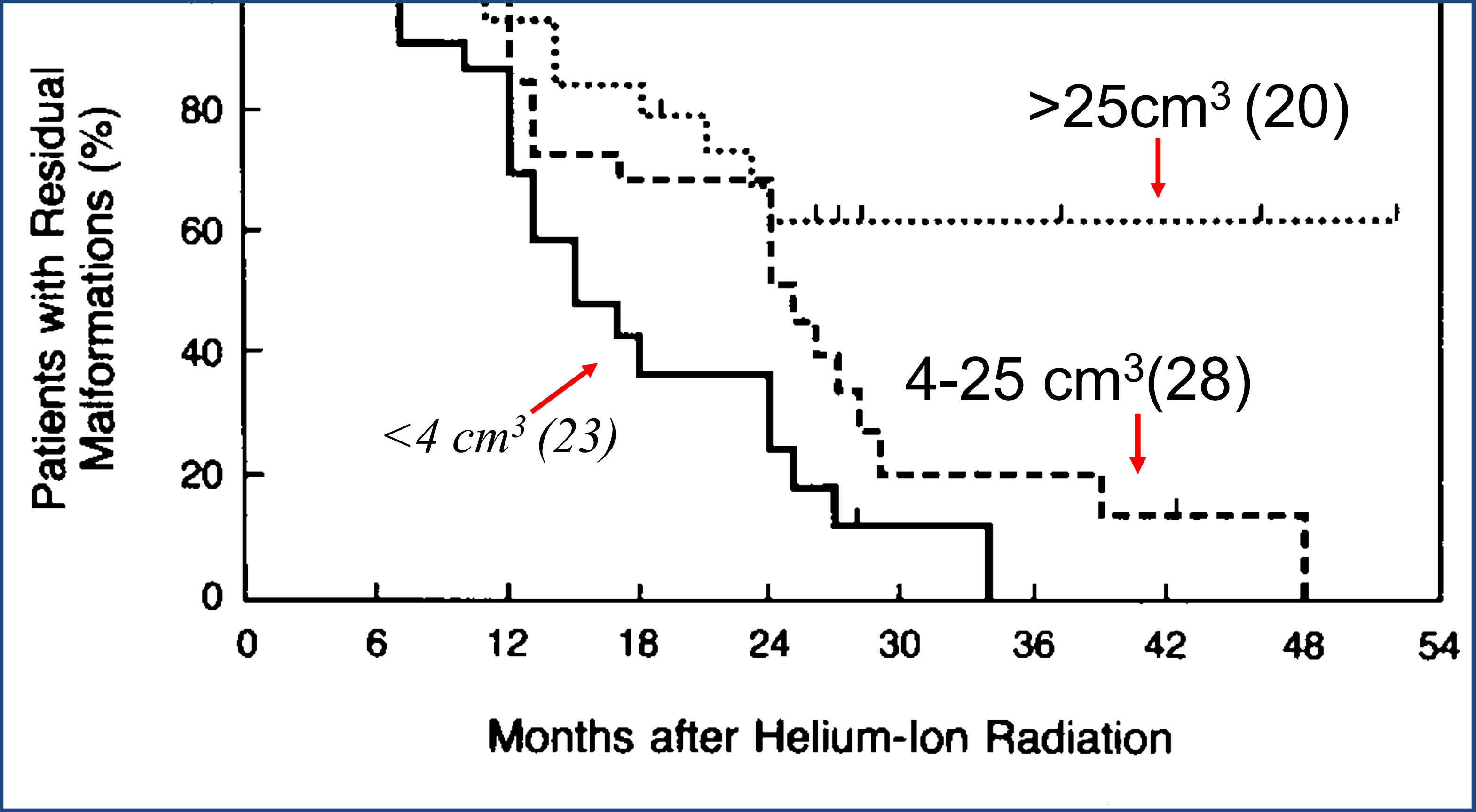
26-yr old
Female-2.5 cm^2
AVM temporal
lobe



21-yr old Male
45 cm^3 AVM
Basal ganglia
And thalamus

Phillips, Kessler, Chuang, Frankel,
Lyman, Fabrikant, and Levy, Int. J. Radiat Bio

Kaplan-Meier Cumulative Obliteration Plots for 71 Patients with Intracranial AVM with Angiography Before and After Treatment with a Single 7.7-19.2 Gy dose of 225 MeV/u Helium



Steinberg, Fabrikant, Mark, Levy, Frankel, Phillips, Shuer, and Silverberg, NEJM, 1990

Precision, He High Dose Radiotherapy: Treatment of Uveal Melanoma

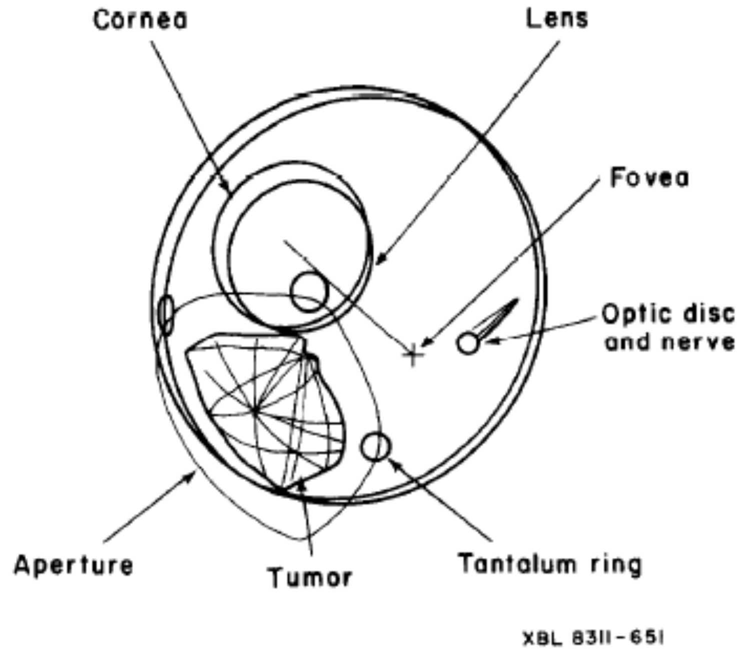
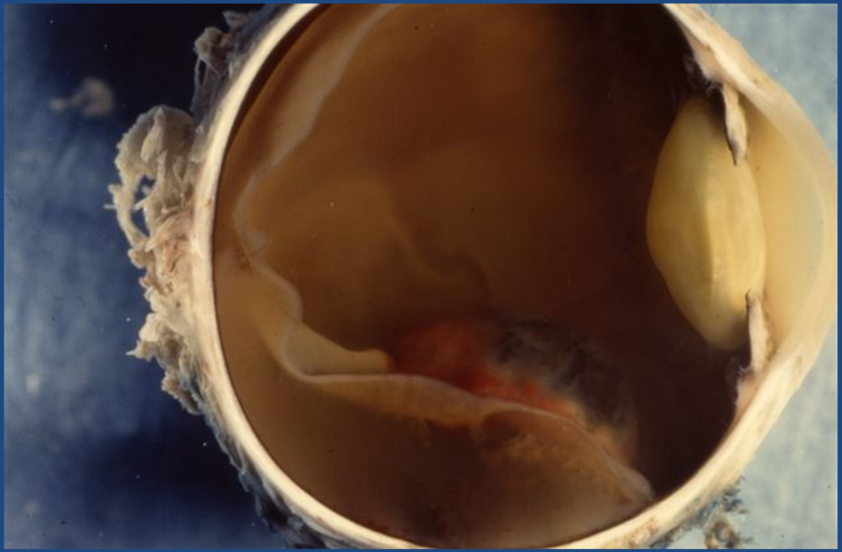
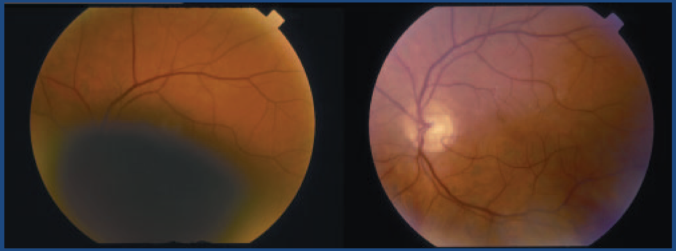


Fig. 3. Output from Massachusetts General Hospital treatment planning program.[7]

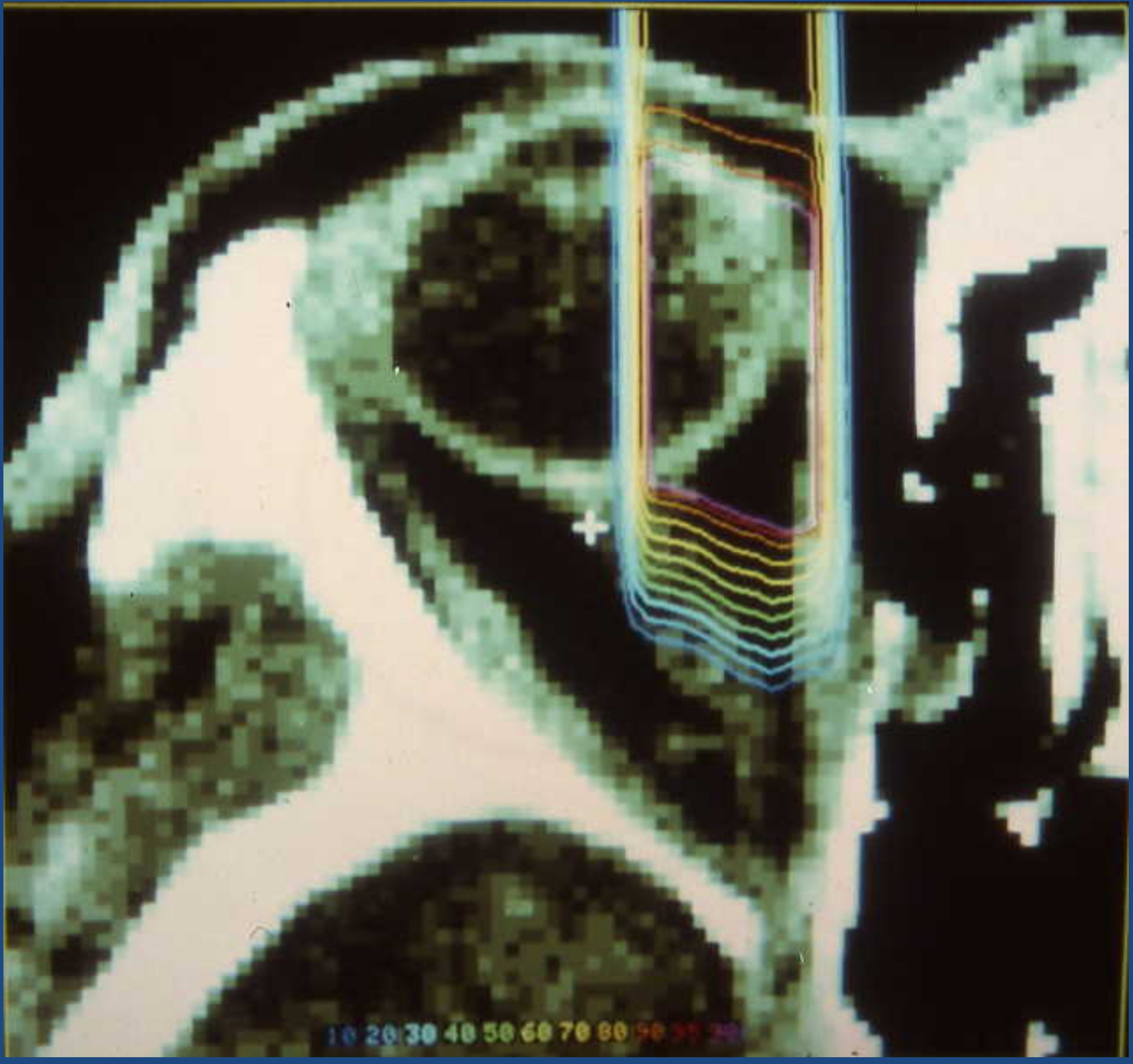


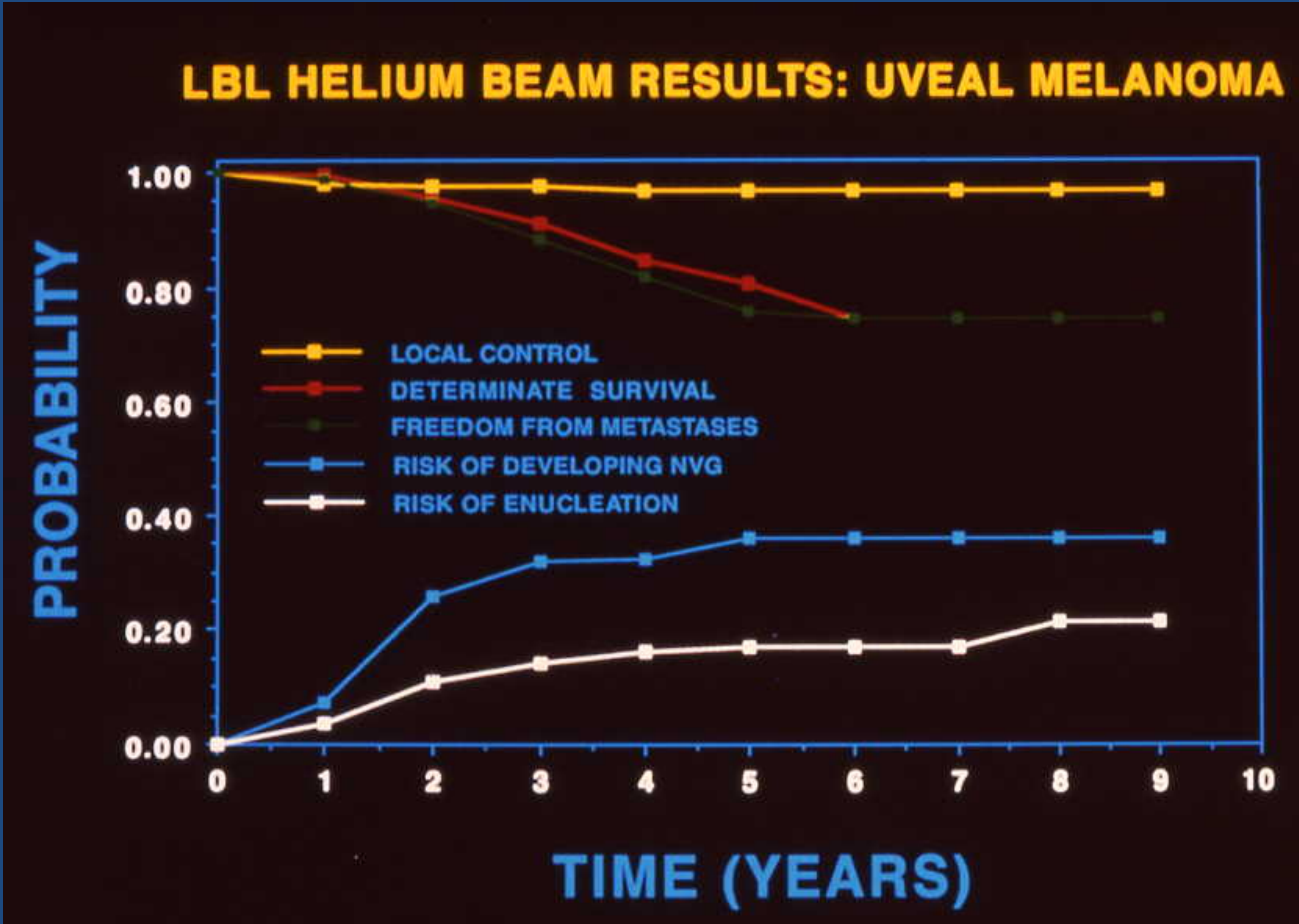


Saunders, Char, Quivey, Castro, Chen, Collier, Cartigny, Blakely, Lyman, Zink and Tobias, Int, J Radiat Oncol Biol Phys 1985,

Gragoudas, Weisenfield Lecture, IOVS, 2006

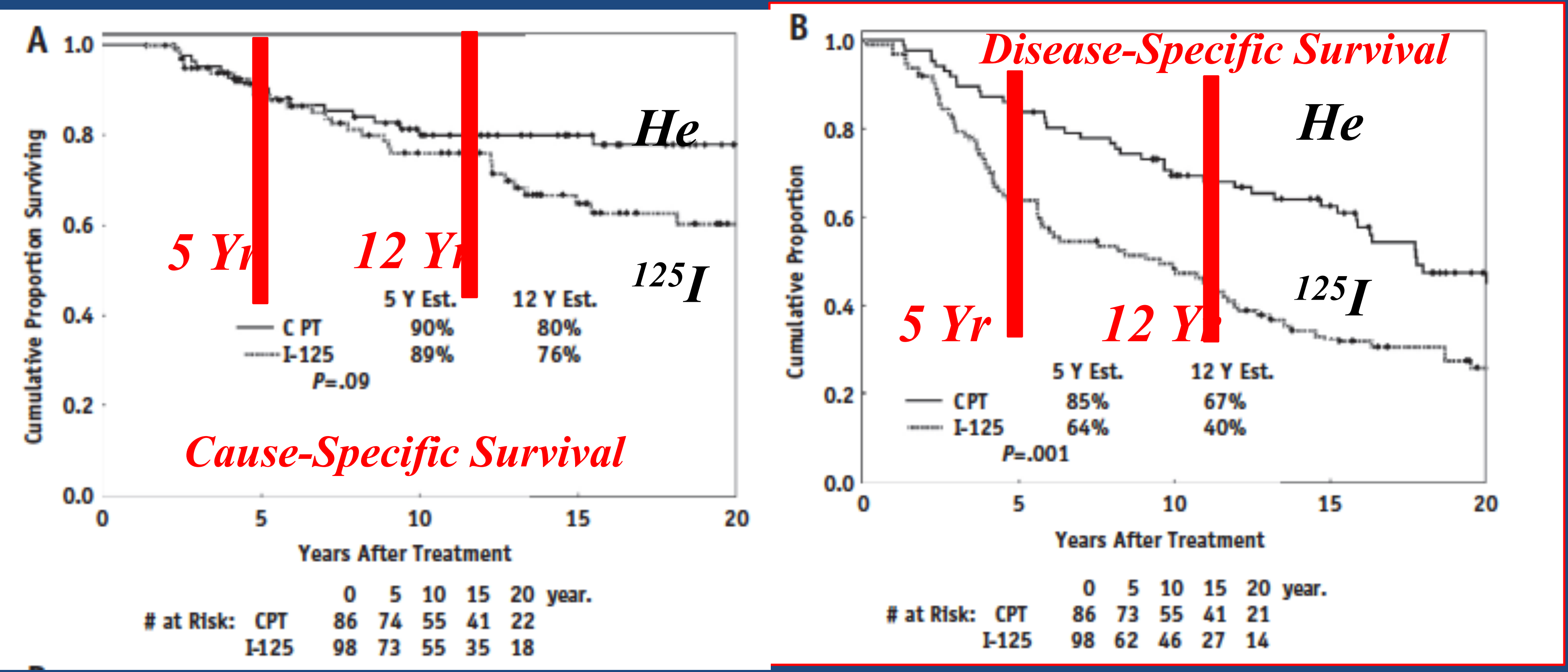
1975-1st Proton treatment of Uveal Melanoma


10 20 30 40 50 60 70 80 90



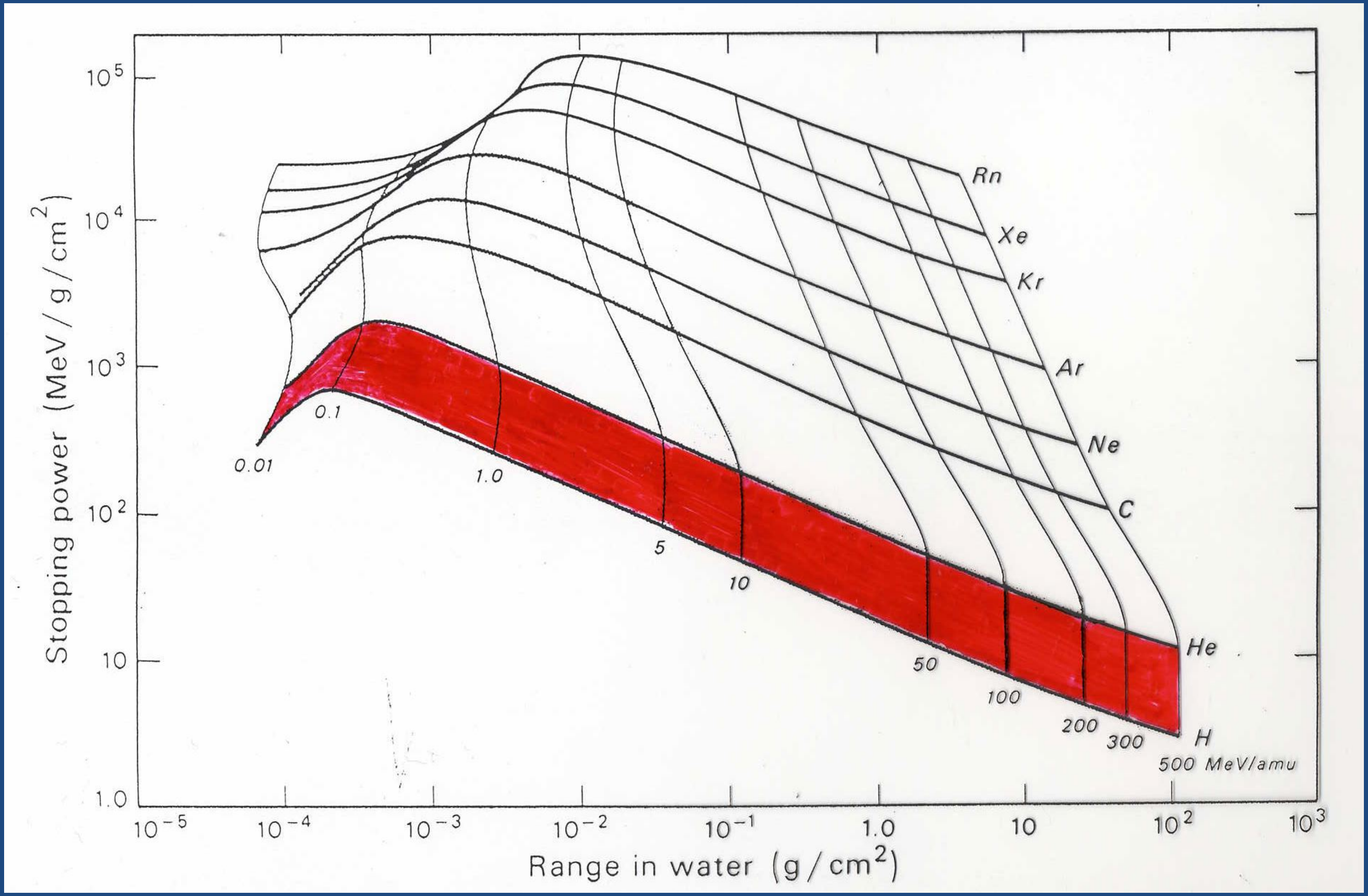
LBL HELIUM BEAM RESULTS: UVEAL MELANOMA
PROBABILITY
1.00
0.80
0.60
0.40
0.20
0.00
LOCAL CONTROL
DETERMINATE SURVIVAL
FREEDOM FROM METASTASES
RISK OF DEVELOPING NVG
RISK OF ENUCLEATION
0
1
2
3
4
5
6
7
8
9
10
TIME (YEARS)

20-Yr. Follow-Up of Phase III Randomized Trial-- Helium vs. ^{125}Iodine Plaque for Choroidal & Ciliary Body Melanoma



Mishra, Quivey, Daftari, Weinberg, Cole, Patel, Castro Phillips, and Char, Int. J. Radiat. Oncol Biol Phys, 2015

Theoretical range energy and stopping power for various heavy ions in water



Steward, 1968

Why Heavier Hadron Beams?

Precision Therapy Conformed to Tumor

Sparing of Normal Tissues

Increased DNA Damage in Tumor

Increased Effect on Hypoxic Tumors

Less Repair of Sublethal and Potentially Lethal Damage in Cell Cycle

Short Overall Treatment Course

Use of Radioactive Beam Component for Treatment Verification

Clinical Trials at LBNL-UCSF, 1975–1992

Prof. Joseph Castro, UC San Francisco conducted the LBNL clinical trials.

Total He ions Pts
1952-1992   2054

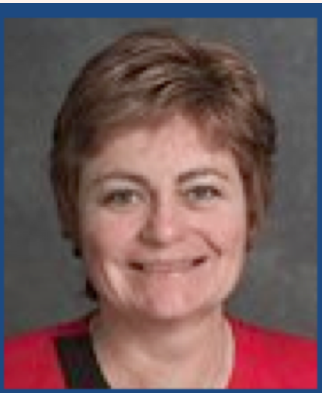
1975-1992	Total treated	NCOG/RTOG
He ions	858 patients	700 patients
Neon ions	433 patients	300patients

1st He patient	*6/75*
1st C patient	*5/77*
1st Ne patient	*11/77*
1st Ar patient	*3/79*
1st Si patient	*11/82*
Total patient treated 1977–1992	*1314*
He patients	*858*
Heavier ions	*456*

Prof. T. Phillips

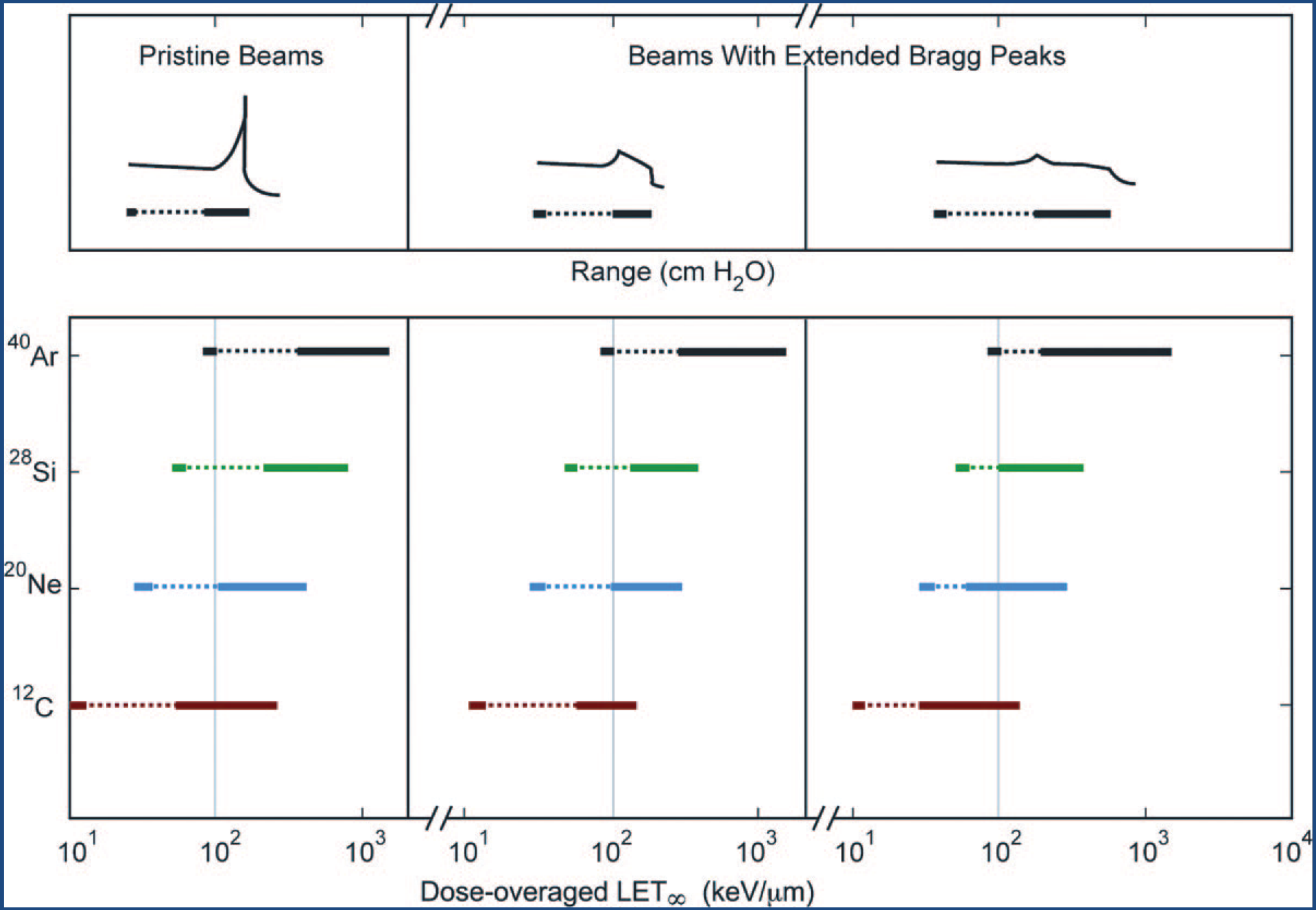
Prof. J. Quivey

Prof. G. Chen



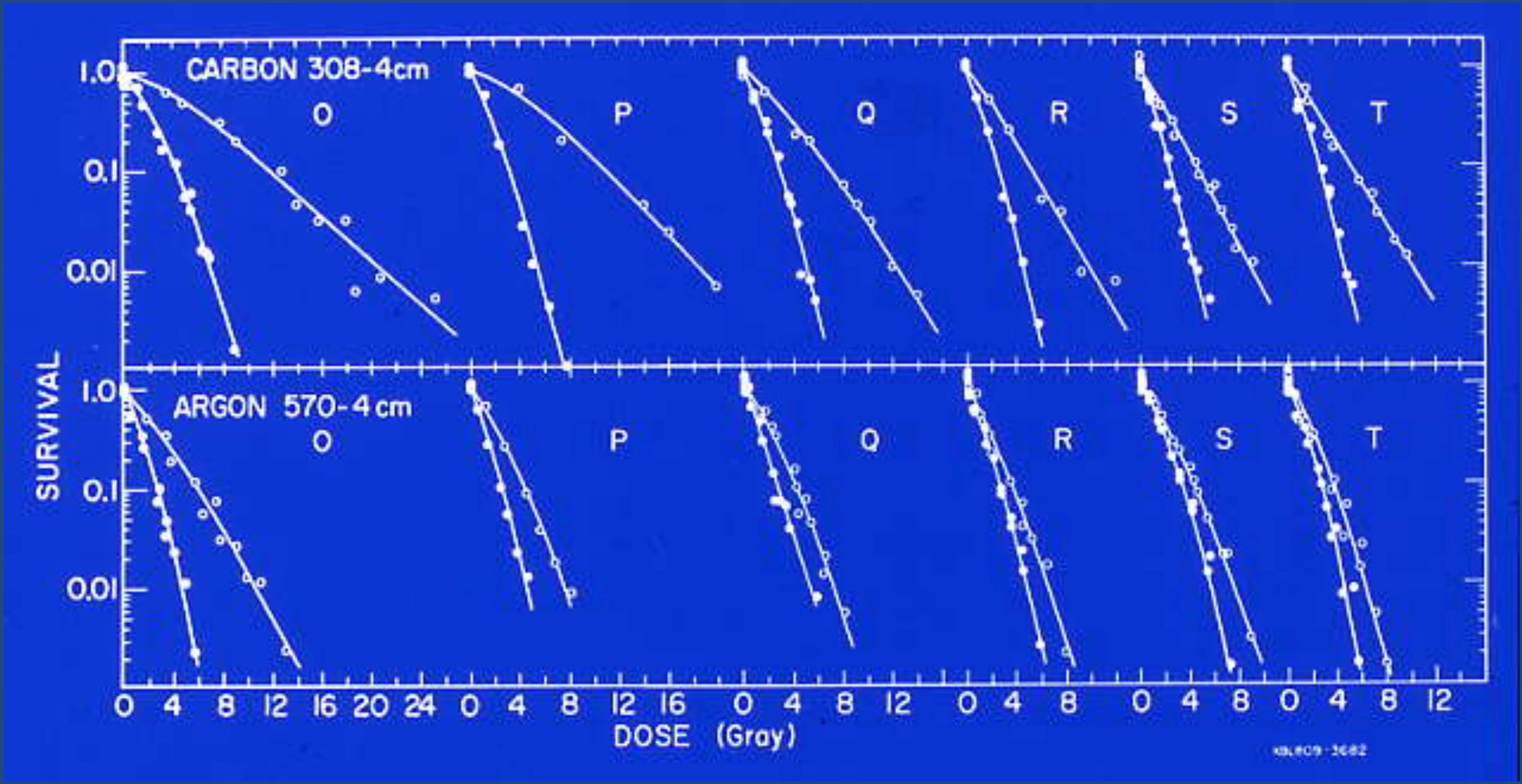
Dr. E. Blakely

LET Ranges for Pristine and Extended SOBP



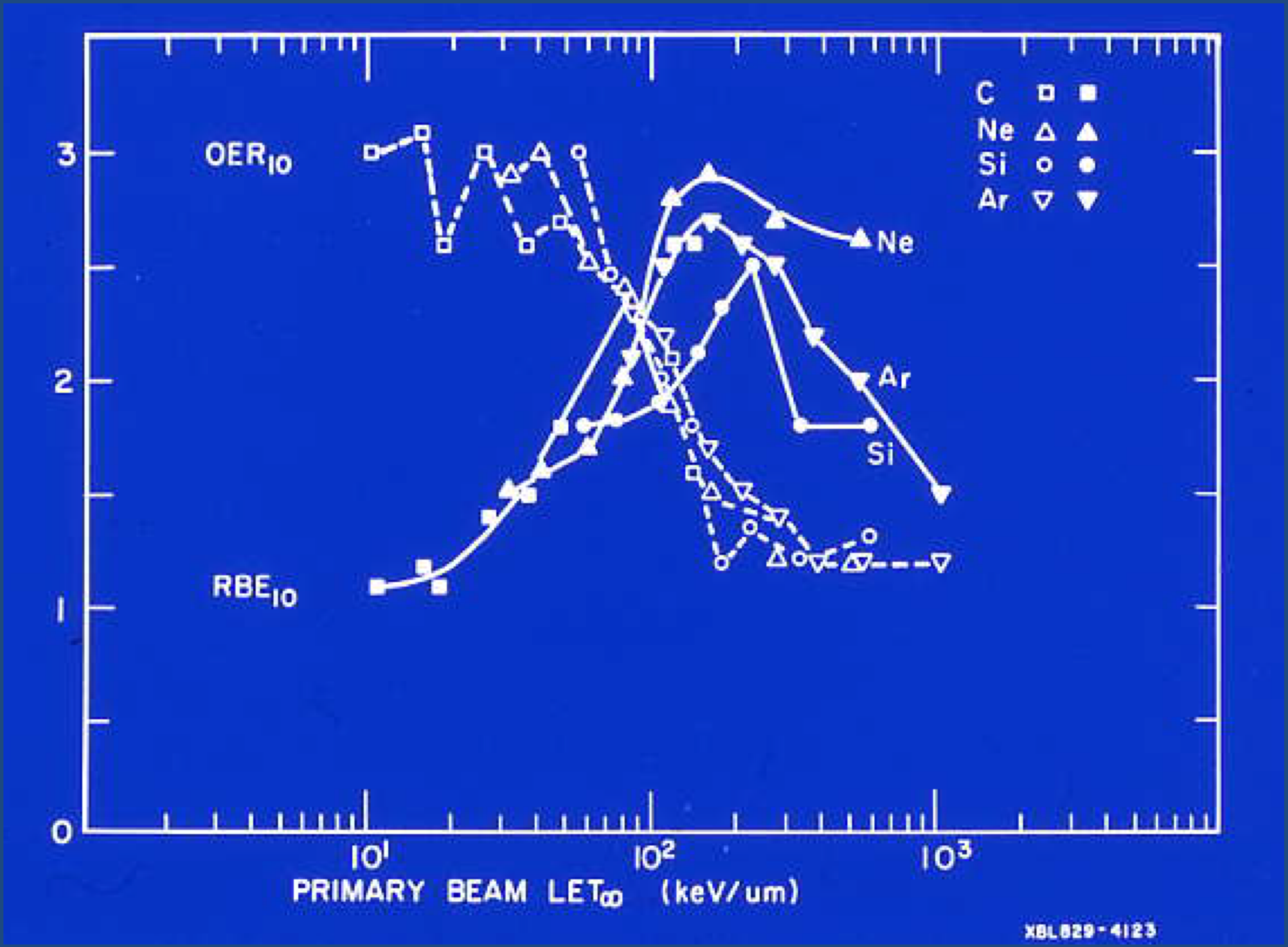
Blakely & Chang, The Cancer J, 2009

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.

Summary Table Comparing Radiation Modalities

HIGH LET ADVANTAGE??	Protons	Helium	Pions	Neutrons	Heavy Ions C	Heavy Ions Ne	Heavy Ions Si	Heavy Ions Ar
PHYSICAL DEPTH-DOSE	+++	+++	+++	no	+++	+++	++	+
RBE	no	+	+	++	++	++	+++	+++
OER	no	+	+	+++	+	++	+++	+++

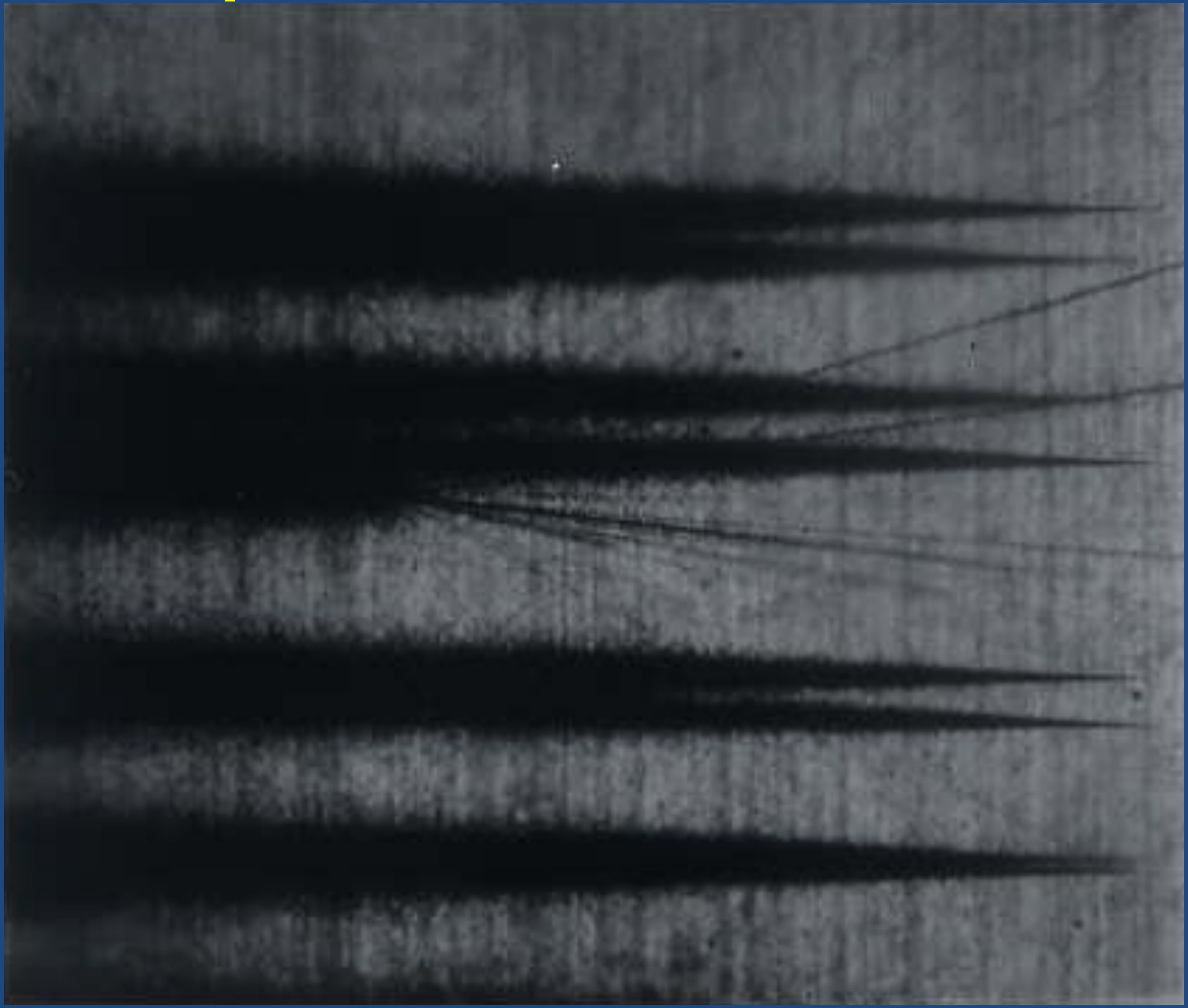
Treatment Outcome Comparing Neon, Neutrons and Conventional Xray Therapy for Selected Types of Tumors

Tumor and Endpoint	Neon	Neutrons	Xray
Macroscopic Salivary Gland Ca			
(Long term local control)	61%	60-70%	25-36%
N=18			
Macroscopic Paranasal Sinus Ca			
(Long term survival)	69%	30+%	32-40%
(Long term local control)	69%	50-86%	N/A
N=10			
Macroscopic Soft Tissue Sarc			
(Long term local control)	56%	50-54%	30-50%
N=12			
Macroscopic Sarcoma of Bone			
(Long term local control)	59%	49-55%	21-33%
N=18			
Locally Advanced Prostate Ca			
(5 yr actuarial local control)	75%	77%	30-50%
N=12			

Reprinted from: Linstadt, Castro and Philips: Neon Ion Radiotherapy: Results of the Phase I-II Clinical Trial. Submitted to Int. J. Rad. Onc. Bio. Phys.

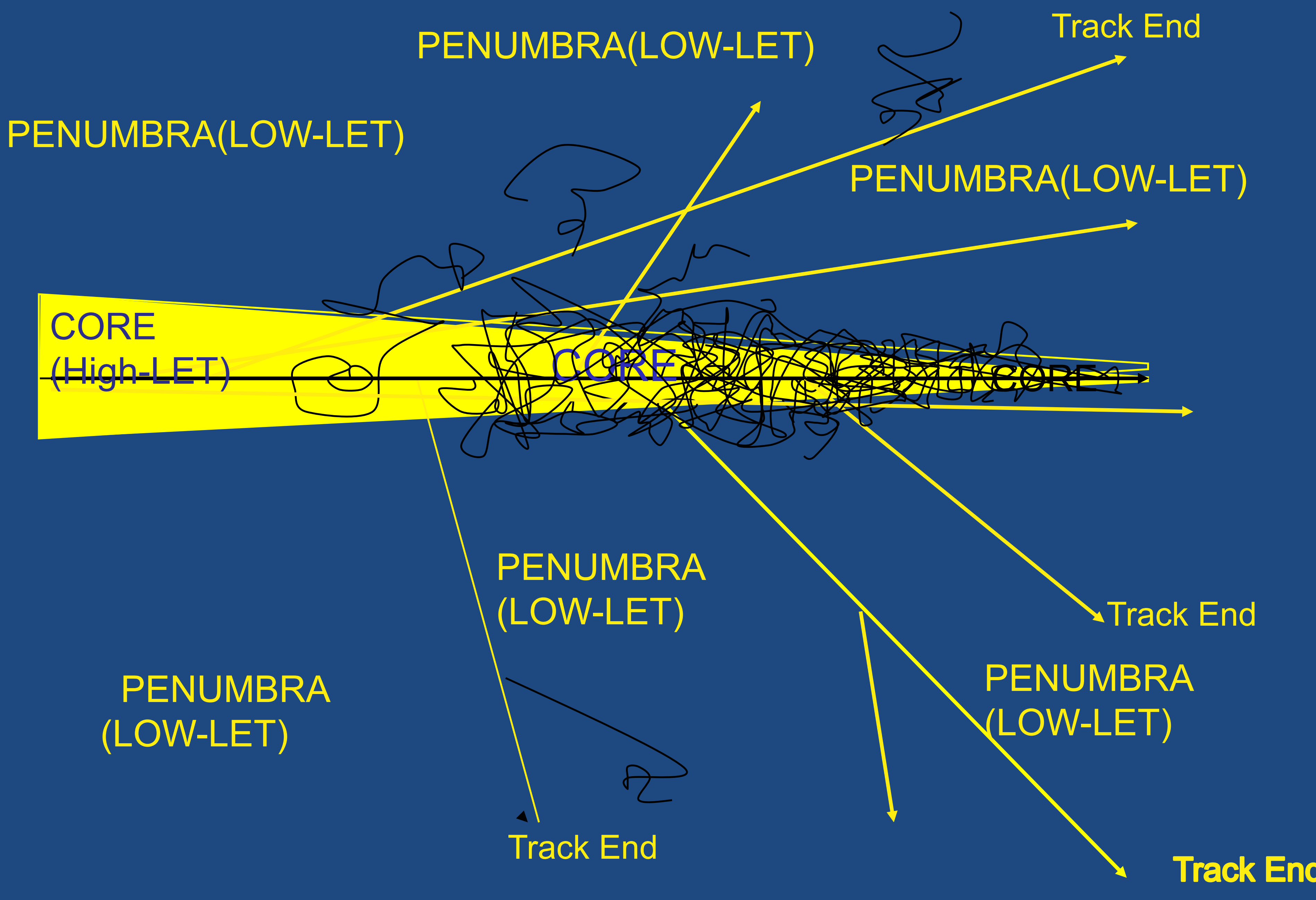
XBL 905-1897

HZE particle tracks in emulsion

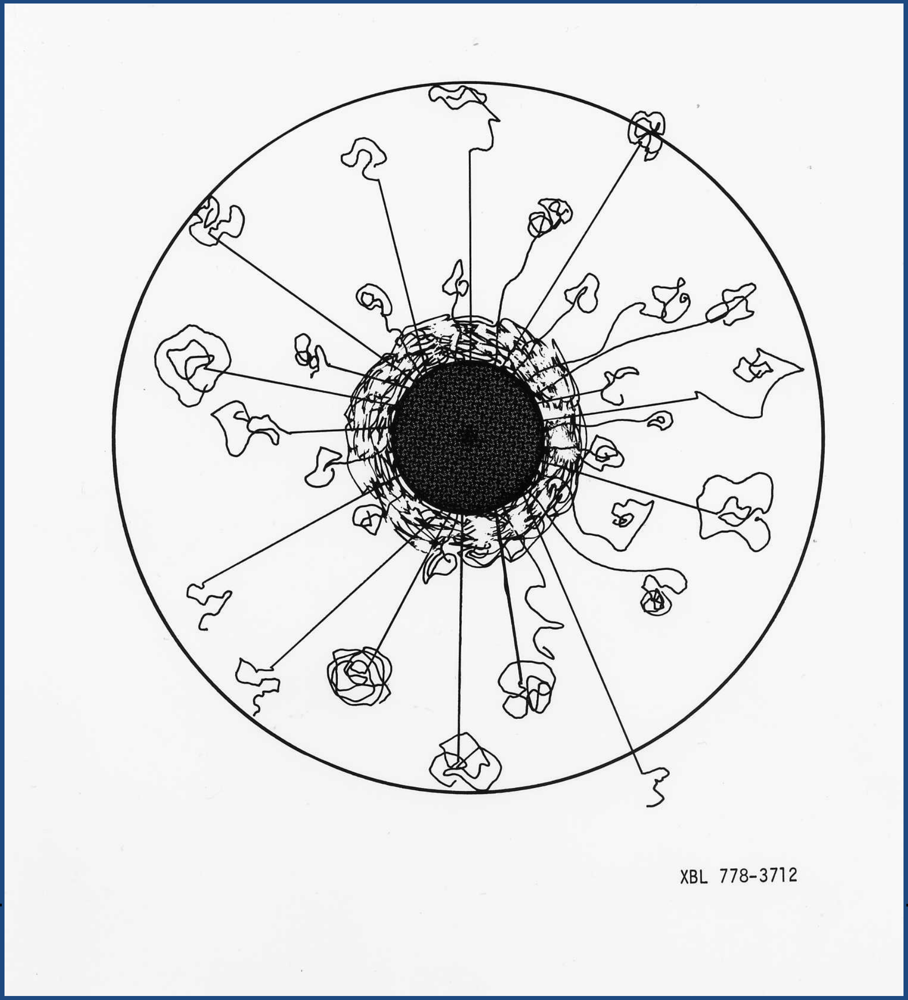


Heckman et al.

Track Structure of HZE Particles

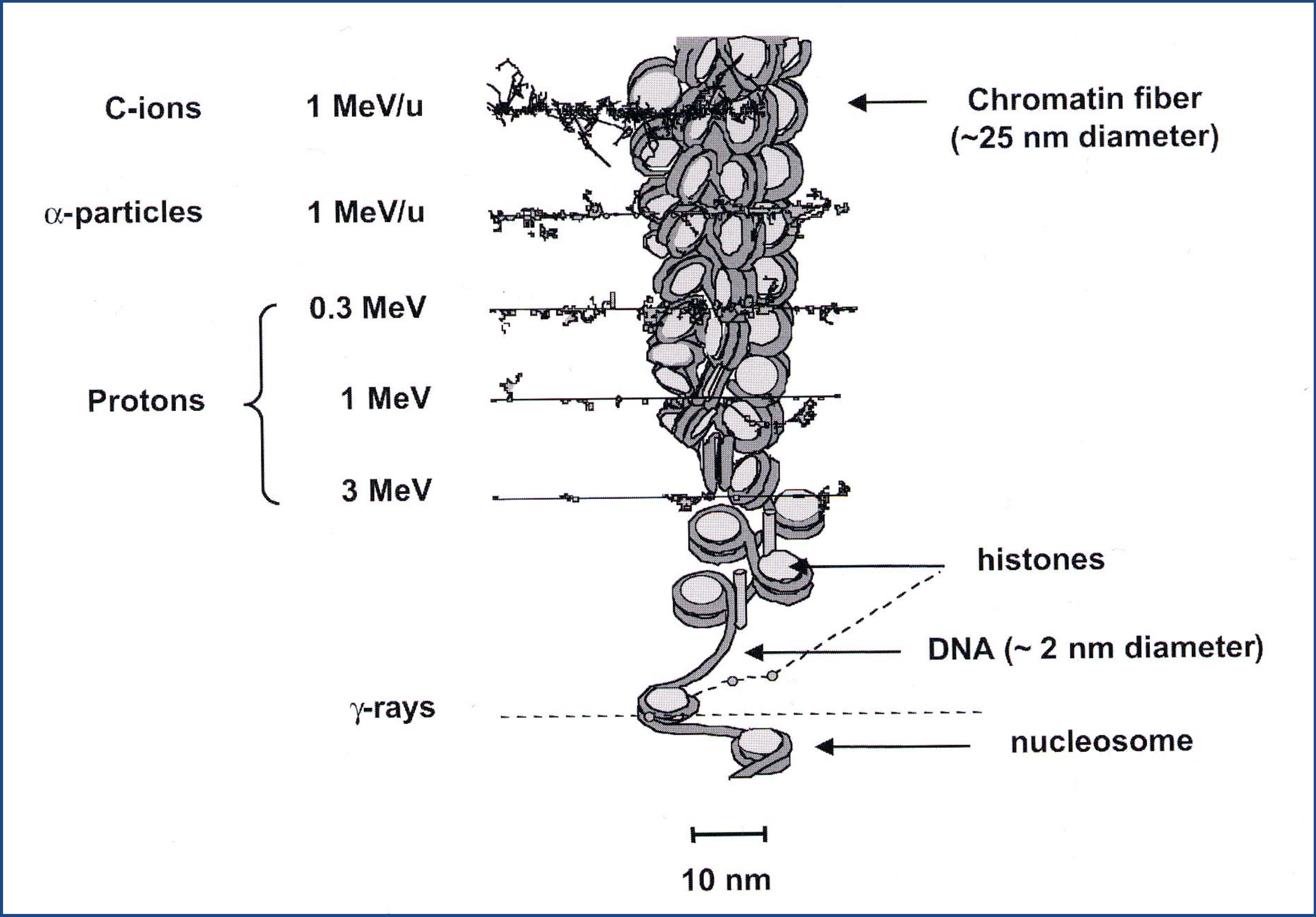


Schematic Cross-Sectional View of a Heavy Particle Track



Chatterjee, 1980

Track-Dependent DNA Targets of Particle Radiation



Belli et al, 2002

IT IS ALL ABOUT THE TRACKS!!

- *If you compare protons and neon ions at the same LET (~30 keV/μm):*
  - *The ion beam with the lower charge (~ 1 MeV protons) has lower velocity and smaller track radii compared to the beam with the higher atomic number (~377 MeV/u Ne)*
  - *More energy is deposited by the lower energy ion (H) in a small target volume.*
  - *But more target molecules are hit by the higher energy (Ne) ion beam due to the delta ray dose*
  - *This leads to both qualitative and quantitative differences between H and Ne.*

Radiation-Induced Oxidative Species

- *Heavy ions and other high-LET ions produce oxidative species that are distinctive from those produced by low-LET radiations*
- *This leads to:*
  - *Decreased Oxygen Enhancement Ratios*
  - *Decreased Cell Cycle Dependence*
  - *Activation/Deregulation of transcriptional gene pathways different from low-LET radiations*
  - *Decreased dependence on tumor cancer promoters*
  - *Development of distinct protective mechanisms*
  - *Unknown role for chronic inflammation*
  - *Uncertainties at low dose*

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

A Personal Perspective on Contributions of the Berkeley Ion Beam Program

- ***New scientific approaches*:**
  - ***To investigate underlying mechanisms of action of densely ionizing radiations on different biological systems***
  - ***To investigate improvements in anatomical and functional imaging of normal and tumor treatments,***
  - ***To develop novel ion beam delivery and treatment planning tools and mathematical and biophysical models to personalize medical care and treatment of disease.***
- ***Opportunities to train other scientists, students, technologists to share the technology***

Charged Particle Radiobiology Needs Continue

- *What are the risks of secondary cancers & late effects?*
- *Can we identify the radiosensitive patient who should be treated with a more conservative treatment plan?*
- *How can we reduce unnecessary dose outside of treatment volume?*
- *Are there pediatric tumors we should not consider treating?*
- *Can specific chemotherapies enhance charged particle therapy?*
- *Can we further optimize with hypofractionation?*
- *What is the best biological model for validating dose effectiveness?*

Factors Hampering Heavy Hadrons

- *Lack of Level 1 Evidence (e.g., Phase III Randomized Clinical Trials)*
- *Cost to build carbon ion clinical facilities*
- *Current lack of insurance reimbursement to maintain a carbon facility*

SUMMARY

- ***Hadron radiations have unique physical deposition patterns, and some novel characteristics of the biological response depending on the radiation type and quality***
- ***There is a need for further basic biological investigations to clarify the significance of the these unique lesions at the molecular, cellular & tissue level.***
- ***There are many powerful new technical tools and genomic and proteomic resources available to radiobiologists to study these effects.***
- ***Theoretical modeling of expected hadron biological effects is important.***
- ***The future scientific opportunities for hadron therapy are promising. Congratulations to the SEEIIST program.***

Acknowledgments

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Special Thanks to Prof. Manjit Dosanjh