Start of Biophysics in Hadron Therapy and LBL

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This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008548

Disclosures

I will discuss investigative use of Hadron Therapy

Affiliation

Retired Sr. Staff Biophysicist

LBNL (DOE National Lab)

Operated by UC Berkeley, CA

Affiliations

Adjunct Research Professor

Dept. Radiation Medicine &

Dept. Basic Sciences

LLU School of Medicine

Commercial

None- Nothing to Declare

HITRI
Heavy Ion Therapy Research Integration

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008548

Goals of Presentation

- *To provide an historical perspective on the early preclinical and Phase I/II trials using charged particle beams for the treatment of cancer in Berkeley, California 1952-1993.*

- *To provide some personal insights for the path forward for particle biophysics and hadron therapy.*

Berkeley Lab is >90 Years Old!

Ernest Orlando Lawrence
Physicist, UC Berkeley
1930's

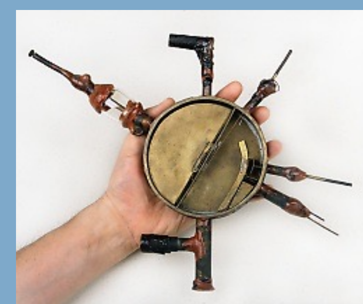
The Radiation Laboratory, 1933

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.

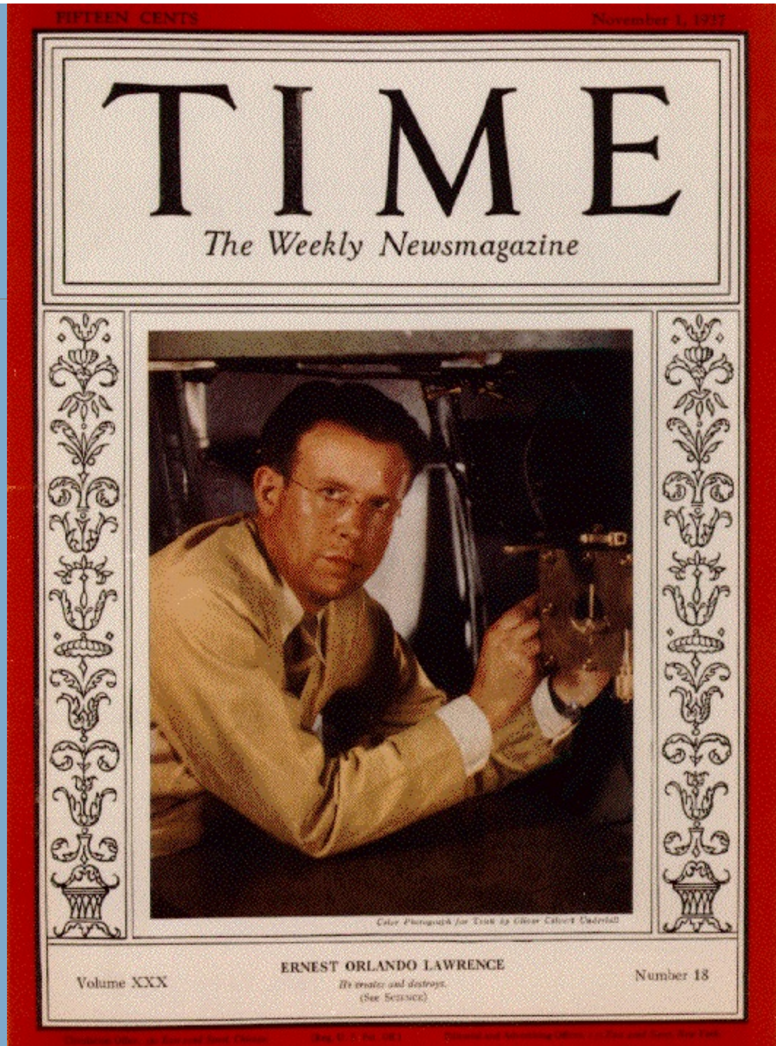
Invention of the Cyclotron

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

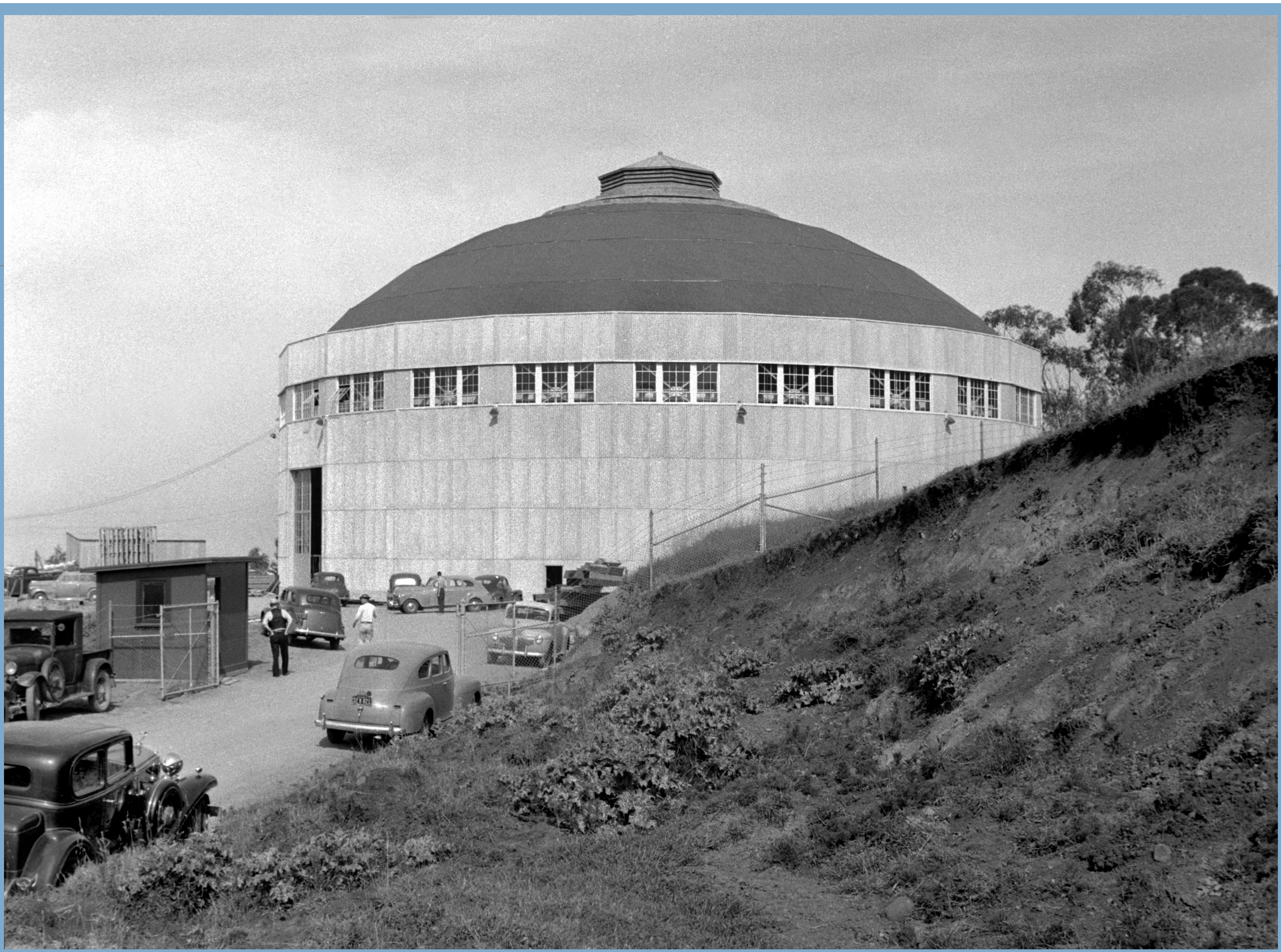


EO Lawrence and MS Livingstone, Phys. Rev 37: 1707 (1931); and MS Livingston, The Production of High-Velocity Hydrogen Ions Without the Use of High Voltages, PhD thesis, University of California, Berkeley (1931).

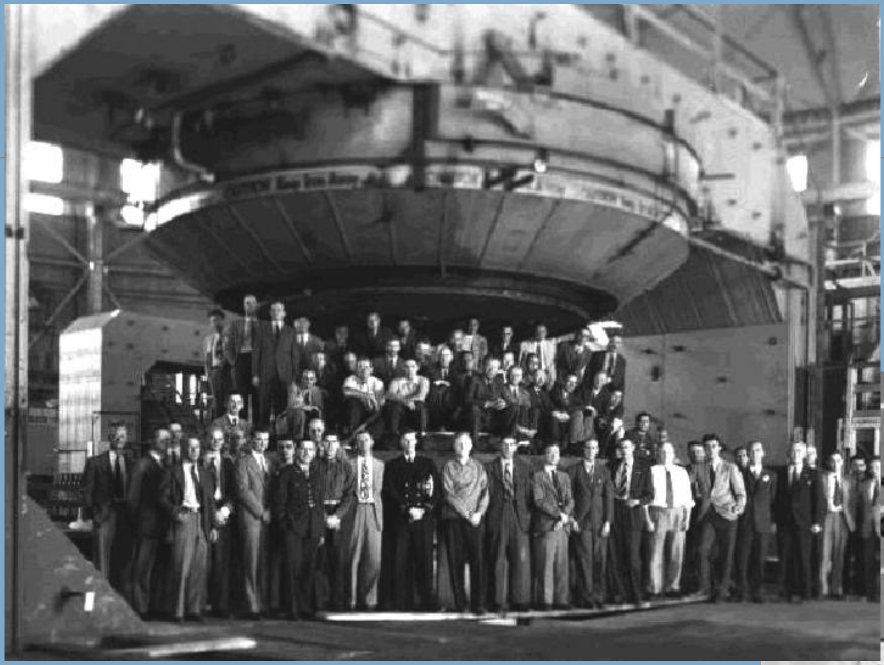


1939
Nobel Prize in Physics

Pioneering Days in the Berkeley Hills Before the 184" Cyclotron Was Built.



184-Inch Cyclotron (1947)

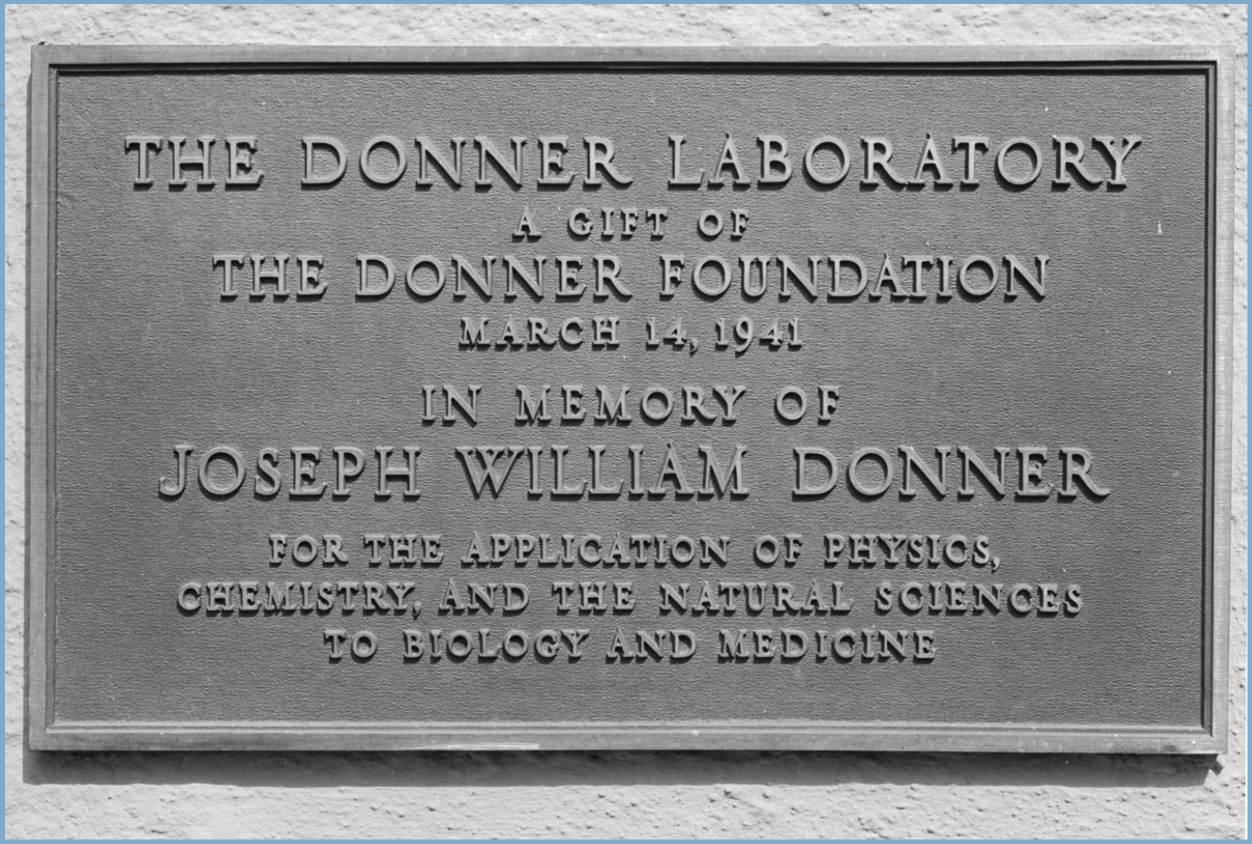


The first beam,
Nov 1, 1947


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

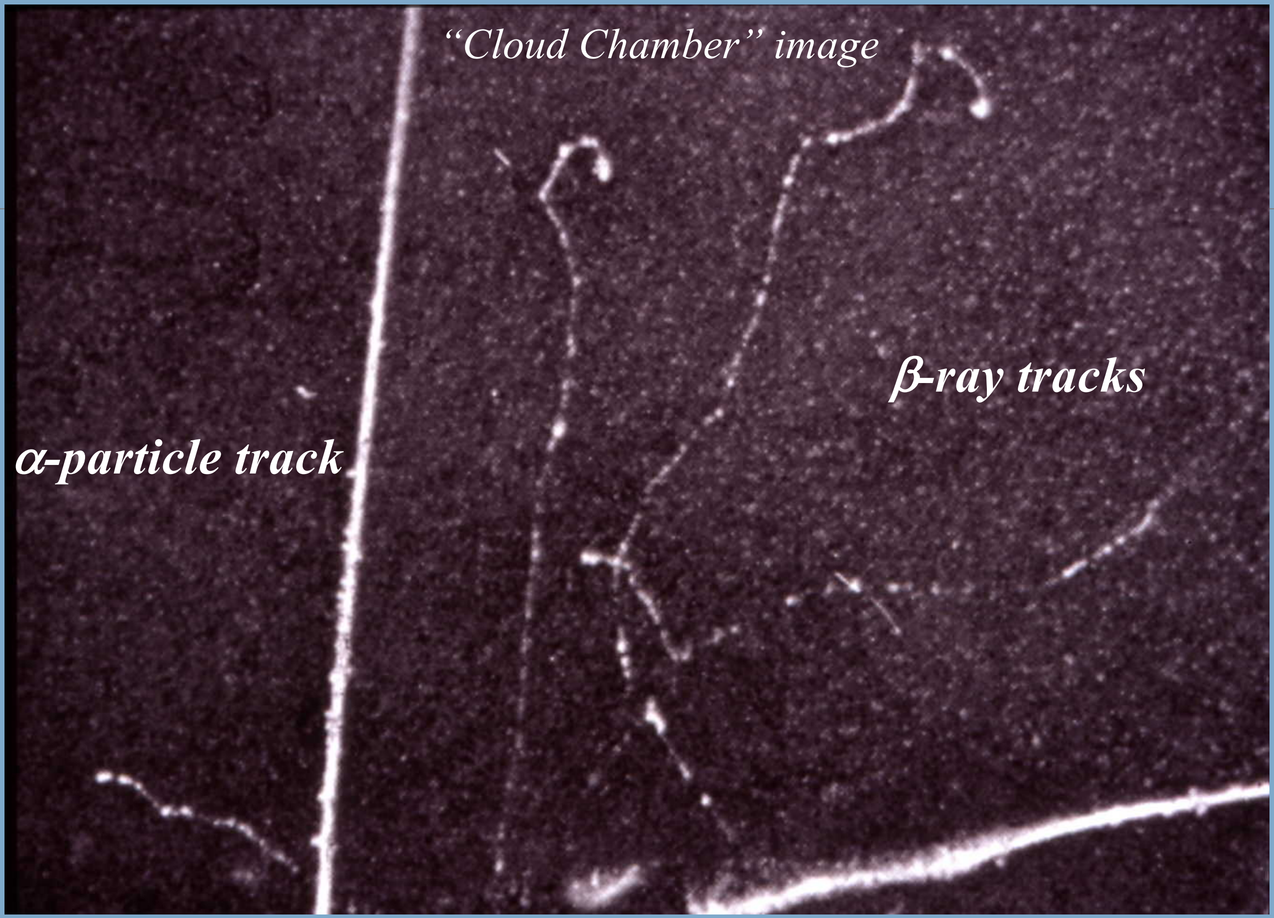
Donner Laboratory Dedication 14 March 1941



Hadron Therapy

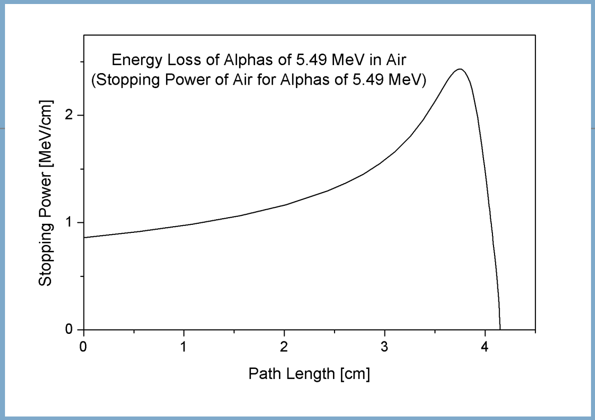
- *First begun in 1938 when neutron beams were used in cancer therapy.*
- *Charged hadron beams (protons & carbon ions) have more favorable depth-dose interaction which is maximal at the end of their range.*
- *Initially in Europe "hadron" therapy meant proton therapy, but "charged particles" includes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

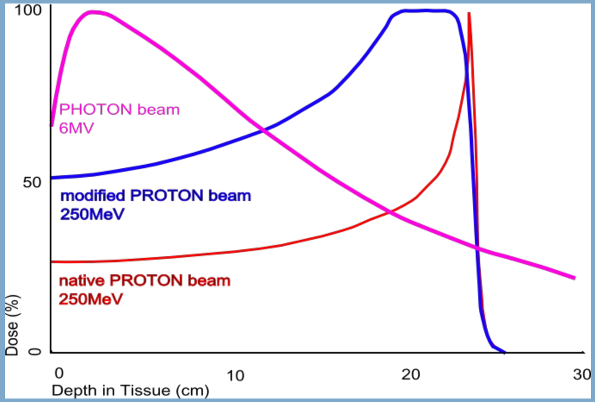
α & β tracks showing the difference in ionizing power of the particles



From the work of M. Curie presented in Rutherford et al., 1930

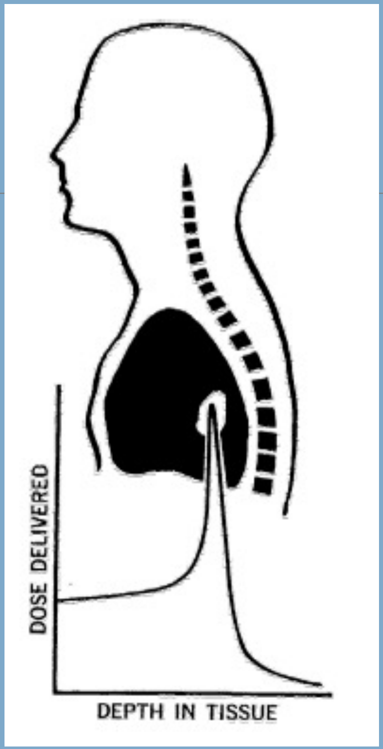
Sir William Henry Bragg first reported "Bragg Curve" 1903





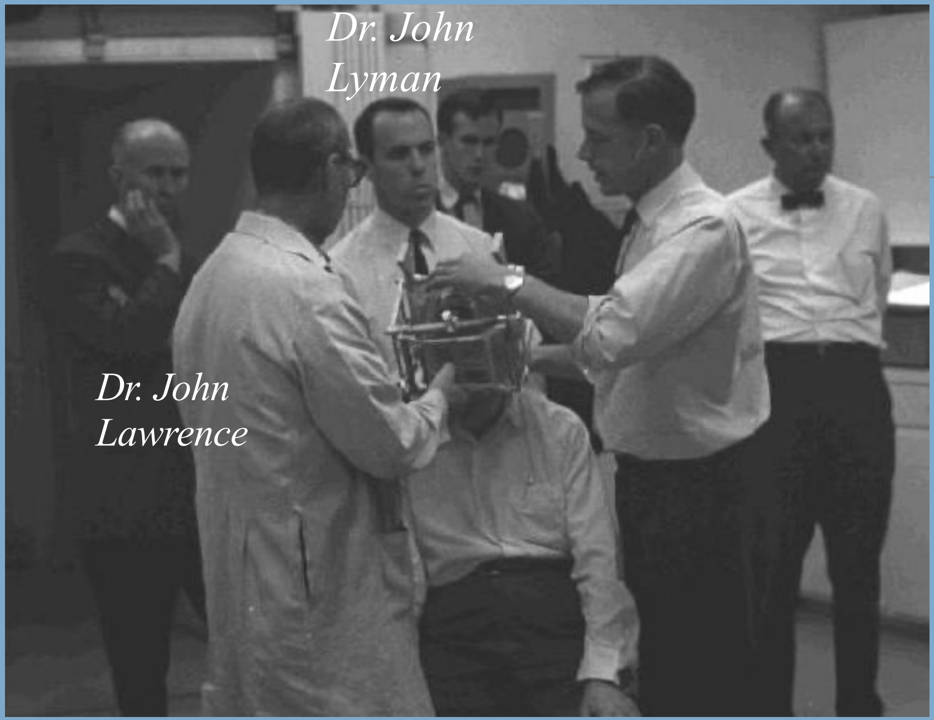
R.R. Wilson and Rationale for Bragg Peak Therapy

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

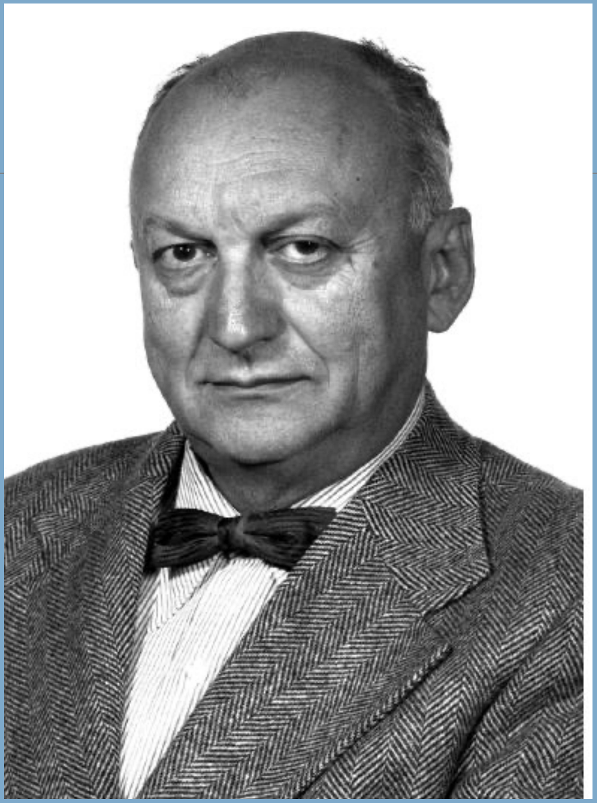


- *Dose localization*
- *Lower entrance dose*
- *No or low exit dose*

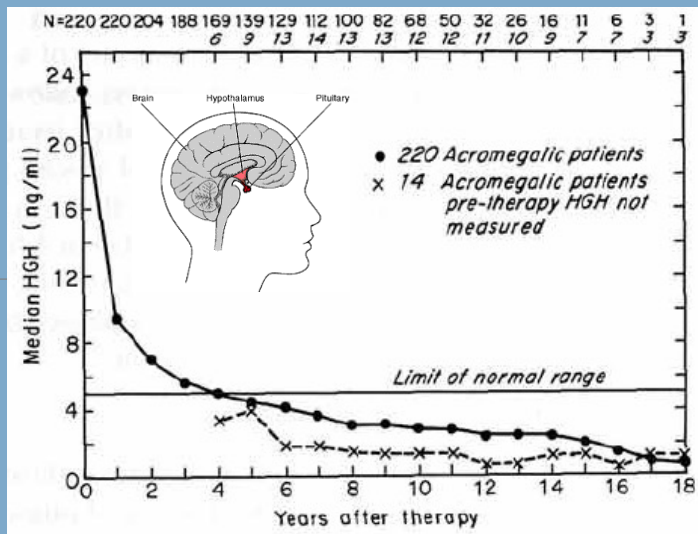
FIRST PROTON THERAPY PATIENT TREATED-SEPT. 1954

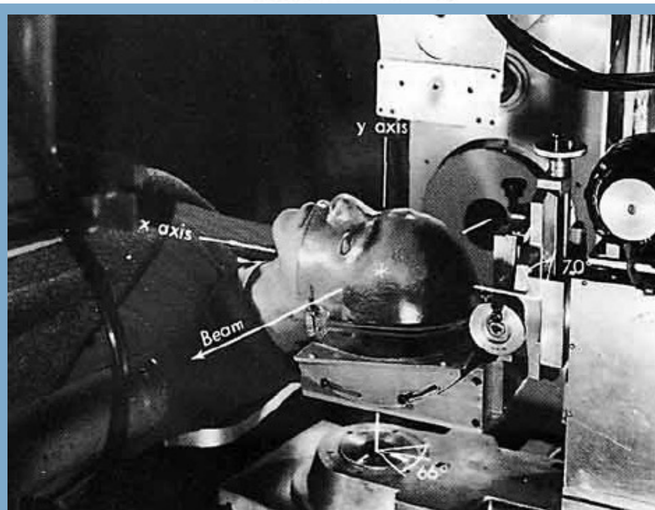


- ***1948: Biology experiments using protons***
- ***1952: Human exposure to deuteron & helium ion beams.***
- ***1954: Human exposure to accelerated protons.***
- ***1956-1986: Clinical Trials– 1500 patients treated***



Prof. Cornelius A. Tobias



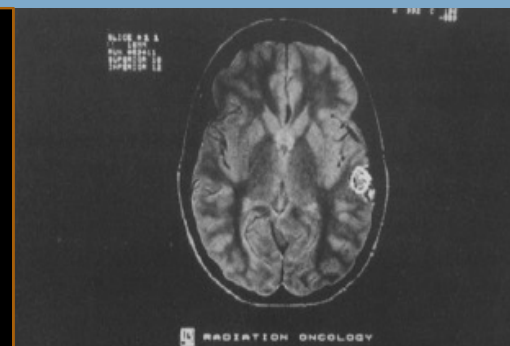


Heavy-Charged Particle Radiosurgery of the Pituitary Gland: Clinical Results of 840 Patients

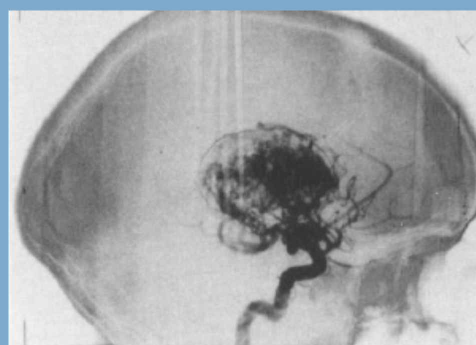
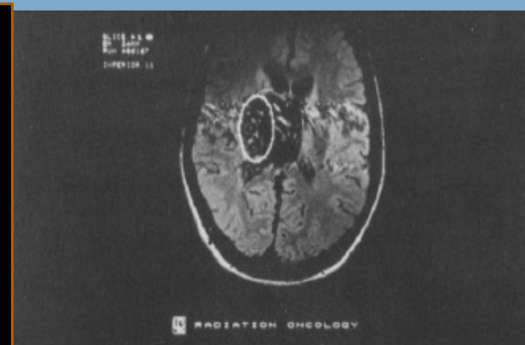
- Initial 30 Pts. Treated with Protons
- Subsequent 820 were treated with He plateau, 30-36 Gy in 3-4 Fx over 5 days.
- Marked and sustained biochemical & clinical improvement observed in majority of the Pts.
- Focal necrosis/nerve injury in only 1%

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

Intracranial Arteriovenous Malformations (AVMs)

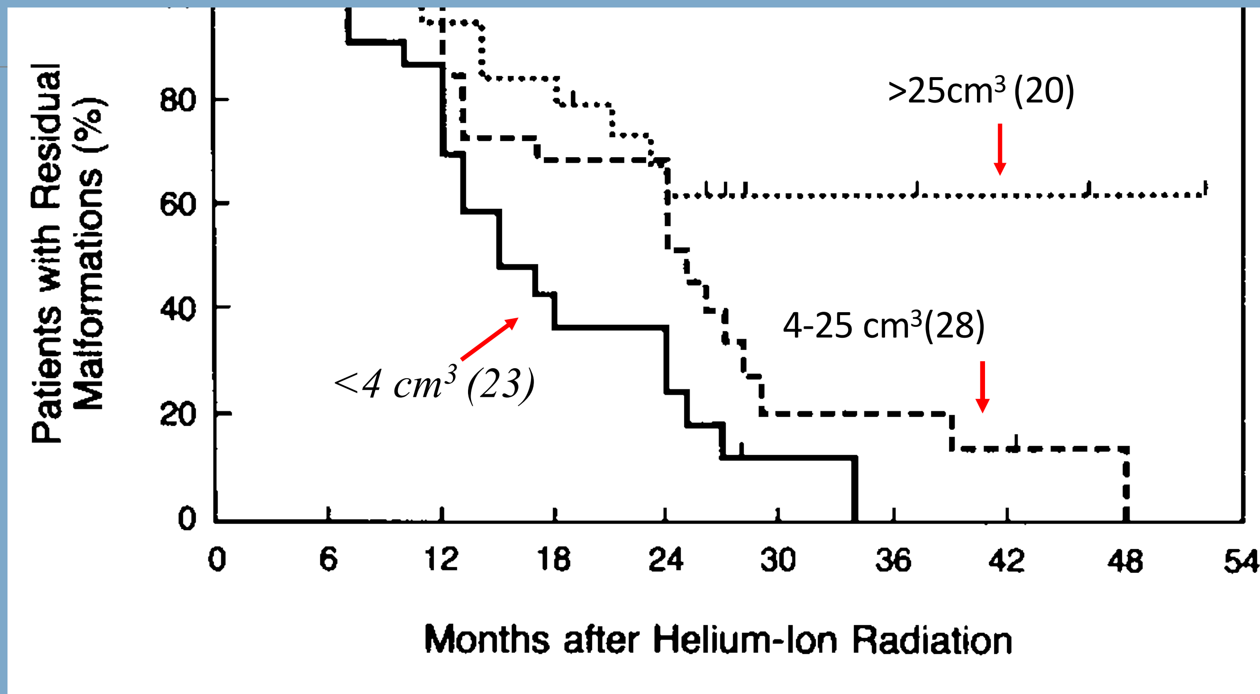
26-yr old
Female-2.5 cm^2
AVM temporal
lobe

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

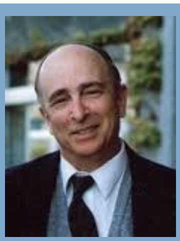
Phillips, Kessler, Chuang, Frankel,
Lyman, Fabrikant, and Levy, Int. J. Radiat Biol Phys 1991

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



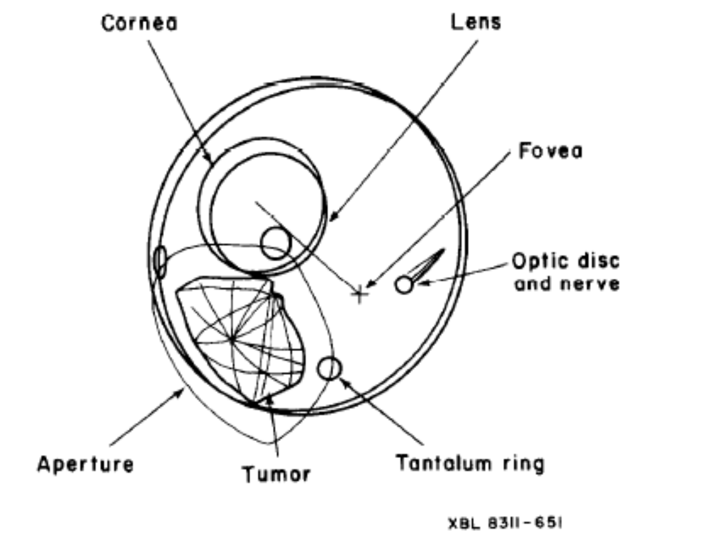
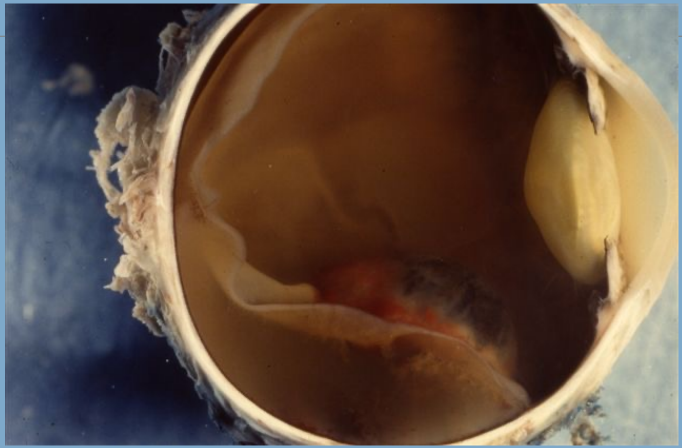
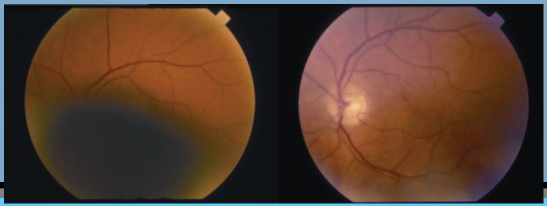


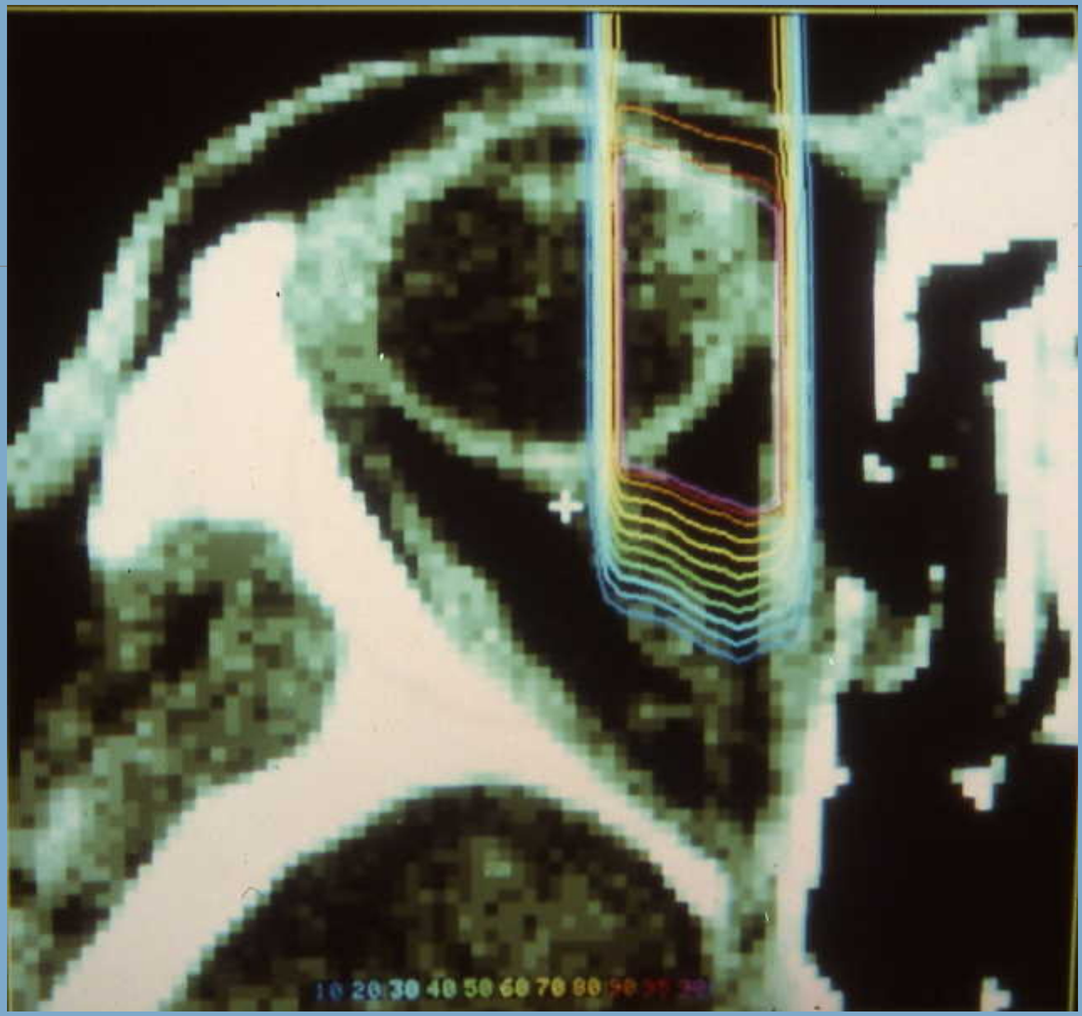
Fig. 3. Output from Massachusetts General Hospital treatment planning program.[7]

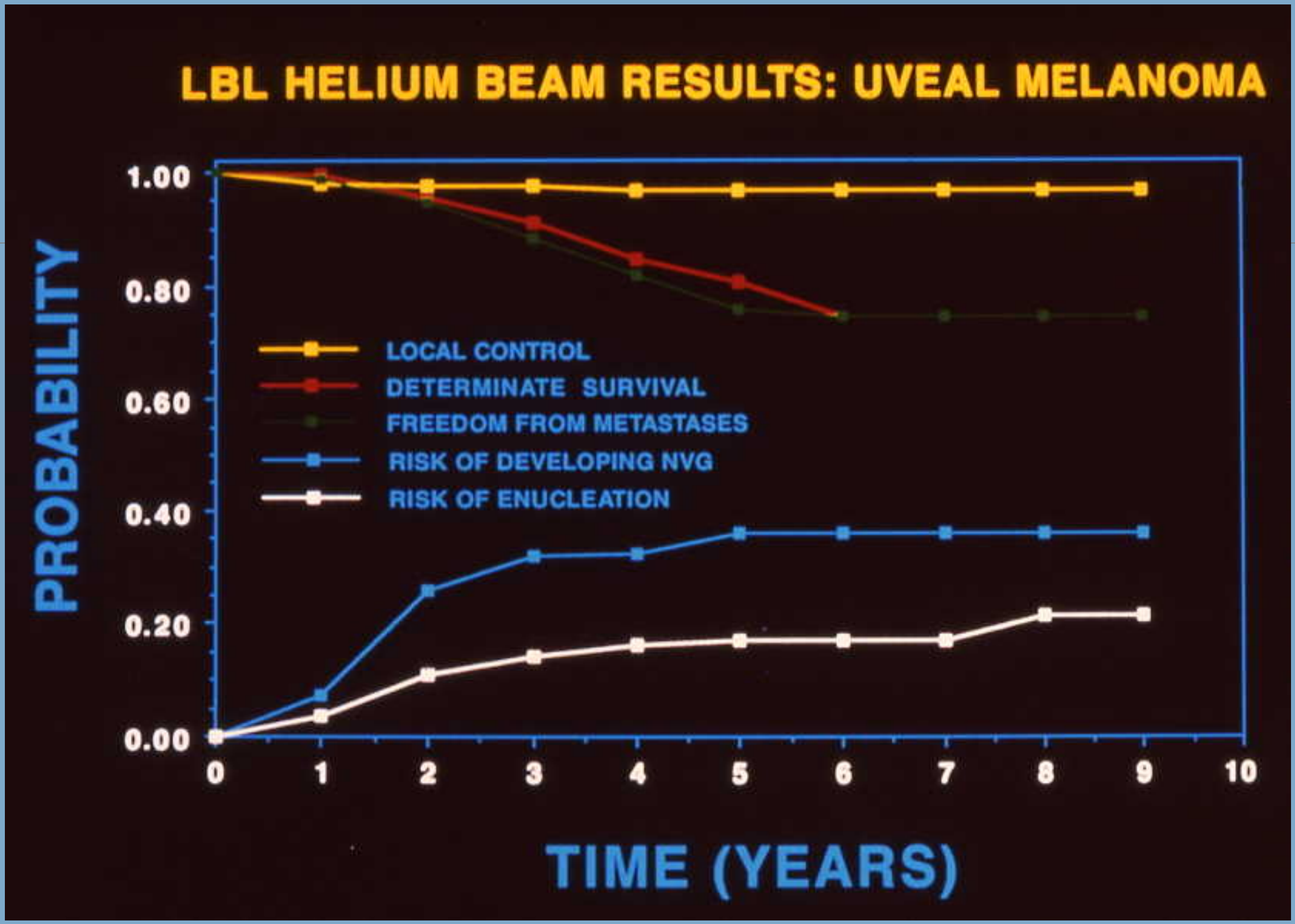


Saunders, Char, Quivey, Castro, Chen, Collier, Cartigny, Blakely, Lyman, Zink and Tobias, Int, J Radiat Oncol Biol Phys, 1985,

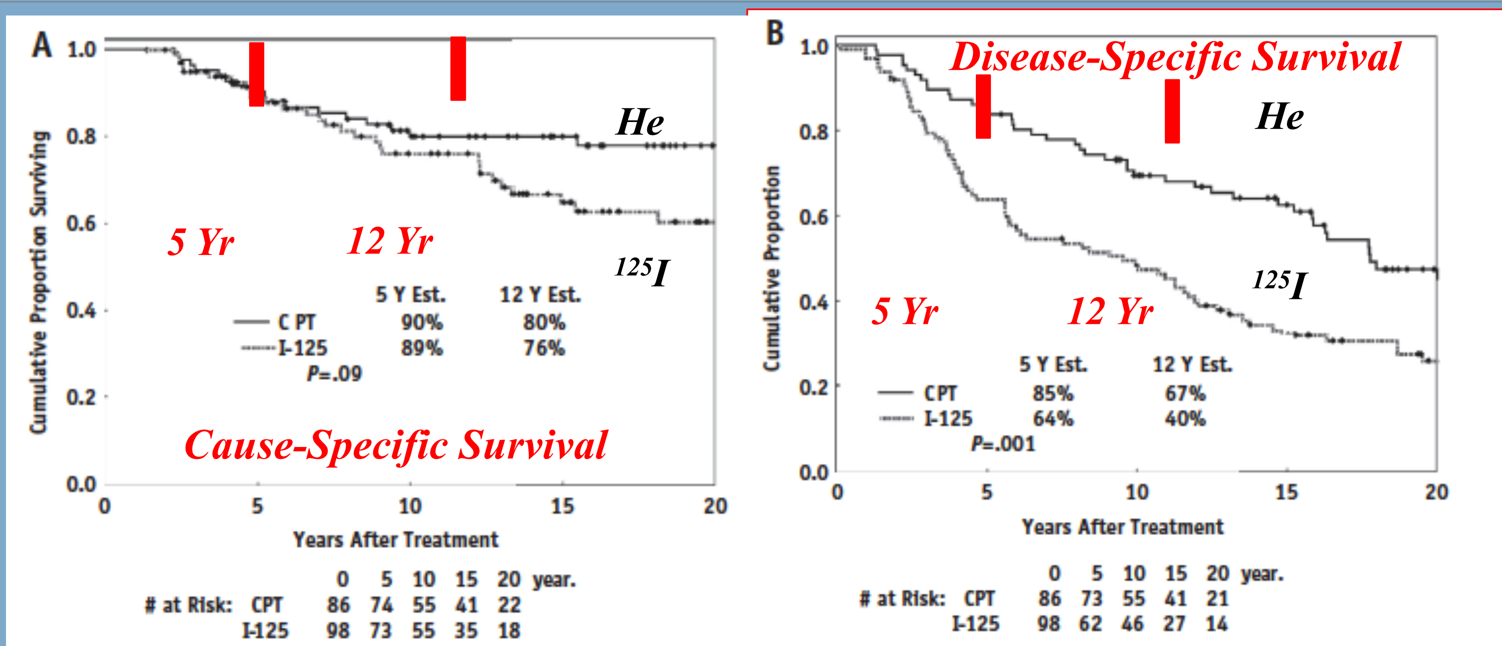


Gragoudas, Weisenfield Lecture, IOVS, 2006
1975-1st Proton treatment of Uveal Melanoma


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

184-Inch Cyclotron and Hadron Therapy

1956 - 1986

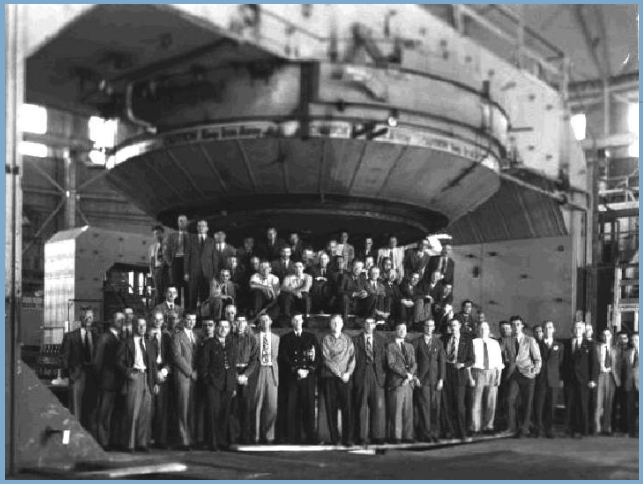
Hadron Therapy

Clinical Trials

1500 patients treated

Patient treatment on ISAH (Irradiation Stereotaxic Apparatus for Humans).

184-Inch Cyclotron and Hadron Therapy



The beginning, 1947

The end, 1986

Bevatron- APS Historic Site Dedication Ceremony

Looking at a model of the Bevatron prior to its construction in 1949 were (left to right) Lloyd Smith, Ed McMillan, Ernest Lawrence, Ed Lofgren, Bill Brobeck, and Duane Shell.

*On **May 11, 2022**. the American Physical Society recognized the Bevatron Particle Accelerator for its contributions to physics*

Al Ghiorso's Idea to Create the Bevalac = Bevatron + Super Hilac

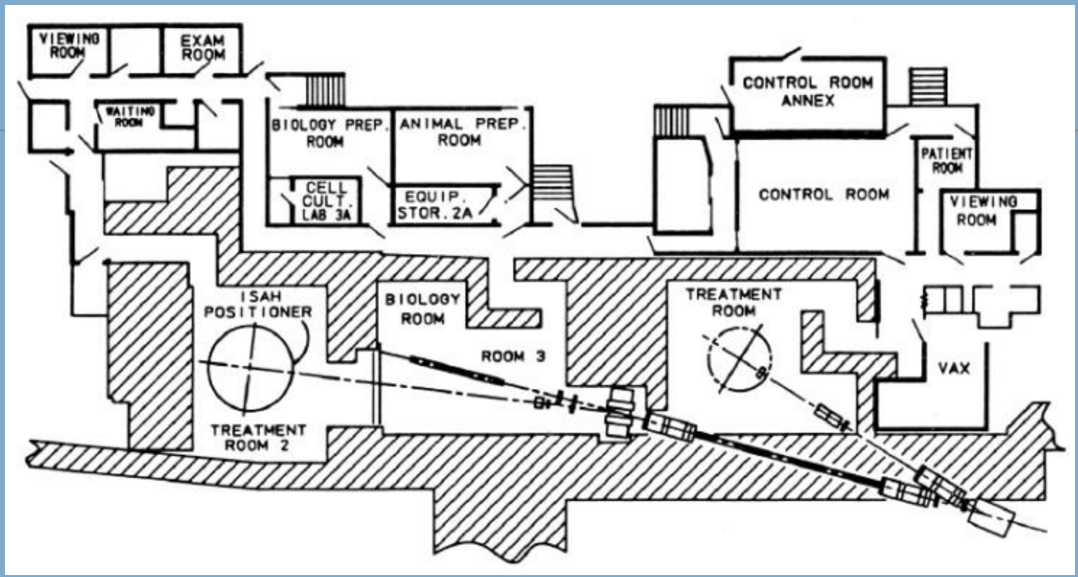
- *In 1974, Transfer Line was completed, connecting the Super HILAC (built in 1958) to the Bevatron (built in 1954)*
- *Thus was formed the world's first accelerator capable of producing high-energy (>1 GeV/amu) beams of any element of the periodic table.*
- *The Bevalac finally ceased operations on February 21, 1993.*

Bevalac (1971-1993) and Hadron Therapy

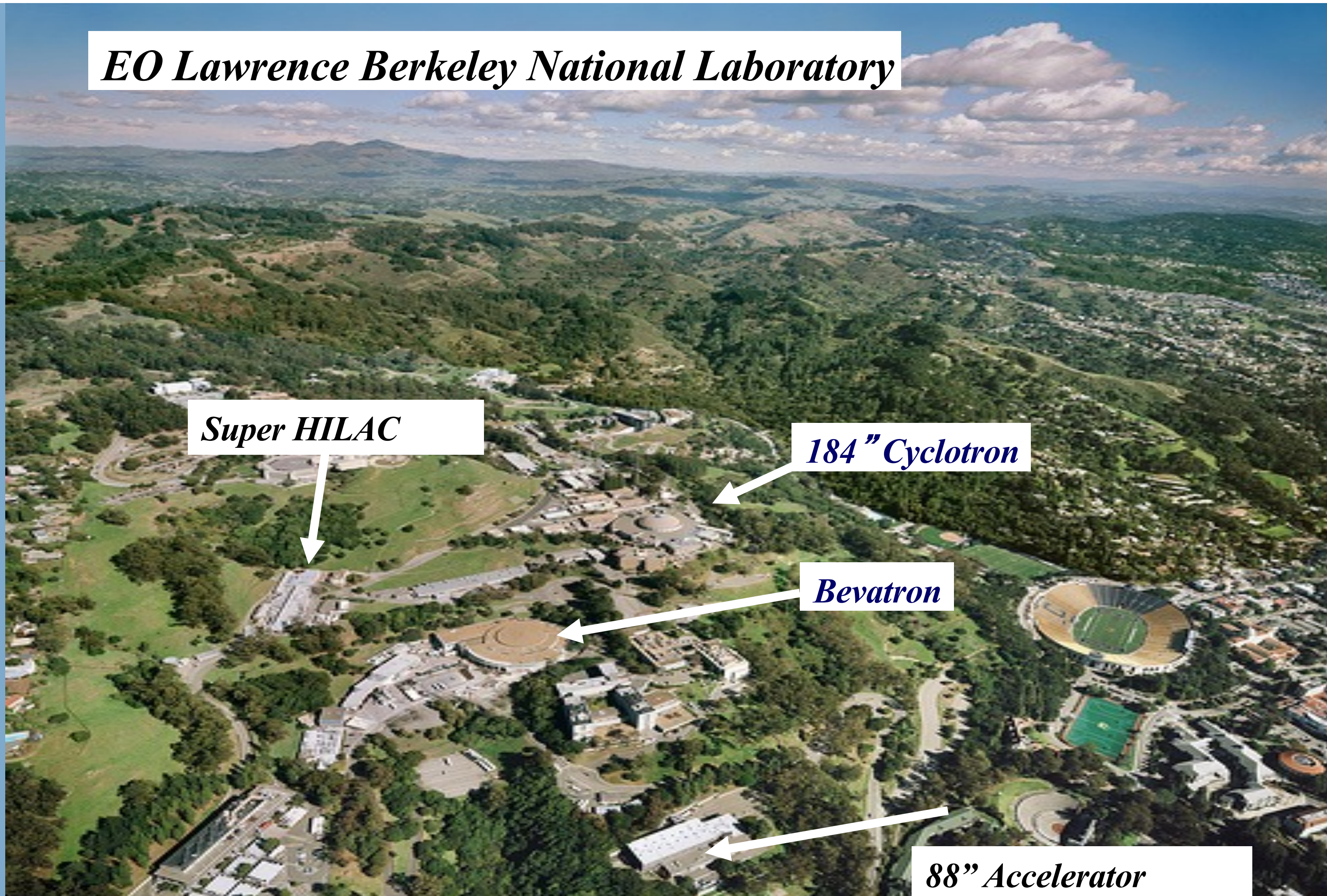
Harry Heckman, Ed McMillan, Cornelius Tobias, Tom Budinger, Ed Lofgren, Walt Hartsough (l. to r.)

Press conference announcing the acceleration of heavy ions in the ***Bevatron*** *(August 1971).*

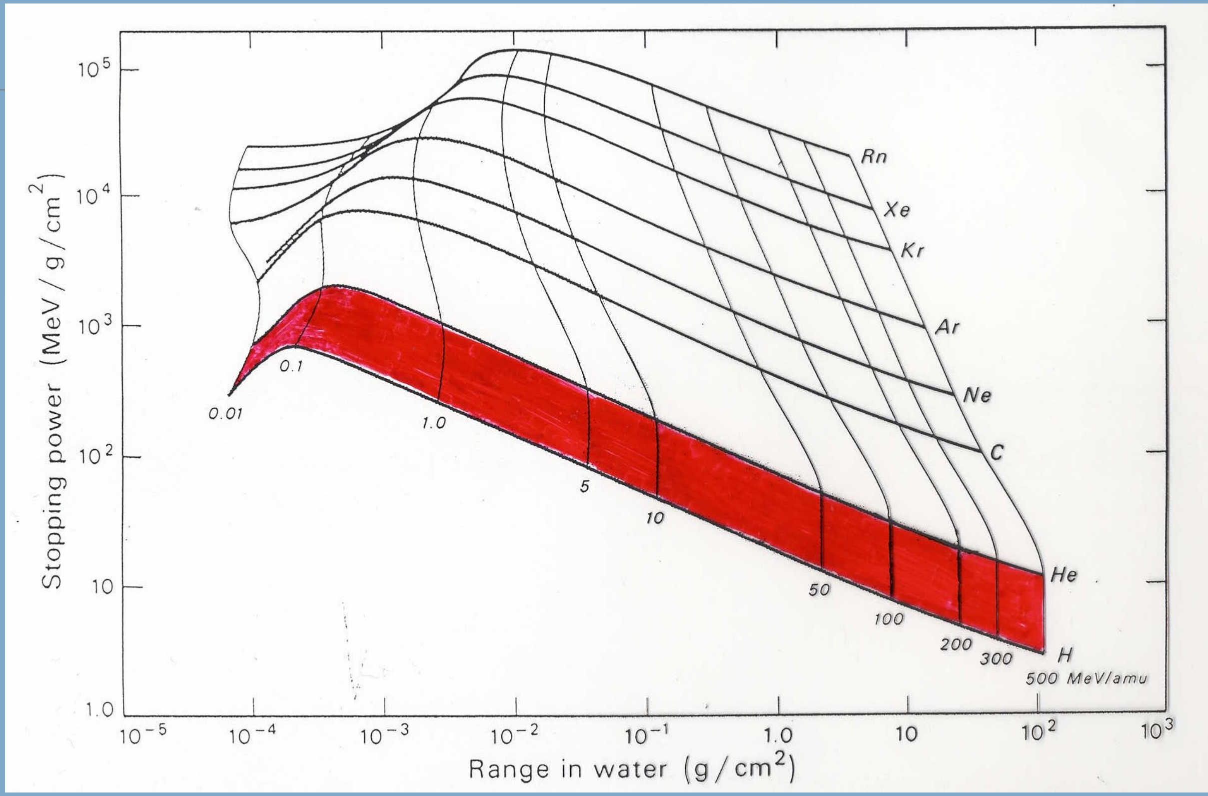
Biomedical Research Programs at the Bevalac



- *1/3 of all Bevalac beam time was dedicated to Life Sciences*
- *Dedicated Biomedical area consisted of:*
  - *Two therapy rooms*
  - *One biology/biophysics area*
  - *Support facilities and patient staging areas*


EO Lawrence Berkeley National Laboratory
Super HILAC
184" Cyclotron
Bevatron
88" Accelerator

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	300 patients

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*

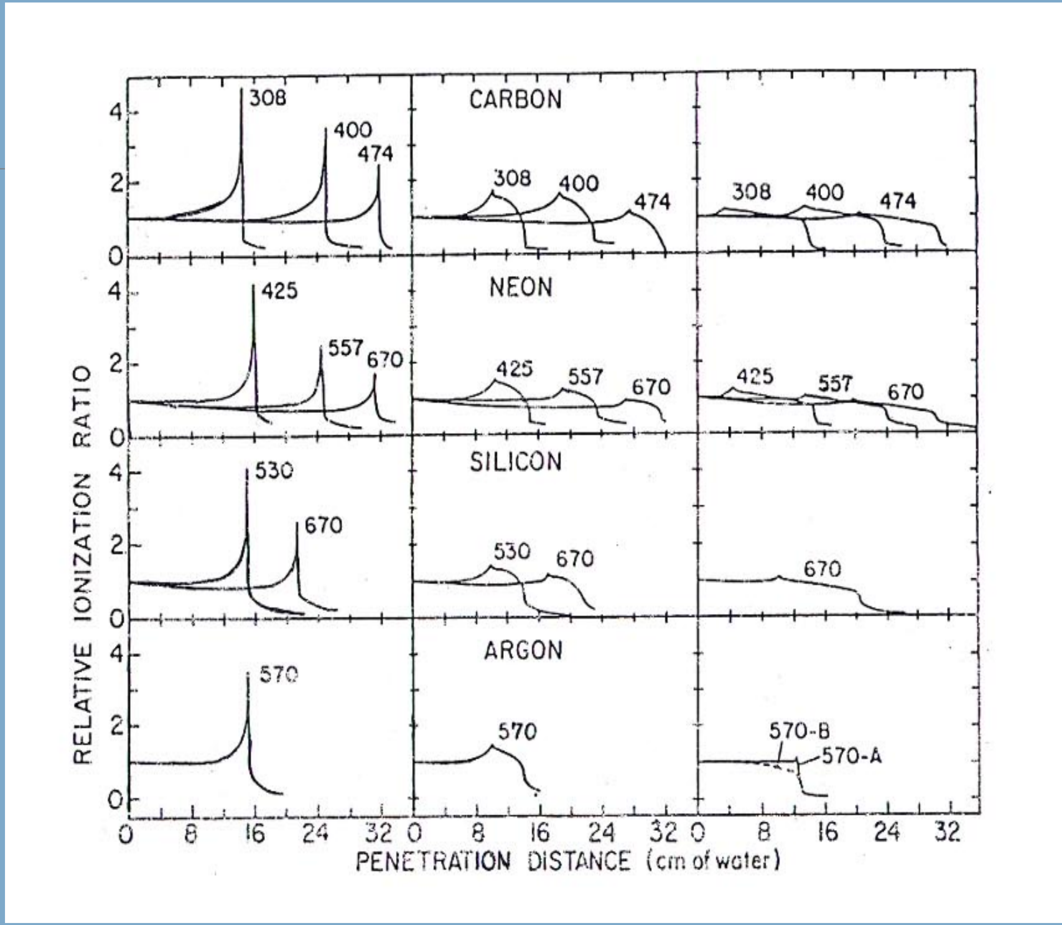
Prof. T. Phillips

Prof. J. Quivey

Prof. G. Chen

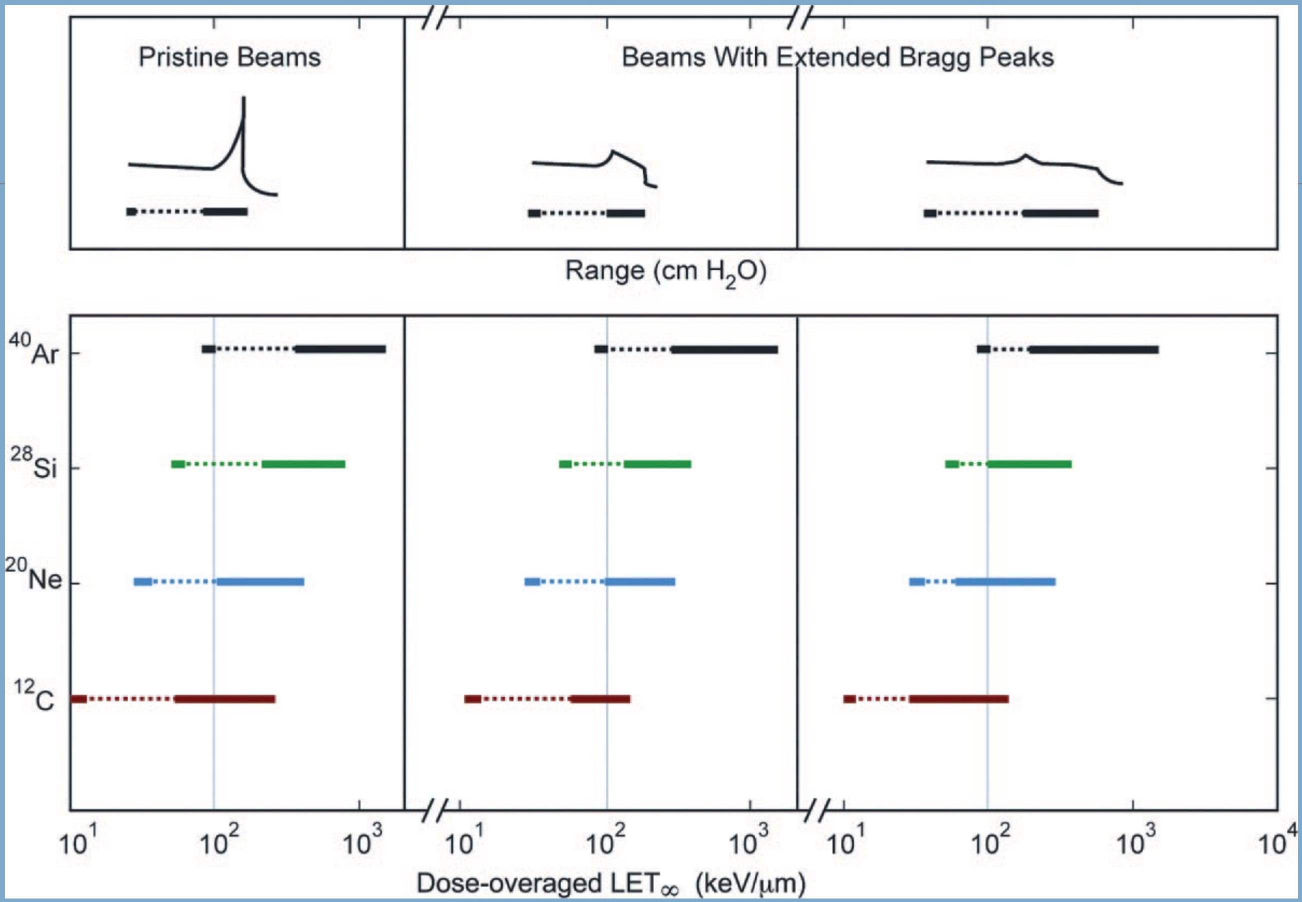
Dr. E. Blakely

Pristine and Extended Bragg Peaks of Carbon, Neon, Silicon & Argon



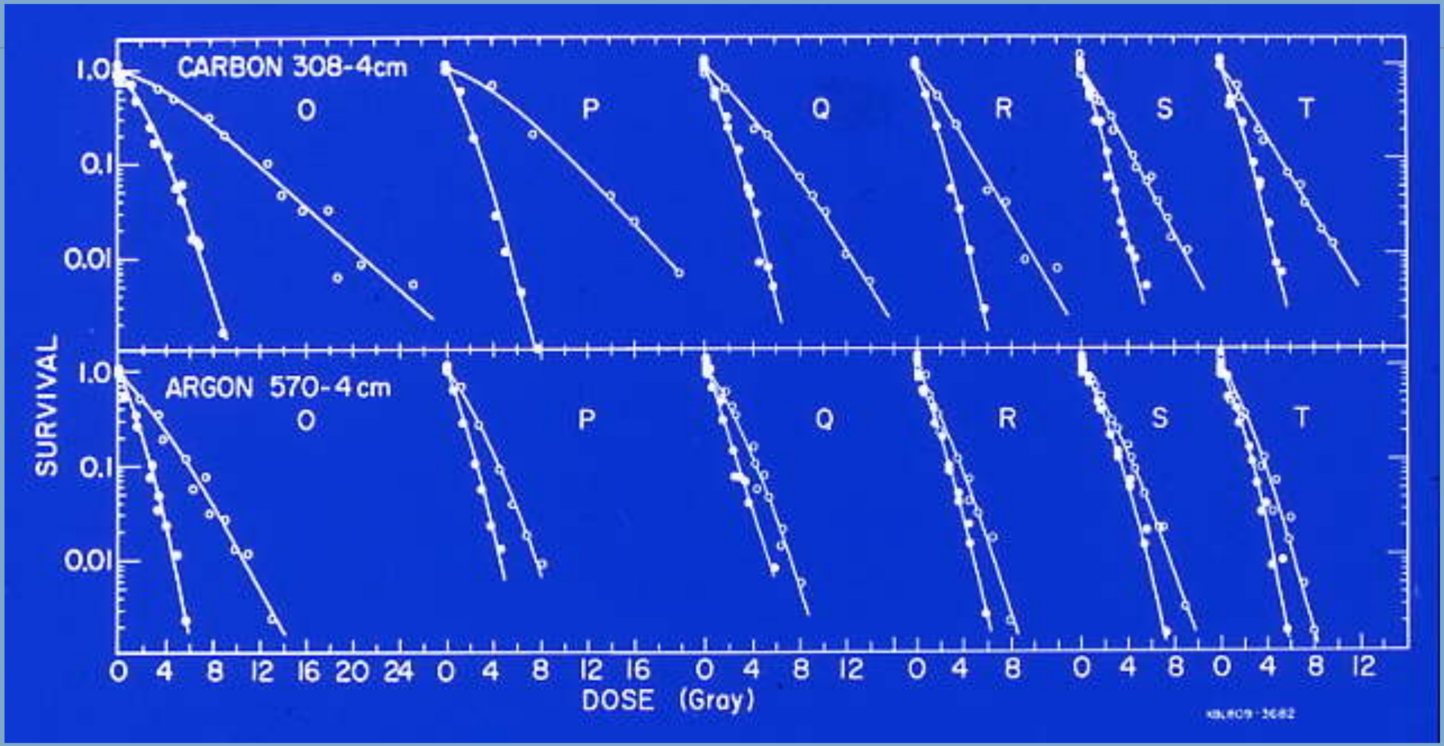
Blakely et al. 1982

LET Ranges for Pristine and Extended SOBP



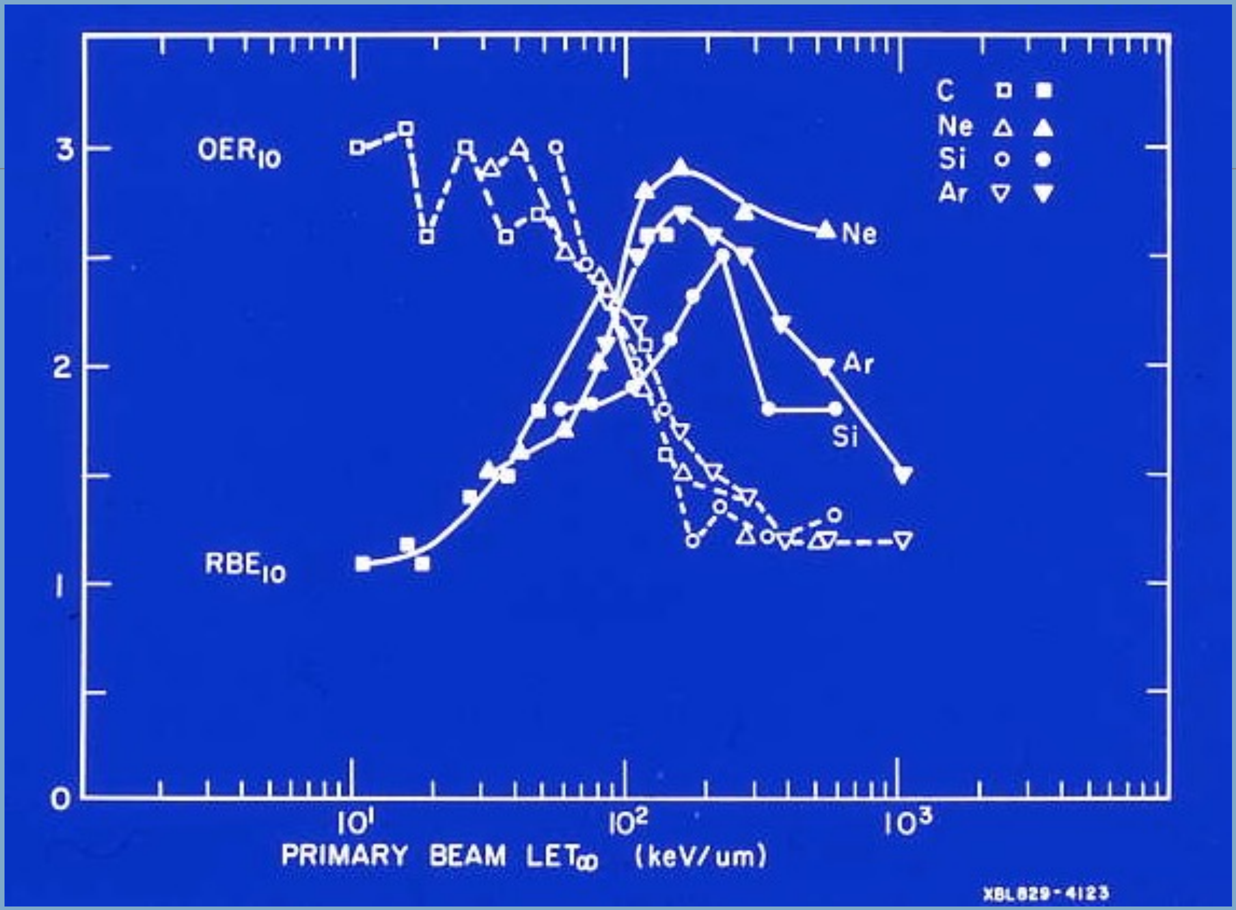
Blakely & Chang, The Cancer J, 2009

Aerobic & Hypoxic Cell Killing with Carbon or Argon Beams

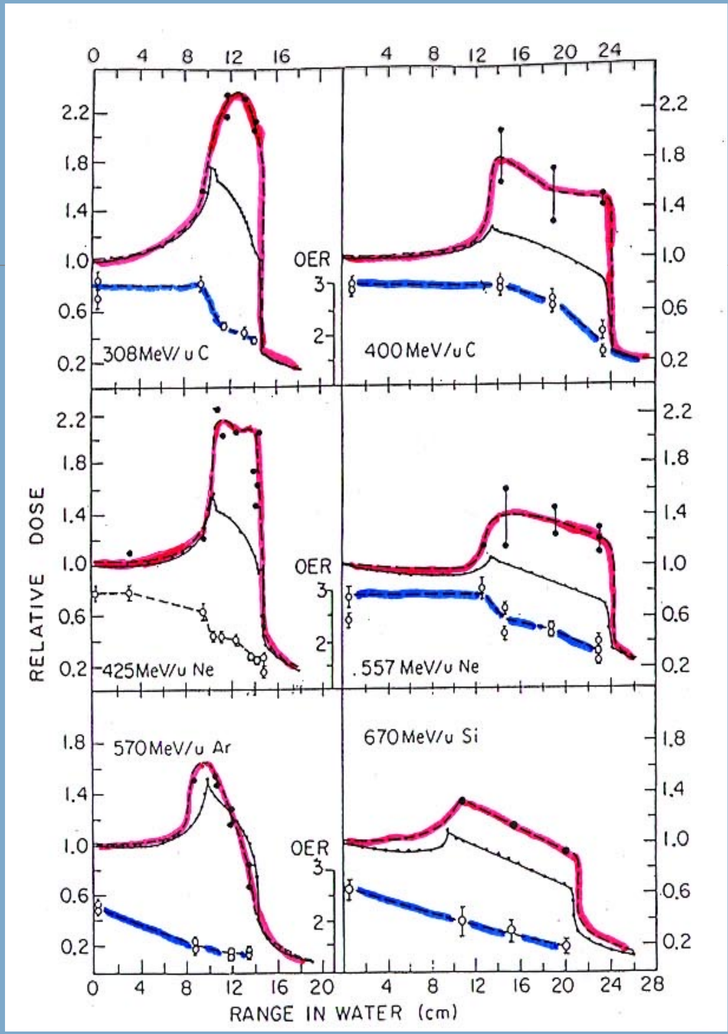


Blakely et al.

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



Blakely et al.



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	+	+	+++	+	++	+++	+++

Blakely et al.

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

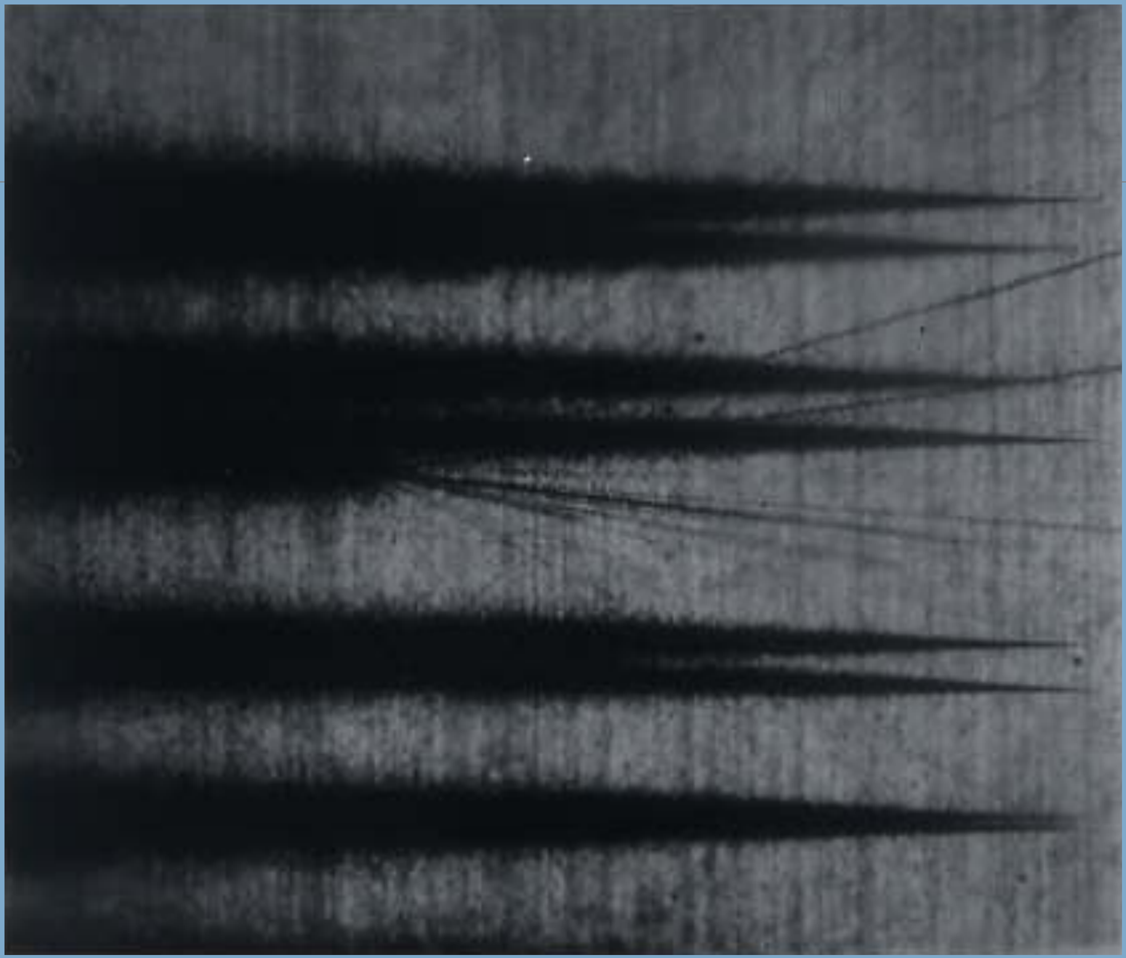
Tumor and Endpoint	Neon	Neutrons	Xray
Macroscopic Salivary Gland Ca			
(Long term local control)	61%	60-70%	25-36%
N=18			
Macroscopic Paranasal Sinus Ca			
(Long term survival)	69%	30+%	32-40%
(Long term local control)	69%	50-86%	N/A
N=10			
Macroscopic Soft Tissue Sarc			
(Long term local control)	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

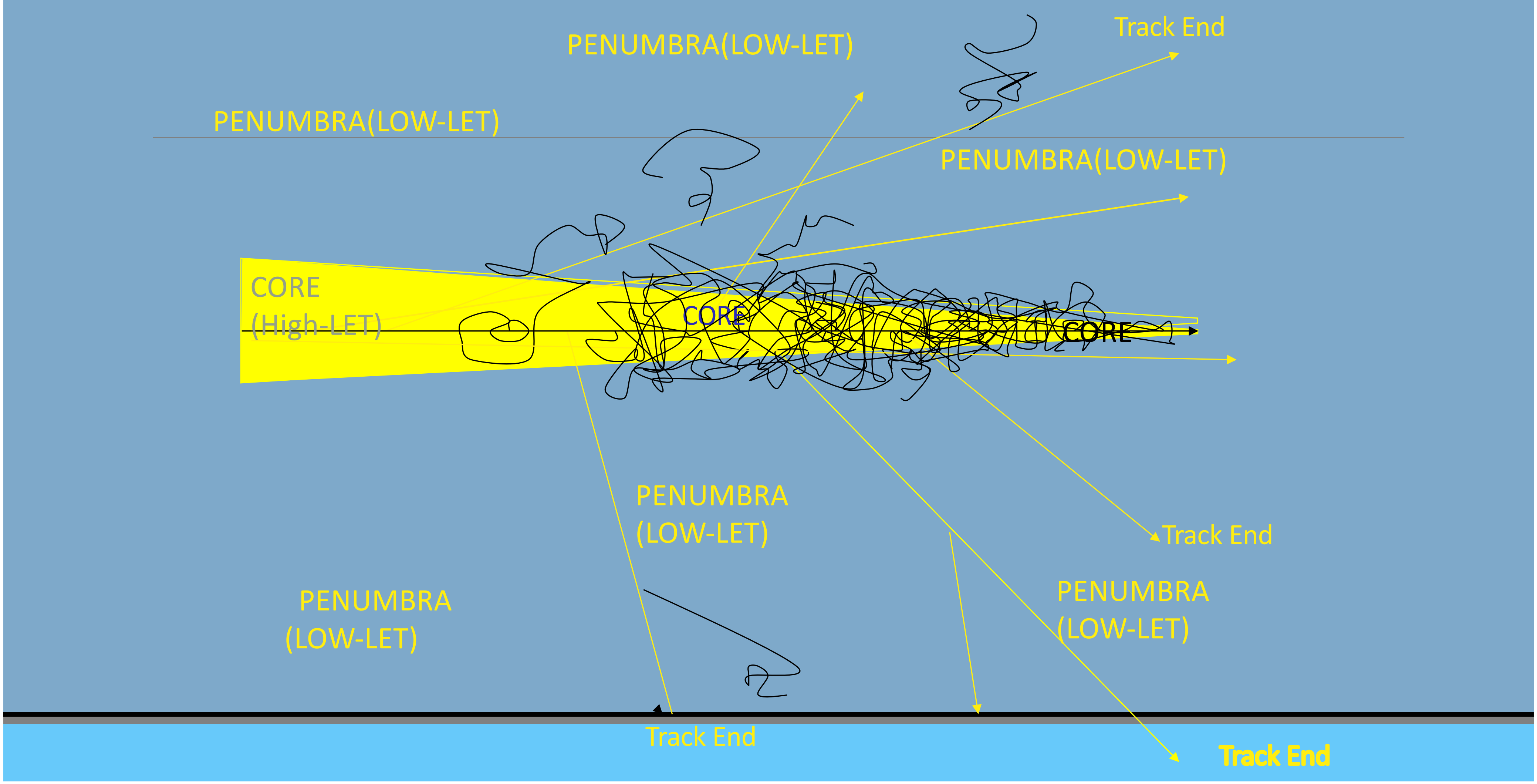
Linstadt et al. , 1991

HZE particle tracks in emulsion

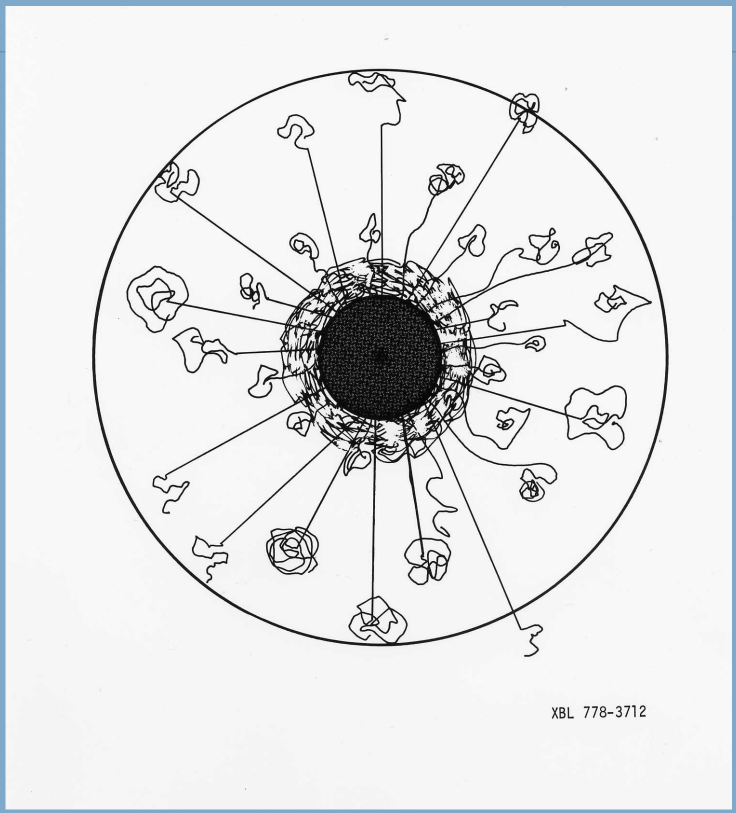


Heckman et al.

Track Structure of HZE Particles

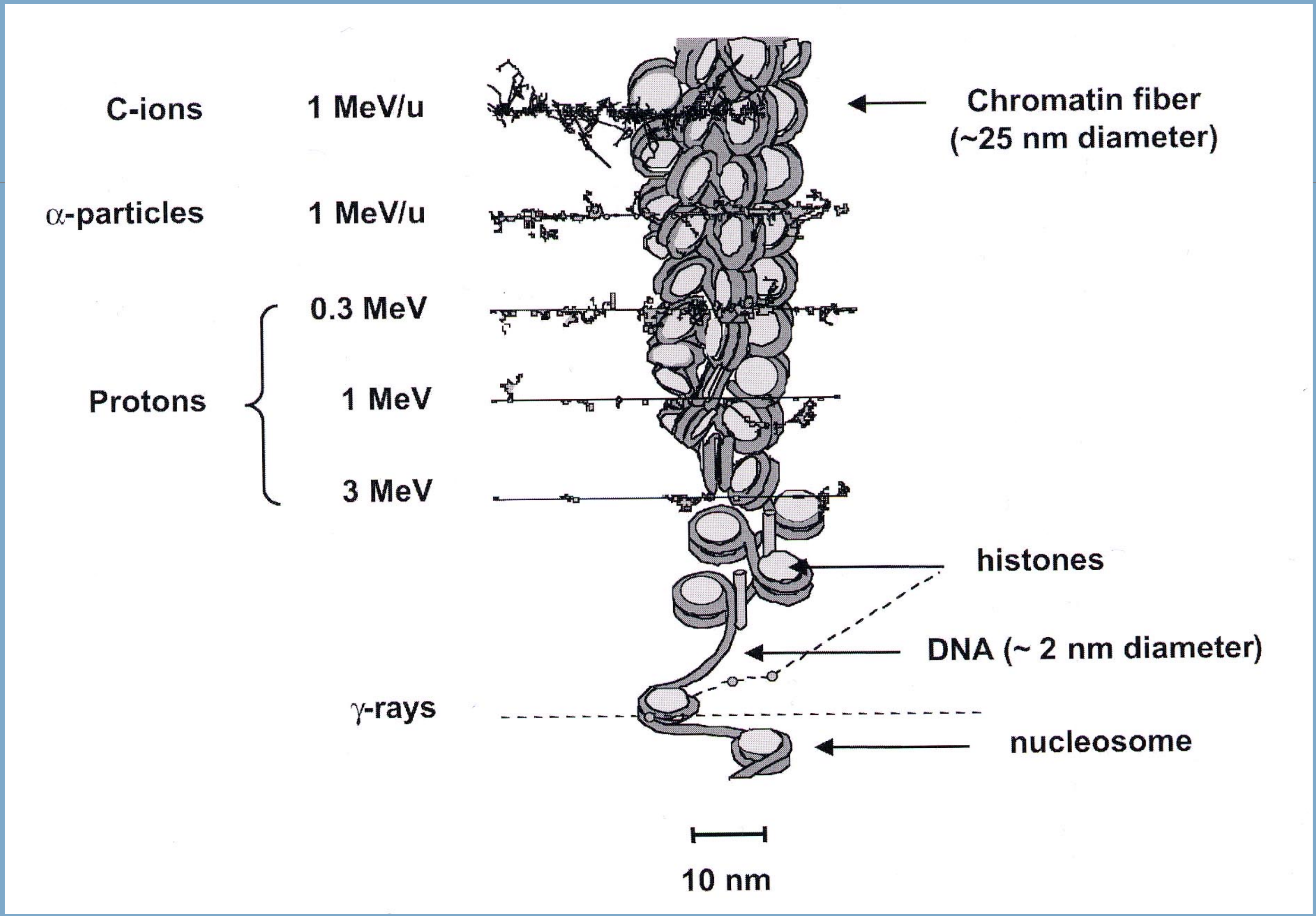


Schematic Cross-Sectional View of a Heavy Particle Track



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/mm):*
  - *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 triggering different damage & repair pathways than low LET radiations*
- *Production of short DNA fragments*
- *Slower repair*
- *Evidence of misrepair*
- *Genomic instabilities*
- *Microenvironmental changes, including stem & immune*
- *LET-dependent gene responses*

A Personal Perspective on Contributions of the Berkeley Charged Particle 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*

Globally in 2020-
~19.3 million new cancer cases
~10.0 million cancer deaths

Worldwide Numbers of Patients Treated with Particle Beams*

Globally in 2040-
Estimate~28.4 million new cancer burden
(Sung et al., 2021)

Ion	Total Pt. #	# Operating Facilities	# in U.S.
Protons.	279,148	95	42
Carbon	41,294	13**	0
		(**all in Europe or Asia)	
He, Ne, π	3,587		
Total	324,029		

- Tabulated by M. Jermann PTCOG for period through December 2021
  www.ptcog.ch
  June 2022

Lancet Oncology 2015; 16: e93-100

Carbon ion radiotherapy in Japan: an assessment of 20 years of clinical experience

Tadashi Kamada, Hirohiko Tsujii, Eleanor A Blakely, Jürgen Debus, Wilfried De Neve, Marco Durante, Oliver Jäkel, Ramona Mayer, Roberto Orecchia, Richard Pötter, Stanislav Vatnitsky, William T Chu

Overall assessment and recommendation

Clinical

NIRS is a pioneer in carbon ion radiotherapy and has contributed major paradigm shifts for radiotherapy and more generally for oncology. Besides improvements over the already favourable results achieved for some rare cancers, such as bone and soft-tissue tumours, the results reported lately support the hypothesis that carbon ion radiotherapy improves outcomes for several common cancers with poor prognosis. Therefore, more patients worldwide should have access to treatments based on carbon ion radiotherapy.

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) needed for FDA approval.*
- *Cost to build carbon ion clinical facilities.*
- *Current lack of US insurance reimbursement to maintain a carbon facility.*
- *Lack of international consensus on treatment planning methods to facilitate comparisons of clinical trials.*

Summary & Conclusions

- *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 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 to optimization of treatment planning for radiotherapy.*
- *The future scientific opportunities for hadron therapy are promising.*

"*This material was prepared and presented within the* ***HITRIplus Specialised Course on Heavy Ion Therapy Research,*** *and it is intended for personal educational purposes to help students; people interested in using any of the material for any other purposes (such as other lectures, courses etc.) are requested to please contact the author.*

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Acknowledgments

Thank you for your attention
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Questions?

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