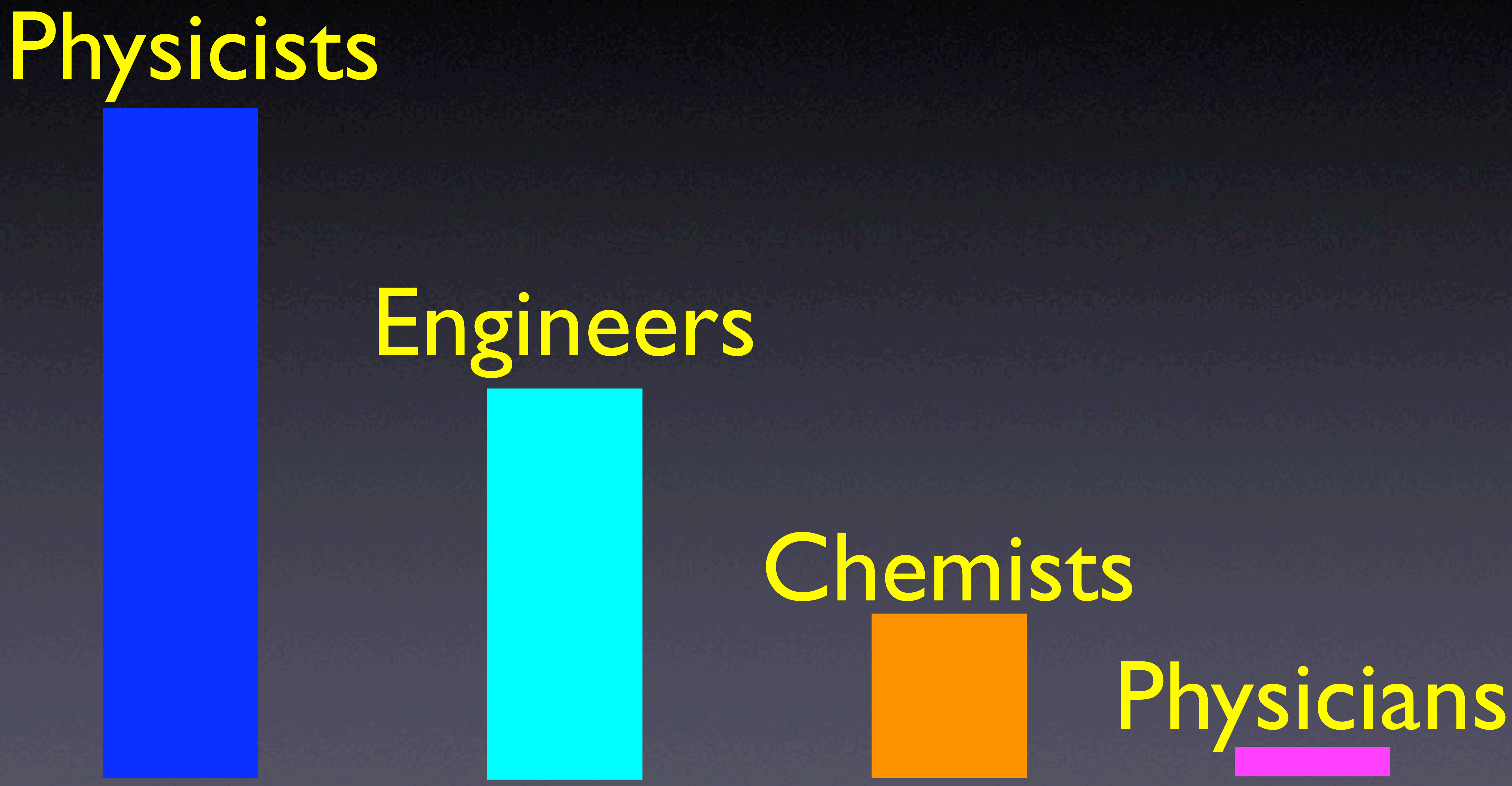
The Case for Light Ions and Carbon Nuclei

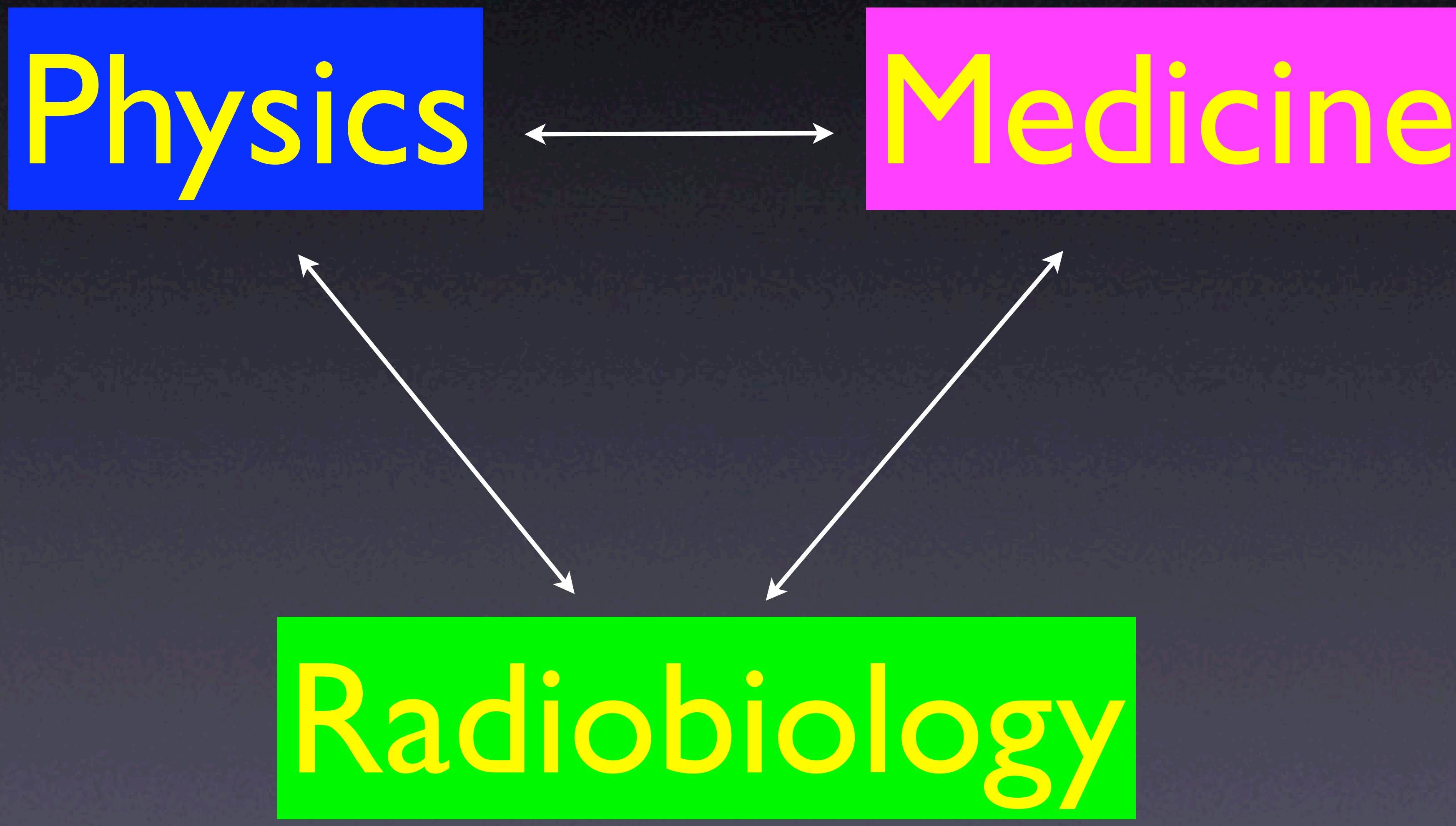
Rich Levy, MD, PhD
ABC Foundation

Formerly: Medical Scientist, LBNL
Professor of Rad Onc, LLUMC

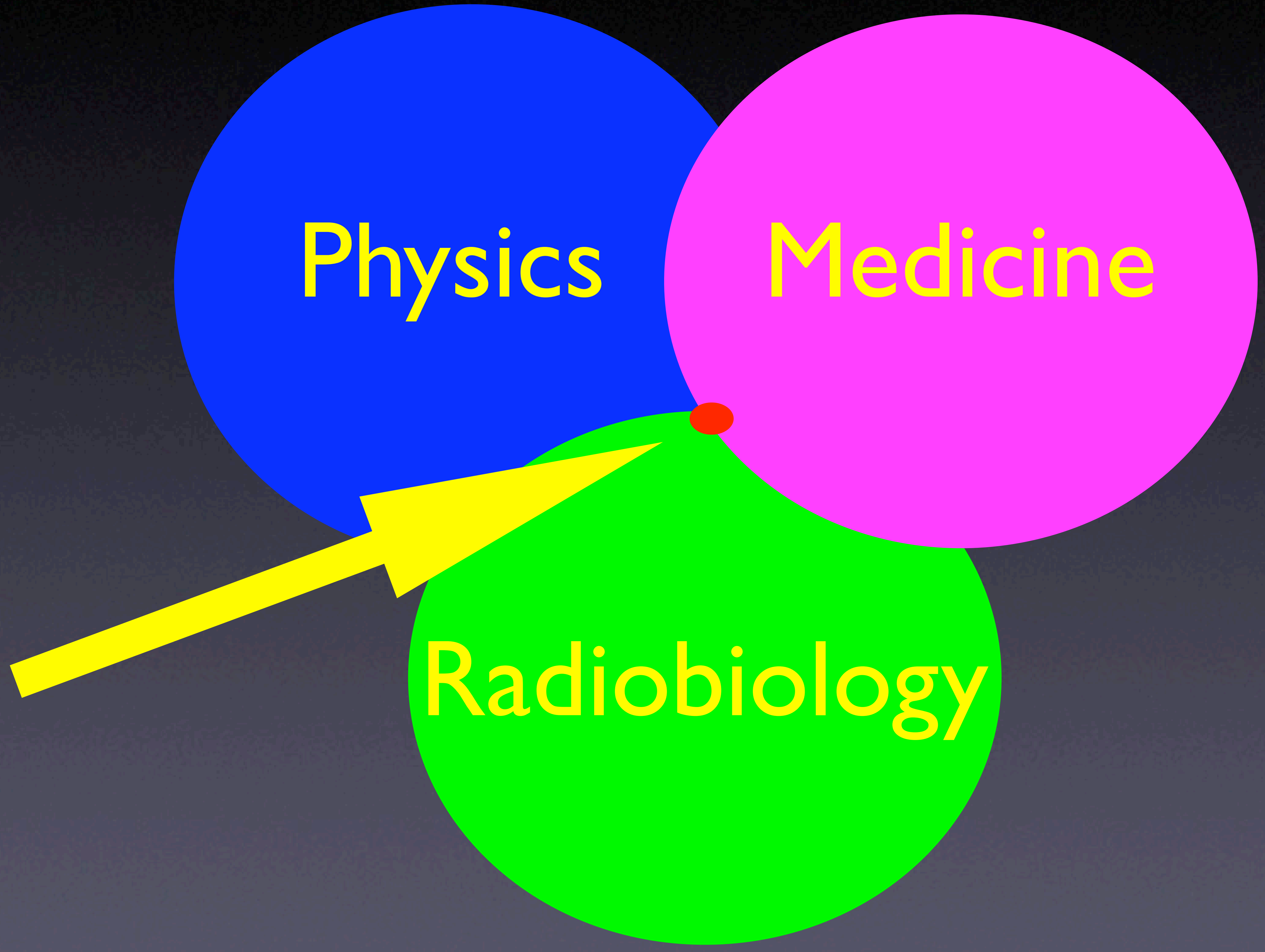
Particle Therapy: Typical Symposium Meeting



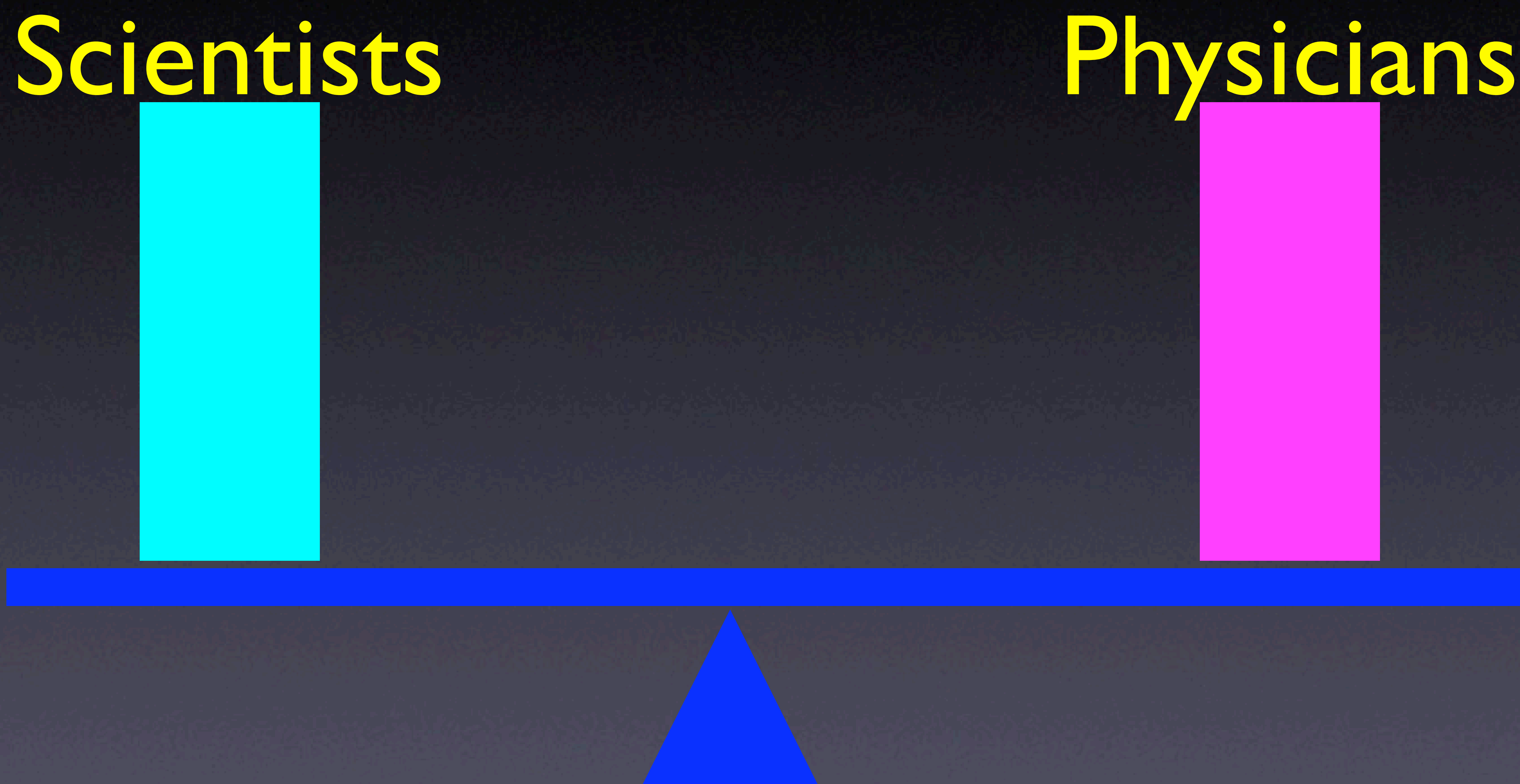
Particle Therapy: The Collaboration Required



Particle Therapy: The Collaboration Thus Far Achieved



Particle Therapy: The Balance Required



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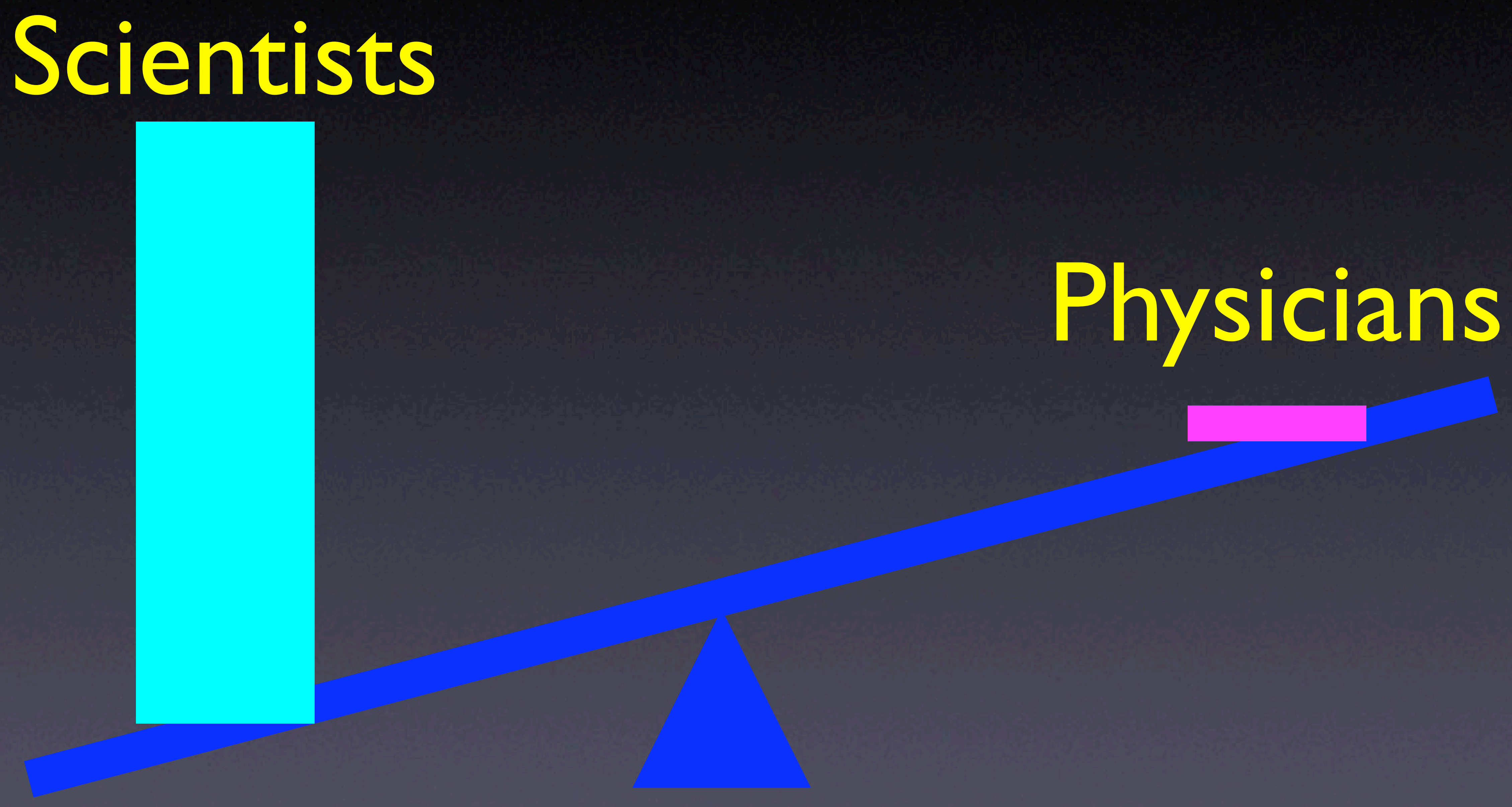

Presentation Overview

- Who am I?
- Introduction to Radiation Oncology
- Historical Overview of Particle Therapy
- Physical and Radiobiological Rationale
- The Future

Who Am I?

- Why am I here?
- Why should you listen to me?

My Interests & "Learned Comments"

Mid 1980s at LBNL, as a Medical Scientist:

1. Stereotactic Radiosurgery
   >"Violates all principles of fractionation!"
2. Image-Fusion (CT-MRI- Angiography)
   >"Too complex, too many computers!"
3. Bragg-Peak Charged Particles
   >"Too complicated, too weird, too expensive!"

Today: "All the above are proven, state of the art!"

BUT, for high-LET ions: same learned comments!

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PhD (Biophysics) - UC Berkeley

Internal Medicine

Radiation Oncology

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Academic Titles

Med Scientist (Research Med/Rad Biophys) - LBNL

Academic Titles

Med Scientist (Research Med/Rad Biophys) - LBNL

Asst Adj Prof (Diagnostic Radiology) - UCSF

Assoc Clinical Prof (Neurosurgery) - SUMC

Full Professor (Radiation Medicine) - LLUMC

Member:
United Federation of Particle Beamers

Introduction to Radiation Oncology

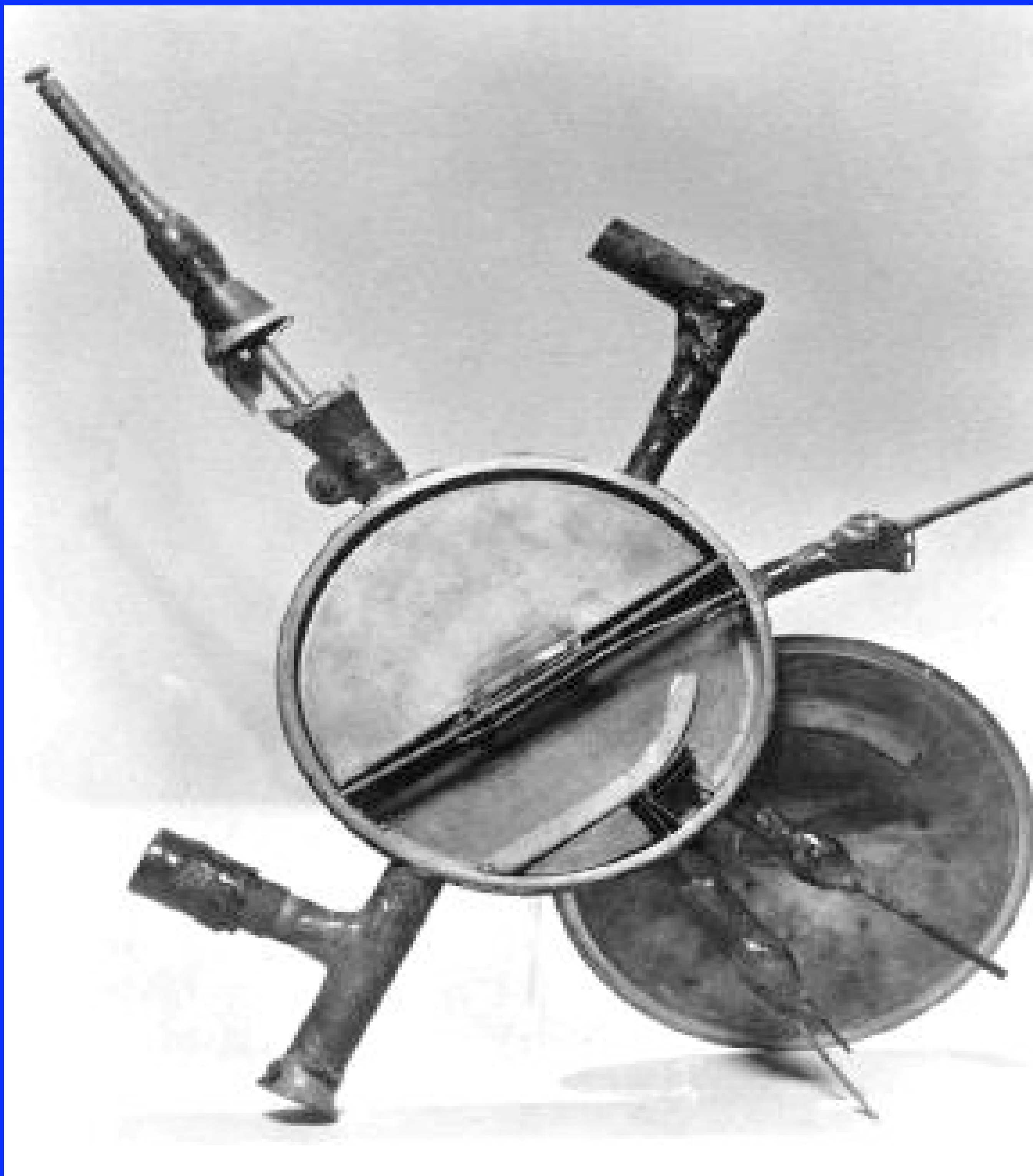
- 1895: Roentgen discovers X-rays
- 1903: Cervical cancer treatment reports
- Early and late adverse sequelae observed
- Must improve "therapeutic ratio"

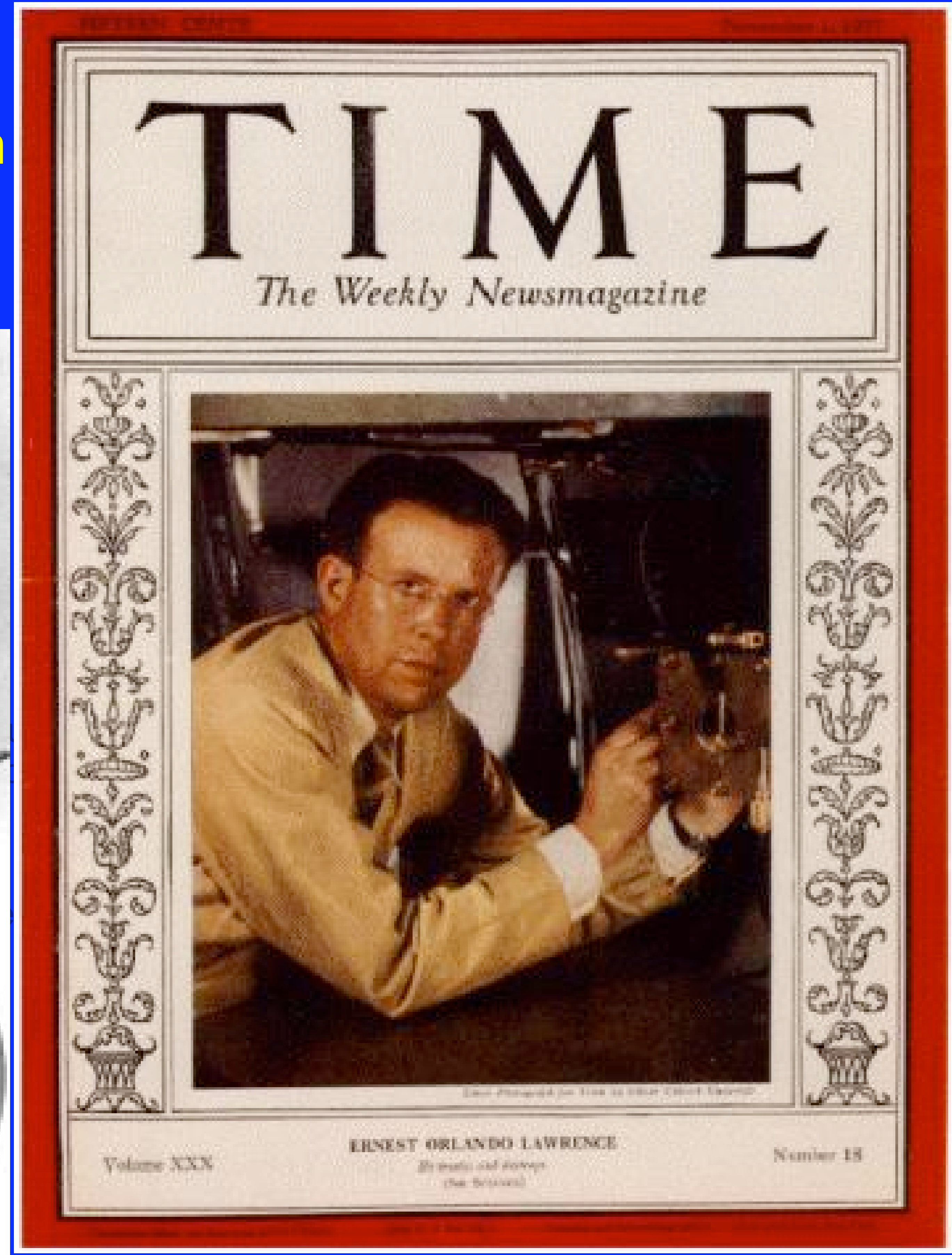
Therapeutic Ratio: Radiobiology

- Dose = effect
- Fractionation
- Target delineation (GTV, CTV, PTV)
- DOSE CONFORMITY!!
- Tumor staging
- IONIZATION DENSITY!!
  - low-LET photons vs high-LET neutrons
  - low-LET particles vs high-LET particles

A Brief History of Charged Particle Therapy

E.O. Lawrence and the Cyclotron
In 1930: First Successful Cyclotron was constructed by Lawrence and Livingston (12 cm diam single Dee)

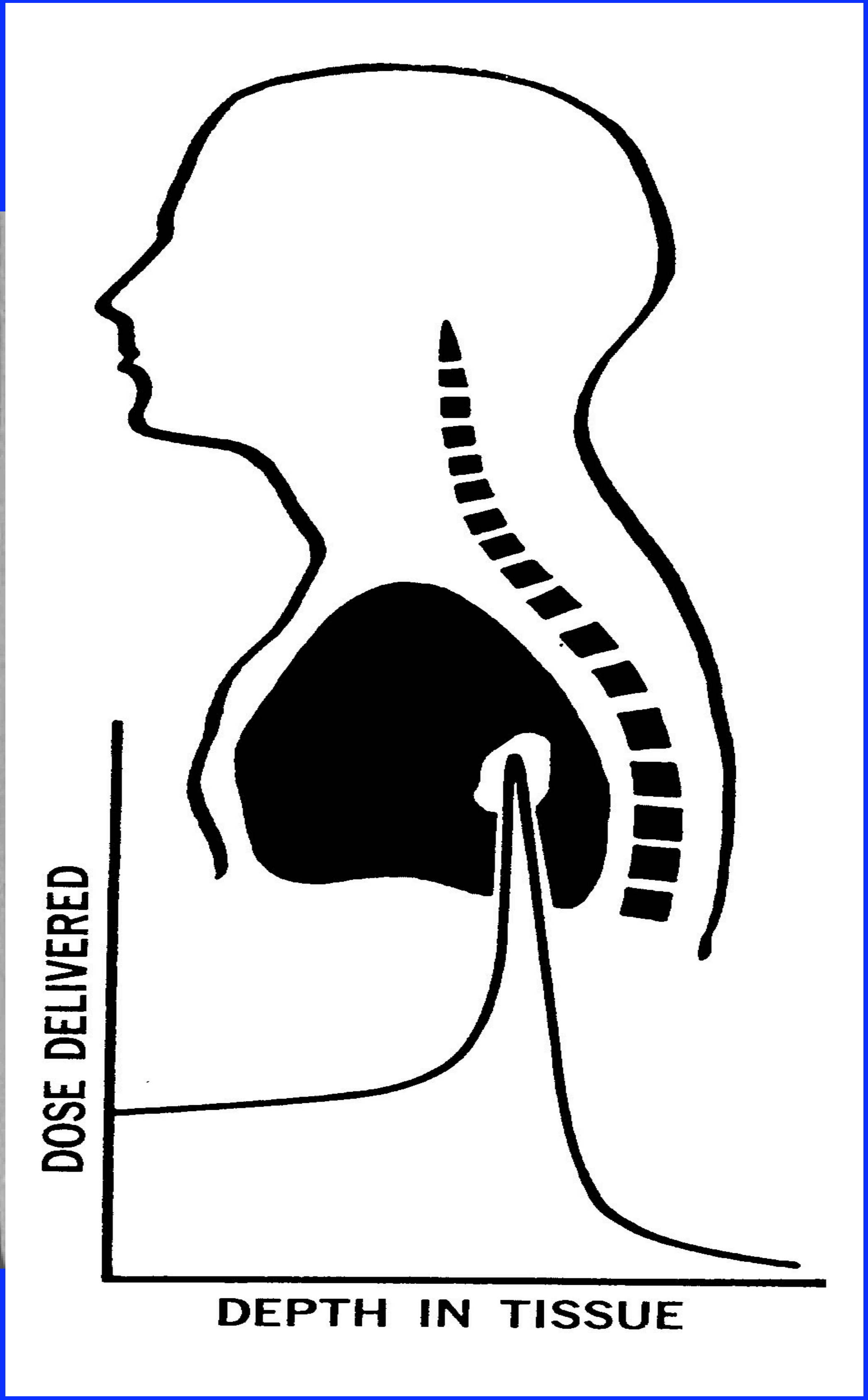




R.R. Wilson and Hadron Therapy

Robert Wilson proposed the use of Bragg Peak for radiation therapy (1946)*

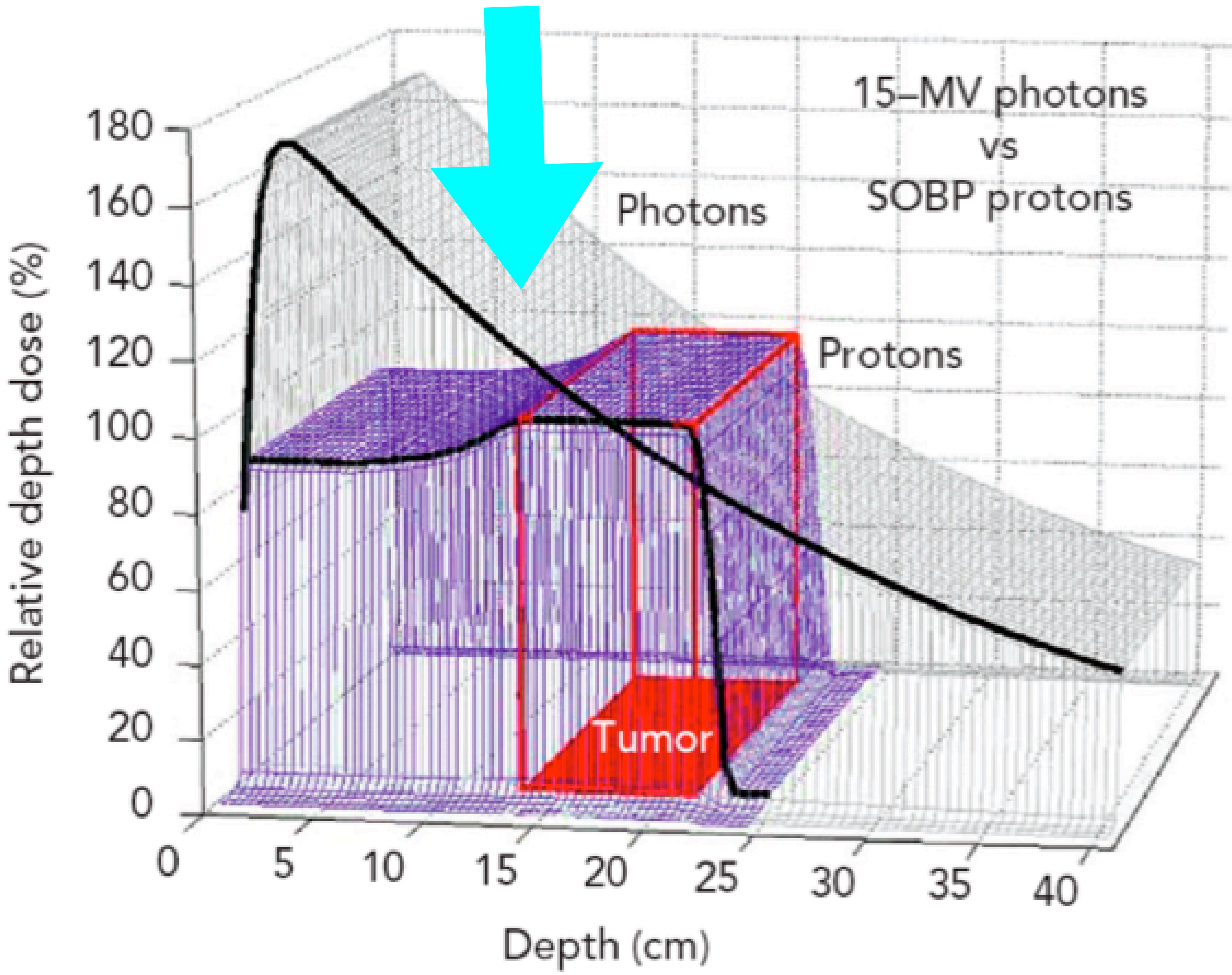
* RR Wilson, "Radiological use of fast protons," Radiology. 1946; **47**: 487-491



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

Physical Rationale for Particles

Depth-Dose Curves of Photon vs. Proton Beams



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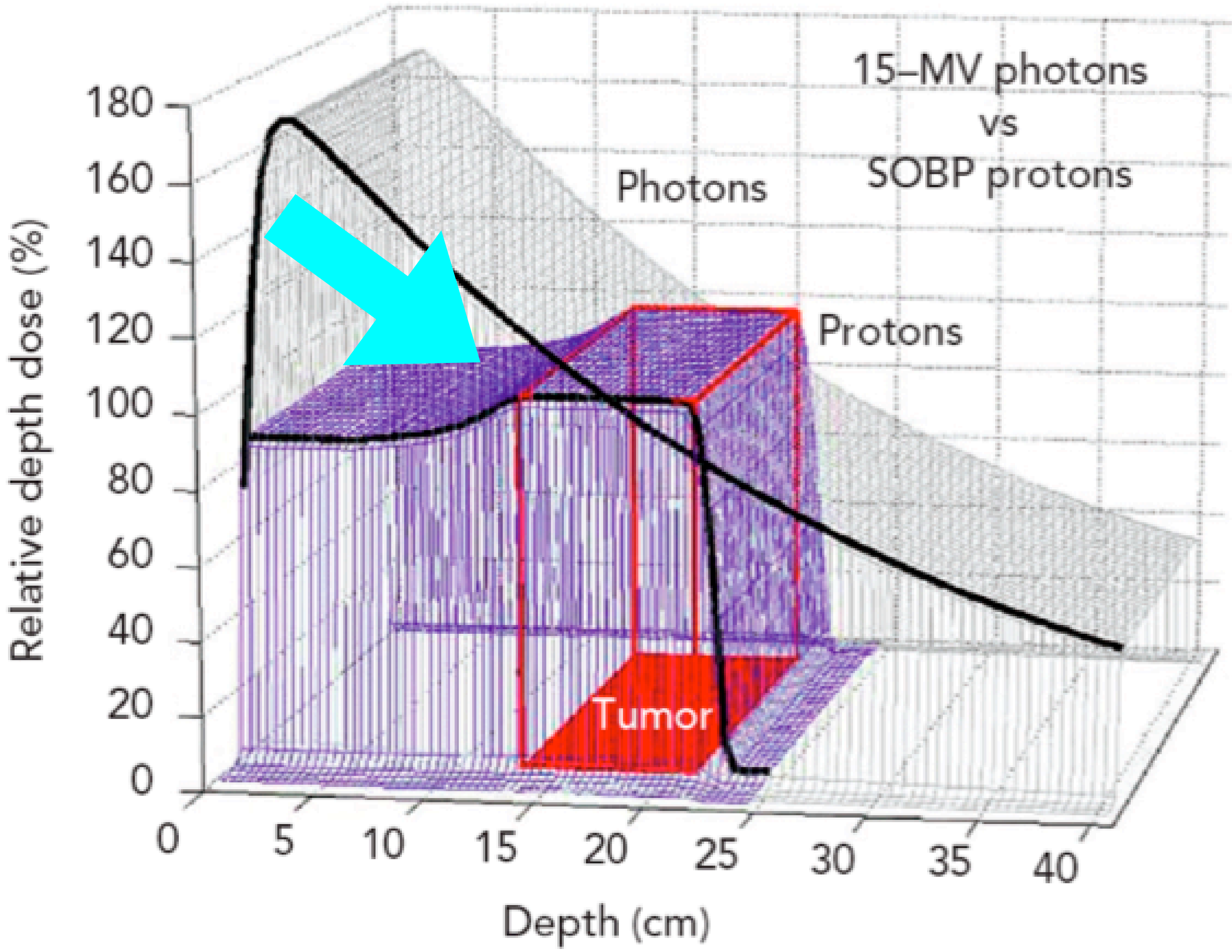
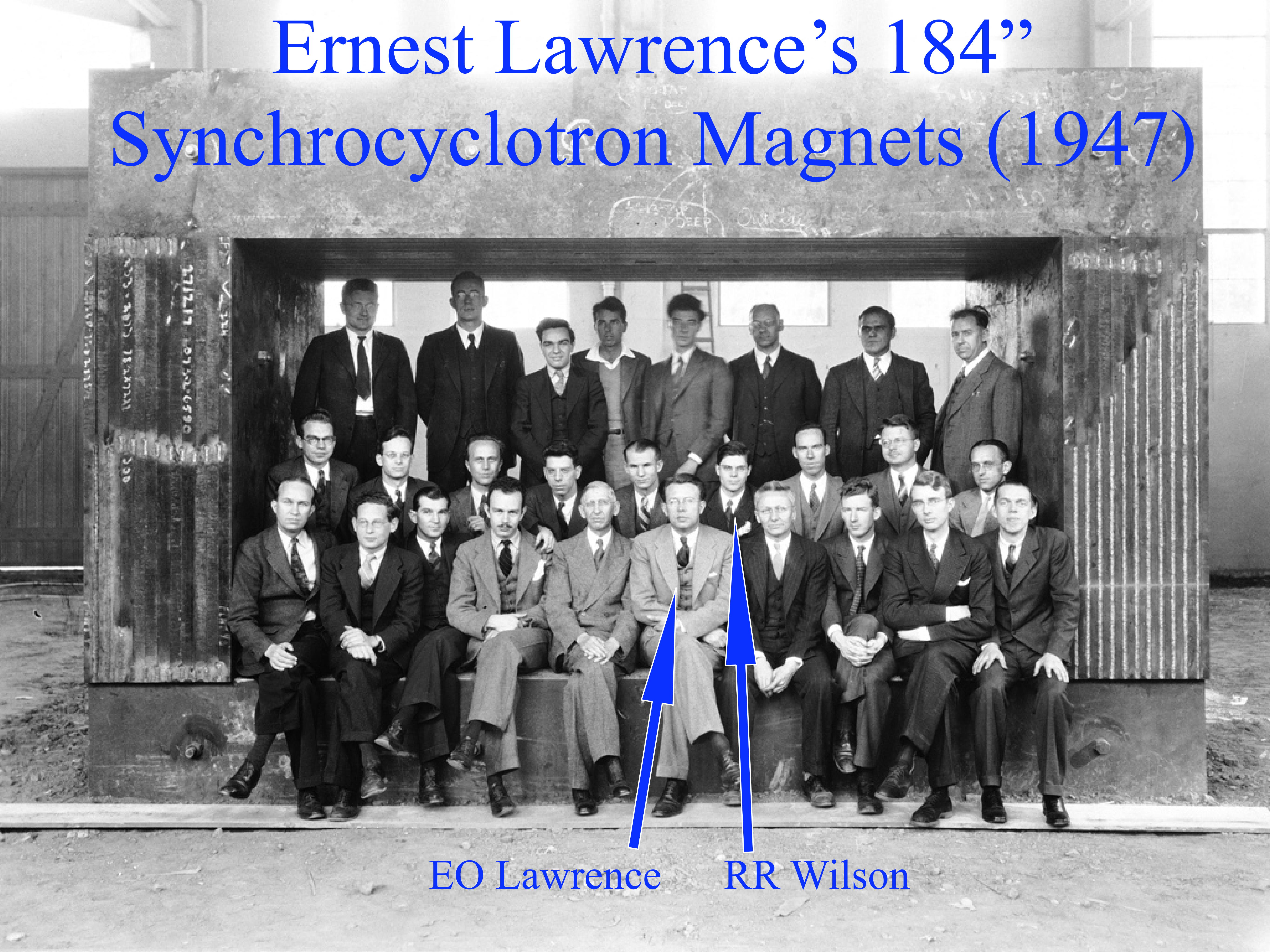


Ernest Lawrence's 184" Synchrocyclotron Magnets (1947)



The first beam: November 1, 1947

The Beginning of Particle Therapy

- 1948- Biology experiments using protons
- 1954- Human exposure to accelerated protons:
  pituitary gland
- 1954 - 1986: Clinical Trials– 1500 patients treated
  with protons and helium nuclei

Cornelius A. Tobias

ISAH:
LBNL, 1950s
(p+ and He)

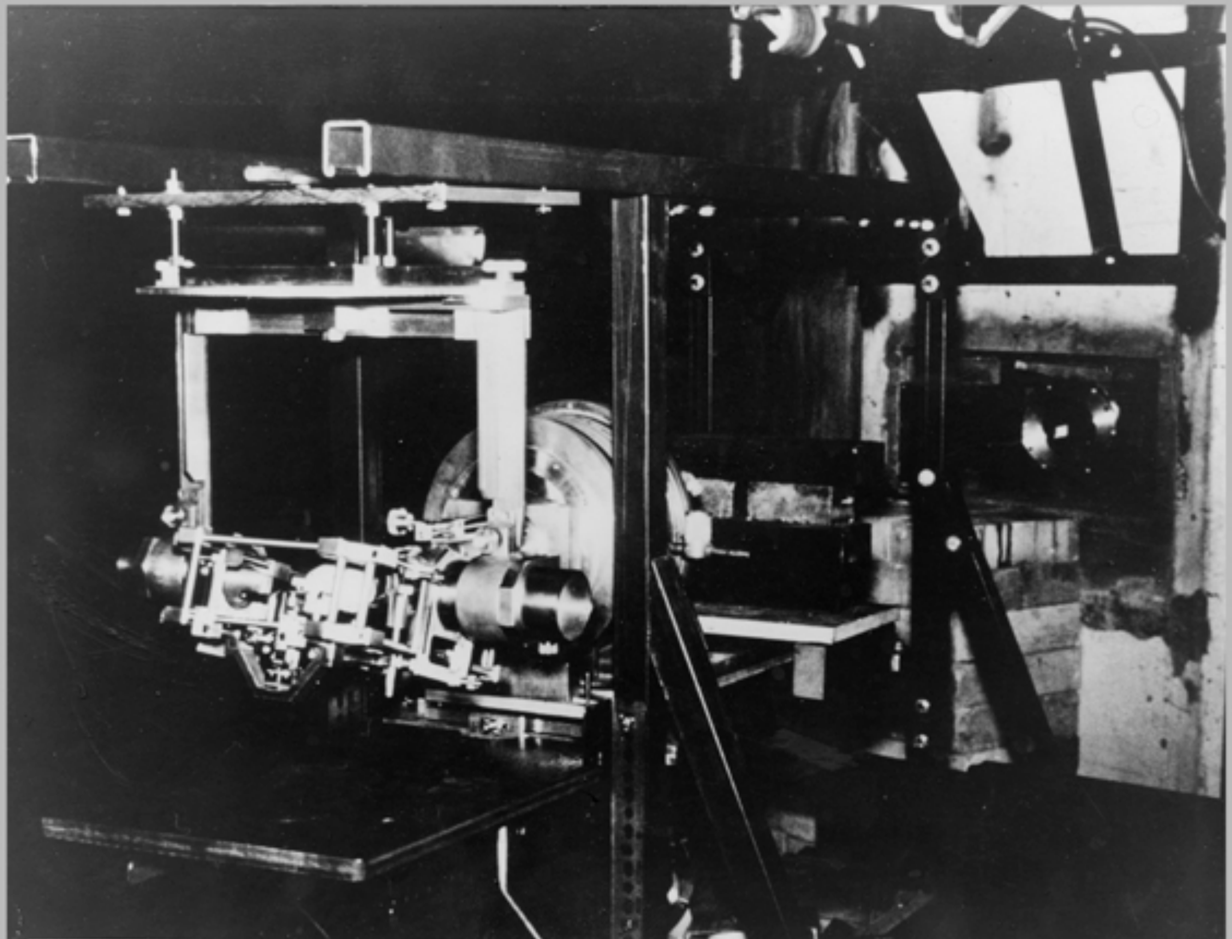
Historical Overview of Particle Therapy: I

- 1930: Ernest O. Lawrence invents cyclotron
- 1946: Robert Wilson proposes particle therapy
- 1947: First beam at 184-inch synchrocyclotron
- 1948: First biology experiments at LBNL
- 1954: First patient treated with protons (pituitary)
- 1957: First cancer treated with protons (Uppsala)
- 1957: First patient treated with helium (pituitary)
- 1975: First cancer treated with heavier ions

Historical Overview of Particle Therapy: II

- 1960s-1970s: Low-LET particle beam treatments expanded to other sites, as 3D imaging evolved.
  - LG Intracranial tumors and AV malformations
  - Paraspinal chordomas and chondrosarcomas
  - Uveal melanomas
  - Head and neck tumors
  - All sites showed excellent clinical results!
    - High local control; Low toxicity

Proton Tx Harvard Cyclotron Lab
(Early 1960's)

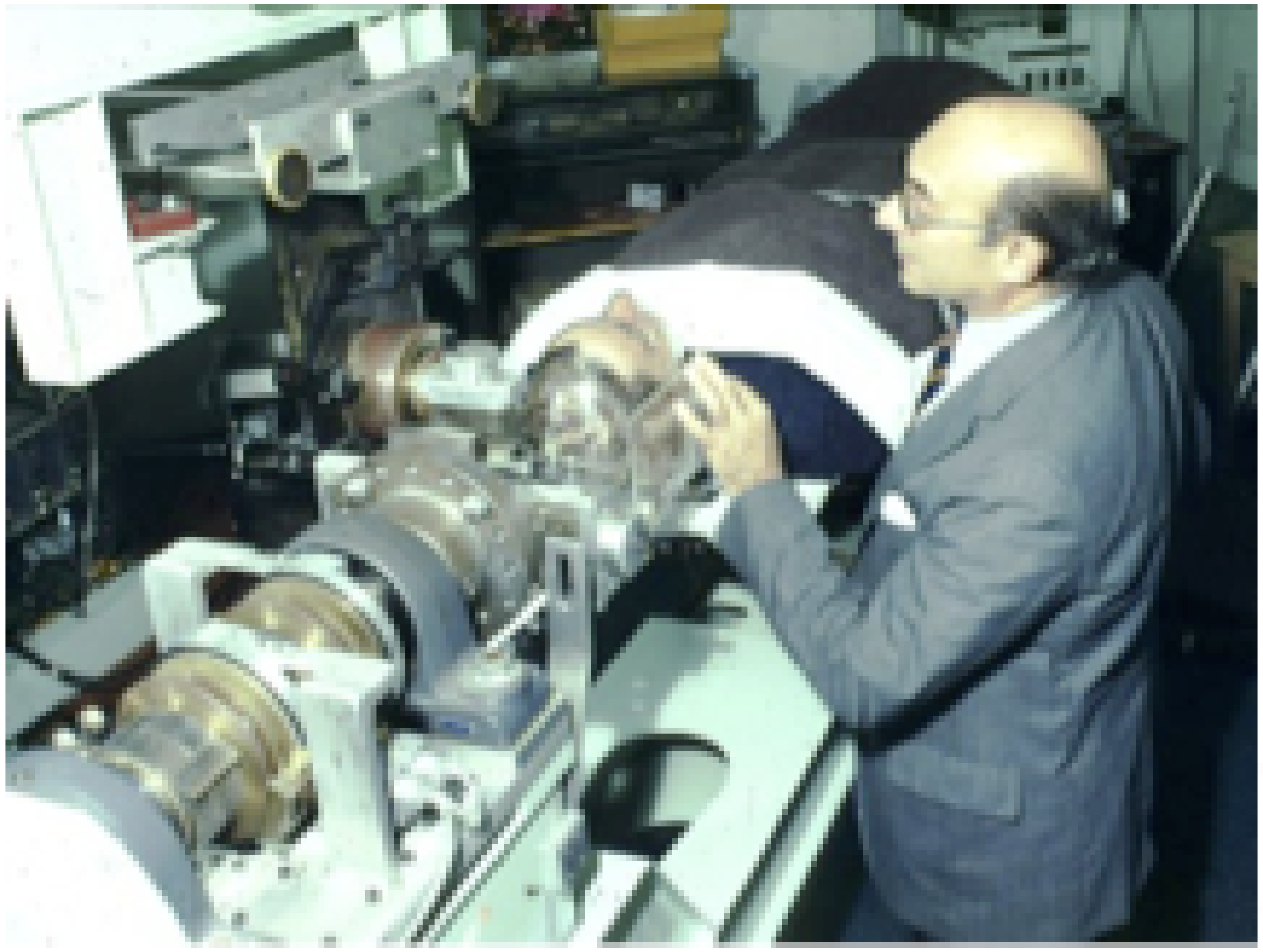


Patient treatments outside the vault in the early 1960's.

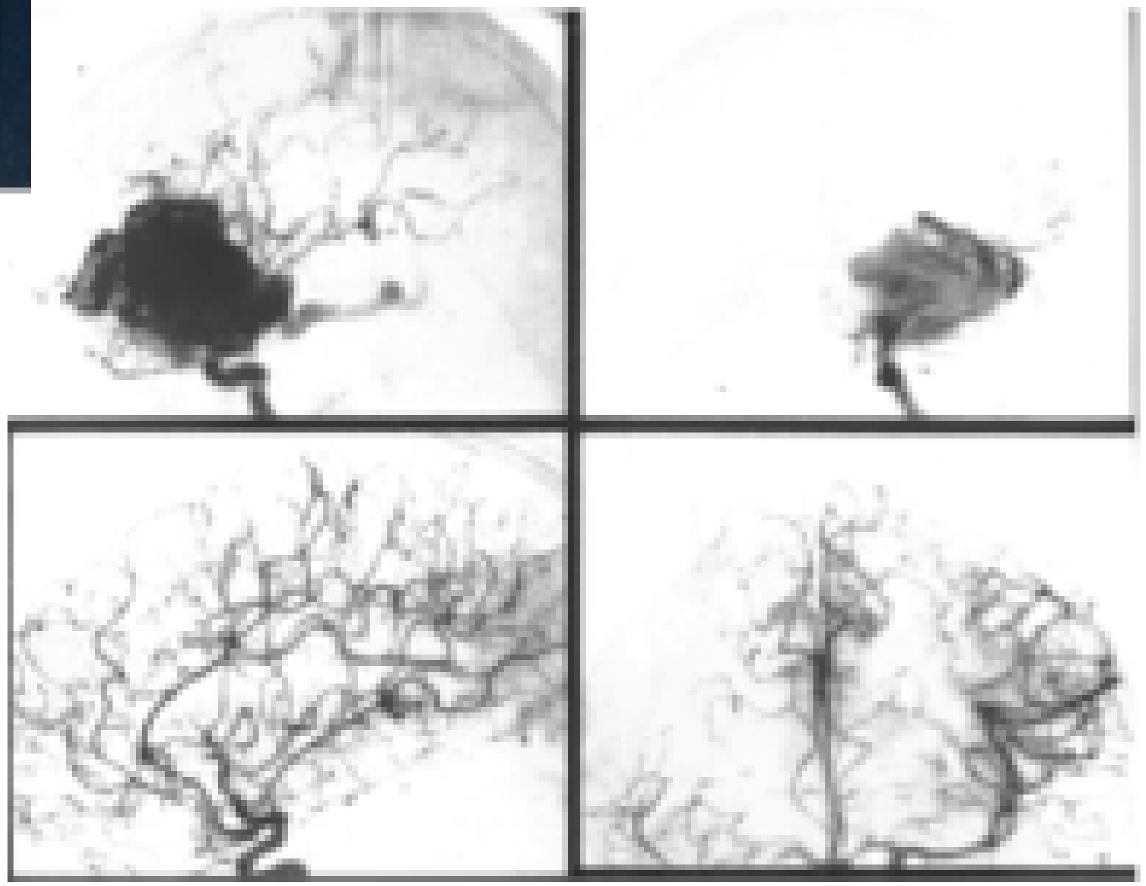
Historical Overview of Particle Therapy: III

- 1970s-present: Still better 3D radiological tools
  - Better target delineation for all sites
  - Better calculation of depth-dose distribution
  - Thoracic tumors
  - Abdominal-pelvic tumors
  - Cranio-spinal irradiation
  - Macular degeneration
  - Most low-LET sites showed excellent results!
    - High local control; Low toxicity

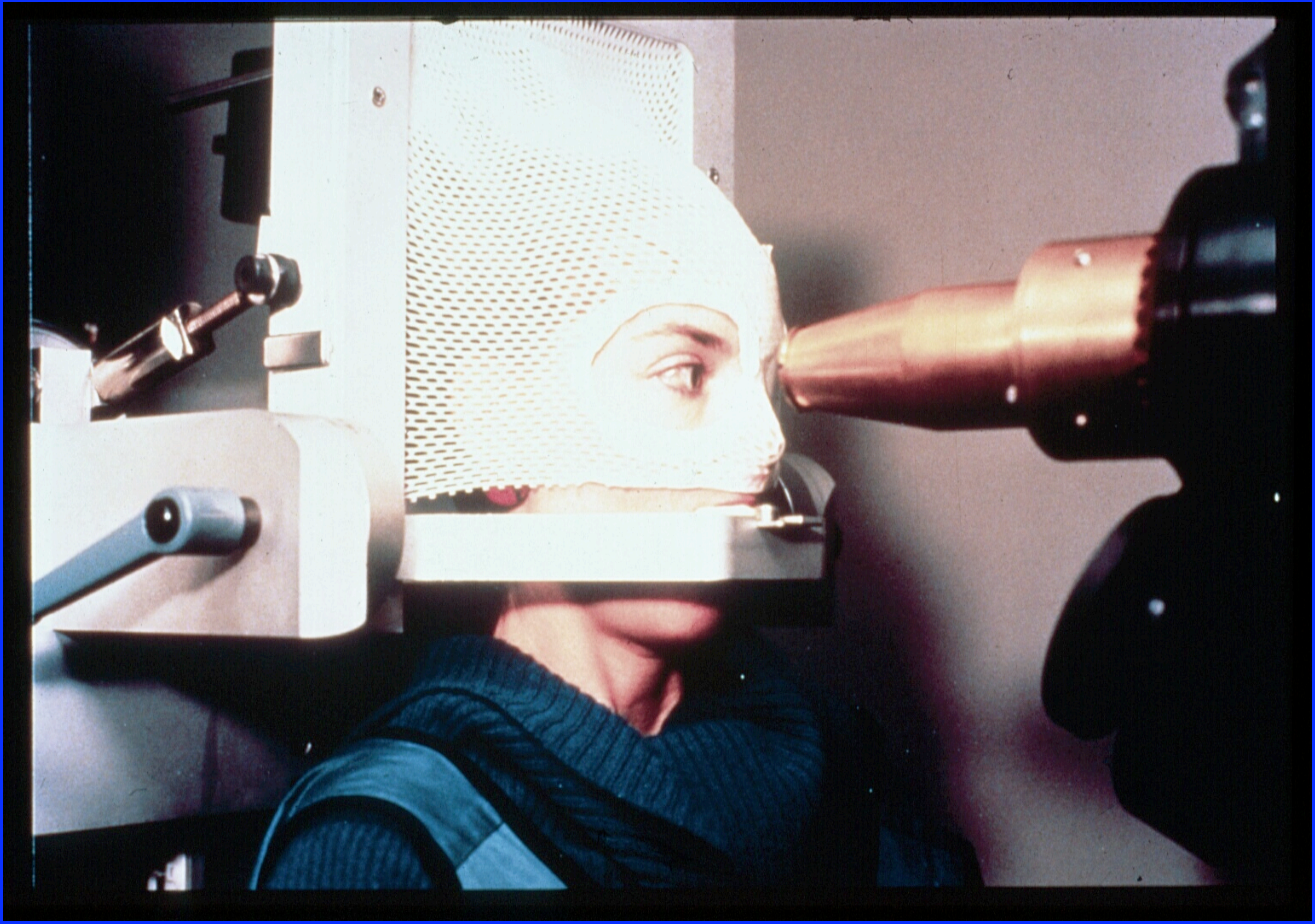
AVM Treatment Using He Ion Beam



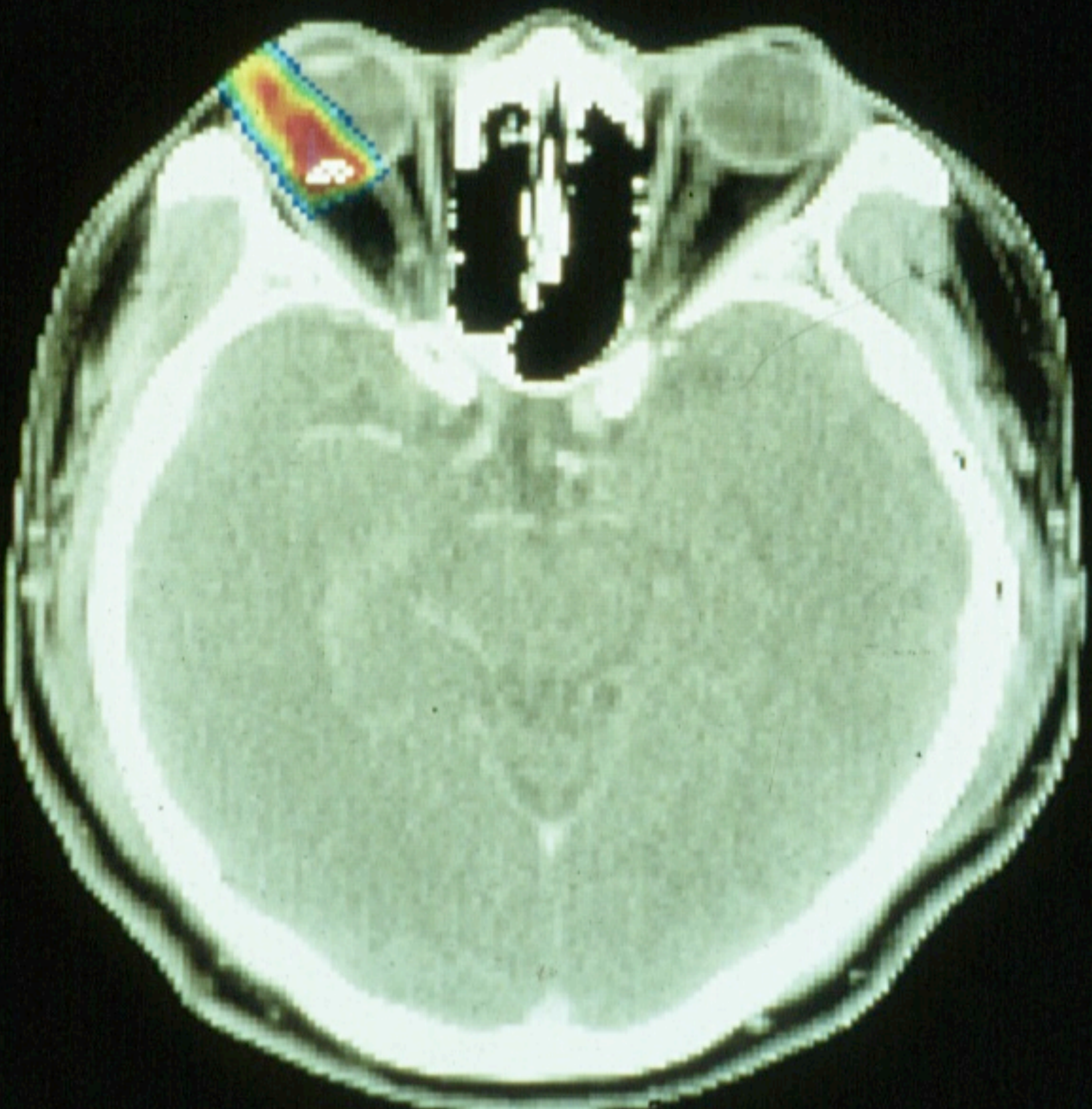
Jacob Fabrikant with an AVM patient on ISAH patient positioner at Bevatron (1987).



LLUMC: 1st pt in Oct 1990 uveal melanoma=SNVM setup

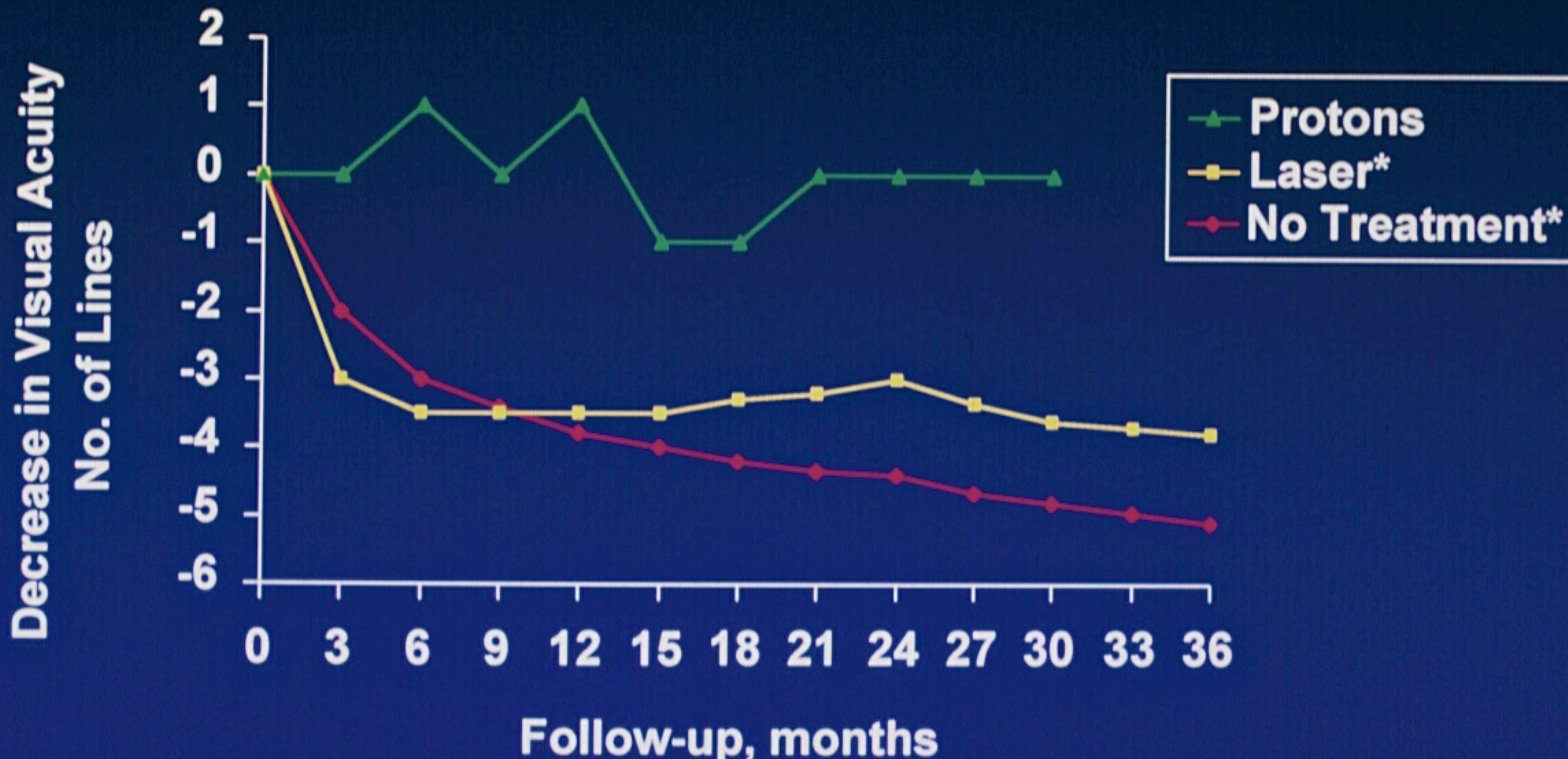


Macular Degeneration (wet type)
14 Gray in 1 fraction; 28 patients



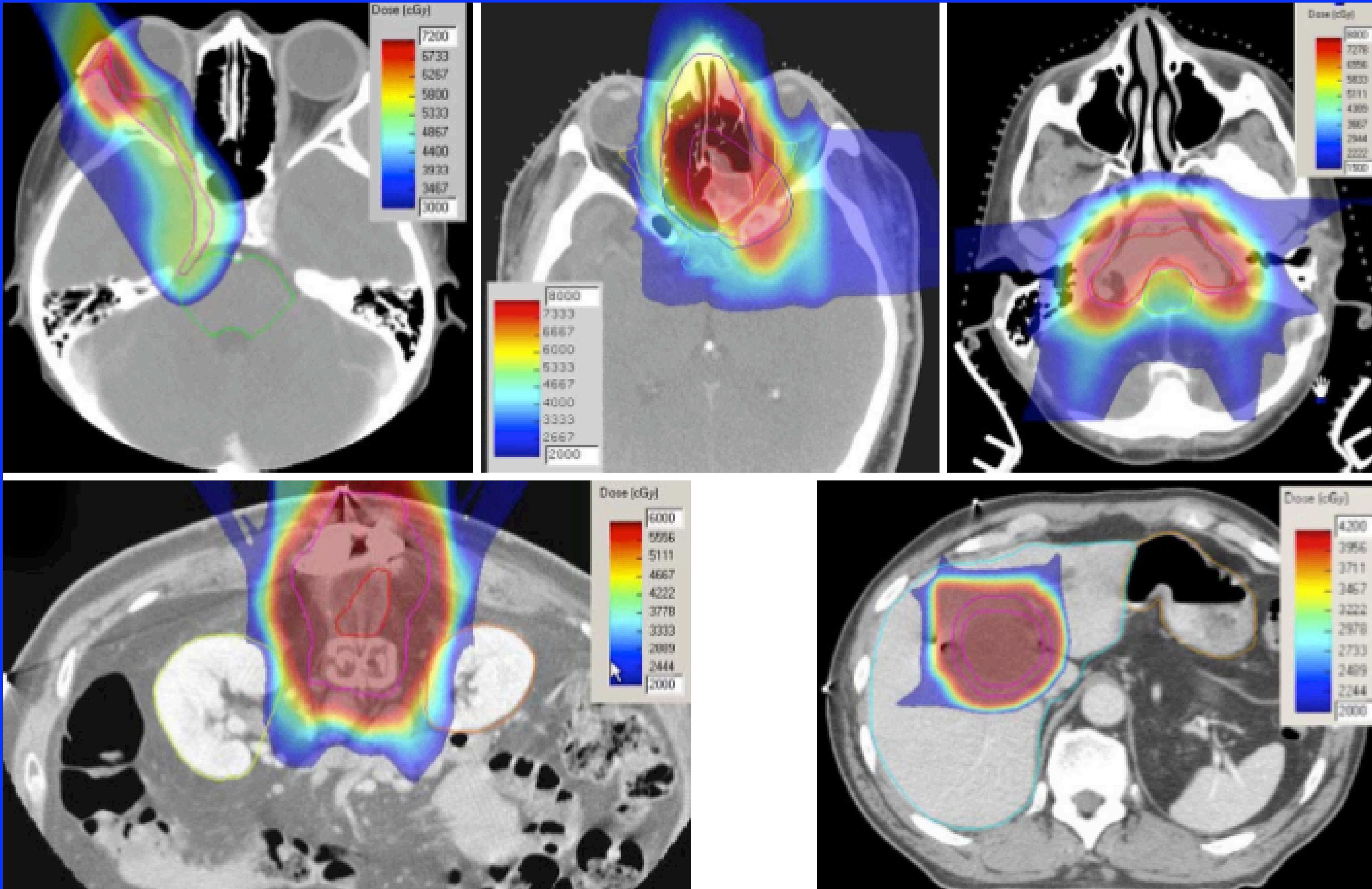
Macular Degeneration

Mean Decrease in Visual Acuity



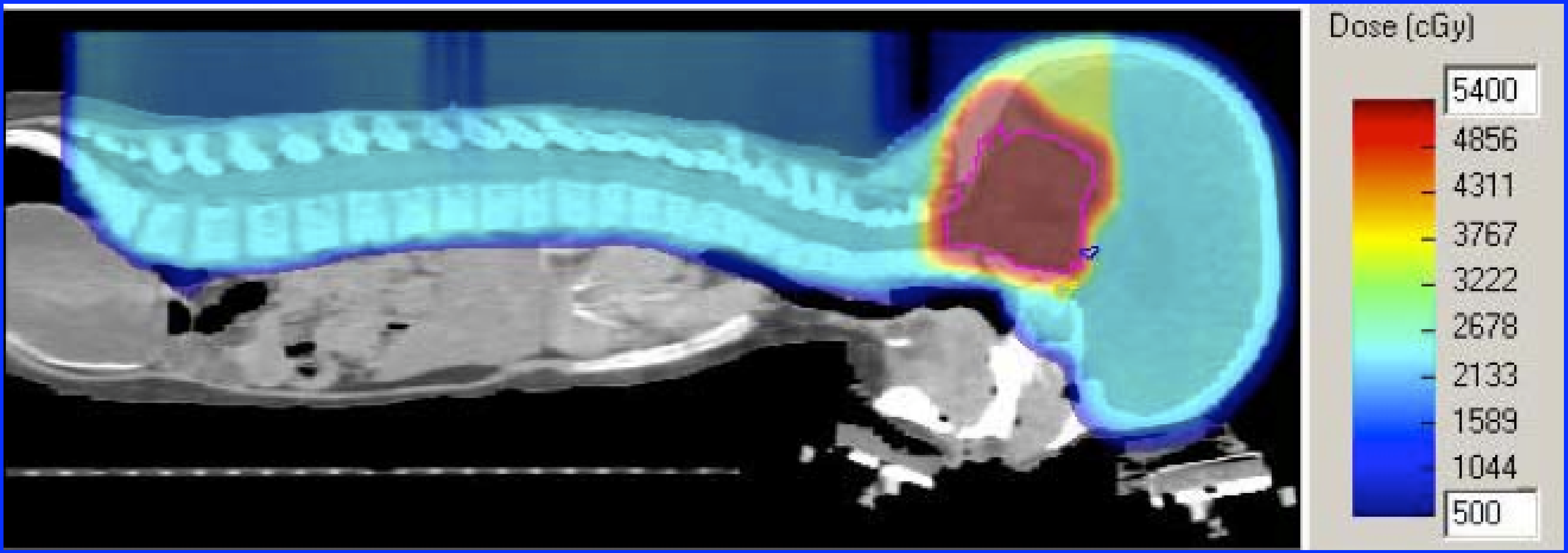
*Arch Ophth. 109: 1220, 1991

Proton Color Wash: 5 Sites



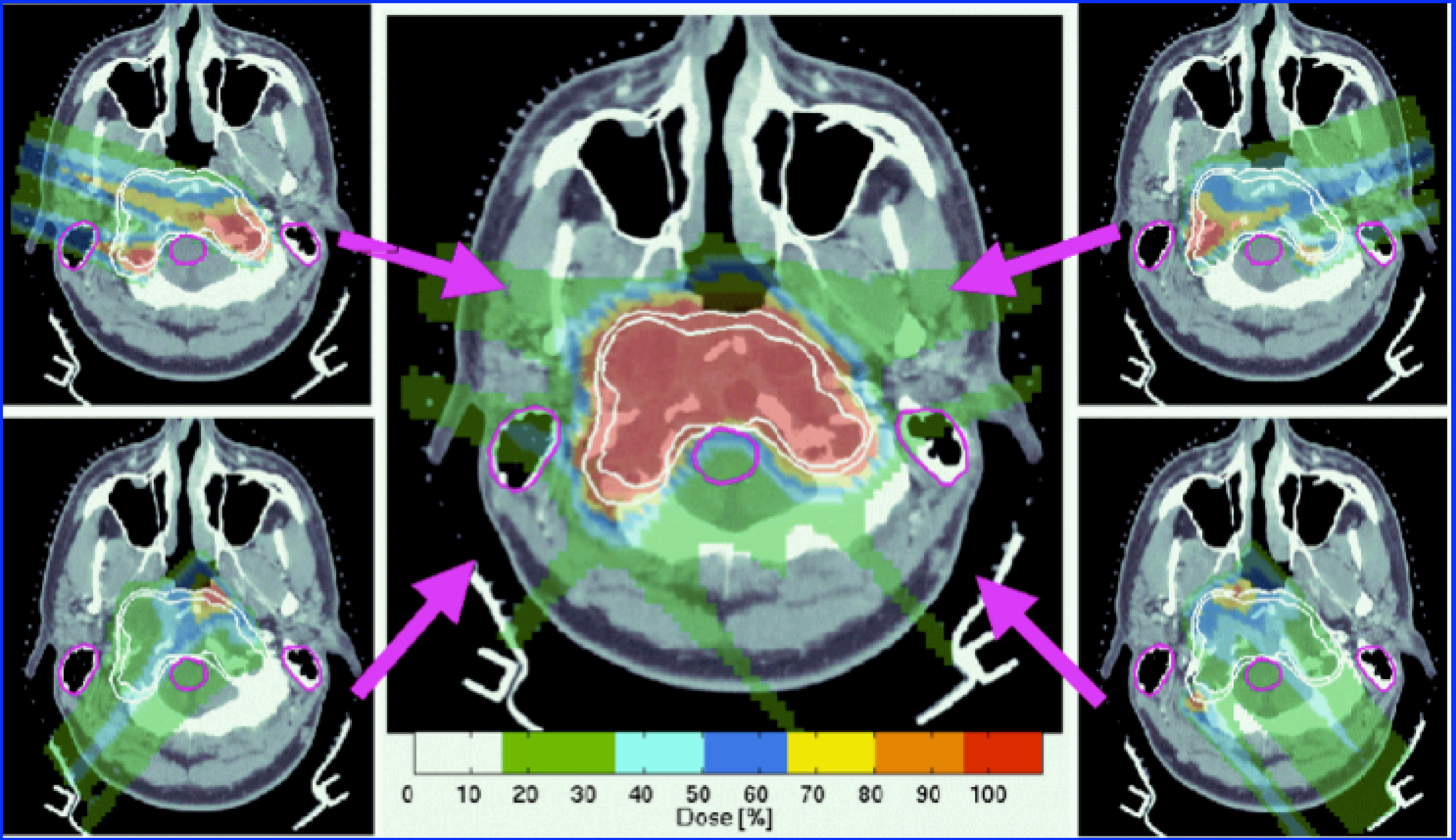
Bussiere and Adams, 2003

Craniospinal Irradiation: Medulloblastoma



Bussiere and Adams, 2003

IMPT Color Wash



Alex Trofimov, MGH

Clinical Cancer Trials at LBNL Bevalac: 1975–1992

J.R. Castro, MD, conducted the LBNL clinical trials.

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 patients treated: 1314

1975–1992

He patients	858
Heavier ions	456

** The beginning of high-LET treatment **

(with charged particles)

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(with charged particles)

Physical Considerations for Particles

- Geometry of Beam Delivery
  - Fixed beam line (horizontal, vertical, diagonal)
  - Gantry based beam delivery
  - Isocentric treatment tables (x, y, z, pitch, yaw, roll)
    - Isocentric Stereotactic Apparatus for Humans
    - HCL/MGH *STAR* System
    - Robotically controlled

Physical Considerations for Particles

- Target Delineation (GTV, CTV, PTV)
  - Absolutely imperative: Know your target!
    - Physical examination
    - Imaging: CT, MRI, PET with various tracers
- Target Motion
  - Respiratory, Cardiac, Peristalsis

Physical Considerations for Particles

Beam Scanning

- Passive Scattering vs Active Beam Scanning
  - Passive scattering: used for decades to SOBP
    - OK for targets of uniform thickness
    - Overshoot for non-uniformly thick targets

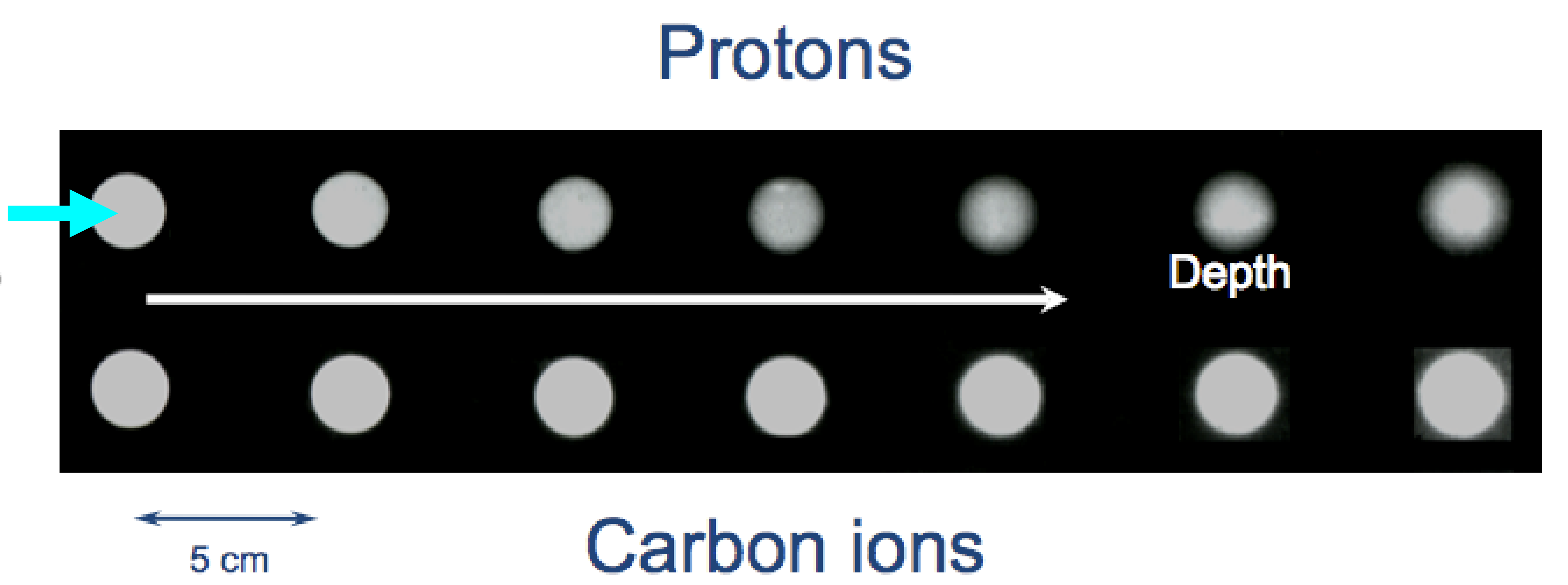
Physical Considerations for Particles

Beam Scanning

- Active Beam Scanning Produces Better Conformity
  - Minimally modulated narrow Bragg peak
  - Sequential magnetic guidance across stacked layers of the target volume
    - Raster scanning (continuous)
    - Step-and-shoot ("spot scanning")

Physical Beam-Scanning Issues

- Lateral penumbra is important!



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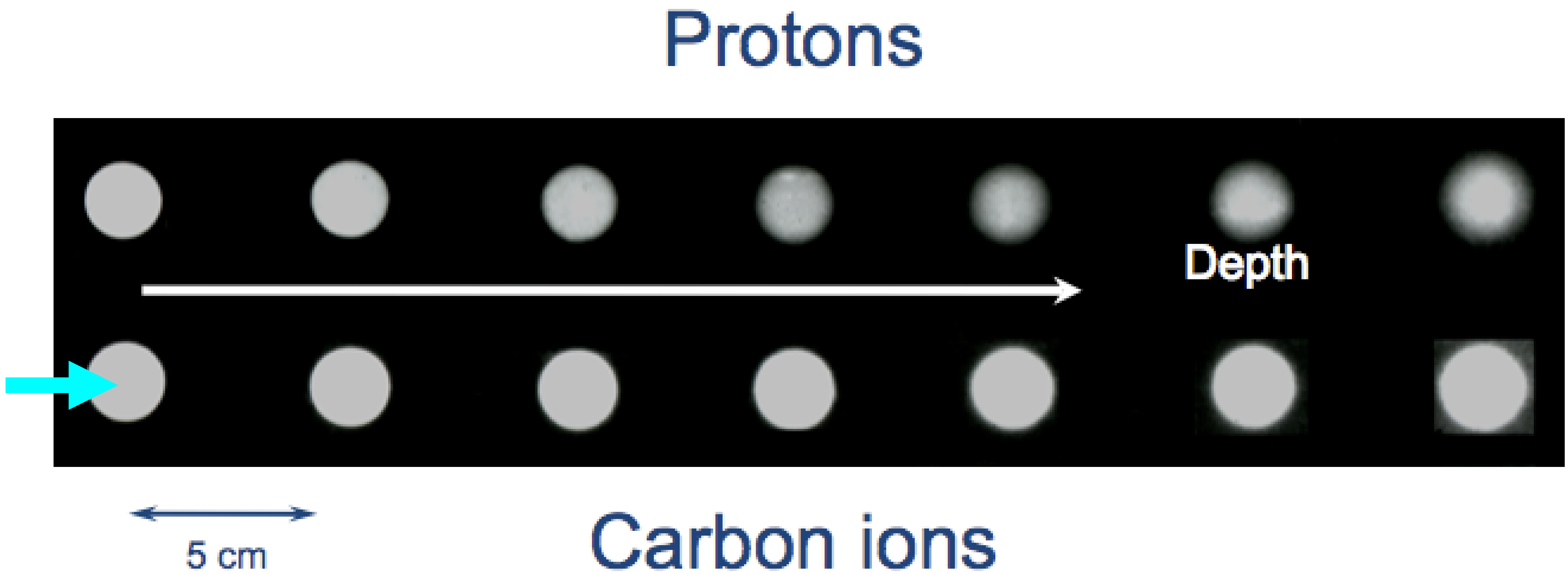
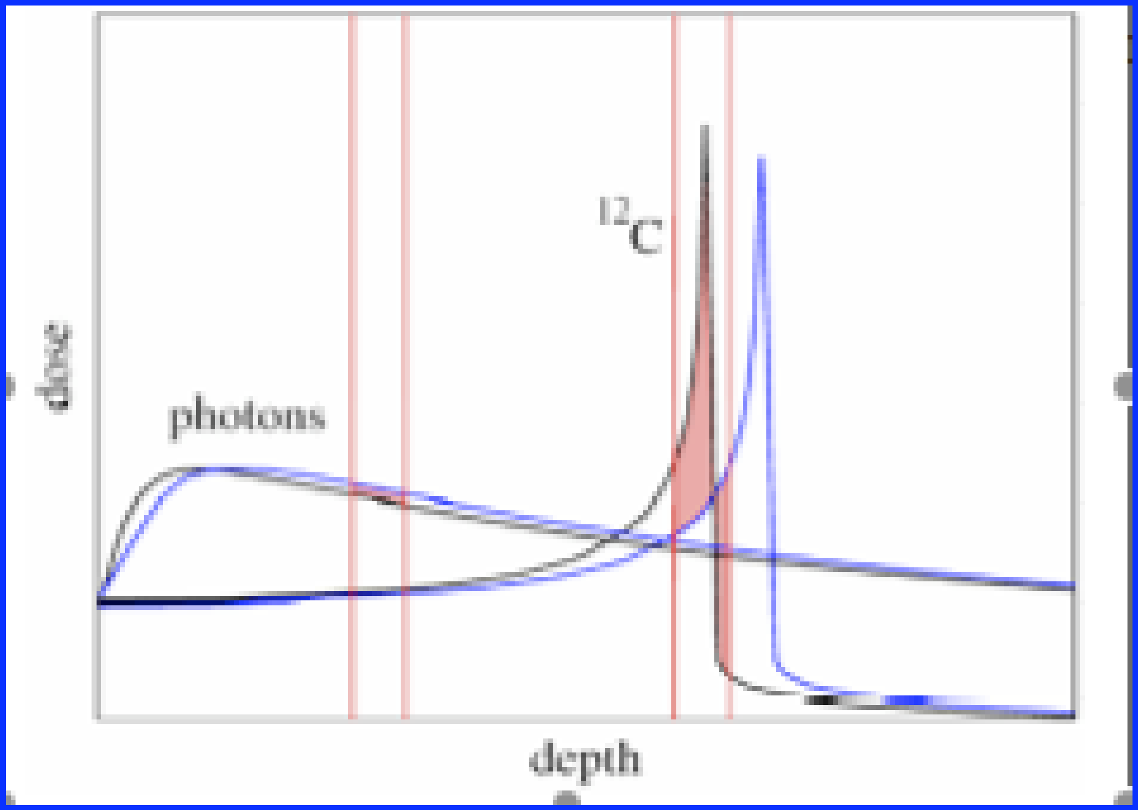


Physical Beam-Scanning Issues

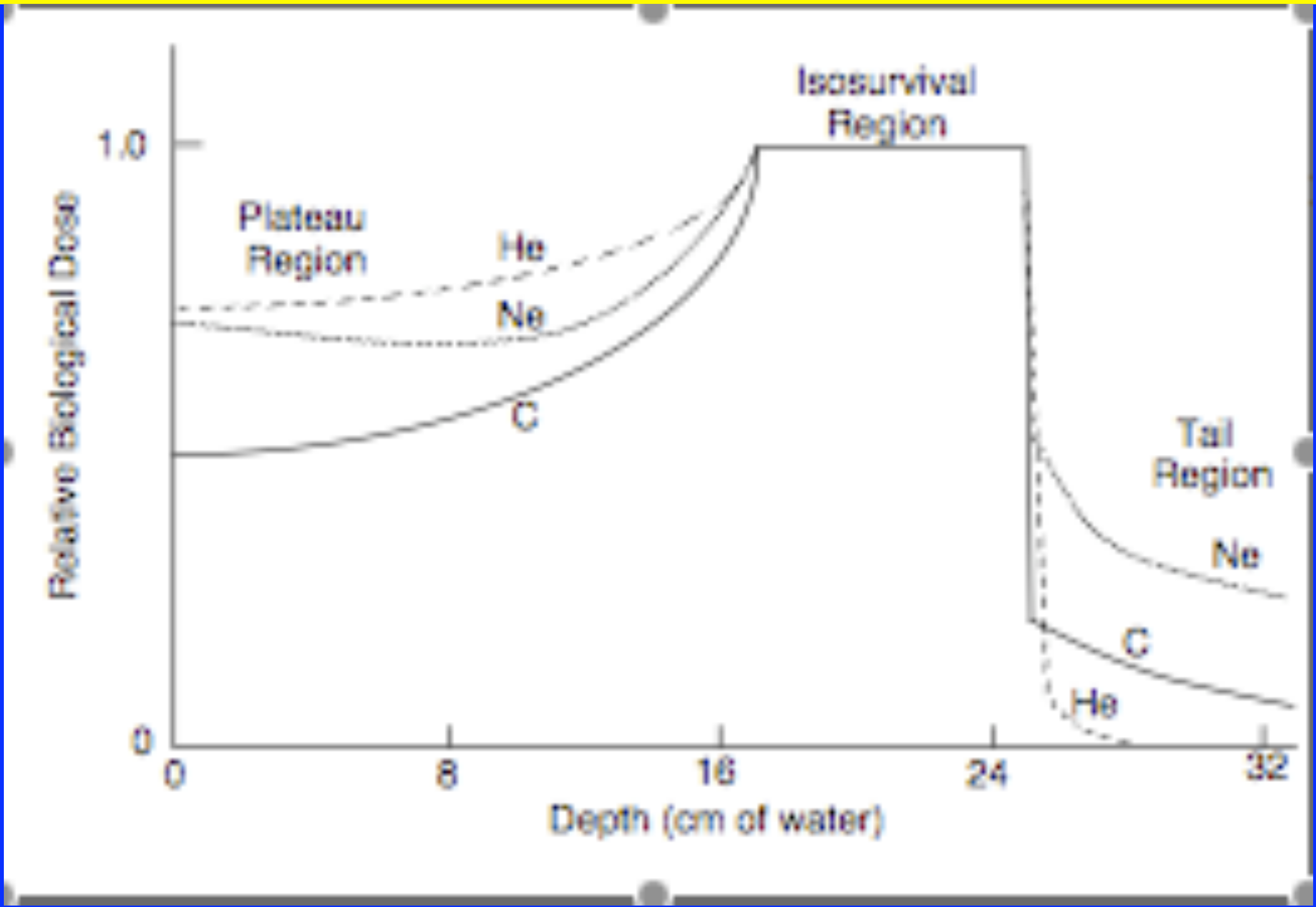
- Better 3-D conformity for irregular targets!
- But, requires high quality magnetic beam guidance!
  - Scan many voxels correctly and quickly.
  - Several scans-through per fraction? Fewer fractions?
    - Respiratory or peristalsis movements?
    - Clinical time constraints?
  - Unanticipated hot or cold spots?
  - Excellent patient immobilization is needed.

Depth-Dose Verification by Positron Emission Tomography



- CT data is quite good for low-LET ions
- Even better range verification is needed for carbon ions in heterogeneous tissue
  - Treatment-table PET: fine energy adjustment

Physical Rationale for Particles



- Depth-Dose Profile
  - relatively small entrance dose (plateau)
  - maximum dose at defined depth (Bragg peak)
  - very low distal dose (tail)

Radiobiologic Rationale for Protons and Heavier Charged Particles

- Radiobiologic Properties
  - Low-LET: protons, helium
    - Single-strand DNA breaks
  - High-LET: carbon, neon
    - Double-strand DNA breaks!
    - Increased RBE in target!
    - Hypofractionation works well!
    - Concurrent chemotherapy symbiosis!

RBE Values for Heavy Charged Particles (vs. 60-Co)

Particle	Peak RBE	Plateau RBE	Peak to Plateau RBE Ratio
Protons	1.2	1.2	1.00
Helium	1.5	1.3	1.15
Carbon	1.8	1.2	1.50
Neon	3.0	2.3	1.30

(RBE values for jejunal crypt cell survival)

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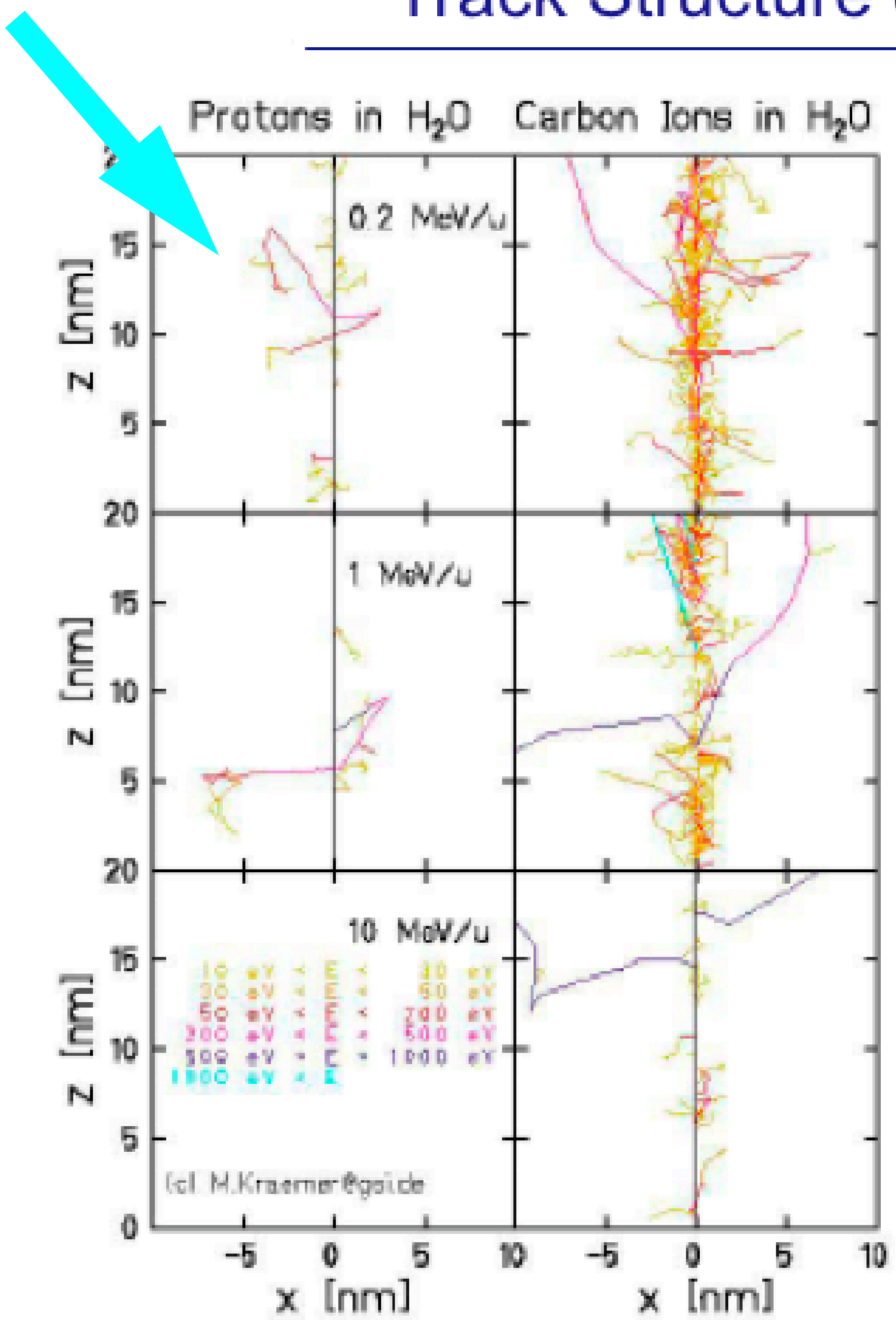
Radiobiological Rationale for Particles

Track Structure of Ions



Carbon ion superior to protons–

- Dose localization
- Biological advantages:
  - high LET to provide significant differences in DNA damage
  - suppression of radiation repair
  - yet avoids some complications with higher-Z ions

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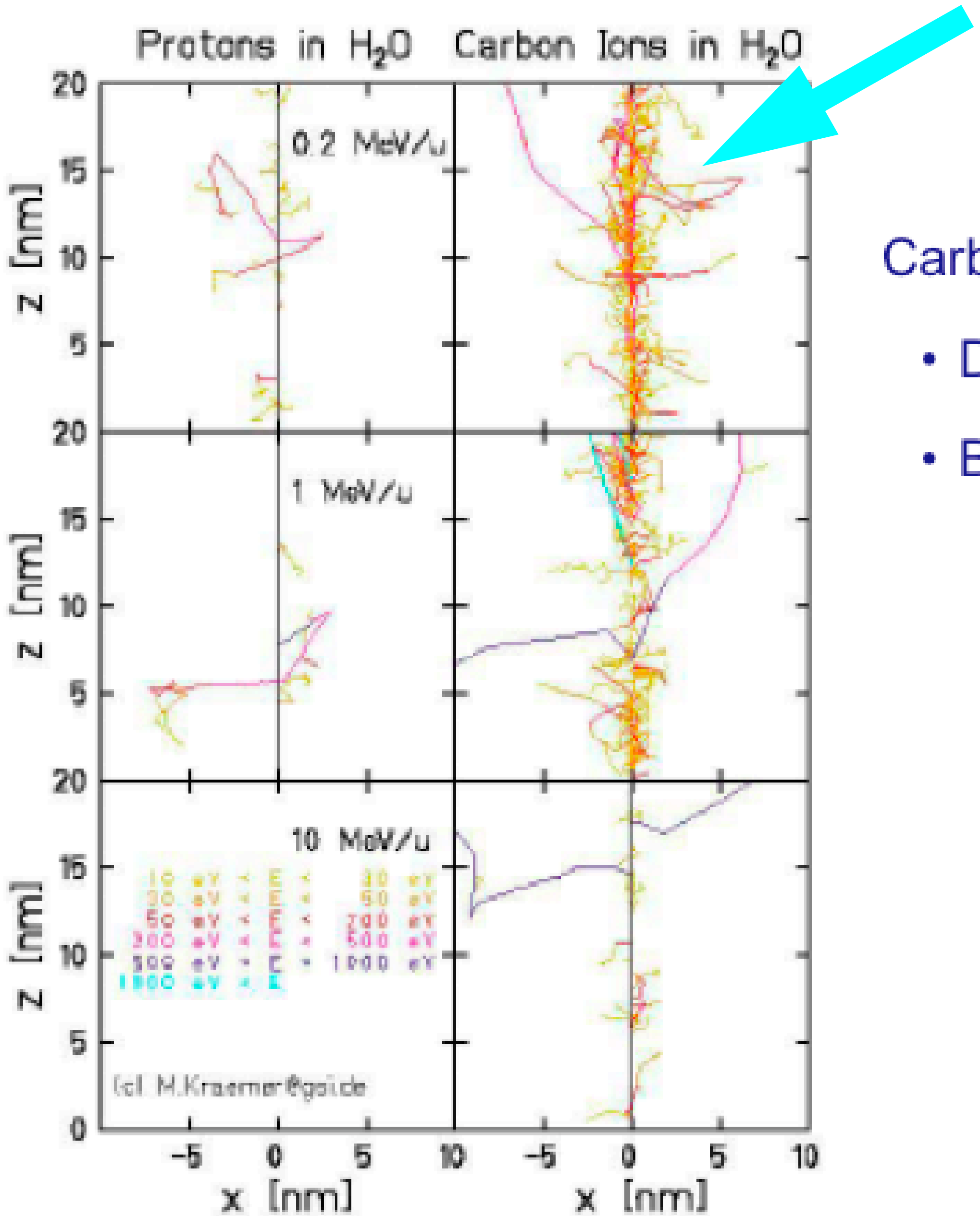

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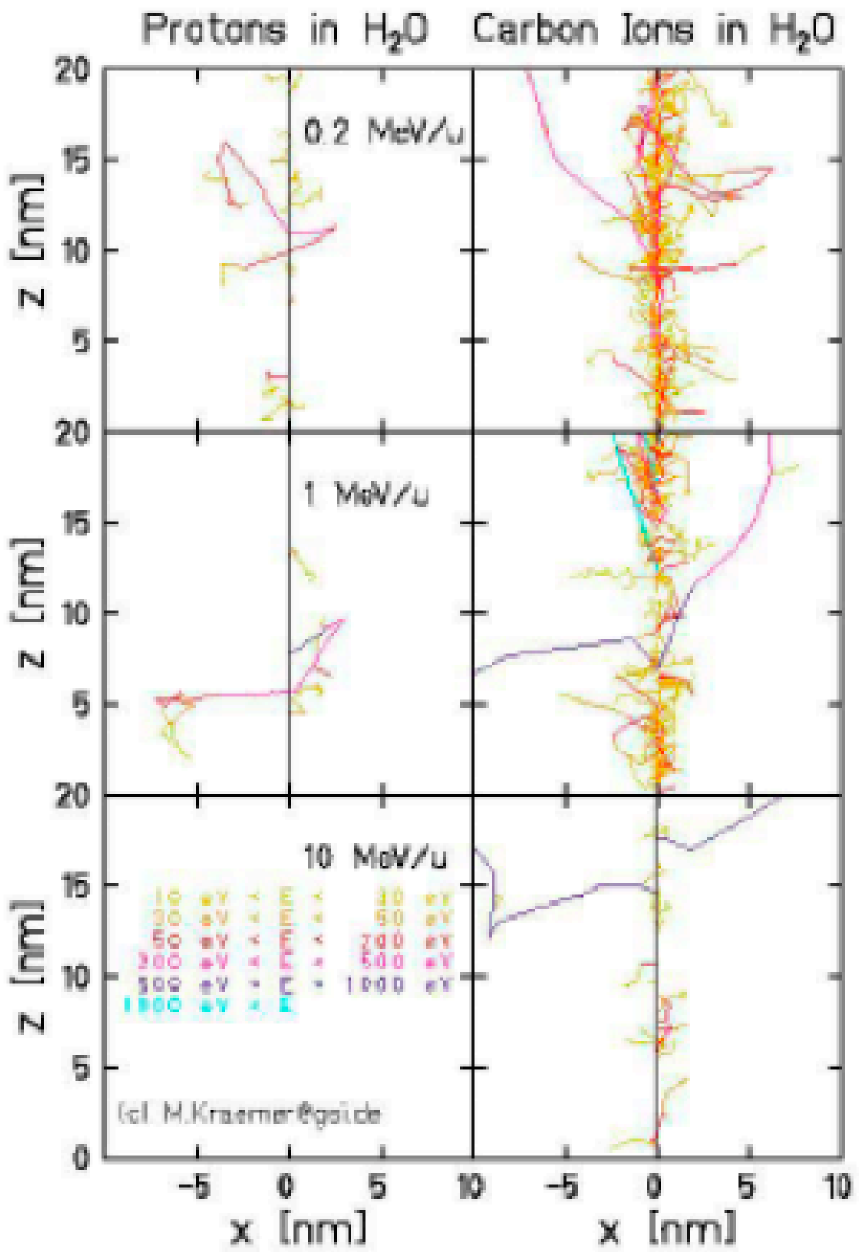

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The Current Status of Particle Therapy

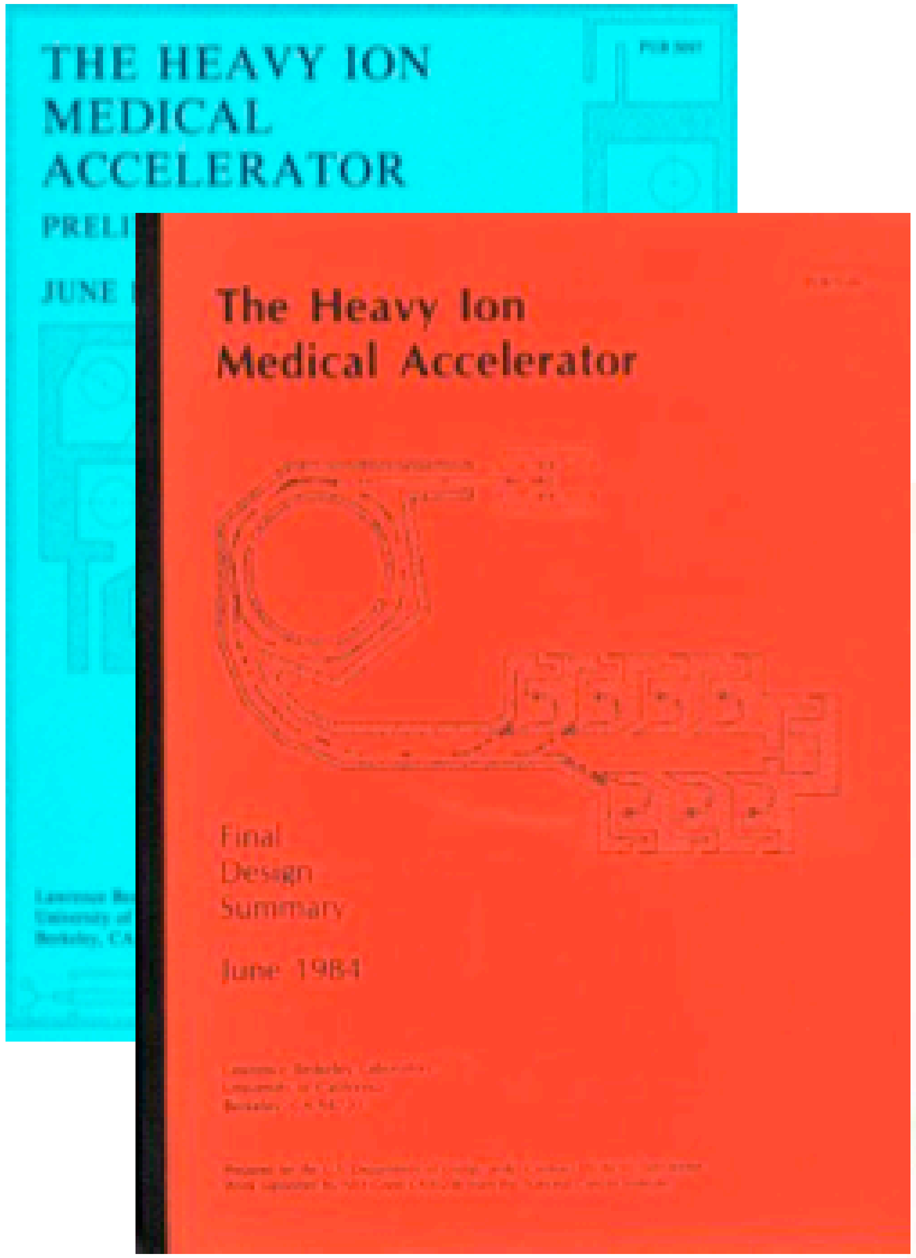
(Worldwide, as of last summer)

- Low-LET (Protons and Helium Nuclei):
  - 55,000 patients from 1954 to present
- High-LET (Heavier Charged Particles):
  - 7,000 patients from 1975 to present

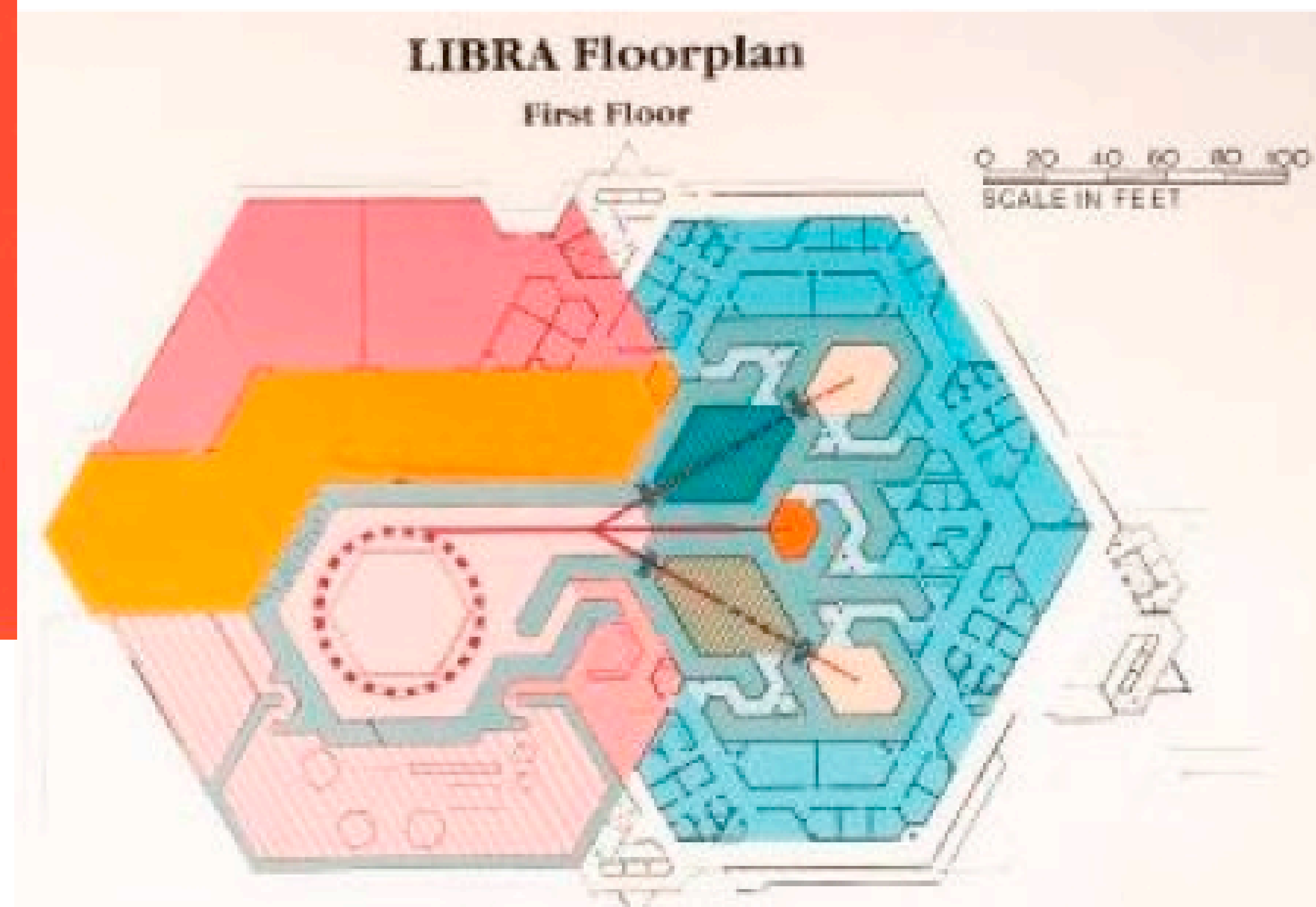
Particle-Selection Capability

- Future clinical trials are best done with all treatment arms in the same facility - less variables!
- Low-LET particles (protons, helium) are time-tested for many common and less-common cancers.
  - Protons vs Helium?
- High-LET particles (especially, carbon) are promising complements to low-LET. *NOT* substitutes!
  - Early high-LET work (Berkeley, Germany, Japan) is looking good.
- Protons for CTV, carbon for GTV boost?

LIBRA Designs at LBNL



1988



Light-Ion Therapy– perspective

Window in Wixhausen's baroque church

"Running light-ion therapy is a big effort -- like the military-industrial complex. It requires close cooperative efforts of medicine, physics, biology and engineering, and big money."

Light-ion therapy–

- Scientific rationale- impeccable
- Clinical results- very promising
- National needs– strong
- Technology– advanced far
- Future– very bright

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Particle Therapy: Accelerator R & D Summary

- GREATER CHOICE OF CHARGED PARTICLES!
- DELIVERED MORE ACCURATELY!
- SMALLER!
- CHEAPER!
- FASTER!

Particle Therapy: Accelerator R & D (I)

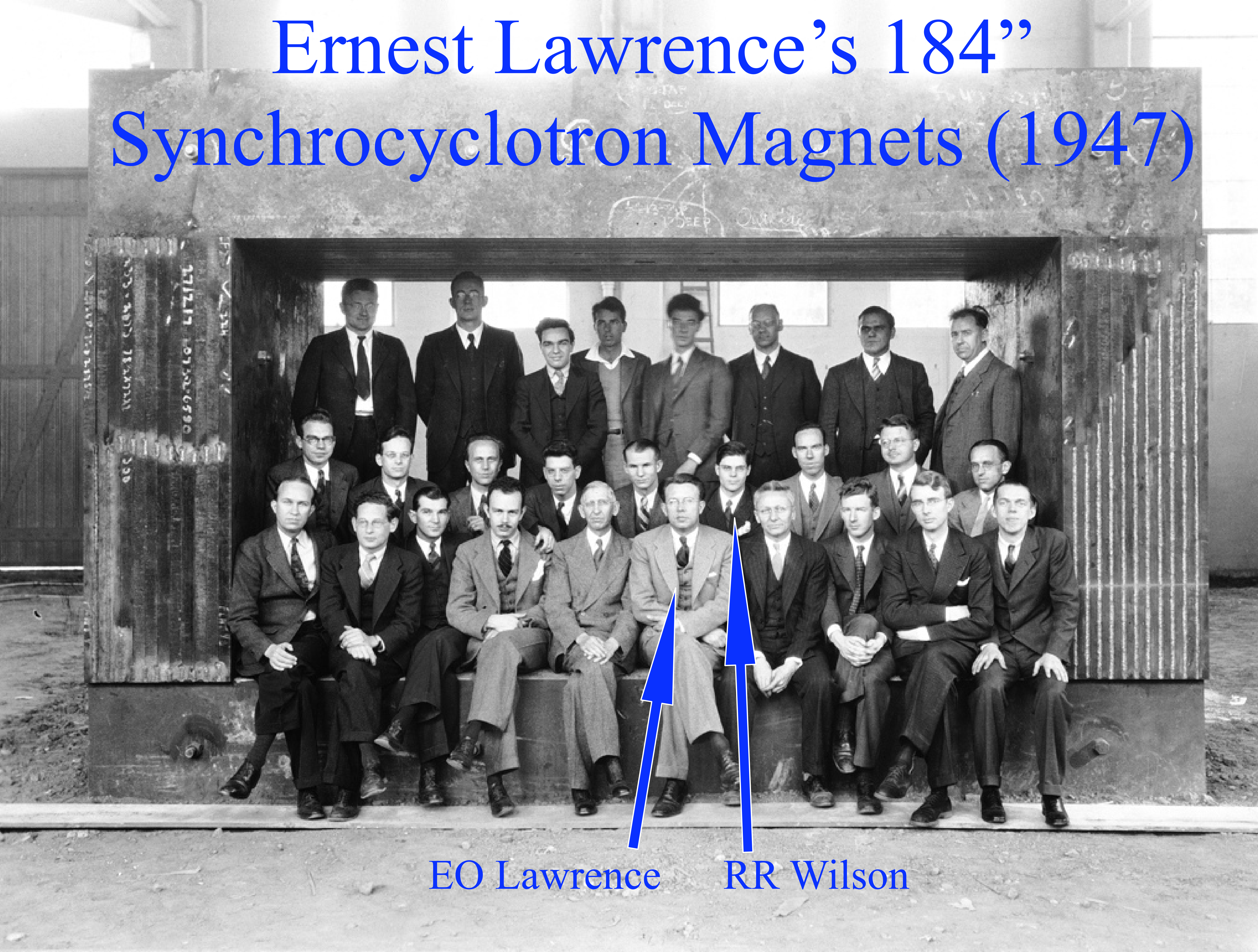
- Delineate the Target: Fuse CT, MRI, PET
- Have Variable-Ion Selection Capability
- Perform Dose-Fractionation Studies
- Design More Compact Accelerator/Gantry
- Use Isocentric Patient Positioning Tables
- Optimize Beam Scanning Speed and Accuracy

Particle Therapy: Accelerator R & D (2)

- Compensate for Target Motion & Distortion
- Integrate RBE Algorithms with Physical Dose Deposition on a Voxel-by-Voxel Basis
- Incorporate PET-Assisted Beam-Energy Adjustment in Real-Time (and use Proton CT) to Further Improve Dose Localization
- Experienced and Dedicated People are Required

The first beam: November 1, 1947

Ernest Lawrence's 184" Synchrocyclotron Magnets (1947)




Ernest Lawrence's
184" Synchrocyclotron
1947-1987


Ernest Lawrence's
184" Synchrocyclotron
1947-1987
JI Fabrikant
CA Tobias
RP Levy

Live long and prosper!

LET'S DO IT!