PUBLIC SEMINAR ON
MEDICAL APPLICATIONS
Accelerating Innovation in Medicine

CERN
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REFLECTIONS AND PERSPECTIVES ON 60 YEARS OF PARTICLE THERAPY

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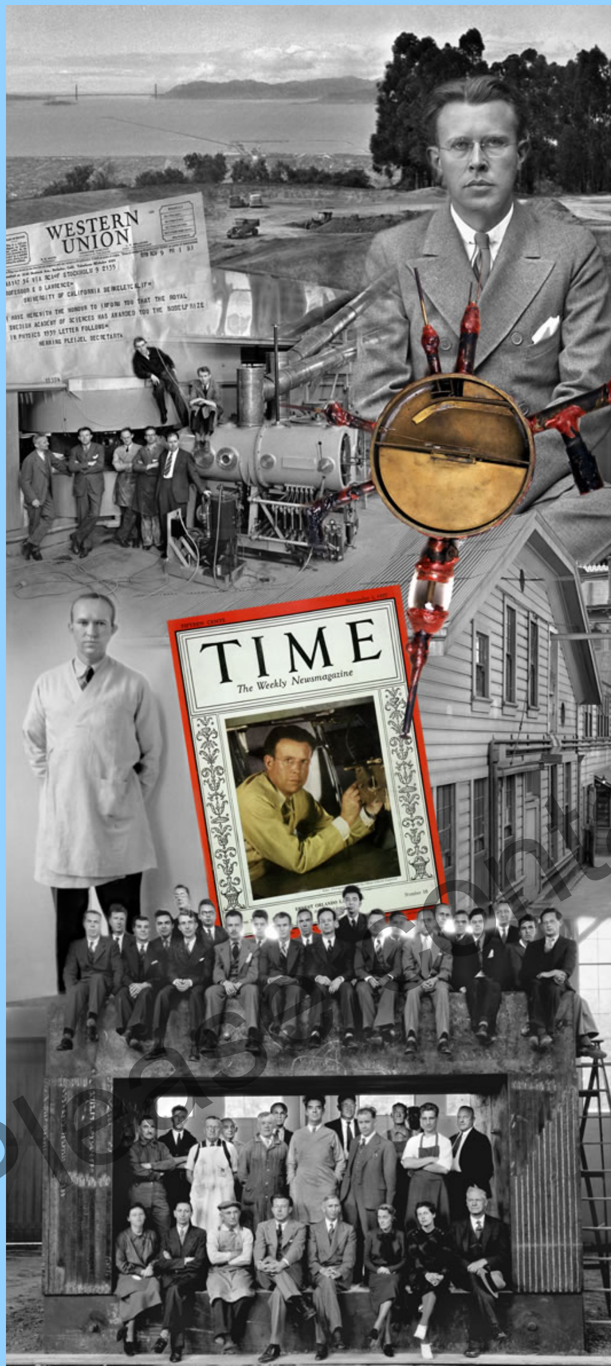
Outline of Presentation

- *Histories of LBNL & CERN*
- *Bonded by Focus on Particle Physics*
- *United by Medical Applications*
- *Particle Detectors*
- *Imaging*
- *Cancer Therapy*
- *Continuing the Dialogue*



1930's

- *E. O. Lawrence came to Berkeley in 1928.*
- *He invented the cyclotron in 1929 that paved the way for the future giant atom smashers of high-energy physics.*
- *In 1931 he opened his "Rad Lab" on the Univ. of California campus at Berkeley.*
- *Together with his physician brother, John and a cast of scientific notables, Lawrence built increasingly larger cyclotrons and expanded the use of these machines from unlocking the secrets of the atom to creating radioisotopes for medical research.*
- *In 1939 E. Lawrence won the Nobel Prize in Physics for his invention of the cyclotron.*

Ernest Orlando Lawrence

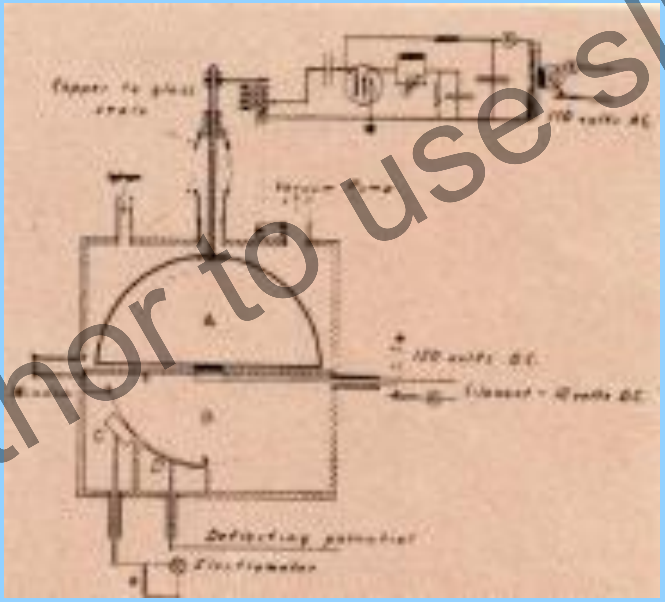
Ernest Lawrence came to Berkeley from Yale to become associate professor of physics in 1928.

The First Successful Cyclotron (1931)

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

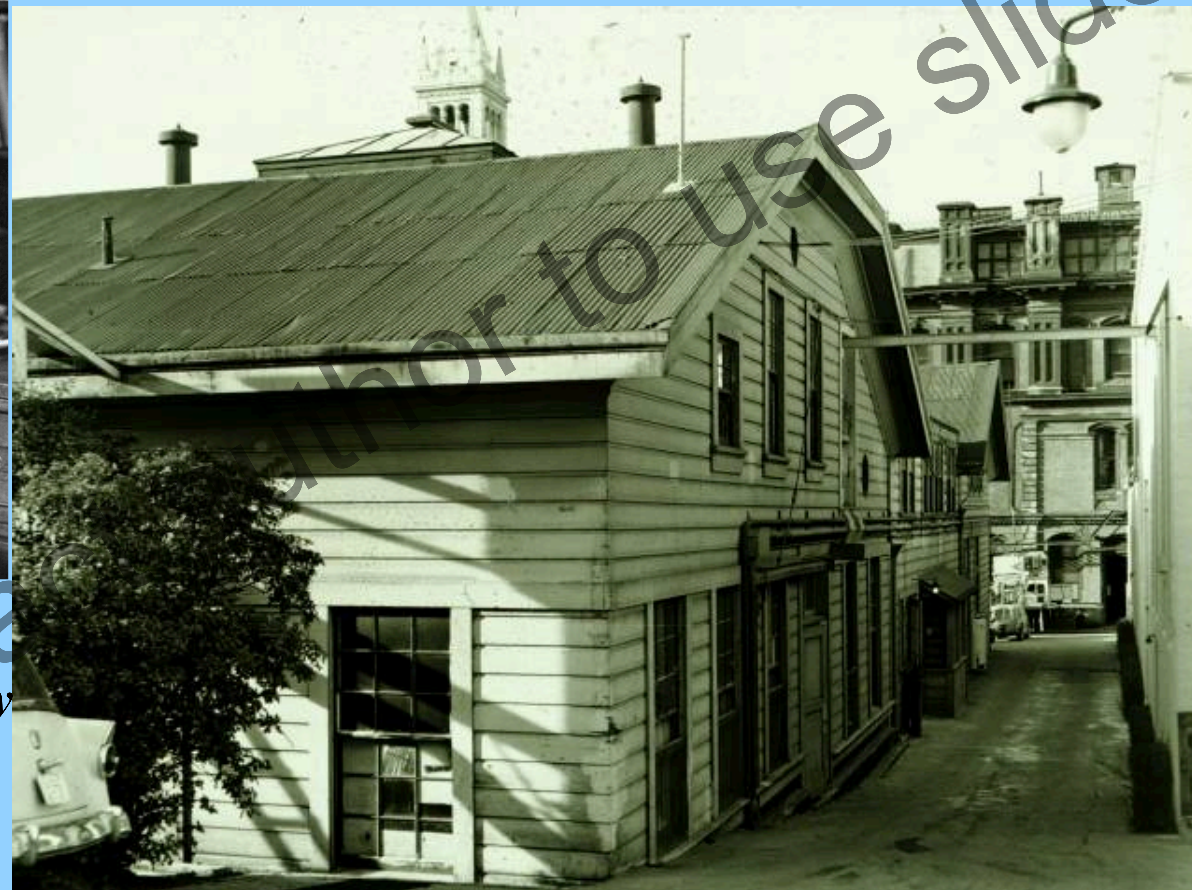
EO Lawrence and MS Livingstone, Phys. Rev 37: 1707 (1931); and MS Livingston, The Production of High-Velocity Hydrogen Ions Without the Use of High *Voltages*, PhD thesis, University of California, Berkeley (1931).

The First Successful Cyclotron Fit In Your Hand



The first cyclotron constructed by Lawrence and M. S. Livingston (1930). The single dee is 13 cm in diameter.

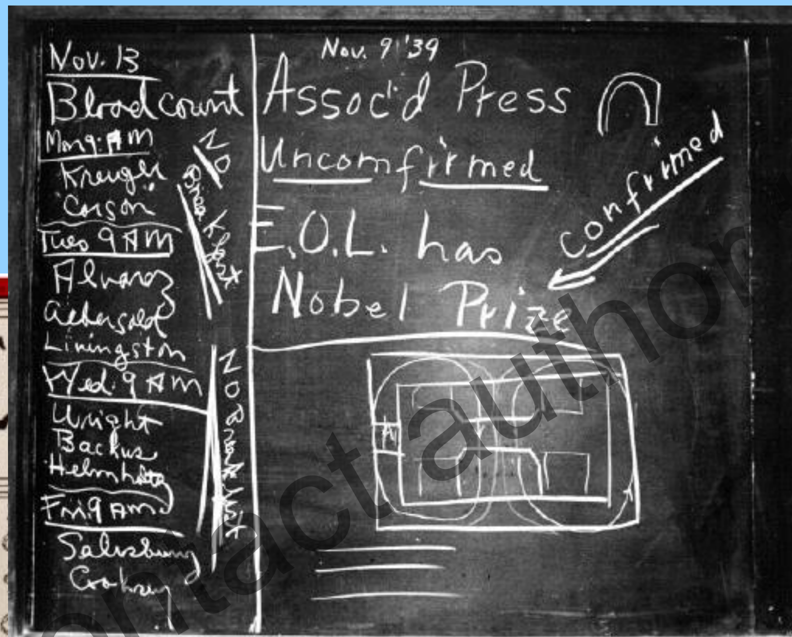
The Radiation Laboratory was established 26 August 1931

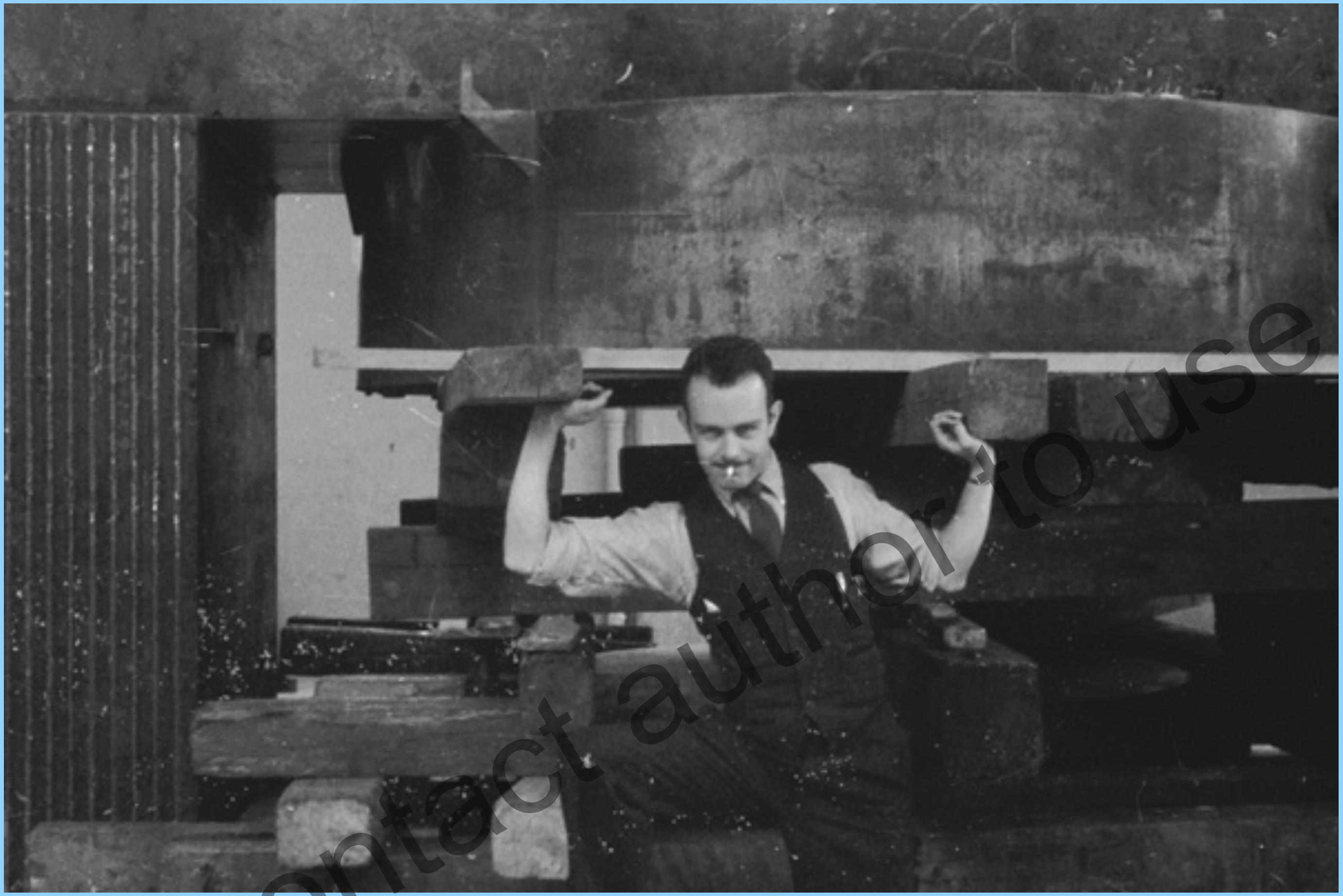


Ernest Lawrence acquired an unused civil engineering laboratory on the UC Berkeley campus to house his first "large" cyclotron.

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.

E. O. Lawrence is awarded the Nobel Prize in 1939 for inventing the cyclotron





1938

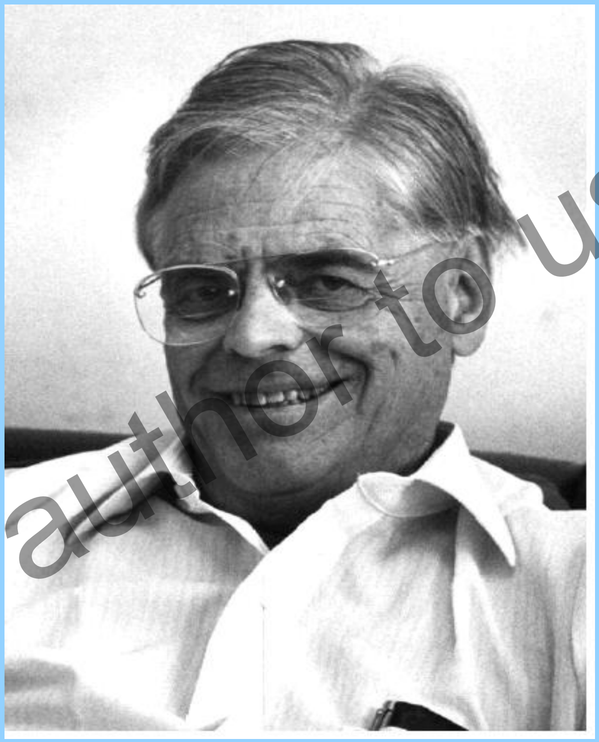
- *Franz Kurie "holding up one of the magnetic poles for the 60-inch cyclotron.*
- *Before going to Berkeley, he earned his Ph.D. at Yale, where he showed that the neutron was neither a "dumb-bell-shaped combination of proton and electron", nor an "onion-shaped combination of an electron embracing the proton".*
- *Consequently, and until the discovery of the quark structure of hadrons, the neutron was assumed to be an elementary particle.*
- *His Kurie plot is used in the study of beta decay.*

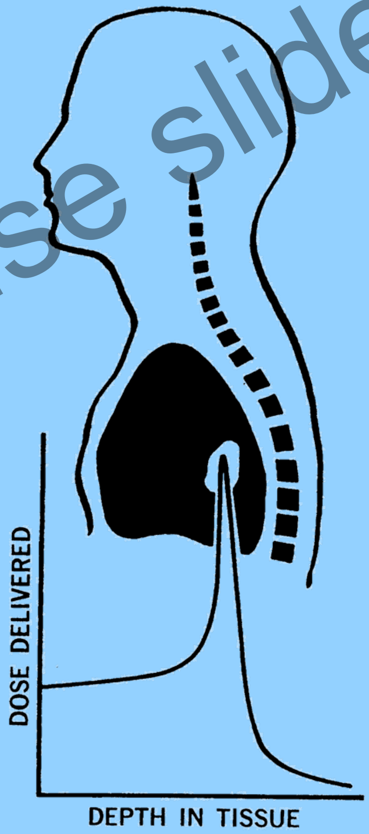
184-Inch Cyclotron

1945

The first beam,
November 1, 1947.

Robert R. Wilson, 1914–2000



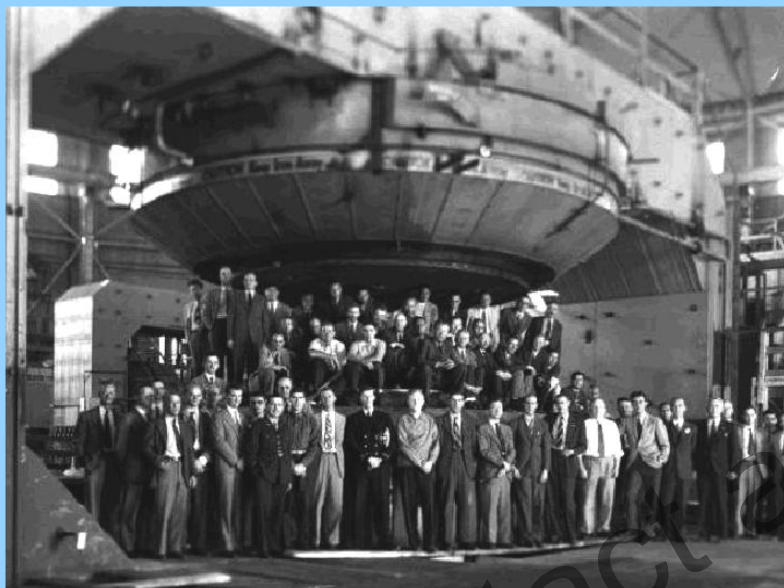


Robert Wilson first proposed use of Bragg Peak for radiation therapy in "Radiological use of fast protons" Radiology 47:487-491 in 1946.

Robert Wilson visited CERN in 1996

184-Inch Cyclotron and Hadron Therapy

The beginning, 1947



The first beam, November 1, 1947

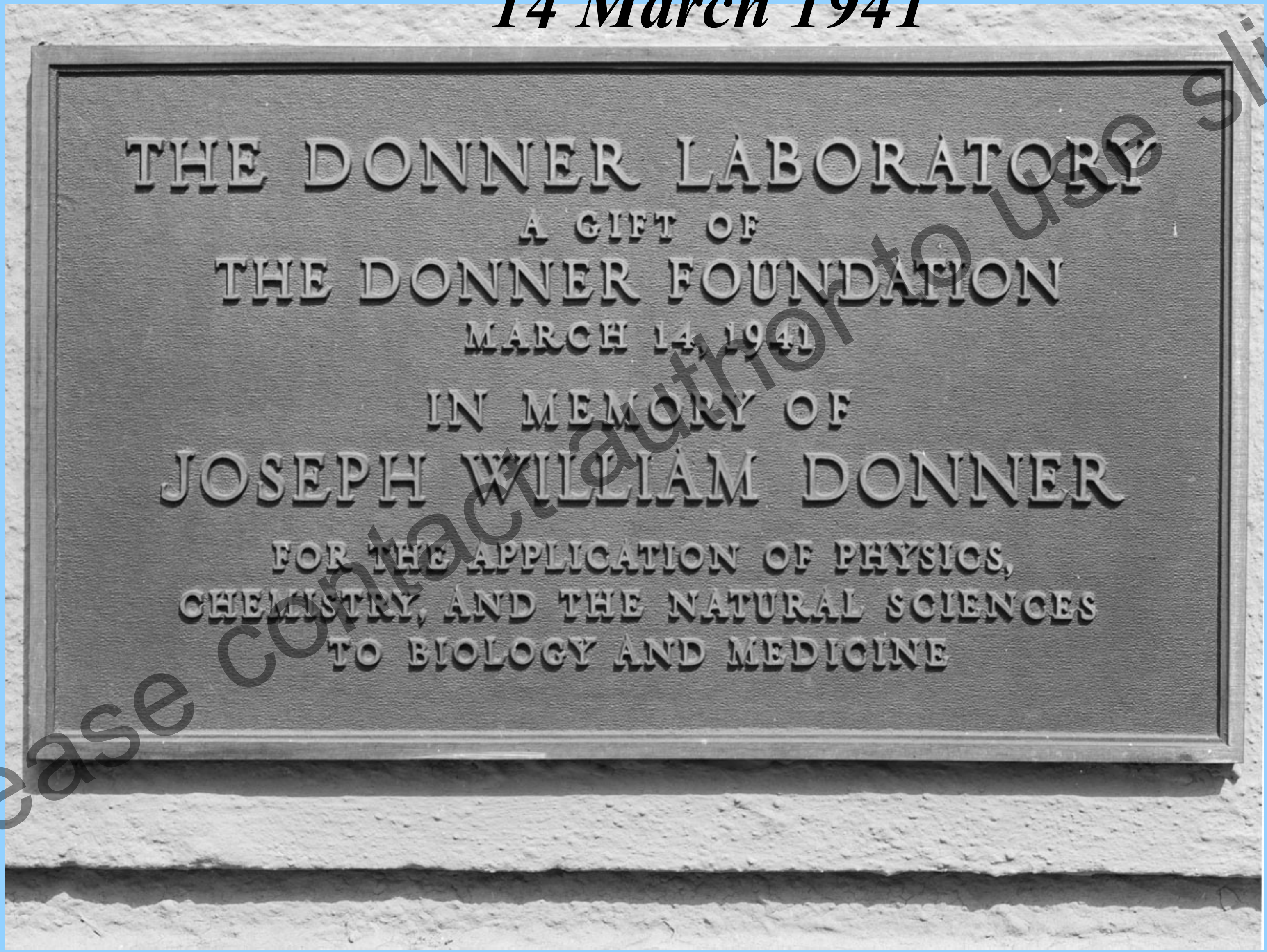
The end, 1986

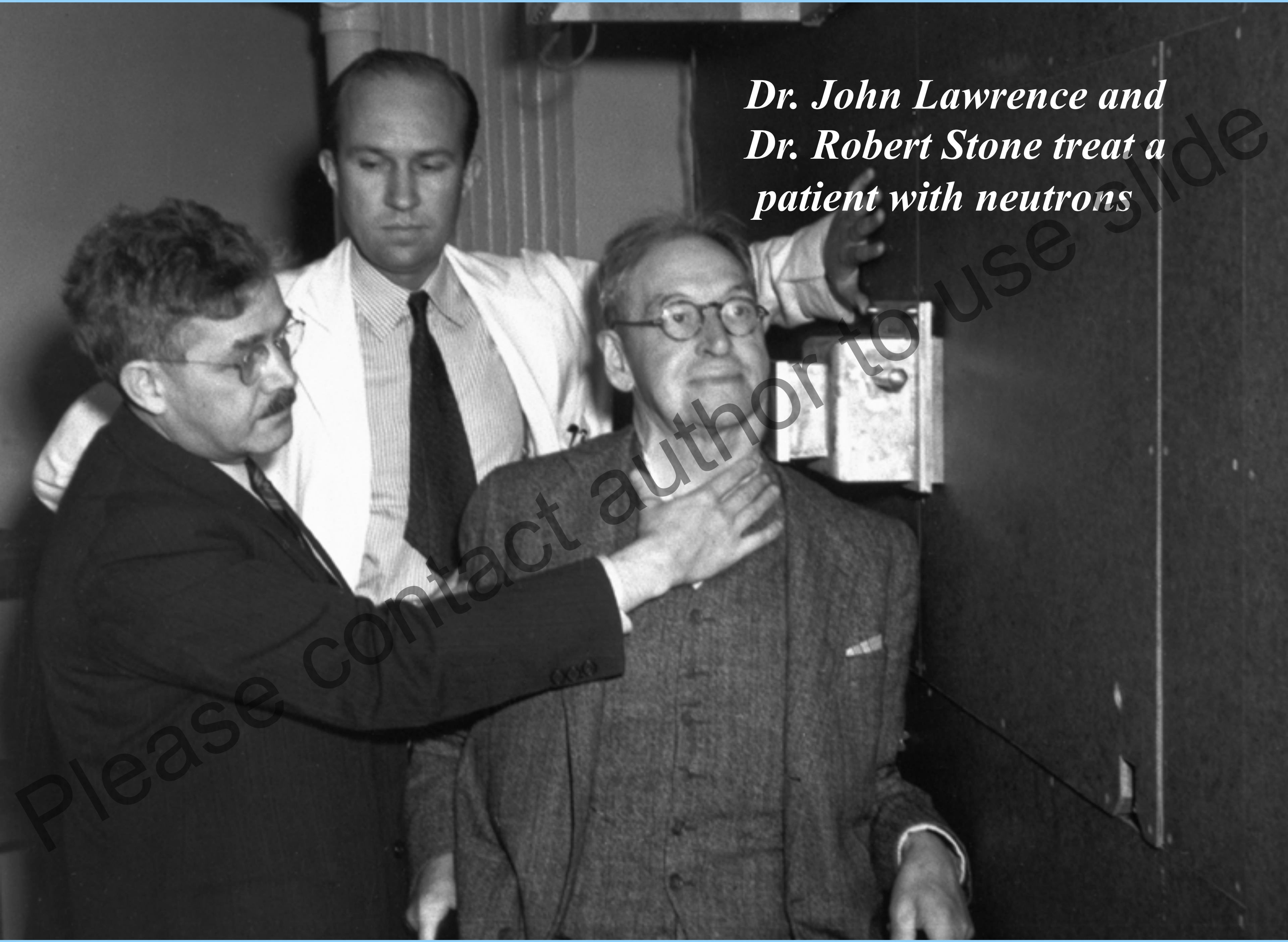
1940's

- *Lawrence's 184-Inch Cyclotron was too large for the UC Berkeley campus, and had to be built at a site in the hills above the campus, which became the Rad Lab's new and current location.*
- *When the U.S. was thrust into WWII, Lawrence mobilized the Rad Lab staff and joined Robert Oppenheimer and other scientific leaders on the Manhattan Project.*
- *Uranium for the first atomic bomb was processed through a type of cyclotron called a calutron, and the second bomb was made from plutonium, an element discovered by the Rad Lab's Glenn Seaborg*

Ernest and John Lawrence who started Donner Biomedical Laboratory at Berkeley Lab that is now the Life Sciences Division

DONNER LABORATORY DEDICATION
14 March 1941





Dr. John Lawrence and Dr. Robert Stone treat a patient with neutrons

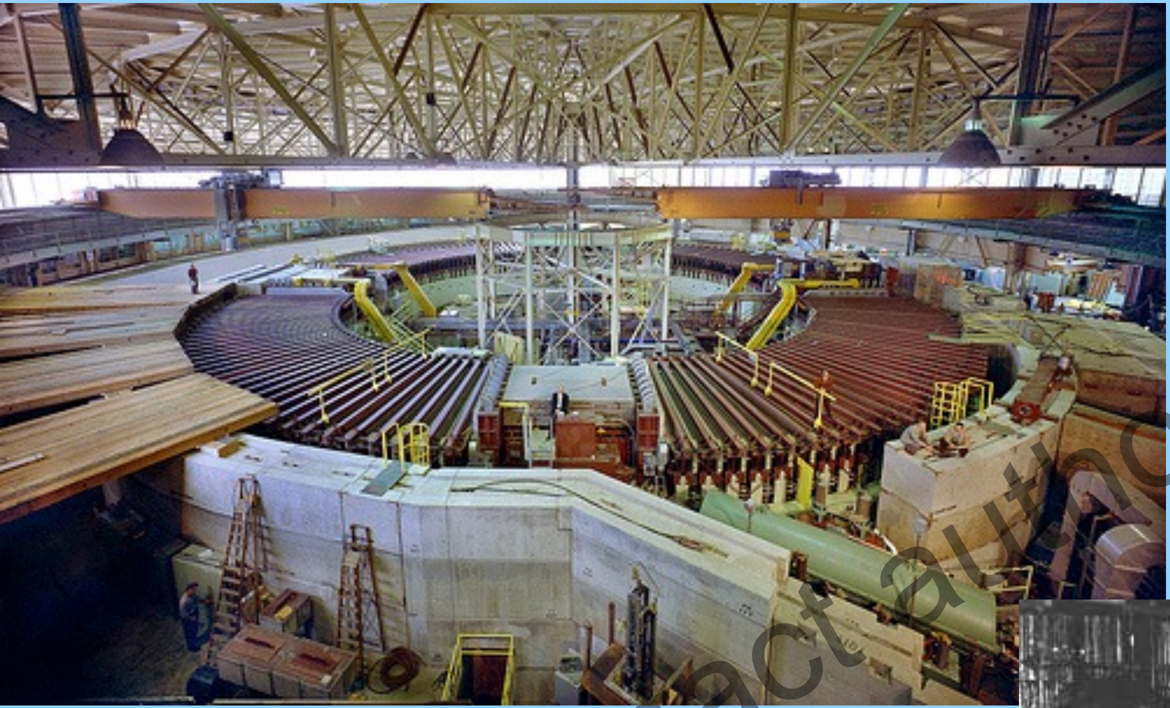
Early Work at Berkeley

E.O. Lawrence placed strong emphasis on medical uses of his cyclotrons.

His brother John H. Lawrence, M.D., became the Father of Nuclear Medicine.

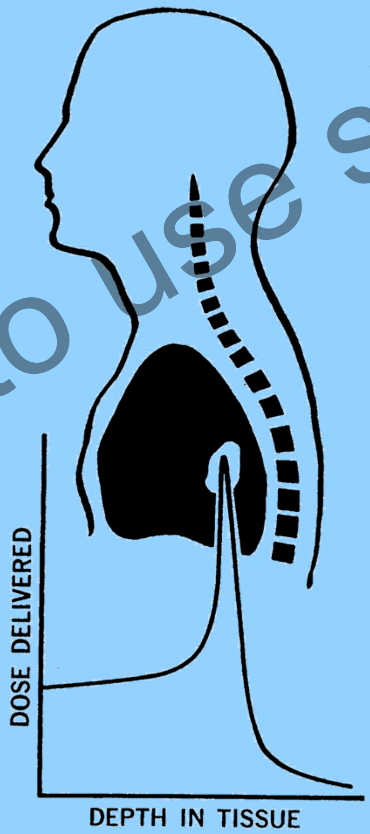
Dr. Hal Anger invented the scintillation Camera known as the Anger Camera.

Bevatron Construction at Berkeley 1949



(Left to right) Lloyd Smith, Ed McMillan, Ernest Lawrence, Ed Lofgren, Bill Brobeck, and Duane Shell.

R.R. Wilson and Rationale for Bragg Peak Therapy

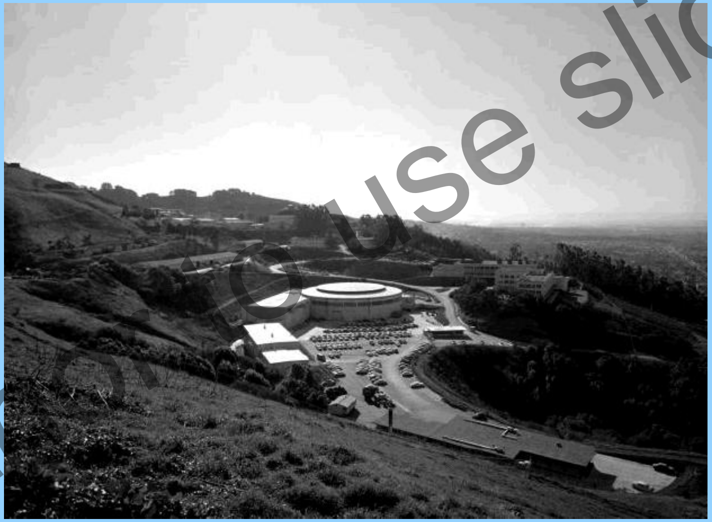


- ***Dose localization***
- ***Lower entrance dose***
- ***No or low exit dose***

In 1946, Prof. Robert Wilson proposed the use of the Bragg Peak for radiation therapy*

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

Bevatron



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.

1950's

- *During the 1950's, Lawrence's Rad Lab enjoyed an unparalleled run of success. For their pioneering discoveries of atomic elements beyond uranium, Glenn Seaborg and Ed McMillan shared the 1951 Nobel Prize in Chemistry.*
- *In 1955, a team led by Owen Chamberlain and Emilio Segre, working at the Bevatron, the Rad Lab's newest and most powerful atom smasher ever, discovered the antiproton, the mirror image counterpart of the normal matter proton. For this discovery, Chamberlain and Segre shared the 1959 Nobel prize in physics.*
- *A few months earlier, on August 27, 1958, Ernest Lawrence died at the age of 57.*
- *In his honor, the Univ. of California Regents renamed the Rad Lab as the Lawrence Berkeley Laboratory*

TRANSURANIUM ELEMENTS

93	NEPTUNIUM	Np
94	PLUTONIUM	Pu
95	AMERICIUM	Am
96	CURIUM	Cm
97	BERKELIUM	Bk
98	CALIFORNIUM	Cf
99	EINSTEINIUM	Es
100	FERMIUM	Fm
101	MENDELEVIUM	Md
102	NOBELIUM	No
103	LAWRENCIUM	Lr
104	RUTHERFORDIUM	Rf
105	HAHNIUM	Ha
106	SEABORGIUM	Sg
107	NIELSBOHRIUM	Ns
108	HASSIUM	Hs
109	MEITNERIUM	Mt
110		
111		

184-Inch Cyclotron and Hadron Therapy

1954 - 1986

Hadron Therapy

Clinical Trials

1500 patients treated

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

Closure of the 184-Inch, 1986.

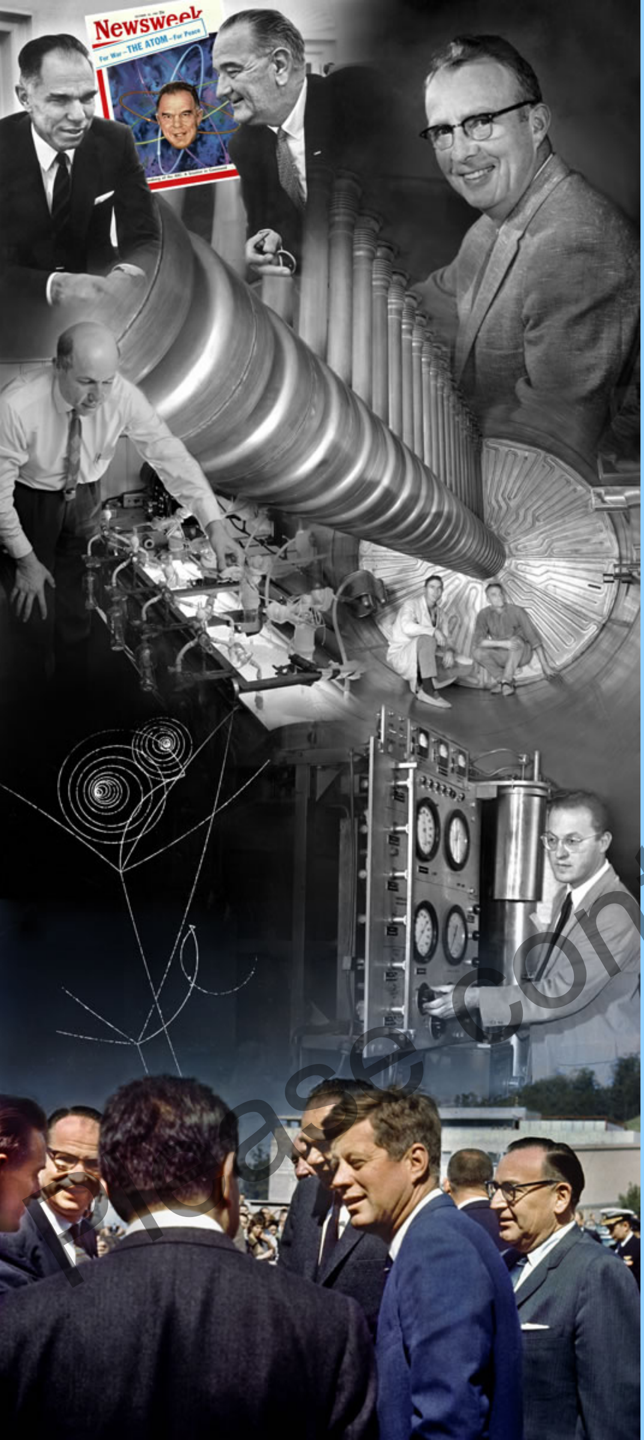
FIRST PROTON THERAPY PATIENT TREATED
September 1954

Prof. Cornelius A. Tobias

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

CERN WAS FOUNDED 29 September 1954

- ***The first meeting of the provisional CERN Council 15 Feb 1952 Key people: Sir Ben Lockspeiser, Edoardo Amaldi, Felix Bloch, Leew Kowarski, Cornelis Bakker, and Niels Bohr***



1960's

- *The 1960's saw a continuation of the Nobel laureate tradition at the Lawrence Berkeley Lab under the direction of Edwin McMillan.*
- *Luis Alvarez, one of the Lab's greatest scientists, invented among many other things a unique type of linear accelerator which he used to discover resonance states in elementary particles. For this work, he won the 1968 Nobel Prize in Physics.*
- *Donald Glaser won the 1960 Nobel Prize in Physics for his invention of the liquid-hydrogen bubble chamber, and Melvin Calvin won the 1961 Nobel Prize in Chemistry for identifying the chemical path of carbon during photosynthesis.*
- *Meanwhile, Nobel laureate Glenn Seaborg worked with President Kennedy and Johnson as the first Chairman of the Atomic Energy Commission and helped forge a nuclear test ban treaty*

1970's

- *Andrew Sessler, an accelerator physicist became the Lab's third director and presided over a new emphasis on energy and environmental sciences.*
- *From atmospheric and indoor air studies, to water quality and seismic research, to the creation of energy-efficient "smart windows", the Lab moved to the forefront in the development of green technologies.*
- *However, particle physics continued to play a major role. This era saw the creation of the SuperHILAC (for super-heavy ion linear accelerator), which could accelerate ions as heavy as uranium, and the invention of the*

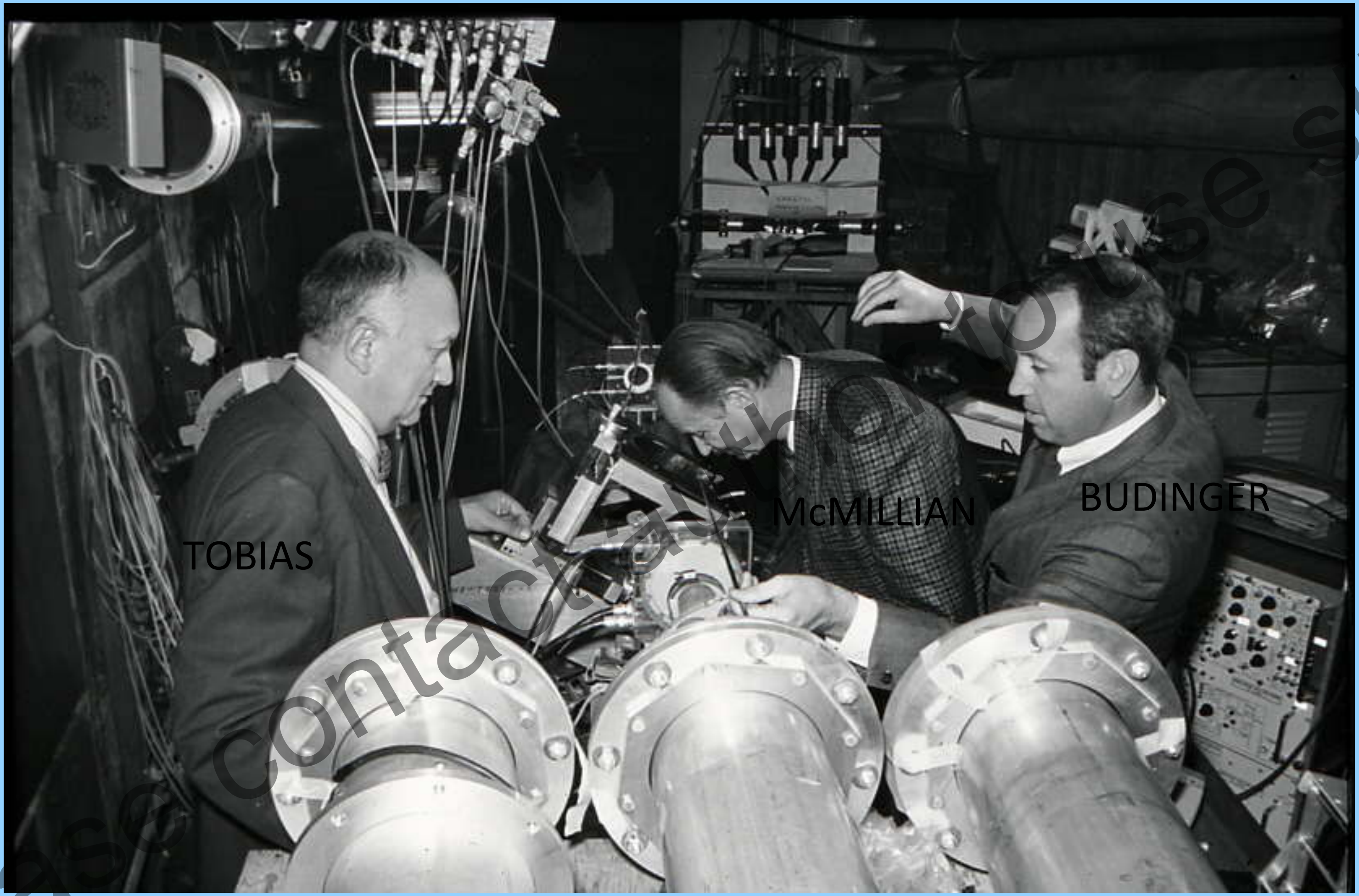
  Time Projection Chamber (TPC), a system for detecting subatomic particles that is still a mainstay of high-energy physics research.

Bevatron/Bevalac (1971-1993) and Hadron Therapy

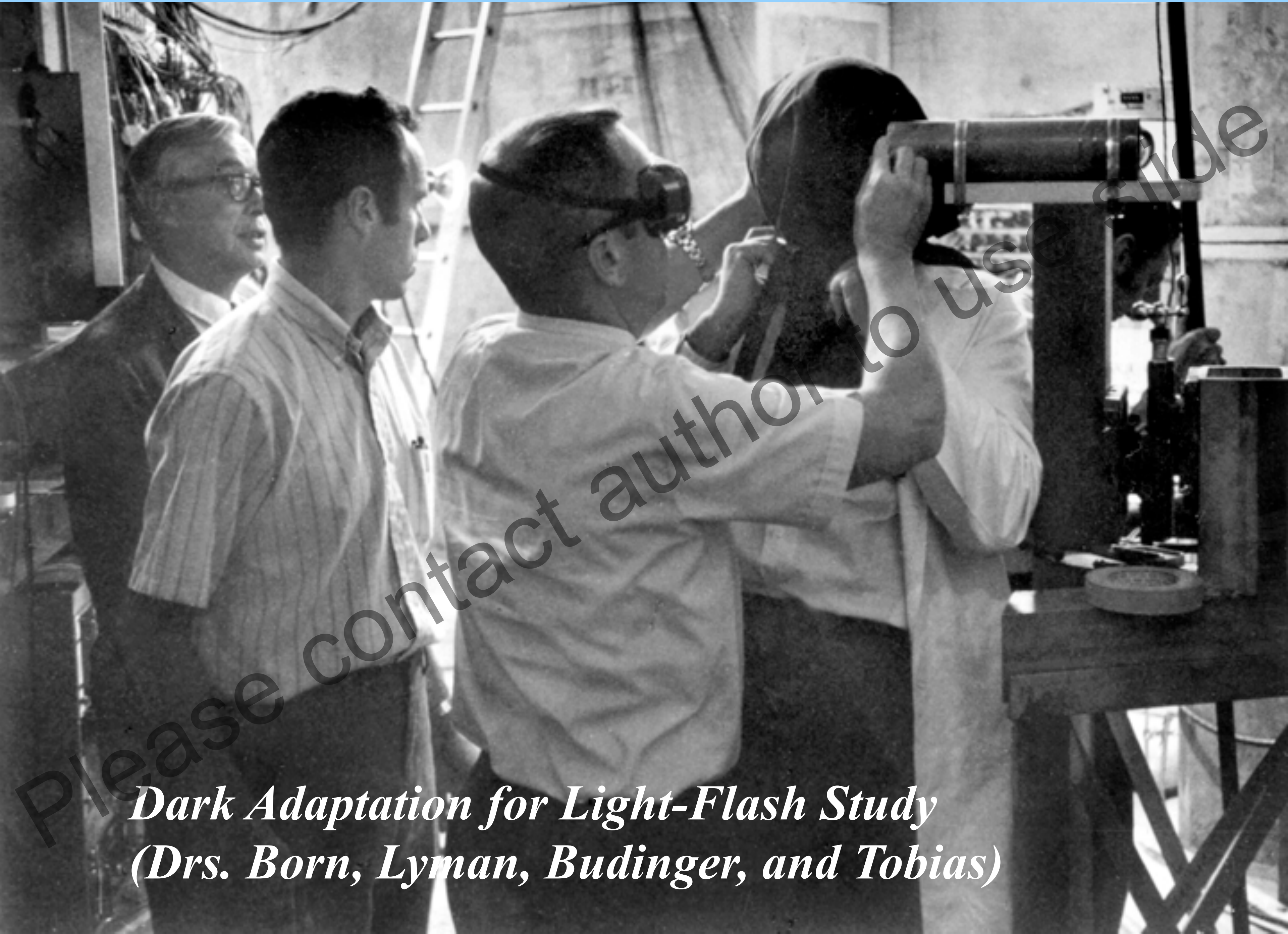
Press conference announcing the acceleration of heavy ions in the Bevatron (August 1971).

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

Space Biology

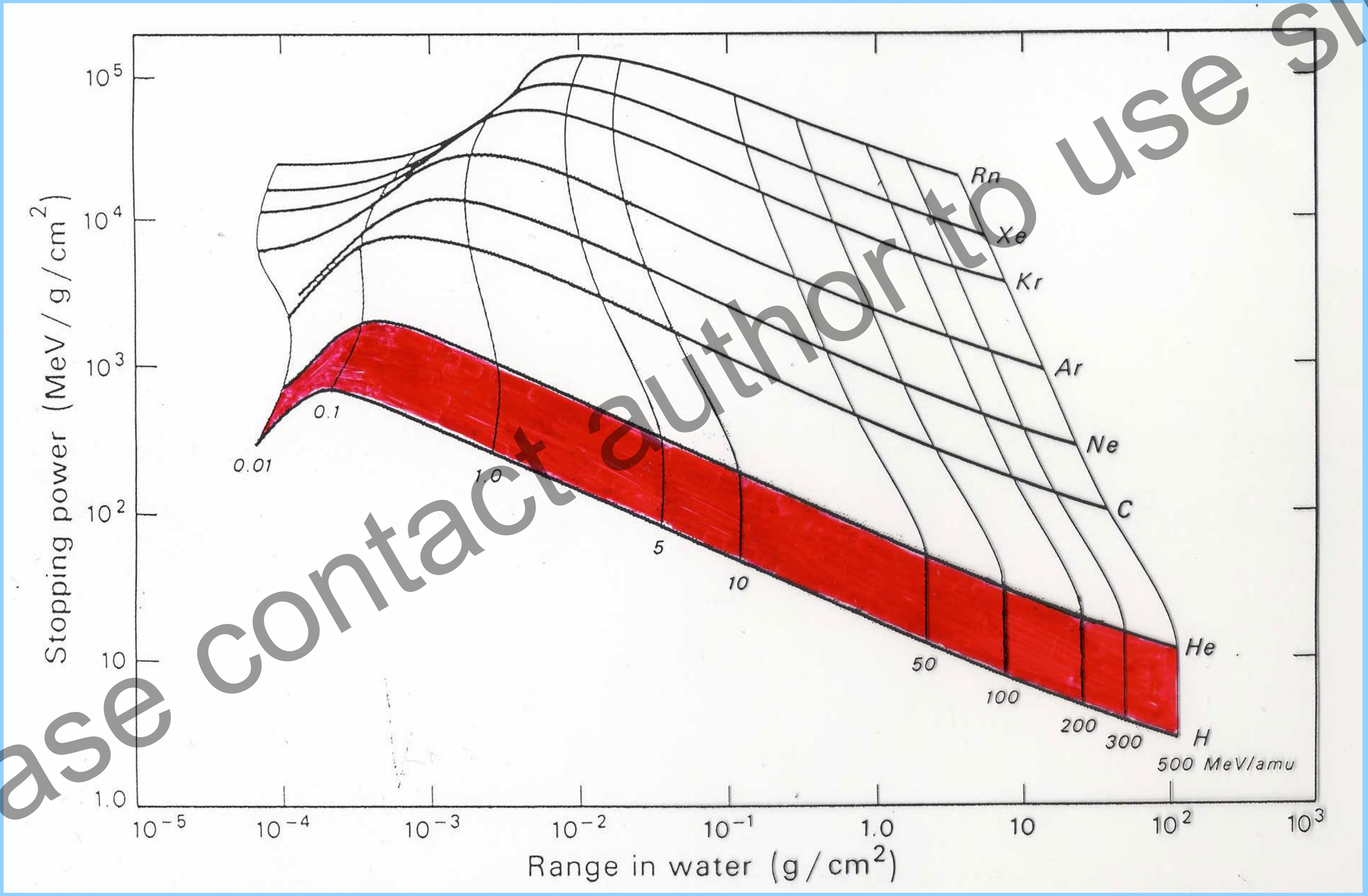


C. A. Tobias predicted the light flash by cosmic rays some 20 years before the astronauts observe them in actual space flights.



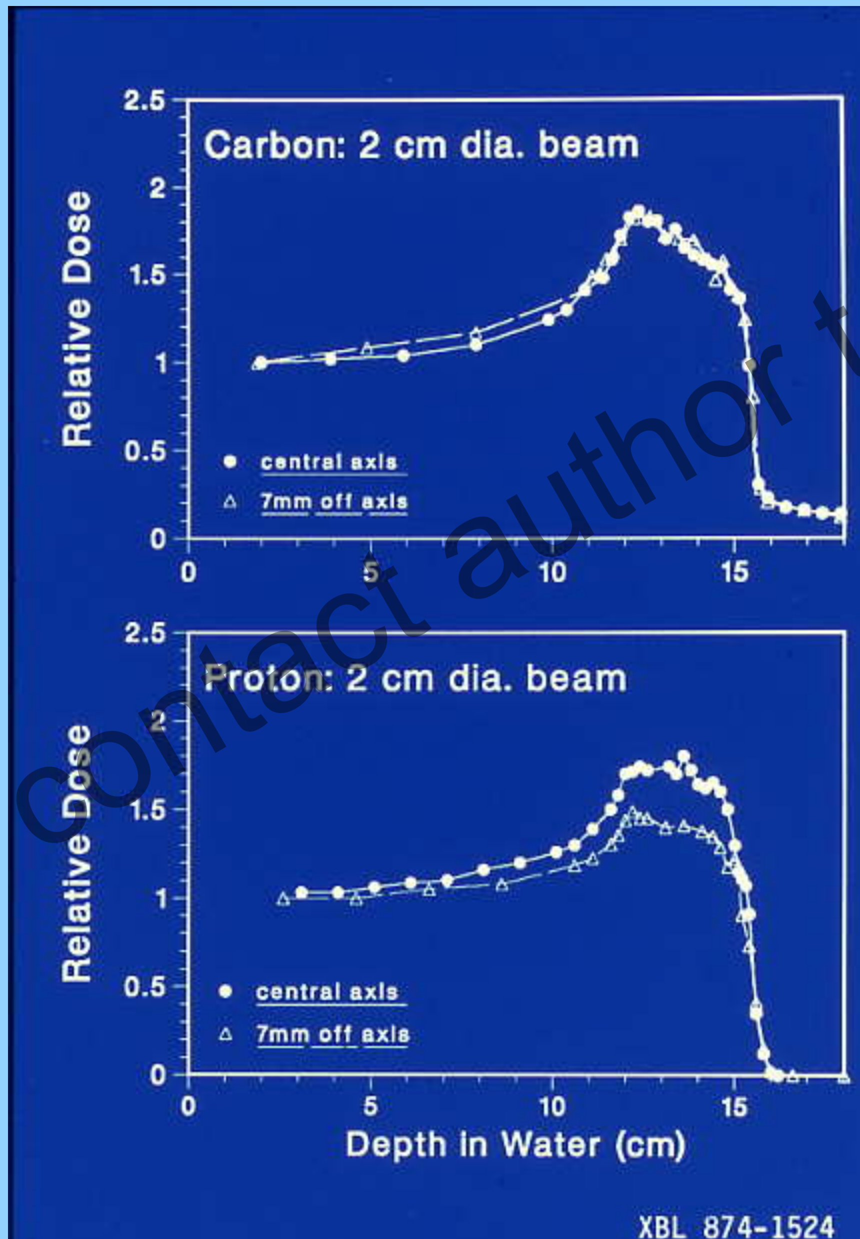
Dark Adaptation for Light-Flash Study
(Drs. Born, Lyman, Budinger, and Tobias)

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

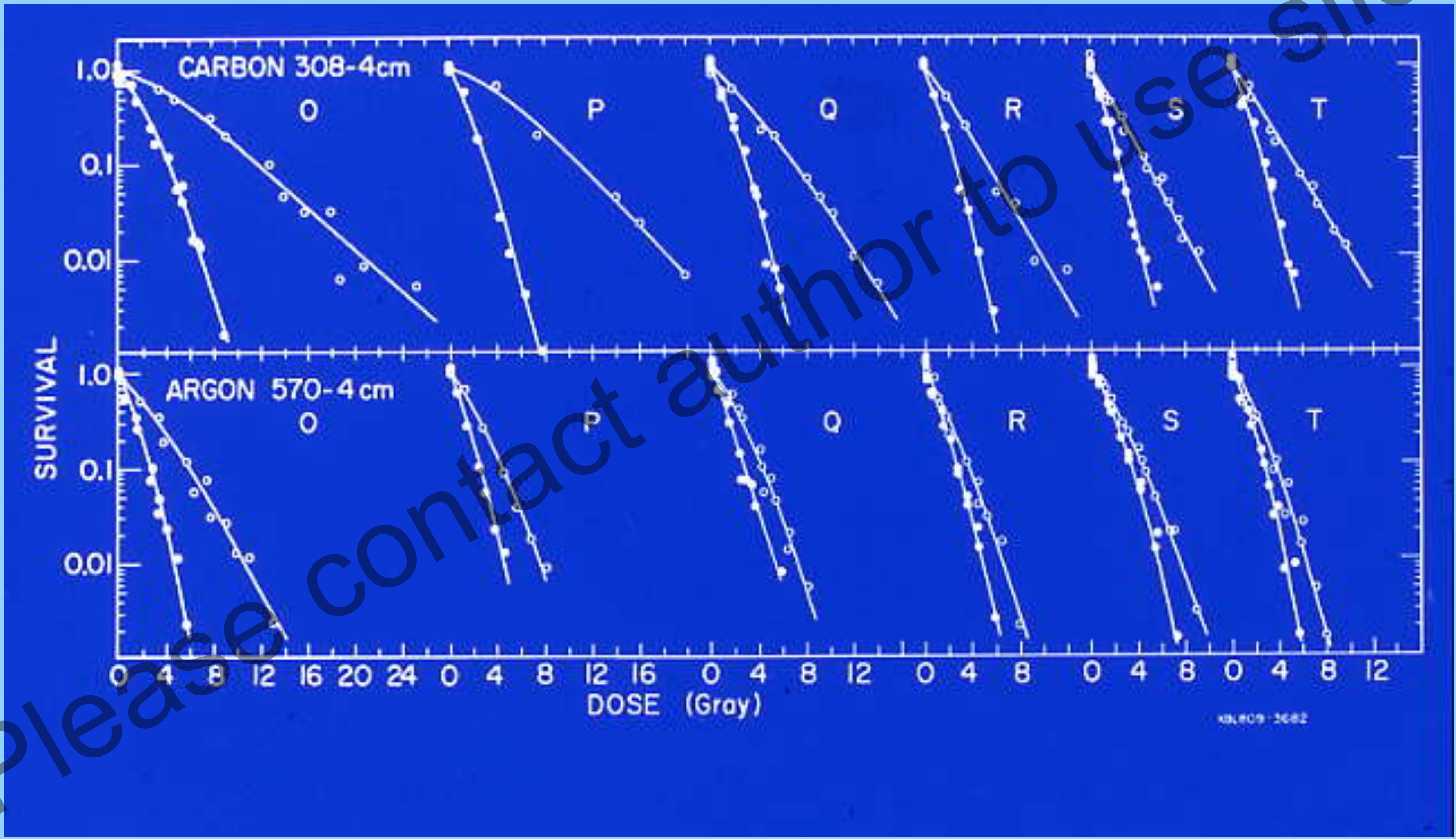


Steward, 1968

Proton & Carbon Extended Bragg curves on and off axis

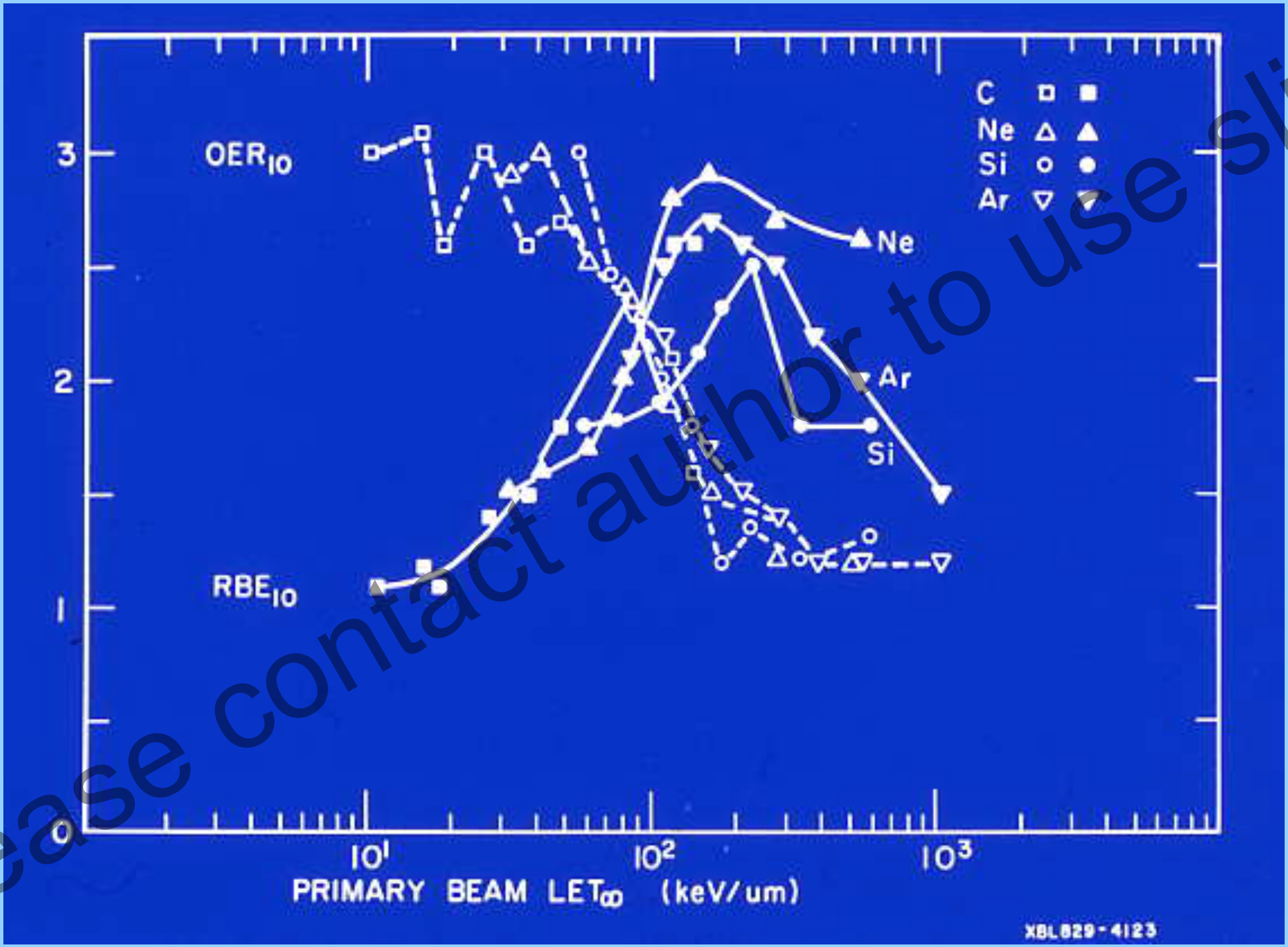


Aerobic & Hypoxic Cell Killing with Carbon or Argon Beams



Blakely

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



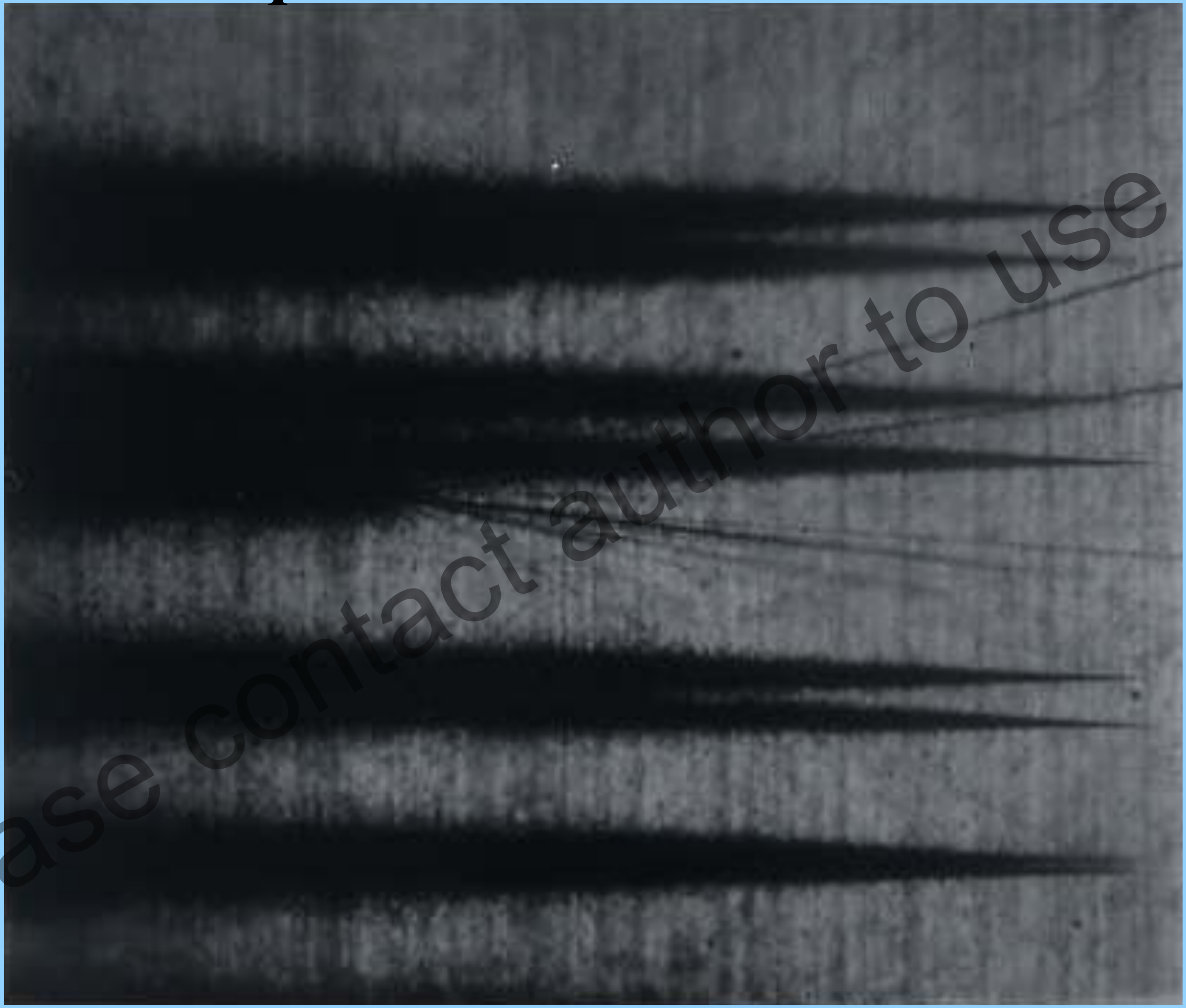
Blakely et al.

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

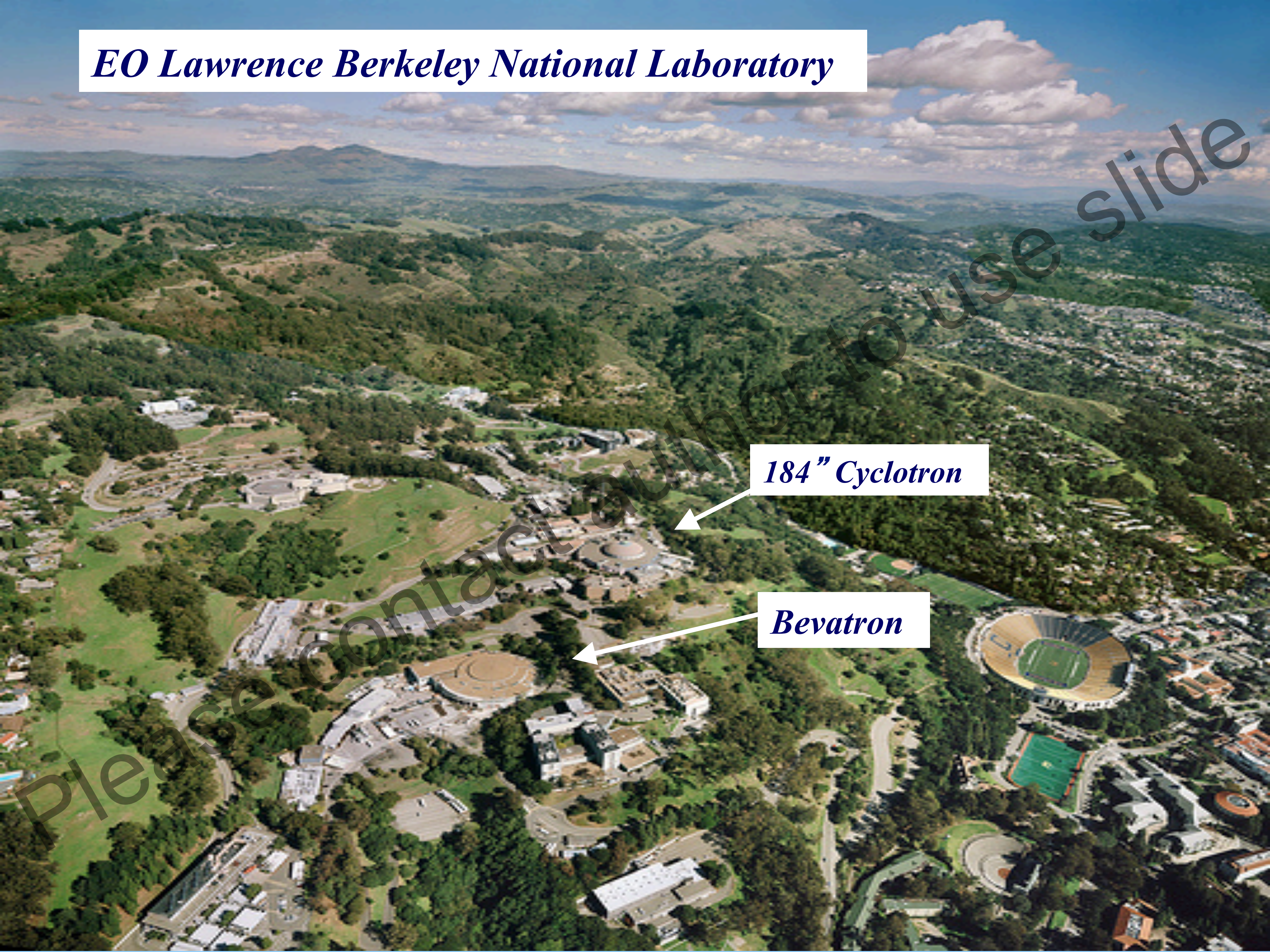
Blakely

HZE particle tracks in emulsion



Heckman et al.

EO Lawrence Berkeley National Laboratory



Al Ghiorso's Idea to Create the Bevalac (1975-1993)

- ***In 1974, a Transfer Line was completed, connecting the SuperHILAC (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.***

Clinical Trials at LBNL-UCSF, 1975-1992

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

1975-1992	Total treated	NCOG/RTOG
He ions	*2054 patients*	*700 patients*
Neon ions	*433 patients*	*300patients*

Prof. T. Phillips

Prof. J. Quivey

Prof. G. Chen

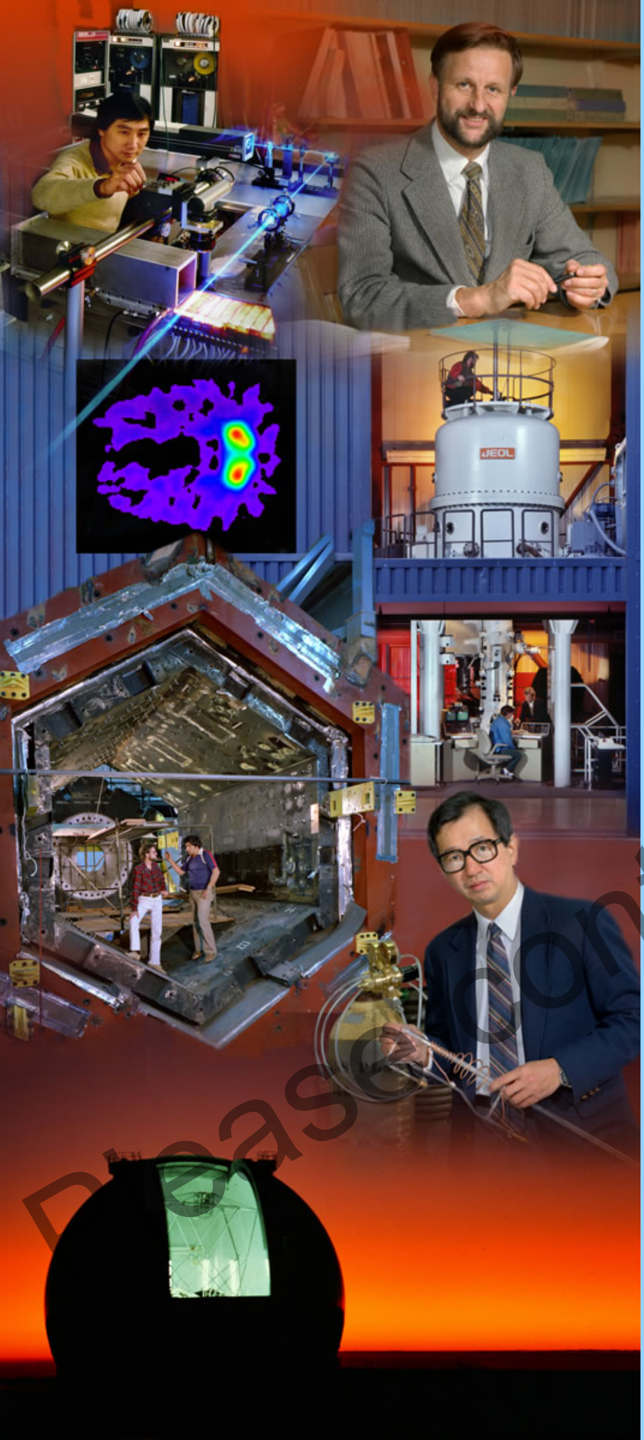
Dr. E. Blakely

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



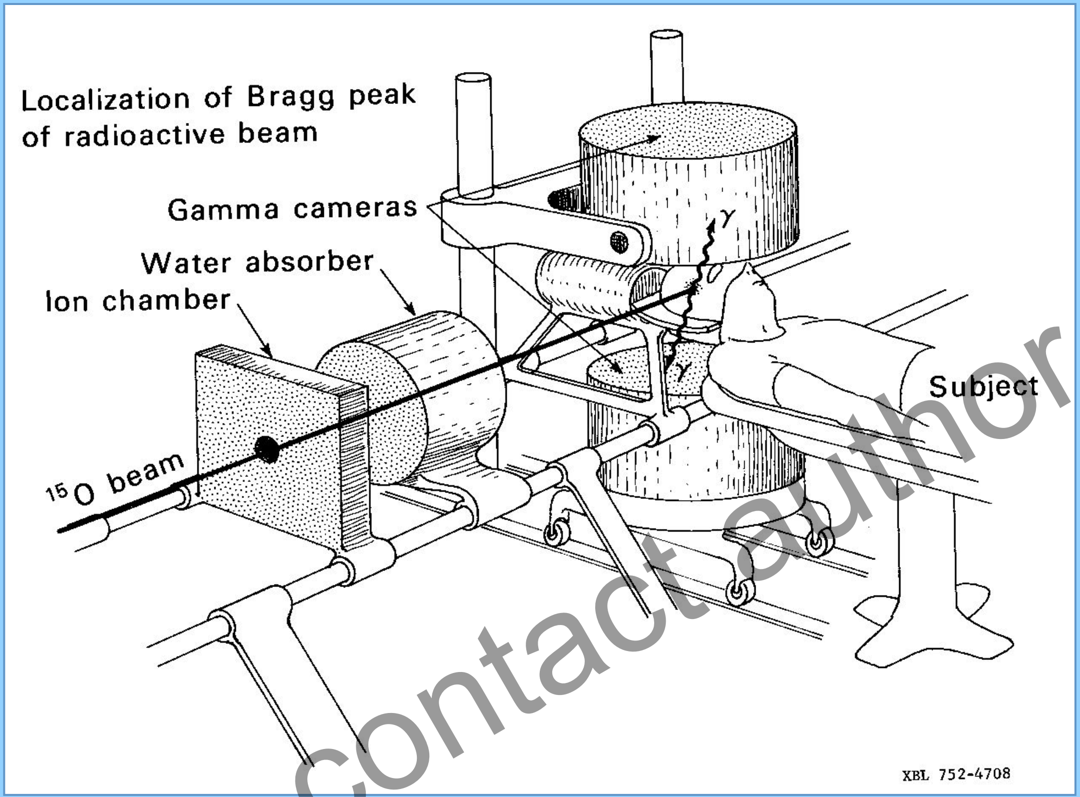
1980's

- *In 1988 Yuan Lee became Lawrence Berkeley Laboratory's ninth Nobel laureate, winning a share of the prize in Chemistry for his "crossed molecular beams" research.*
- *During the 1980's, the Lab under its fourth director, David Shirley, the first non-physicist, opened the National Center for Electron Microscopy (NCEM), home to the world's most powerful electron microscopes, launched the Center for Advanced Materials, invented the segmented mirror for the Keck Ten Meter Telescope, collaborated with the Stanford Linear Accelerator Center on the Positron-Electron Project, a matter-antimatter collider used to create and study new types of quarks, and broke new ground in Positron Emission Tomography studies of the brain.*

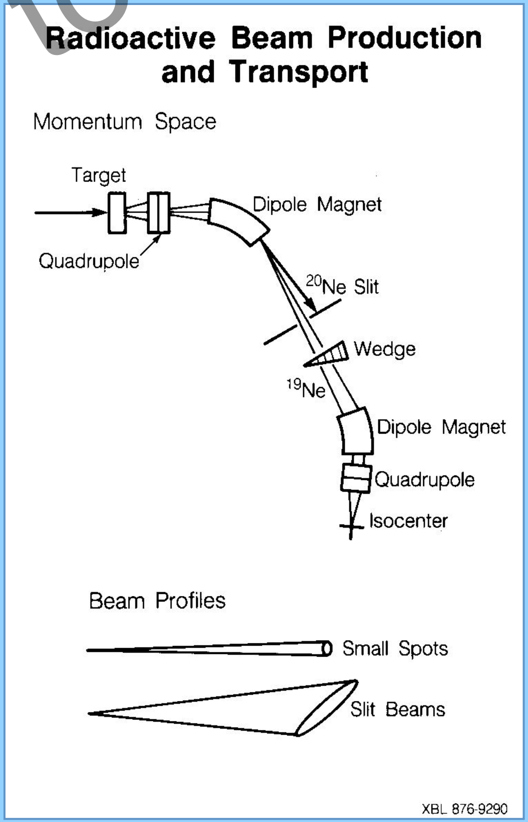
Development of Therapy Delivery Methods

- ***Tumor Localization***
  - ***Tumor localization by CT, MRI, PET and radioactive beam produced at the Bevalac***
  - ***Patient immobilization and verification of beam delivery through accurately transferring information among these data sets.***
- ***Beam Delivery Methods***
  - ***Wobbler***
  - ***Raster scanner***
  - ***3D conformal therapy delivery***
- ***Beam-Delivery Control Code and Therapy Planning Code***
  - ***The computer code used to control the beam in the human therapy facility was an innovative system of the highest quality***
  - ***Unblemished safety record in human cancer therapy***

Tissue Ranging Using Radioactive Beam

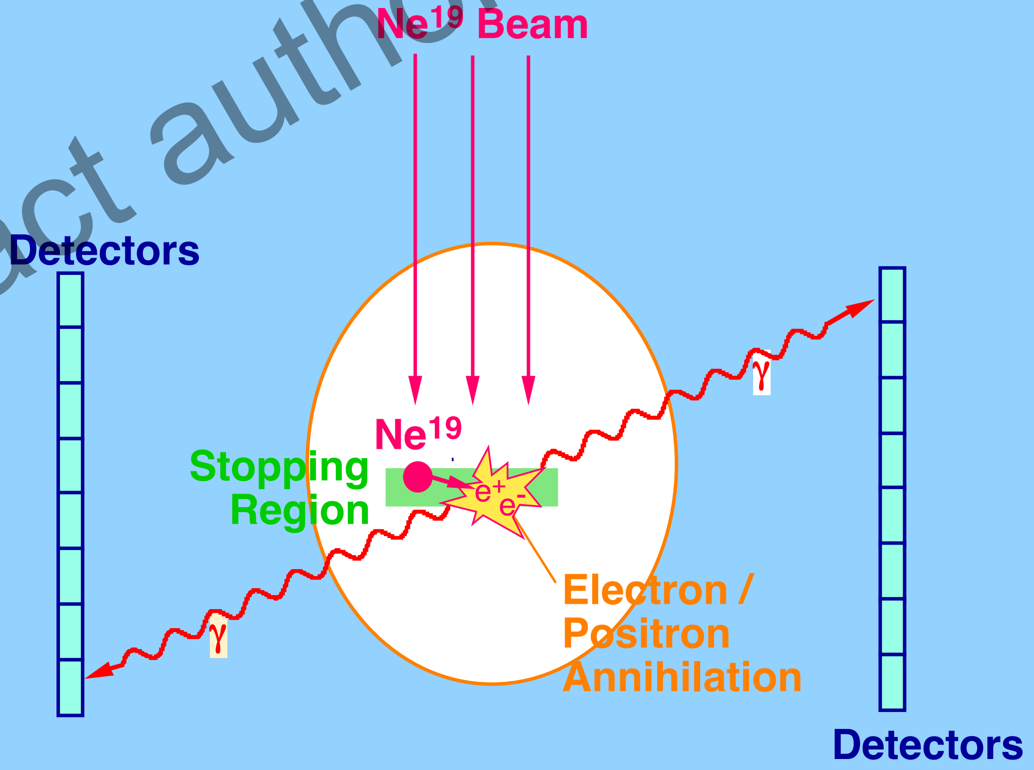


1975



Positron Emitter Beam Analyzer (PEBA)

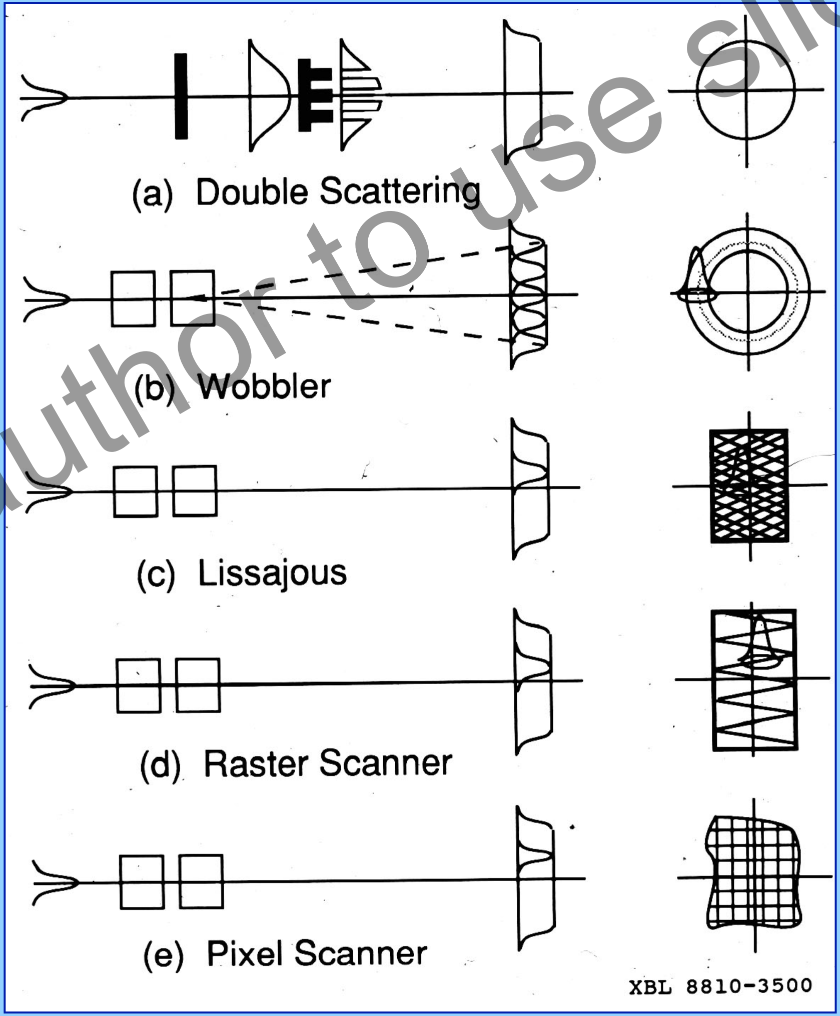
- ***An instrument that collects gamma rays from positrons emitted at the end of range of radioactive nuclei and imaged them as PET scanners does.***
- ***The instrument was more sensitive than PET scanners of the time, as it took advantage of the fact that the position of the beam in a plane transverse to its direction was known.***



Developed New Beam Delivery Methods

Goals:

- *Better conformation of dose to irregular shape*
  - *Modulation of SOBP*
- *Better utilization of beams*
- *Higher beam quality*
  - *Decrease in fragmentation losses*
- *Maintaining sharp field edges*
  - *Reduction in scattering and straggling*

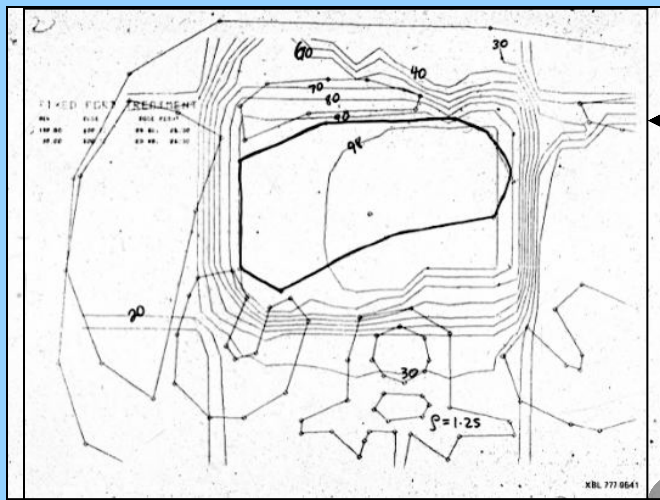


Treatment Planning

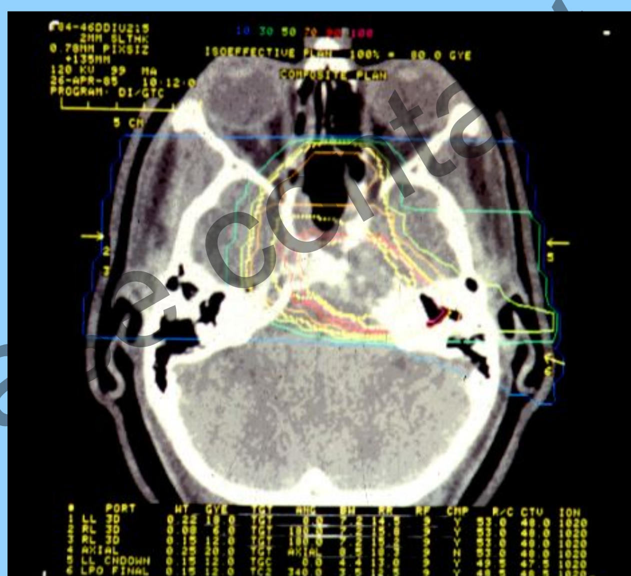
- ***Development of one of the first and best 2D and 3D therapy planning programs for the use of ionizing radiation including charged particles in human cancer therapy.***
  - ***The combined efforts of many computer scientists, biologists, biophysicists, mathematicians, accelerator physicists, graduate students and physicians.***
  - ***Many of the innovations and techniques begun at LBL were incorporated in later treatment planning programs for conformal xray therapy, stereotactic radiotherapy, therapy other charged particles centers and throughout all of radiation oncology.***

Evolution of Therapy Planning

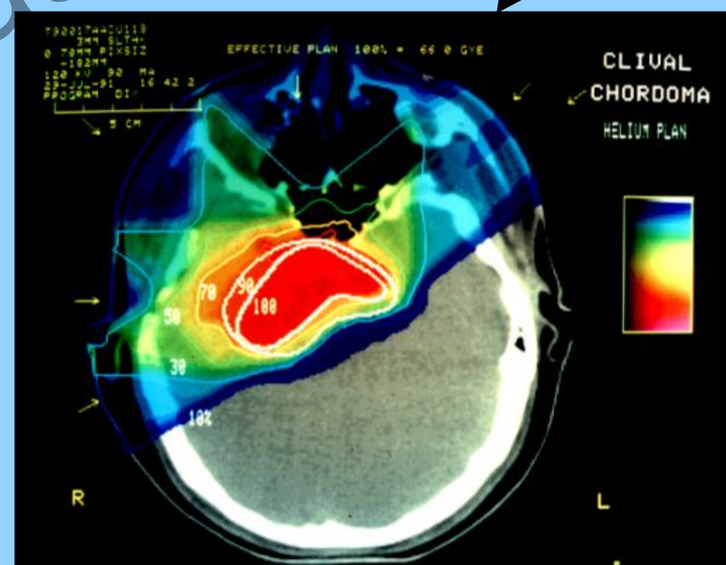
1977



1985

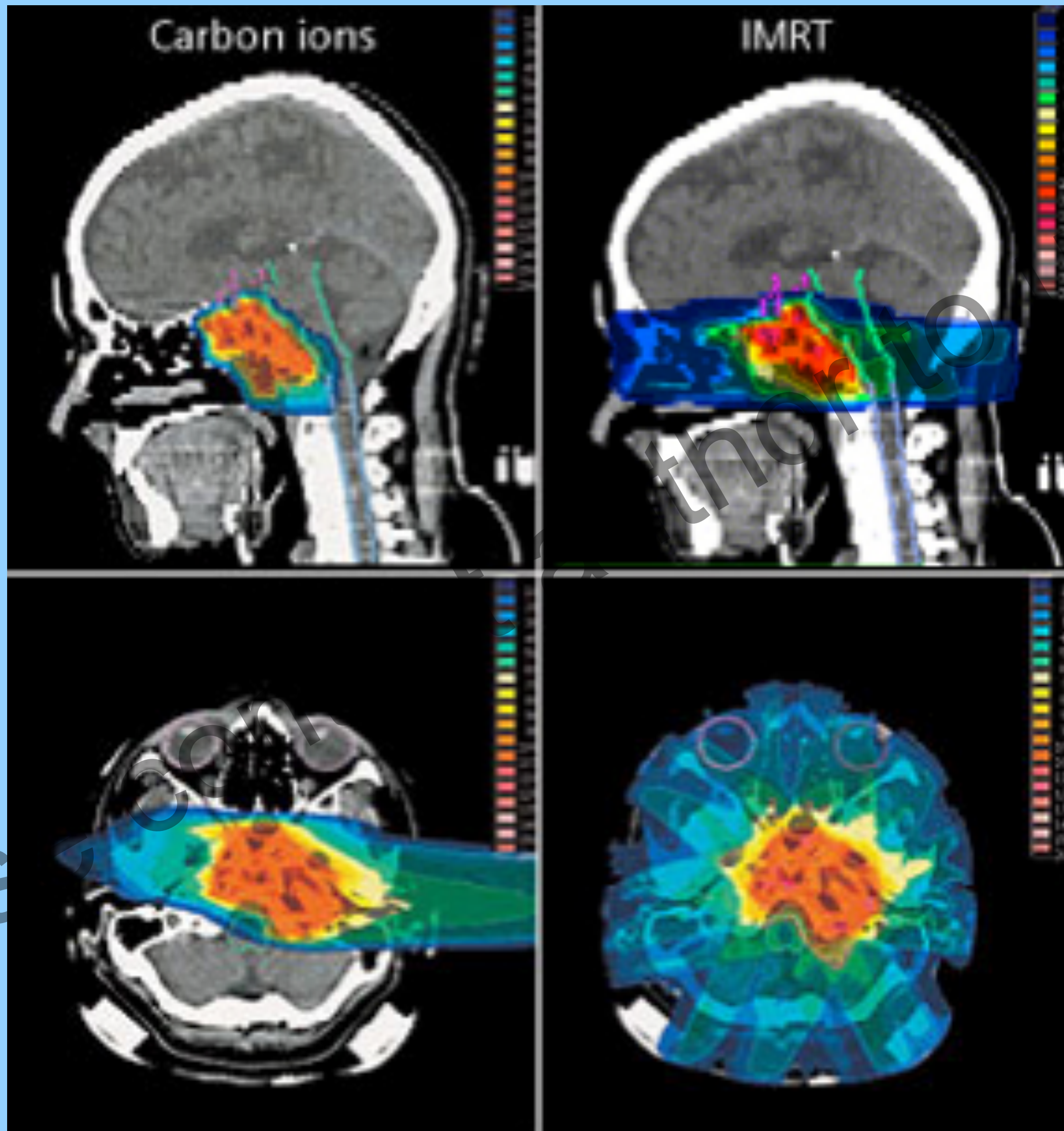


1992



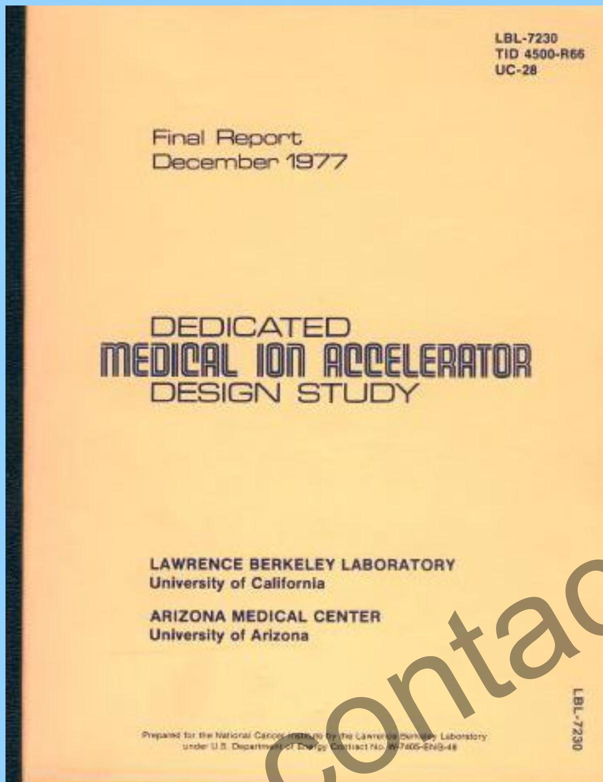
Carbon Beam vs. Photon Therapy

Carbon ions
1 field



Photons (IMRT)
multiple fields

Medical Accelerator Designs at LBNL


LBL-7230
TID 4500-R66
UC-28

Final Report
December 1977

DEDICATED
MEDICAL ION ACCELERATOR
DESIGN STUDY

LAWRENCE BERKELEY LABORATORY
University of California

ARIZONA MEDICAL CENTER
University of Arizona

Prepared for the National Cancer Institute by the Lawrence Berkeley Laboratory under U.S. Department of Energy Contract No. W-7405-ENG-48

LBL-7230

1977

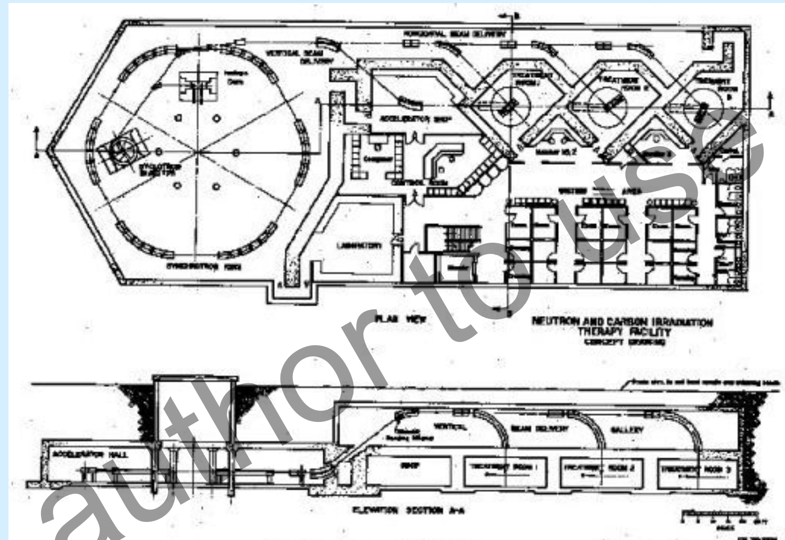


FIG. 37: Conceptual Facility Layout

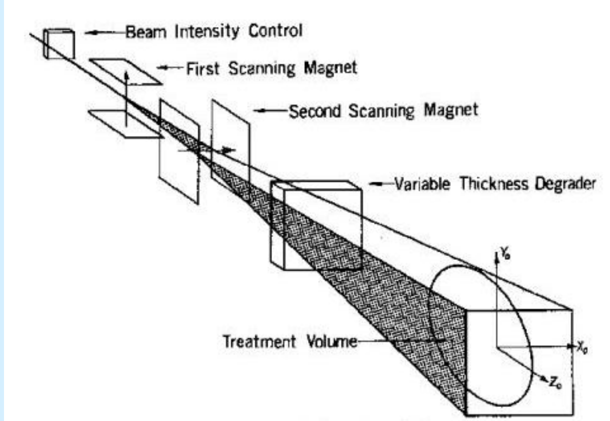


FIG. 26: Schematic depiction of scanning method.

Medical Accelerator Designs at LBNL

1988

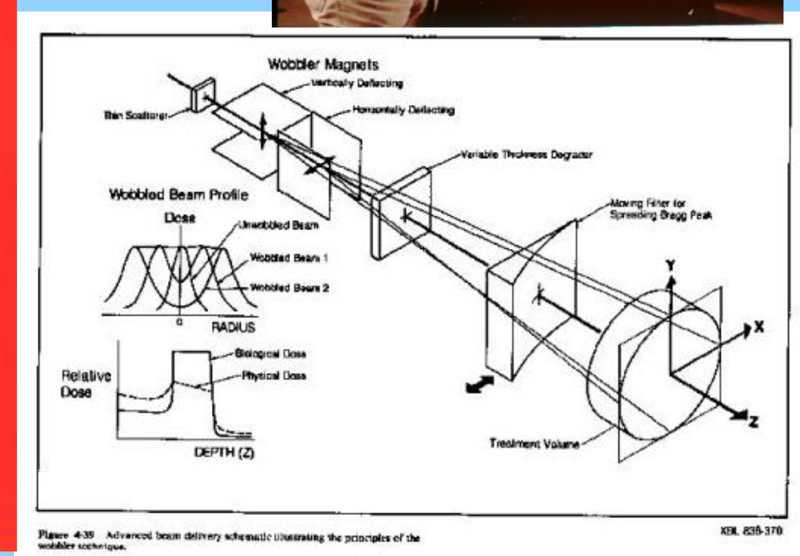


Figure 4-39 Advanced beam delivery schematic illustrating the principles of the wobbler technique.

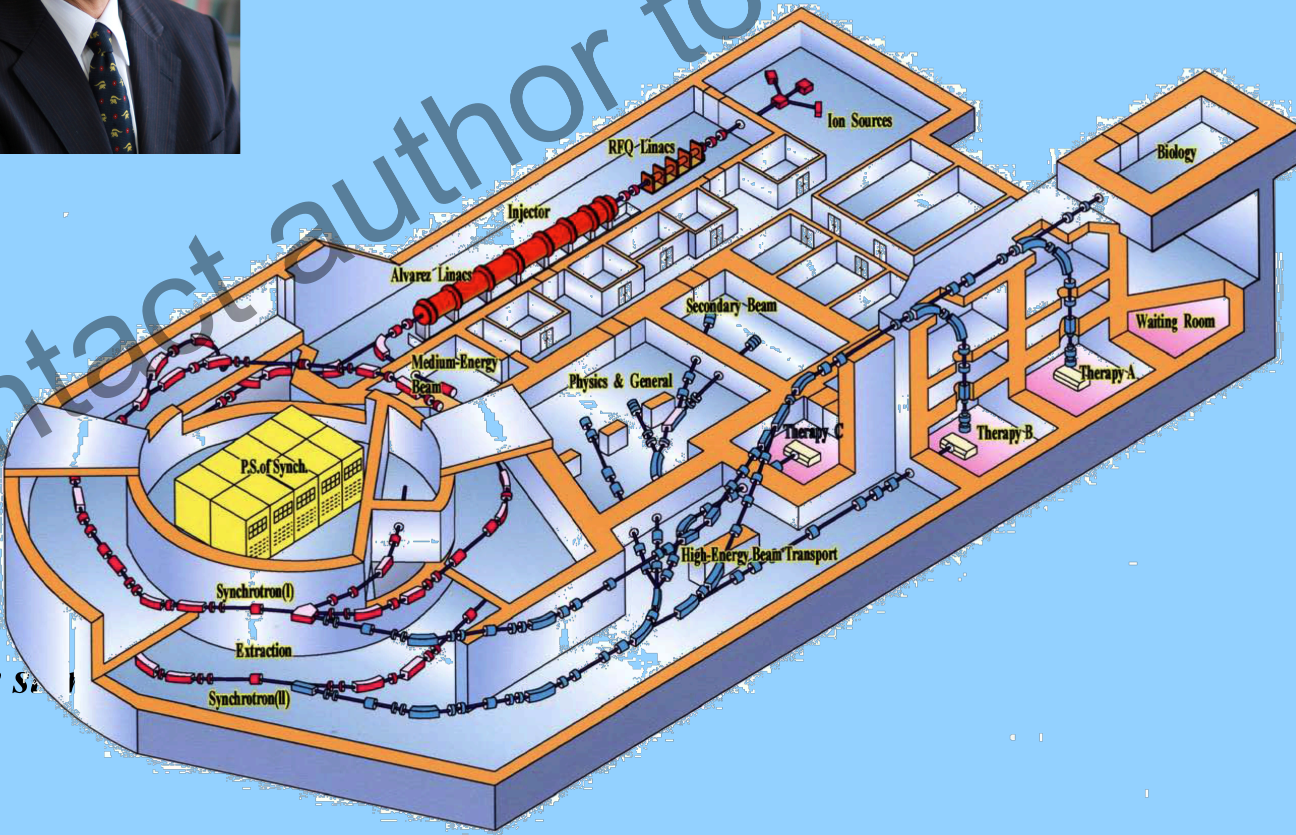
1990's

- *In the 1990's, under the direction of Charles Shank, the Lab became the Lawrence Berkeley National Laboratory, or Berkeley Lab, and its research truly spanned from the infinite to the infinitesimal.*
- *The Gammasphere probed nuclear collisions and starred in a movie, the discovery of dark energy confirmed Einstein's intuition, the Sudbury Neutrino Observatory (SNO), revealed neutrino mass, a low-tech device for purifying water became invention of the year.*
- *The COBE satellite and Relativistic Heavy Ion Collider (RHIC) brought us snapshots from the dawn of time, the Advanced Light Source began a new era in synchrotron studies, and NERSC, the National Energy Research Scientific Computing Center, ushered in a new age for scientific computing.*

Heavy Ion Medical Accelerator at Chiba (HIMAC) at NIRS, Chiba, Japan (1992)

Prof. Hirohiko Tsujii

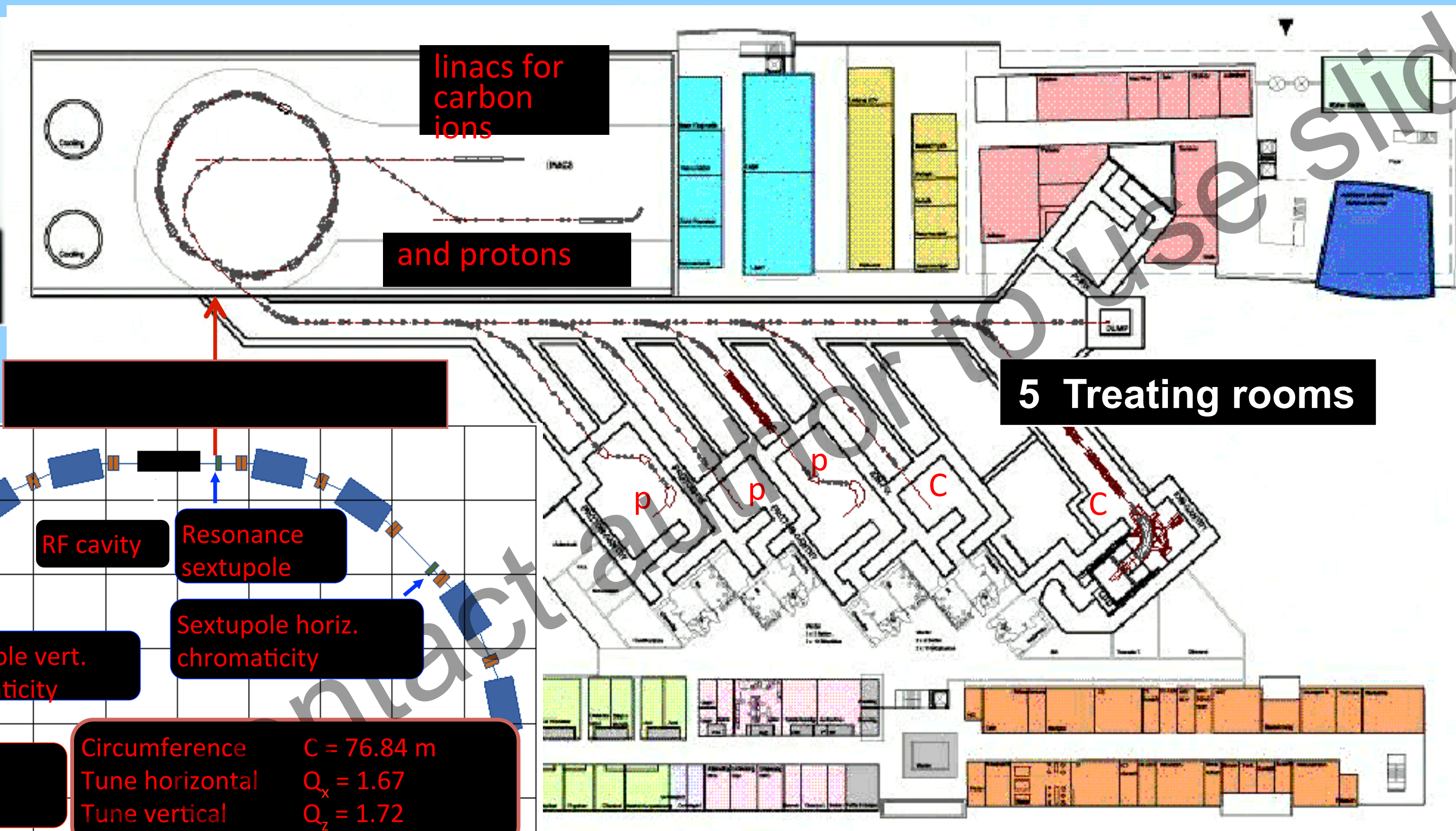
Prof. Yasuo Hirao



1994: Carbon-ion radiotherapy s
2010: Treated >5000 patients
2011: New Treatment Facility

The origin: Proton Ion Medical Machine Study (PIMMS)
TERA 25 man years, MedAustron 10 man years

Ugo Amaldi



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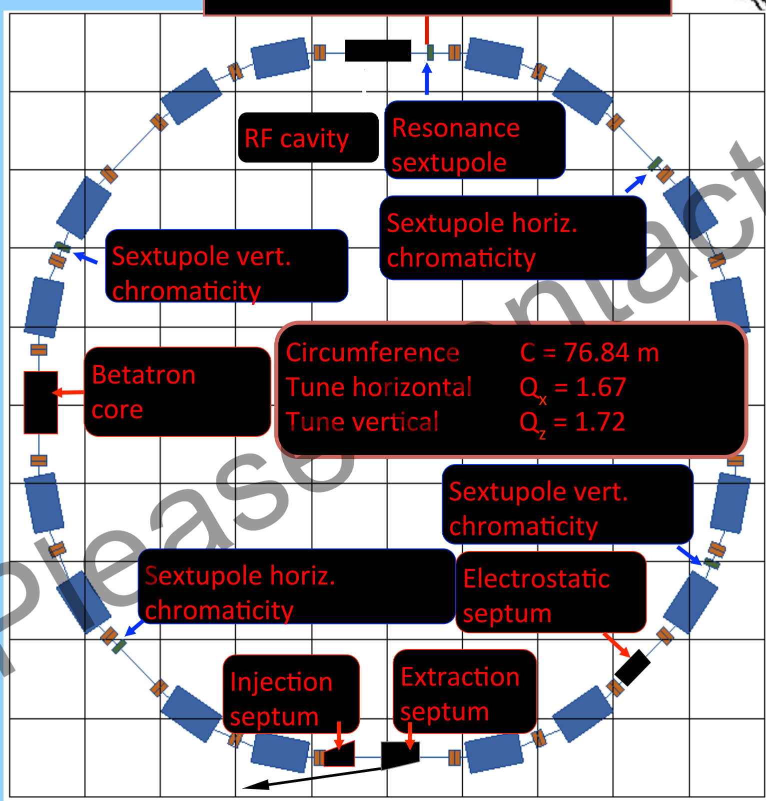
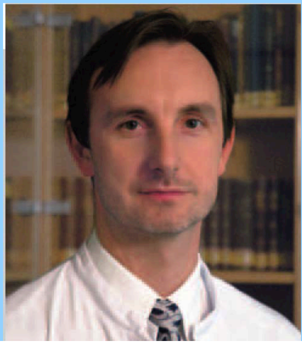


Optimized synchrotron for constant spill Project Leader: Phil Bryant

Chair of PAC: Giorgio Brianti

1996-2000

Heidelberg Ion Therapy (HIT, 2009)



Prof. Dr. J. Debus

Prof. G. Kraft

Dr. T. Haberer

HIT – two ion sources, a linac and a synchrotron, with 2 fixed beam lines and one with a rotating gantry

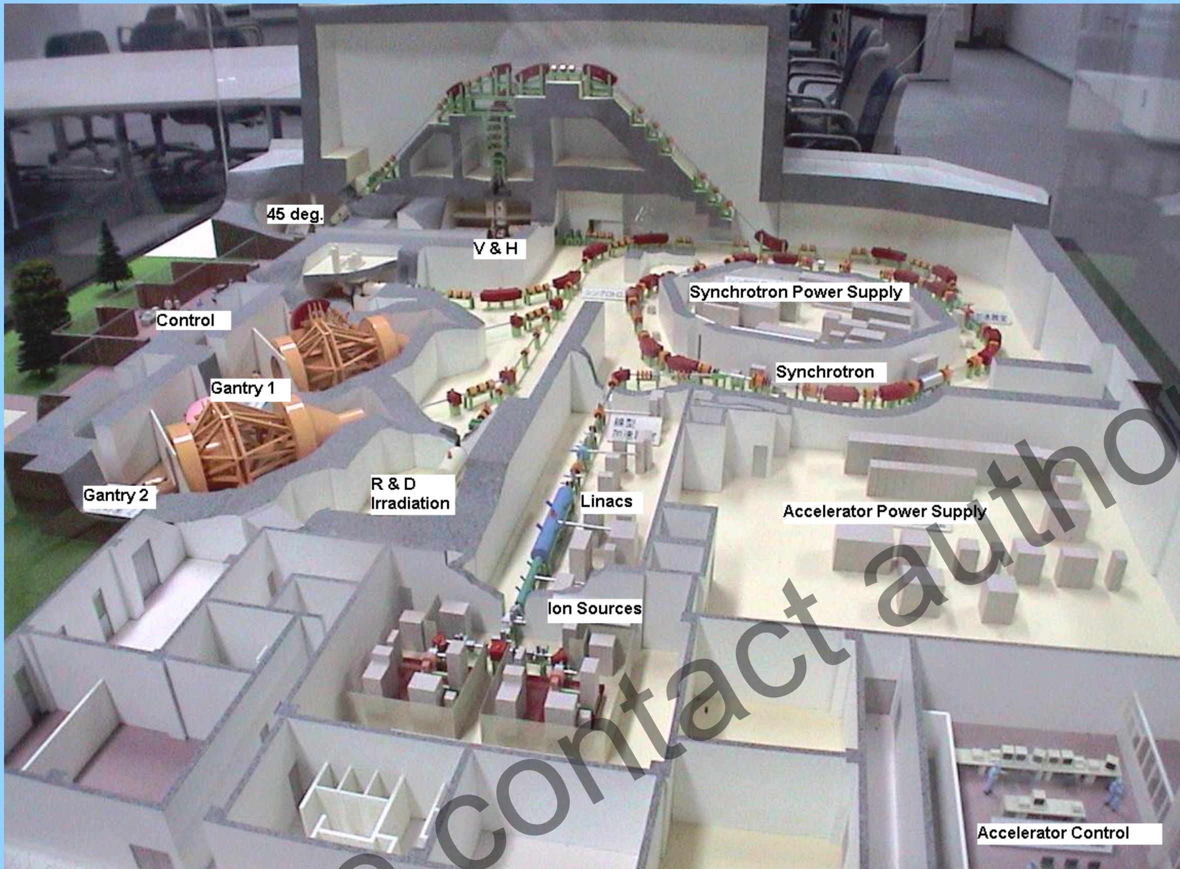
2000's

- *In 2004, Steven Chu became the Lab's sixth director and 10th Nobel laureate.*
- *The Lab got big on nanotechnology with the opening of its Molecular Foundry, a center devoted to nano-scale research, and started the first Synthetic Biology Department, where promising developments in anti-malarial and anti-AIDS drug research are already being realized.*
- *Lab researchers also plunged into carbon sequestration, exploring such possibilities as deep-ocean storage, and looked to apply information gained from sequencing the human genome to the development of new diagnostics and therapies.*
- *Another area ripe for exploration is the explosion of stars deep in outer space. SNAP, the SuperNova/Acceleration Probe, hopes the study of such phenomena will shed new light on dark energy.*

Summary of Berkeley Lab's Center for Beam Physics (CBP) Contributions to the LHC through the US-LARP program and within the Accelerator & Fusion Research Division

- ***Ideas***
  - *CBP incubated highly relevant contributions to LARP and the LHC*
  - *Ideas led to:*
    - *Luminosity monitor*
    - *SPS feedback design for electron cloud mitigation*
    - *Contributions to the Crab Cavity proposal*
- ***Tools and Infrastructure***
  - *Software modeling assets provided the backbone for many studies*
    - *Electron Cloud (WARP, POSINST), BeamBeam3D, Space Charge (IMPACT)*
- ***People***
  - *The integration of beam physics and accelerator technology at LBNL provides a unique, ideal mix of expertise and tools for the US-LARP at CERN*

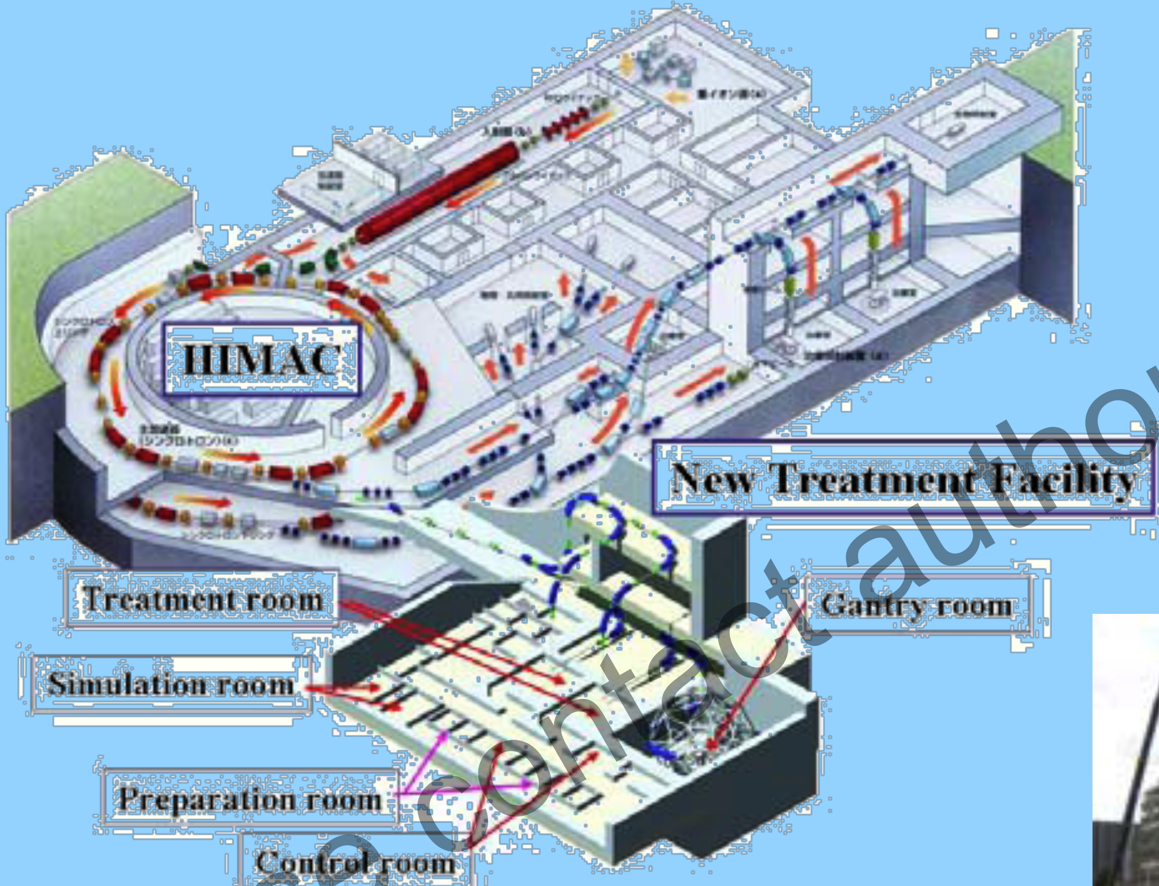
HIBMC, Hyogo (2001)



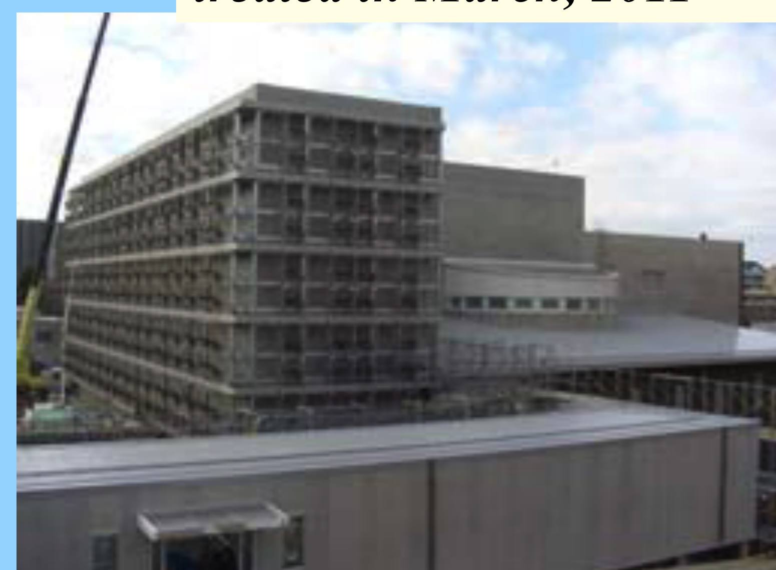
Synchrotron

- *70–230-MeV protons with 2 gantries*
- *70–320 MeV/nucleon ^{12}C beam with one each horizontal, vertical and 45° oblique fixed beams*

NIRS HIMAC Expansion (2011)



The first patient was treated in March, 2011



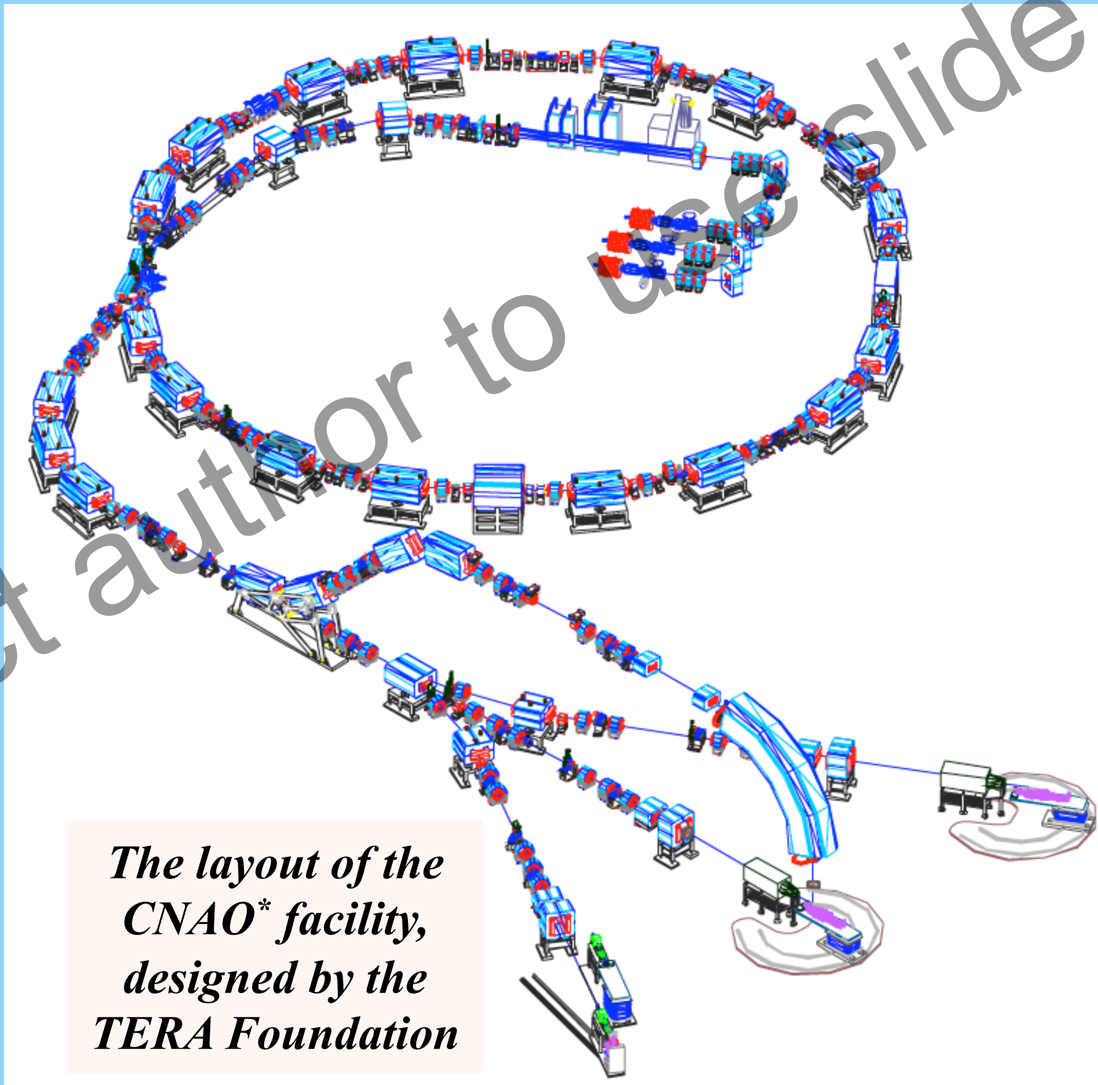
Koji Noda (NIRS), 2nd NIRS-CNAO Symp., Pavia, Italy, 21st March, 2010.

CNAO Facility, Pavia, Italy (2010)*

Prof. Ugo Amaldi

Prof. R. Orecchia

Dr. Sandro Rossi



The layout of the CNAO facility, designed by the TERA Foundation*

**Centro Nazionale di Adroterapia Oncologica*

THE BEGINNING ON TWO CONTINENTS

Berkeley, California, USA 26 August 1931

Geneva, Switzerland 29 September 1954

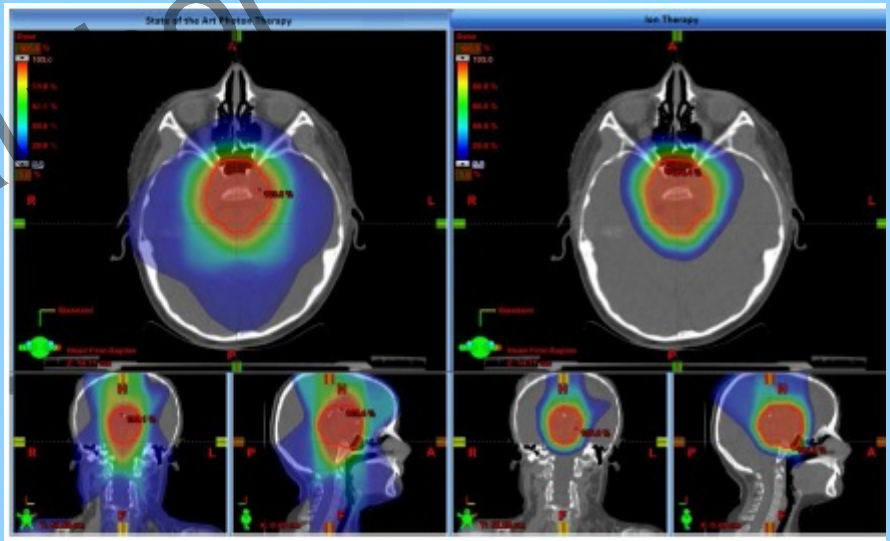
Continuing the Dialogue

Dr. Manjit Dosanjh

- *CERN has coordinated and catalyzed the ENLIGHT European platform promoting International Research and Development, Networking and Training for students and staff from facilities planning or using Hadron therapy across Europe.*
- *ENLIGHT*
- *PARTNER*
- *ULICE*
- *ENVISION*
- *ENTERVISION*

Path Forward: DOE-NCI Workshop on Ion Beam Therapy, Bethesda, MD, January 2013

- ***More than 60 participants from medicine, physics, biology & business were charged with addressing 4 topics:***
  - ***Charge 1:*** *Identify pertinent clinical applications and radiobiological requirements*
  - ***Charge 2:*** *Assess corresponding beam requirements for future treatment facilities*
  - ***Charge 3:*** *Assess the corresponding beam delivery system requirements*
  - ***Charge 4:*** *Identify R&D activities needed to bridge the gap*



NIH/NCI----Planning for a National Center for Particle Beam Radiation Therapy Research (P20)

PAR-13-096 (due May 21, 2013) & PAR-13-371 (due Jan 21, 2014)

The purpose of this Funding Opportunity Announcement (FOA), issued by the National Cancer Institute (NCI) of the National Institutes of Health (NIH), is to encourage and support planning efforts for establishing a Center for Particle Beam Radiation Therapy (PBRT) Research….. The goal of this FOA is to provide the awardees with funding to enable inclusion of necessary resources (expertise or facilities) to carry out basic, translational, and clinical research complementary to a clinical PBRT facility……The necessary expertise and efforts would be provided by a multidisciplinary team of basic, translational, and clinical Researchers, including physicists, engineers, biologists, and physicians, while the research facilities may include, by way of example, cell culture laboratories, vivarium, and clinical anesthesia units for pediatric patients….. It is expected that this effort will result in a national research resource capable of successfully competing for and securing the funding required to operate a specialized research center for clinical PBRT. This FOA is designed to support solely the planning for a Research Center at a separately funded PBRT facility, and not the PBRT facility itself.

2010's

IN PROGRESS

- *In 2009, Paul Alivisates became the Lab's seventh director.*
- *Berkeley Lab currently has six main science thrusts*

  --soft x-ray science for discovery

  --climate change and environmental sciences

  --matter and force in the universe

  --energy efficiency and sustainable energy

  --computational science and networking

  --biological science for energy research (JBEI)
- *Berkeley Lab is host to six major National User Facilities:*

  --Advanced Light Source

  --The National Center for Electron Microscopy

  --National Energy Research Scientific Computing Center

  --The Energy Sciences Network

  --The Molecular Foundry

  --The Joint Genome Institute
- *The BEVALAC has been dismantled, and only the 88" accelerator remains in operation.*

Future Hadron Therapy in the SF Bay Area?

SF Bay Area P20 planning application—NAPTA
(North American Particle Therapy Association)
Led by UCSF and colleagues at LBNL, Stanford & SLAC
Supported by numerous international and national experts

Principal Investigator
Dr. Mack Roach, III
Chairman, Dept. of Radiation Oncology

Pending NCI Decision by October 2014

Summary

- *LBNL and CERN share a similar history, and a focus on the physics and medical applications of accelerators and each have benefitted from the research of the other.*
- *At present the challenge for the U.S. is support for the design and construction of medical accelerators to allow radiobiological research and medical trials to proceed to Phase III trials for cancer therapy.*

ACKNOWLEDGEMENTS

- *I wish to gratefully acknowledge the following individuals who provided assistance with slide material*

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--Dr. William Chu

--Dr. Manjit Dosanjh

--Dr. Maurice Garcia-Sciveres

--Dr. Stephen Gourlay

--Dr. Alessandro Ratti

--Dr. Reinhard Schulte

- Supported by

---**NASA** Grant # *NNJ11HA941*

---*Office of Science,& Office of BER of the **USDOE** under Contract # DE-AC02-05CH11231*

---***CERN***

THANK YOU FOR YOUR ATTENTION

There are no commercial disclosures, and views and opinions are those of the speaker.