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Rationale for, and Development of, the World's First Hospital-based Proton Therapy System at Loma Linda University Medical Center

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Proton therapy was deemed necessary for radiation medicine because of unacceptable side effects patients experienced with conventional X-ray therapy. Such effects sometimes compromised treatment due to normal-tissue injury. Injuries arose from the uncontrollable pattern of ionization delivered by these particles, as well as the inability to identify targets with sufficient precision.

Robert R. Wilson, from Lawrence Berkeley Laboratory (LBL), described the superior attributes of protons for radiotherapy [1]. Heavy charged particles pass through patients' tissues, maintaining a predictable path owing to their mass, while their charge attracts and removes electrons from the targeted tissues, thus leading to cell death. Other attributes of heavy charged particles, in particular protons, arise because their velocity is inversely proportional to their ionization capabilities. Thus, upon entering the patient's skin, velocity is at a maximum and ionization is minimized. As protons approach their target, to a depth determined by the beam energy, velocity decreases as ionization events increase. Protons stop abruptly at the targeted depth and ionization intensifies; this forms the Bragg peak, as is seen with all heavy charged particles (Fig. 1). In addition, proton beams display low ionization density (low LET), which allows some repair of normal-tissue injury.

Studies were ongoing with helium and carbon ions, as used at LBL [2]; pions, as used at Los Alamos Meson Physics Facility (LAMPF) [3]; and protons, as used at Harvard Cyclotron Laboratory (HCL) [4,5]. These pioneers employed research equipment in physics laboratories. Their excellent work and clinical results formed the basis for understanding advantages and deficits of these particles.

In 1970 the author was recruited to Loma Linda University Medical Center (LLUMC) to develop a dedicated radiation oncology service. Among his goals were to bring heavy-charged-particle therapy to patients of the institution, and to develop precision in therapy planning, which he had already begun to do as a means of improving X-ray therapy. The precision of heavy charged particles could not be exploited fully without precise target delineation, and in any case, more-precise therapy planning would benefit patients treated by any form of external-beam therapy.

Preparing Specifically for the LLUMC Proton Facility

In 1970, a study was done to assess the feasibility of a heavy-charged-particle facility at LLUMC. The study demonstrated that designing a patient-dedicated facility was then premature because: 1) imaging modalities were inadequate to visualize the true extent of tumor; 2) computer-assisted treatment planning systems did not exist, forestalling accurate placement of any ionizing beam and development of an optimal treatment plan; and 3) computing technology was not available to adequately perform heavy-charged-particle treatment in a clinical setting.

The author decided to first address the problem of inadequate imaging for treatment planning. He had begun working on the problem in the late 1960s, in consultation with Ivan Neilsen, a physicist at Loma Linda University. After 1970 they and others continued this effort, and in 1971 began using an ultrasound-based, computer-assisted treatment-planning system [6]. The system enabled more-precise photon therapy planning but remained inadequate due to lack of detail and density data. Computed tomography (CT) provided such data; when it became available in the mid 1970s, LLUMC purchased one of the first General Electric CT scanners and interfaced it with their treatment planning system [7]. This pioneering work was recognized at international meetings; one attendee referred to it as the "missing link" in radiation oncology (Fig. 2). In subsequent years CT-based radiation therapy planning was adopted by radiation oncologists worldwide, and many accelerator manufacturers developed computer-assisted planning systems. This advance enhanced all forms of external-beam radiotherapy, photon and heavy-charged-particle alike.

Throughout the 1970s and early 1980s, as precision therapy planning was becoming common, James M. Slater and LLUMC colleagues monitored heavy-charged-particle therapy as it was being practiced in research settings. Slater was a part-time faculty member at LAMPF, where he assisted in patient treatments with pions. He also visited LBL, where helium ions and heavy ions were used, and referred some patients there. As these studies progressed, it became clear that pions and heavy ions were unsuitable for routine radiation therapy, mainly owing to excessive damage to normal cells admixed with tumor cells. These considerations made a low-LET proton beam more attractive. With patient needs as the prime consideration, Slater therefore chose proton beams because of their combination of capabilities: a low entrance dose; a Bragg peak that can be modulated to encompass a broad range of target volumes; a sharp dose fall-off that spares irradiating tissues distal to the beam; and low-LET behavior in tissue. The superior dose distribution of proton beams was the most important consideration because of the need to reduce normal-tissue injury.

Developing the LLUMC Facility

By the mid 1980s, deficiencies identified by the 1970 LLUMC feasibility study had been largely overcome. Computer-assisted, CT-based planning, further developed at LLUMC, was spreading world-wide [8]. Imaging was expanding: magnetic resonance imaging (MRI) and positron emission tomography (PET) promised further precision in therapy planning. Computers were becoming capable of controlling the beam precisely. The author began recruiting a team of like-minded physician colleagues [9].

LLUMC thus was ready to proceed in developing a hospital-based proton therapy system. Although some faculty and administration had lingering concerns, David Hinshaw, Sr., Vice-president for Medical Affairs, strongly supported the project. Representatives of approximately 35 industrial and engineering firms were invited to visit LLUMC for a presentation; the firms were asked, in essence, whether they would partner in developing the pioneering accelerator and facility. All declined; a senior engineer at Siemens told Slater that the project would be too great a change of direction for the companies. Subsequently, the author visited major international high-energy physics laboratories and assessed their potential as possible collaborators.

In late 1984, the author and Herman Suit, of Massachusetts General Hospital, conferred about their mutual interest in proton therapy and agreed that a symposium would help to focus the emerging interest in a hospital-based facility. Slater approached Fermilab administration, specifically the director, Leon Lederman, and the deputy director, Philip Livdahl. Fermilab supported the idea; in January 1985, 93 physicists from international high-energy physics laboratories met to discuss design requirements for a hospital-based proton facility. A second meeting was held at Fermilab in August, followed by formation of the Proton (now Particle) Therapy Co-operative Group (PTCOG), which began meeting semi-annually at international institutions and continues today.

Slater participated in meetings at Fermilab and PTCOG from 1985-1989. Early in this period he sought active collaboration with Fermilab, then the world's premier designer and fabricator of synchrotrons and related components. Although a U.S. Department of Energy (DOE) facility, and thus not engaged in private ventures, Livdahl assured Slater that Fermilab could collaborate under DOE's "work for others" proviso, designed to promote technology transfer. Lederman supported the collaboration, as did the Universities Research Association, which operated Fermilab for DOE. This high-level peer review was important when federal support later was sought to augment funding committed by LLUMC. During this period, Slater arranged for LLU faculty, administrators, and Board of Trustees members to visit Fermilab; the visits alleviated scientific and financial concerns of many LLUMC personnel. LLUMC and Fermilab signed an agreement for a conceptual design study in January 1986, followed by an agreement for an engineering design about a year later.

Slater announced the collaboration at an early PTCOG meeting. PTCOG members and institutions played an important consulting role and added peer-reviewed, scientific cachet to the project. The author chaired one of its three committees that discussed specifications for an accelerator, facility, and clinical applications.

Slater and Fermilab physicists agreed that the accelerator should be a synchrotron (Fig. 3), chiefly because beam energy must be rapidly variable to permit flexibility in beam delivery. Changing energy was the key to treating a variety of tumors of various depths and sizes within the body. Specific design requirements were: 1) safety for patients and therapy personnel; 2) easy maintenance and upgradeability; 3) a control system interfaced with a treatment planning system to fully control each patient's set-up and treatment, yet nonetheless simple to operate; 4) sufficient reliability to treat at least 200 patients per day and also support research projects. Several Fermilab physicists and engineers worked on the design and construction of the proton accelerator. The fundamental design was led by Lee Teng, of Fermilab and Argonne National Laboratory [detailed in refs 10,11].

Fermilab personnel were responsible for designing and fabricating the synchrotron and the transport system for carrying the beam to four treatment rooms, three having gantries, and one room containing three beam lines for research purposes. To assist in transferring the accelerator and its associated technology to the medical center, LLUMC acquired an industrial partner, Science Applications International, Inc. (SAIC), selected by Fermilab.

The control system was LLUMC's responsibility. Three LLUMC engineers were sent to Fermilab to participate in developing the accelerator and treatment room control systems. Their objective was to devise an integrated control system, based on the needs of a medical facility, and to maintain and continually upgrade the entire system when it was in clinical operation. Differences of opinion arose between the LLU engineering team and Fermilab physicists, owing to fundamentally different concepts of what the control system must do. James M. Slater, realizing that the LLUMC team better understood the medical needs, transferred the team from Fermilab to LBL, to study control systems used there. From this, and experience accumulated in working with radiation physicists at LLUMC and the University of Utah, the engineers designed the control system for LLUMC.

Slater coordinated the project. Timely development was emphasized: timing in planning, fabrication, and installation was as important as the successful operation of component parts because of high monthly construction costs. Pre-building arrangements with the purchasing department, suppliers, labor unions, and all primary and secondary contractors avoided delays and disputes, and resulted in the ability to take early partial occupancy for installing heavy subsystems such as three rotating gantries, based on an HCL design; the first ever used to transport a proton beam. Several teams operated collegially, maintaining regular intercommunication. There were eight teams, each having tasks relevant to the overall engineering design; LLUMC, Fermilab, and the architectural firm, NBBJ, of Seattle, Washington, provided staff for each team. Weekly team meetings were supplemented with monthly meetings with hospital and university administrators, and periodic meetings were held with outside reviewers; these helped to keep all aware of progress and problems.

The building was designed to treat patients safely and efficiently; be erected within budget; provide facilities for patients, practitioners, and for scientist education and research; and be modifiable as new technology appeared. Design requirements were based on clinical experience and patients' needs. These resulted in a facility with five beam lines in four treatment rooms, three containing rotating gantries, and a separate research room with three beam lines. Clinics, treatment rooms, patient preparation areas, waiting rooms, animal research facilities, and offices were sited for optimal efficiency. It includes a beam-delivery system developed by LLUMC engineers with guidance from physicists and engineers at LBL. [detailed in refs 10,11]

The facility was ready for clinical operation in October 1990. By then the LLUMC team had grown to approximately 30 engineers, as they prepared to maintain and continually upgrade the accelerator and proton center. As LLUMC administration desired that the team form an independent company to reduce expenses, the firm now known as Optivus Proton Therapy, Inc. was formed.

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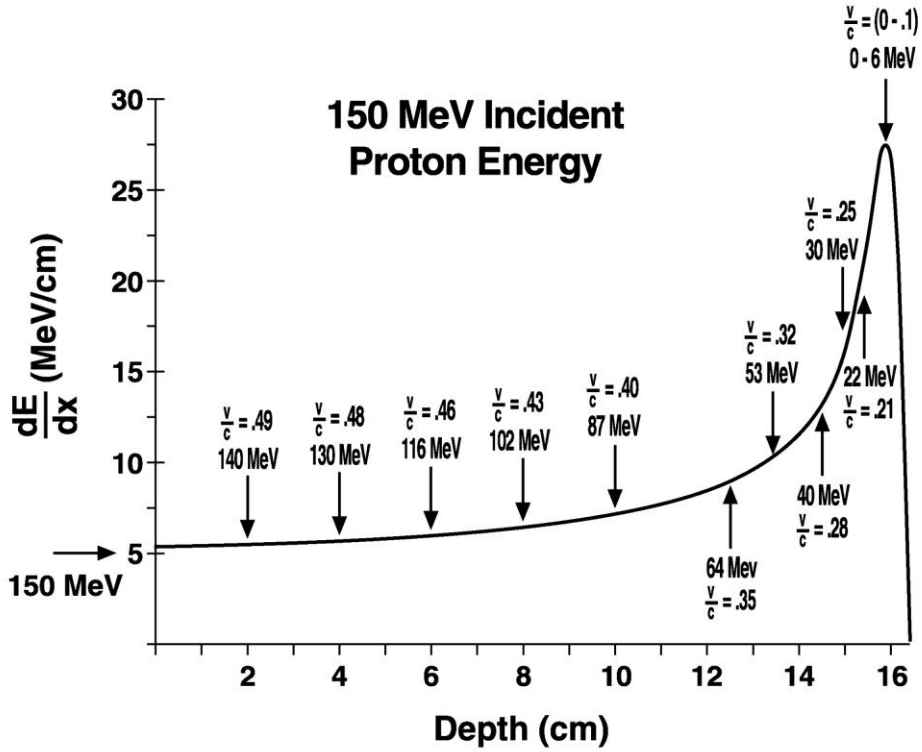

Figure 1. Bragg curve for a single 150-MeV proton beam. The velocity of the particle is compared to the velocity of light (v/c). As the particle enters the patient, it loses energy (velocity). At about 1/3 the velocity of light (64 MeV; v/c = .35) a dramatic increase in ionization events begins to occur; at about 1/10 the velocity of light, the interactions stop and energy deposition drops off precipitously. No radiation dose is deposited beyond this depth in tissue. Courtesy of George B. Coutrakon, Ph.D.

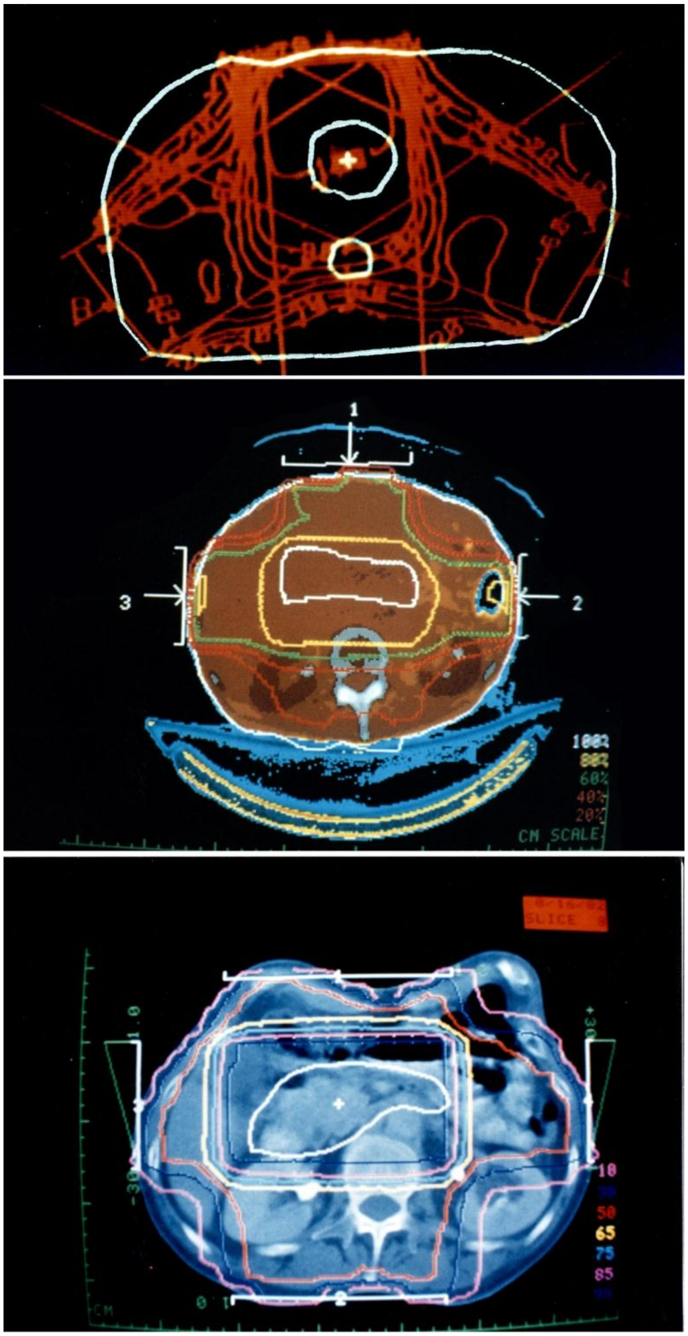

Figure 2. Three iterations of computer-assisted radiation therapy planning developed at LLUMC. Top (1971-72): image from ultrasound-based radiotherapy planning system. Middle (1975-76): image from CT scan-based planning system. Bottom (1986): image from refinement of CT-scan-based system. CT scans enabled inclusion of tissue-density data into the planning process.

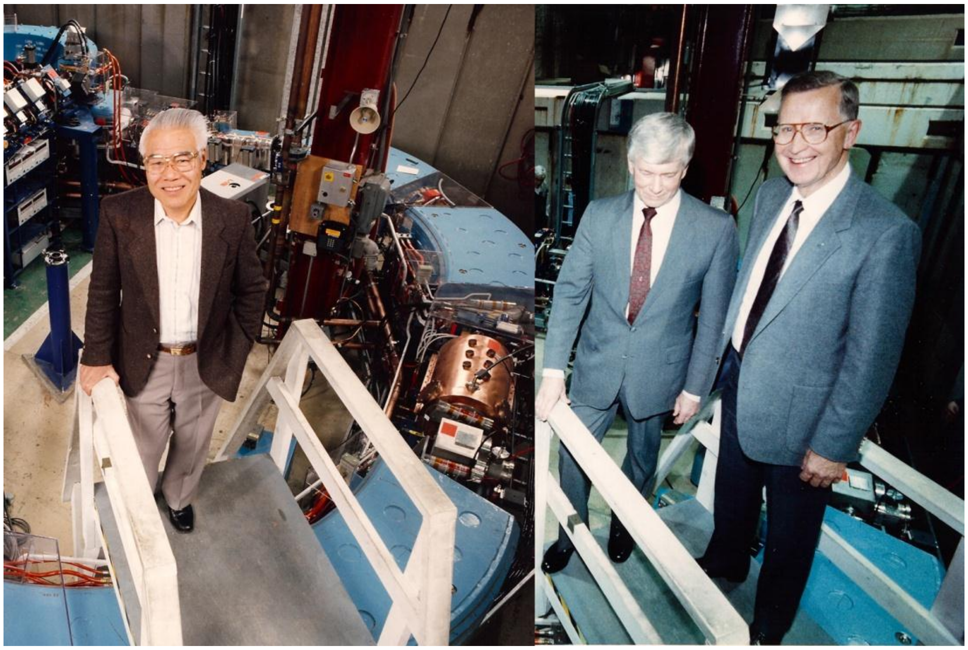

Figure 3. Composite image from photographs taken during construction of LLUMC proton synchrotron at Fermilab, 1987-1988. Left, Lee Teng; center, James Slater; right, Philip Livdahl.