



# New Clinical and Research Programs in Particle Beam Radiation Therapy: The University of California San Francisco Perspective

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## Historical Flashback

The first phase I/II clinical trial involving the application of particle beam radiation therapy (PBRT) with ions heavier than protons was initiated at the University of California, San Francisco/Lawrence Berkeley National Laboratory (UCSF-LBNL) in 1975 [1–4]. This trial prospectively evaluated tumor responses to PBRT and collected information on the late effects. The last trial extension, submitted to the National Institutes of Health/National Cancer Institute in 1991 by Drs Castro, Phillips, and others from UCSF-LBNL, was awarded an outstanding score. The main goals of the proposed 5-year extension were (1) to complete phase II and III trials in selected, specific tumor sites, (eye, paranasal sinuses, skull base, juxtaspinal area, brain, bone, soft tissue, biliary tract, prostate) and (2) to begin clinical studies with the unique dynamic conformal treatment delivery system available only at LBNL. This would permit 2D-raster scanning to be combined with variable modulation and dynamic collimation, affording a unique opportunity to study the benefits of optimized dose localization with heavy charged particles.

After tailoring individualized PBRT ion treatments for nearly 2500 patients for 17 years, the facility at Berkeley Laboratory was closed by the Department of Energy in 1992, owing to budget constraints. Proton beam therapy for uveal melanoma continued at the UCSF-LBNL Crocker Laboratory, with some noteworthy successes [5]. Following the lead in Berkeley, several other hospital-based heavy ion therapy facilities were developed in Japan, Germany, and Italy [6, 7].

## Current Status

Unfortunately, as the cost of PBRT centers remains high (~\$200M, USD), and evidence-based randomized trials for the enhanced efficacy of such therapies remain scant, there are currently no heavy ion beam facilities in the United States. There is wide consensus that to justify the development of such a facility, definitive studies (ie, randomized trials) are needed to prove that high-linear energy transfer ion beam radiation therapy results in improved cost-effective outcomes, compared to treatment with low-linear energy transfer protons or advanced x-ray-based therapy such as intensity-modulated radiation or stereotactic body radiation therapy [8, 9].

On February 10, 2015, the US President's Office of Science and Technology Policy announced the National Cancer Institute's selection of 2 P20 planning grants. The North

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### Editorial

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American Particle Therapy Alliance (NAPTA), a collaborative effort between leading academic institutions in the United States, US national laboratories, and leading PBRT centers in Japan and Germany, was 1 of the 2 recipients. Our proposal titled “NAPTA: Optimizing Clinical Trial Design and Delivery of Particle Therapy for Cancer” was awarded to lay out a future for ion beam therapy research in the United States.

## The Future: A New Approach

NAPTA intends to build a future for ion therapy by integrating and developing the clinical, biological, and technical know-how necessary to build a National Center of PBRT Research to include ion beams from protons to carbon and possibly oxygen. As a first step to reach this goal, the NAPTA P20 has the following overall specific aims in the first 2 years:

1. To transform existing groups and institutions with clinical interest in performing R&D work in PBRT into a network of functional teams with a common vision for research and development and clinical studies involving PBRT. To provide the organizational structure within NAPTA to synergistically align these teams.
2. To complete a pilot research project showing how we can move the field forward in addressing issues related to physical range uncertainty and integrating the development of “new knowledge” in radiation biology into treatment planning for assessing biological dose distributions.
3. To begin planning for the next 2 major phases to follow the P20 planning grant:
  - a. To facilitate the development of new, low-cost, compact/efficient designs, for ion accelerators, ion gantries, treatment planning systems, and imaging technology in the treatment room for adaptive planning and quality assurance/verification.
  - b. To enhance clinical PBRT research by developing the infrastructure for treating all patients within common protocols shared by all partner institutions and using common technology in the United States in synergy with similar efforts in Europe and Japan.

With this approach, NAPTA aims at developing synergy and commonality between cutting-edge technology and clinical trial designs across the United States and internationally, in order to achieve a thorough investigation of the value of PBRT. Through this endeavor, we will allow the US medical accelerator industry to reach the highest level of technical standards in manufacturing crucial components of future PBRT facilities. At UCSF, we have identified a site for such a center to be built and have developed a timeline and business model with high potential for sustaining a National Center for PBRT Research and Therapy.

Over the next several years, in collaboration with a number of national and international investigators and laboratories, we will launch a series of trials leveraging existing technology to challenge the null hypothesis that heavy-charged PBRT is required to improve survival and local control of selected cancers. This slow but steady progress and steadfast commitment to this research area will allow us to finally address the key 7 major challenges to advancing this field, which we call by the acronym *RESIDUE*:

1. **R**adiation biology to address uncertainty in optimal fraction sizes and doses and RBE (biological)
2. **E**xchange of technology, funding, and infrastructure between academic centers, health care payers, industry, and funding agencies (operational)
3. **S**ize/weight of accelerators and gantries (engineering/physics)
4. **I**ntegration of technology to advance key areas from beam acceleration and delivery, through treatment planning and image guidance (engineering/physics)
5. **D**efining the patient population to be studied; that is, “who really needs PBRT” (clinical)
6. **U**ncertainties of dose and range in treatment planning (physics)
7. **E**vidence of clinical effectiveness and cost-effectiveness (societal)

## Conclusions

NAPTA will determine the means to resolve the *RESIDUE* challenges through the full spectrum of opportunities for clinically viable PBRT: biological, operational, engineering/physics, clinical, and societal. The set of unique challenges, ranging from radiation biology to cost-effectiveness and complex operational issues, will require new strategies and broad support from both public and private sectors.

## ADDITIONAL INFORMATION AND DECLARATIONS

**Conflicts of Interest:** The authors have no conflicts to declare.

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