

THE UNIVERSITY OF WASHINGTON CLINICAL CYCLOTRON A SUMMARY OF CURRENT PARTICLES AND ENERGIES USED IN THERAPY, ISOTOPE PRODUCTION, AND CLINICAL RESEARCH

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Abstract

The University of Washington Clinical Cyclotron (UWCC) is a Scanditronix MC50 compact cyclotron installed in 1983. The cyclotron has now been in operation for 30 years and has been used to treat approximately 3000 patients. Its primary purpose is the production of 50.5 MeV protons used to bombard a beryllium target to produce neutrons for fast neutron therapy. The unique nature of the cyclotron is its variable frequency Rf system, and dual ion source chimneys; it is also capable of producing other particles and energies.

Our facility is now sharing beam time among multiple users:

- Fast neutron radiotherapy.
- Development of a Precision Proton Radiotherapy Platform.
- In vivo verification of precision proton radiotherapy with positron emission tomography.
- Routine production of 211-At.
- Routine production of 117m-Sn.
- Cyclotron based 99m-Tc production.
- Cyclotron based 186-Re production.
- Proton beam extracted into air, demonstrating a visual Bragg peak.
- Neutron hardness testing for electronic subsystems.

These multiple projects show the uniqueness of our hospital based facility and our commitment to therapy, radioisotope research and production, and clinical investigations.

HISTORY

In January 1979, the National Cancer Institute (NCI) published a Request For Proposal (RFP) for a “Clinical Neutron Therapy Program”. The RFP requested medical centers, which met minimum qualifications outlined in the RFP, to respond with proposals to establish Clinical Neutron Therapy Programs utilizing dedicated neutron generators. The RFP outlined three major phases for the project: Acquire a high LET neutron generator to be dedicated to the project, acquire the necessary facilities to house the generator and treatment rooms, and undertake six years of clinical trials according to established protocols.

In April 1979, the University of Washington (UW) submitted a formal proposal to the NCI. In all, eleven medical centers responded to the NCI with proposals.

In September 1979, a contract between the NCI and the UW was awarded to build a Clinical Neutron Therapy

Program. The NCI also awarded contracts to three other medical centers: MD Anderson Cancer Center, University of California at Los Angeles, and The Fox Chase Medical Center.

A RFP for the clinical neutron therapy equipment was issued by the UW in November 1979. Bids were submitted by The Cyclotron Corporation (TCC), Nucletronix/Scanditronix (SCX), and CGR-Medical. All manufacturers proposed a fixed-energy isochronous AVF cyclotron as the core of their neutron therapy system. Proton beam energies ranged from 42–60 MeV depending on manufacturer and machine specifications.

A variable energy option was added so that different dose distributions and comparative neutron beam studies could be performed over a range of energies at one facility. The variable energy option was also seen as giving the cyclotron more flexibility for research purposes. Although not intended for radioisotope production under the NCI contract, the use of the cyclotron for this purpose was envisioned in a separate grant proposal for the production of short-lived and positron-emitting isotopes.

In February 1980, SCX was selected as the vendor. The SCX system was judged to have a number of advantages in magnetic field, Rf, vacuum, extraction, ion source, and beam transport systems. In addition to the technical advantages, the SCX system offered the low bid among the three vendors for the “complete” system.

February 14, 1980, purchase order T-485501 was issued by the UW to SCX for the clinical neutron therapy equipment at a cost of \$4,700,000. The core of the system is a MC50 cyclotron.

Subsequent to execution of the initial fabrication contract, permission was sought and granted by NCI to modify the design of the cyclotron to provide for the addition of deuteron acceleration capability. SCX gave assurance that this modification would not detract from the neutron production capability nor affect its reliability. This late change was very important to the flexibility of the cyclotron and the role it currently plays in research at the UW.

March 1980 – September 1982, Cyclotron and related equipment was fabricated at the SCX facility.

November 1982, Treatment units and beam line components delivered to UW.

April 1983, Cyclotron delivered to the UW.

June 1983, First beam on the therapy target.

October 19, 1984, First patient treated!

PROTONS

(All beam currents quoted are at target location)

50.5 MeV H⁺ 70 μA

Fast Neutron Radiotherapy

The 50.5 MeV Proton beam was the original design purpose of the University of Washington Clinical Cyclotron (UWCC). Impinging on a Beryllium target housed in an isocentric gantry, this is the beam that generates the neutron flux for radiotherapy. Target currents initially ran at 60 μA, but internal cyclotron modifications were made so that target currents now operate at 70 μA.



Figure 1: Patient positioned under the isocentric gantry in the neutron therapy treatment room.

Increased interest in proton beam research has led us to convert our second neutron treatment room to a dedicated proton research room. Current projects include:

50.5 MeV H⁺ 5 pA

Proton Beam Activated PET

Proton therapy is characterized by a sharp falloff in dose at the distal edge of the Bragg peak, which offers therapeutic benefits but also a need for verification of proton range in the patient. Proton-induced radioisotopes were imaged in the murine model, and Monte Carl simulations were used to infer delivered radiation dose from these images. This technology will allow in vivo verification of precision proton radiotherapy for radiobiological studies in mice and may eventually be translated for clinical use [1].

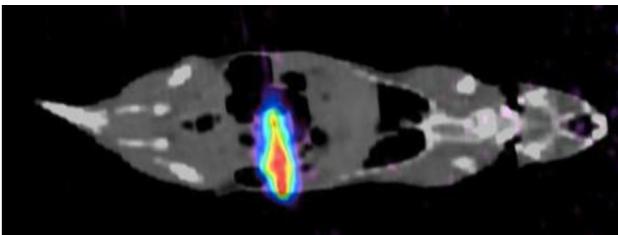


Figure 2: Fused PET/CT of irradiated mouse.

30 and 35 MeV H⁺ 3-5 pA

Precision Proton Radiotherapy Platform (PPRP)

The PPRP will open a new window of study in the biology of proton radiation therapy. The beam is specifically designed to provide a highly collimated beam (2 mm) of low energy protons (30 and 35 MeV), which results in a high-LET Bragg peak at approximately 8 mm deep in tissue. This makes the platform suitable for a variety of in vitro and in vivo experiments. The beam has been fully characterized with an extensive series of measurements coupled with a Monte Carlo simulation, and radiobiology experiments are now underway [2].

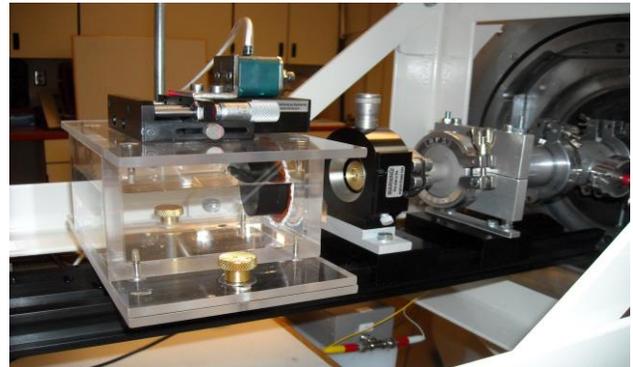


Figure 3: Proton Precision Radiotherapy Platform located in the proton research room.

16, 18, 20, 24 MeV H⁺ 20 μA

Cyclotron Based Tc-99m Production

Tc-99m can be directly produced with the MC50 cyclotron via the Mo-100(p,2n) reaction. A liquid molybdate solution was used in a standard “PET style” target and the irradiated solution was processed with an automated chemistry unit that purified the Tc-99m and recycled the Mo-100. Beam energies from 16 to 24 MeV (emulating typical PET cyclotrons) were used and the Tc-99m produced was used to efficiently label a pharmaceutical sestamibi kit [3].



Figure 4: BruceTech liquid target module attached to the vault research beam line.

6.8 MeV H_2^+ 300 nA

“Show and Tell”

The cyclotron has the capability to produce low energy protons by accelerating H_2^+ molecules. Recently developed and extracted into air, we use this beam as a demonstration of our cyclotron's multiuse capacity.

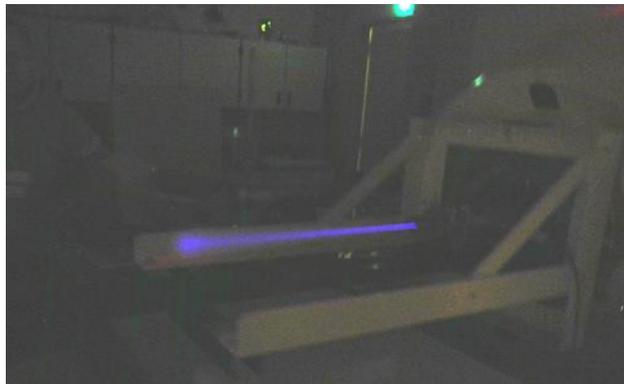


Figure 5: H_2^+ beam extracted into air in the proton research room.

DEUTERONS

(All beam currents quoted are at target location)

18, 20, 22, 24 MeV D^+ 20 μA

Cyclotron Based Rhenium-186 Production

The irradiation conditions and isolation chemistry for cyclotron based production of High Specific Activity Re-186 is being developed. This particular radionuclide is of interest as a medical isotope because chemically, it behaves nearly identically to the well studied and established imaging radionuclide, Tc-99m. The major difference with Re-186 is that in addition to a gamma photon of 137.2 keV (nearly identical energy to the 140.5 keV gamma photon of Tc-99m) it also emits a therapeutic beta particle with 1.1 MeV decay energy, making it a true "theranostic" radionuclide. This would potentially allow clinicians to image and treat patients with the same radionuclide, reducing variability introduced with "matched radionuclide pairs" (e.g. In-111 and Y-90) [4].

ALPHAS

(All beam currents quoted are at target location)

Initially, operation with alpha particles was not part of the cyclotron program. The alpha program started in early 1990 with an unstable 1 μA at 28 MeV. Early development was not very serious, and it remained a side project until late 1997 when a greater demand for Astatine-211 emerged. Modifications to the central region geometry, ion source power supply, ion source slit geometry, cathode button design, and beam-line modifications have contributed to the current status of the Alpha beam. After the addition of a new beam line at the zero degree port of the

switching magnet, a dedicated target station for isotope production with alpha beams became available in 2002. It is designed for solid targets installed at a 10 degree slant.

29 MeV He^{2+} 50 μA

Cyclotron Based Astatine-211 Production

The At-211 produced with the cyclotron is used to study possible new therapies for various forms of cancer (e.g. lymphoma, leukemia, prostate) and for bone marrow ablation. After the At-211 is chemically isolated from the irradiated bismuth target, it is attached to biologically active molecules that can localize to tumor cells. Once localized to a tumor cell, the high energy alpha decay of At-211 is sufficient to cause that cell's death. The research group is working to optimize the attachment of At-211 to biologically active molecules and their delivery to tumor cells with minimal damage to normal cells [5].

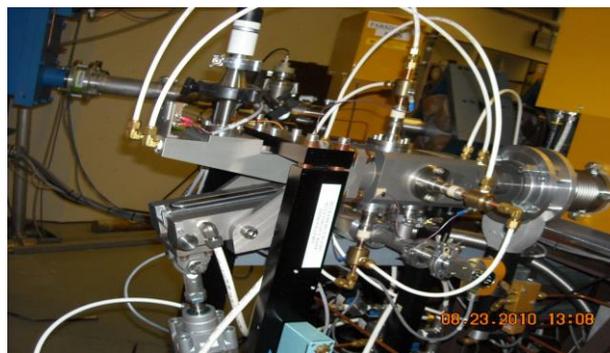


Figure 6: The alpha beam isotope production station.

47.3 MeV He^{2+} 60 μA

Cyclotron Based Tin-117m Production

Cardiovascular diseases represent a leading cause of death and, specifically, a ruptured coronary vulnerable plaque (VP) accounts for about 70% of fatal acute myocardial infarctions and/or sudden death and a high incidence of stroke in unstable carotid plaque. Despite this, there are no available methods that can both image (monitor) and treat these problems. Recently, Sn-117m labeled annexin has found successful application in pre-clinical and clinical studies for this purpose. Biological labeling demands high specific activity (>1000 Ci/g) that can only be produced with accelerators. This isotope was produced at the University of Washington MC50 employing the $Cd-116(\alpha,3n)Sn-117m$ reaction at 47.3 MeV and electroplated Cd-116 targets. Yields of ~150 $\mu Ci/\mu Ah$ and specific activities up to 22,000 Ci/g were routinely achieved. A novel chemical separation/purification method was used to produce the radioisotope which was subsequently chelated to aminobenzyl-DOTA and conjugated to annexin V-128 for these in-vivo studies. Promising initial results of both integrated imaging and therapeutic modalities are emerging [6].



Figure 7: Top – ^{209}Bi target on aluminum backing used in the production of At-211 , Bottom – ^{116}Cd target on copper backing used in the production of Sn-117m .

CONCLUSIONS

After 30 years, the cyclotron facility is running well continuing its mission to treat cancer patients with fast neutron radiotherapy. Important decisions were made early in the design process of the cyclotron. Including a variable frequency Rf system and dual ion source chimneys gave the UWCC many tools and great flexibility in supporting multiple research projects, demonstrating the unique nature of this hospital based facility.

REFERENCES

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