

Brookhaven National Laboratory: Radioisotopes for Medical Imaging and Disease Treatment

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The before and after images are stunning: A prostate cancer patient riddled with metastatic tumors that disappear after just 3 potent treatments (Fig. 1). “Two patients underwent these treatments and they were cured,” said Cathy Cutler, PhD, director of the Medical Isotope Research and Production Program at the U.S. Department of Energy (DOE) Brookhaven National Laboratory (BNL). “Their cancer was gone. *This* is what we want to do—supply this material so that more patients can get this treatment,” she said.

The material is a molecule tagged with ^{225}Ac , a radioactive isotope. When designed to specifically bind with a protein on the surface of cancer cells, the radiolabeled molecule delivers a lethal, localized punch— α particles that kill the cancer with minimal damage to surrounding tissues. ^{225}Ac can only be produced in the large quantities needed to support clinical applications at facilities that have high-energy particle accelerators. “This is why I came to Brookhaven,” Cutler said in a recent talk highlighting her group’s work. “We can make these α emitters, and this is really giving doctors a chance to treat these patients.”

Radiochemistry Redux

BNL and the DOE Isotope Program have a long history of developing radioisotopes for uses in medicine and other applications. These radioactive forms of chemical elements can be used alone or attached to a variety of molecules to track and target disease. Among the notable BNL suc-

cesses are development in the 1950s and 1960s of the $^{99\text{m}}\text{Tc}$ generator and ^{18}F -FDG, respectively. These 2 radiotracers went on to revolutionize medical imaging. As an example, ^{18}F -FDG emits positrons (positively charged cousins of electrons) that can be picked up by a PET scanner. Because rapidly growing cancer cells take up glucose faster than healthy tissue, doctors can use PET and ^{18}F -FDG to detect and monitor the disease. “FDG turned around oncology,” Cutler said. Instead of taking a drug for months and suffering toxic side effects before knowing whether a treatment is working, “patients can be scanned to look at the impact of treatment on tumors within 24 hours, and again over time, to see if the drug is effective—and also if it *stops* working.”

Symbiotic Operations

Although $^{99\text{m}}\text{Tc}$ and ^{18}F -FDG are now widely available in hospital settings and used in millions of scans each year, other isotopes are more difficult to make. They require the kind of high-energy particle accelerator found only at world-class physics labs. “Brookhaven is one of just a few facilities in the DOE Isotope Program that can produce certain critical medical isotopes,” Cutler said.

BNL’s linear accelerator (linac) was designed to feed beams of energetic protons into physics experiments at the Relativistic Heavy Ion Collider (RHIC), where physicists are exploring the properties of the fundamental building blocks of matter and the forces through which they interact. But because the linac produces the protons in pulses, Cutler explained, it can deliver them pulse-by-pulse to different

From the Newsline Editor: The FY 2018 budget submitted to Congress by the White House in February calls for drastic cuts of as much as \$900 million in funding to programs in the Department of Energy (DOE) Office of Science and \$2 billion in other DOE offices. The DOE Office of Science and Brookhaven National Laboratory (BNL) in particular have for decades provided not only new knowledge to advance nuclear medicine but also the radioisotopes that continue to power innovations in the field. As Congress begins the process of analysis, negotiation, and reconciliation on the FY18 budget, we urge members of the nuclear medicine community to share with their legislators articles such as this recent release from BNL, highlighting the essential role that federal science plays in powering both diagnostic and therapeutic applications to benefit millions of patients each year.

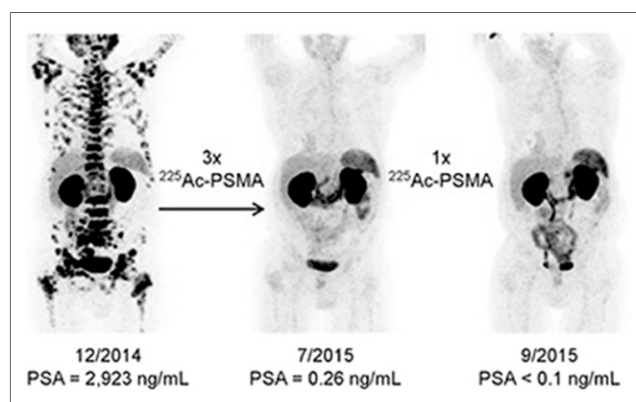


FIGURE 1. Before and after images show how a molecule labeled with ^{225}Ac delivers cell-killing α particles directly to tumors, eradicating metastatic prostate cancer. The BLIP team aims to increase the production of ^{225}Ac so that scientists can conduct large-scale trials to advance clinical use of this lifesaving treatment. Image from Kratochwil et al., *J Nucl Med.* 2016;57:1941–1944.

facilities. Operators in Brookhaven's Collider-Accelerator Department deliver alternating pulses to RHIC and the Brookhaven Linac Isotope Producer (BLIP). "We operate these 2 programs symbiotically at the same time," Cutler said. "We combine our resources to support the running of the linear accelerator; it's cheaper for both programs to share this resource than it would cost if each of us had to use it alone."

Tuning and Targets

BLIP operators aim the precisely controlled beams of energetic protons at small puck-shaped targets. The protons knock subatomic particles from the targets' atoms, transforming them into the desired radioactive elements. "We stack different targets sequentially to make use of the beam's reduced energy as it exits one target and enters the next in line, so we can produce multiple radionuclides at once," Cutler said. Transformed targets undergo further chemical processing to yield a pure product that can be injected into patients or a precursor chemical that can easily be transformed into the desired isotope or tracer on site at a hospital.

"A lot of our work goes into producing these targets," Cutler said. "You would be shocked at all the chemistry, engineering, and physics that goes into designing one of these pucks—to make sure it survives the energy and high current of the beam, gives you the isotope you are interested in with minimal impurities, and allows you to do the chemistry to extract that isotope efficiently."

Cutler recently oversaw installation of a new "beam raster" system designed to maximize the use of target materials and increase radioisotope production. With this upgrade, a series of magnets steers BLIP's energetic particle beam to "paint" the target, rather than depositing all the energy in one spot. This cuts down on the buildup of target-damaging heat, allowing operators to increase beam current and transform more target material into the desired product.

Meeting Increasing Demand

The new raster system and ramped up current helped increase production of one of BLIP's main products, ^{82}Sr , by more than 50% in 2016. ^{82}Sr has a relatively long half-life, allowing it to be transported to hospitals in a form that can generate a short-lived radiotracer, ^{82}Rb , which has greatly improved the precision of cardiac imaging. " ^{82}Rb mimics potassium, which is taken up by muscles, including the heart," Cutler explained. "You can inject ^{82}Rb into a patient in a PET scanner and measure the uptake in heart muscle to precisely pinpoint areas of decreased blood flow when the heart is under stress. Then surgeons can go in and unblock that coronary artery to increase blood flow before the patient has a heart attack. Hundreds of thousands of patients receive this life-saving test because of what we're doing here at Brookhaven."

Driving an 80-Ton Truck into a Tumor

BLIP also produces several isotopes with improved capabilities for detecting cancer, including metastatic tumors, and monitoring response to treatment. But rising to meet the demand for isotopes that have the potential to *cure* cancer may be BLIP's highest calling—and has been a key driver of Cutler's career. "We want to go beyond imaging to therapy," she said, noting the promise of designing molecules to deliver cancer-killing radiation with extreme precision. "This is where I started as a chemist at the University of Missouri—designing molecules that have the right charges, the right size, and the right characteristics that determine where they go in the body so we can use them for imaging and therapy," she said. "If we can target receptors that are overexpressed on tumor cells, we can selectively image these cells. And if there are enough of these receptors expressed, we can deliver radionuclides to those tumor cells very selectively and destroy them."

Radionuclides that emit α particles are among the most promising isotopes, because α particles deliver high energy and traverse very small distances. Targeted delivery of α energy would deposit very high doses—"like driving an 80-ton semi truck into a tumor"—while minimizing damage to surrounding healthy cells, Cutler said. "Our problem isn't that we can't cure cancer; we can ablate the cancer. Our problem is saving the patient. The toxicity of the treatments in many cases is so significant that we can't get the levels in to kill the cancer without actually harming the patient. With α particles, because of the short distance and high impact, they are enabling us to treat these patients with minimal side effects and giving doctors the opportunity to really cure cancer."

Making the Case for a Cure

One experimental treatment Cutler developed using ^{177}Lu while still at the University of Missouri worked favorably in treating neuroendocrine tumors, but did not achieve a cure state. ^{225}Ac , which is more difficult to produce, has shown more promise—as demonstrated by the prostate cancer results mentioned above. Right now, DOE's Oak Ridge National Laboratory (ORNL) makes enough ^{225}Ac to treat about 50 patients each year. But almost 30 times that much is needed to conduct the clinical trials required to prove that such a strategy works before it can move into routine medical practice.

"With the accelerator we have here at Brookhaven, the expertise in radiochemistry, and experience producing isotopes for medical applications, we—together with partners at ORNL and DOE's Los Alamos National Laboratory—are looking to meet this unmet need to get this material out to patients," Cutler said.

BLIP is funded by the DOE Isotope Program, managed by the Office of Science's Nuclear Physics program. RHIC is a DOE Office of Science User Facility.