The Paradox of Using Radionuclides To Treat Disease

Thomas E. Albrecht-Schmitt

Department of Chemistry and Biochemistry, Florida State University, Tallahassee, Florida 32306, United States

New method for the large-scale production of $^{119m}\text{Te}$ and $^{119}\text{Sb}$ may allow for significant expansion in the use of these radionuclides to treat disease.

Approximately 40% of us will hear at some point in our lives that we have cancer, and nearly 25% of those that hear this grave news will perish from this disease. Paradoxically, while most of us immediately associate radiation with diseases such as cancer, since the Nuclear Age began in the closing years of the 19th Century we have known that radioisotopes and radiation can be used to image, diagnose, and treat disease. Recently, Kozimor and co-workers have discovered a new way for the large-scale isolation and production of $^{119}\text{Sb}$ that may enable targeted radiotherapeutic applications (see Figure 1). This radionuclide shows special promise of potentially delivering lethal doses of radiation to targeted diseased cells, reducing side-effects by leaving adjacent healthy tissue unharmed.

As early as 1899, X-rays were applied to successfully treat skin cancer. Shortly thereafter, radium from the Curie’s laboratory found similar uses in the treatment of Lupus and many forms of cancer. Unfortunately, this was rapidly followed by the misuse of radioactive materials for everything from treating virtually every ailment to making glowing clocks, wristwatch faces, and children’s nightlights, and even to intentionally mutating flowering plants to create exotic flowers. Radium became snake oil, and this calamity climaxed with the deaths of the so-called "Radium Girls," who perished from ingesting large amounts of radium while painting watches. Following these events, nuclear medicine continued under many guises for decades thereafter so as not to be lumped in with mistakes of the past, and many books have been written to describe these events both for technical and general audiences. Notably, in the last 20 years, nuclear medicine has become more societally accepted. This shift in perception is perhaps because enough of general public has come to understand that it can be safely applied to ease, and even cure, what ails us.

In particular, alpha radiotherapy has emerged over the past decade as one of the best methods for treating disease and, in cases when it cannot be cured, to improve quality of life by easing chronic pain. The most significant advantage of alpha therapy is that this radioactive decay mode delivers all of its energy (typically in the MeV range) to only a few layers of cells. Thus, the damage can be localized to the area where it is needed, such as the destruction of a tumor with minimal damage to the surrounding tissue. Perhaps the best-known recent victory in this area is the medication Xofigo, whose production was recently acquired by Bayer because of its broad success. Xofigo relies on obtaining $^{223}\text{Ra}$ from the $^{227}\text{Ac}$, and the subsequent delivery of this radionuclide to diseased areas of bones. The purification of $^{223}\text{Ra}$ from $^{227}\text{Ac}$ is shown in Figure 1. This radionuclide shows special promise of potentially delivering lethal doses of radiation to targeted diseased cells, reducing side-effects by leaving adjacent healthy tissue unharmed.

Figure 1. Kozimor and co-workers report on a large-scale production method for $^{119m}\text{Te}$ and $^{119}\text{Sb}$ from proton bombardment of Sb target containing natural abundance antimony. X-ray absorption spectroscopy has been used to understand solution speciation to develop improved separation of the $^{119m}\text{Te}$ parent from the $^{119}\text{Sb}$ daughter. The latter will be used in targeted radiotherapy. Reprinted with permission from ref 2. Copyright 2019 American Chemical Society.
the actinium parent is no small feat and is accomplished by a team at Oak Ridge National Laboratory using robotic hot cell facilities. This treatment can substantially decrease chronic pain caused by metastatic prostate cancer. Many of these patients must make difficult decisions in choosing between unbearable pain or sedation/addictions from opioids. Drugs like Xofogo and Lexidronam, an older medication for treating pain associated with metastatic bone cancer that contains β-emitting $^{153}$Sm, offer alternatives to addictive and debilitating pain killers and significantly improve quality of life and end of life care.

Among successful and emerging radiotherapeutics, $^{119}$Sb has unique potential in targeted therapeutic applications for low energy electron-emitting isotopes (Auger electrons). These electrons have a biological path length of about 10 μm, which is the width of a single cell. To date, developing $^{119}$Sb-based drugs has been slow in comparison to other radionuclides. This is primarily associated with limited access. Typically, $^{119}$Sb is prepared in cyclotron facilities in reasonable quantities (0.1–1 Ci). Production routes often involve irradiation of isotopically enriched $^{119}$Sn targets. Unfortunately, the relatively short $^{119}$Sb half-life ($t_{1/2} = 38.19(22)$ h) and limited production capabilities present a bottleneck for distribution of usable activity for medical experimentation.

The new $^{119}$Sb production and separation method described by Kozimor and co-workers represents an exciting leap forward for targeted radiotherapeutic uses of Auger-emitting isotopes. It offers the opportunity to greatly increase access to $^{119}$Sb beyond the relatively limited number of medical institutions that have colocated $^{119}$Sb production sites. The team demonstrated that large quantities of $^{119}$Sb could be generated by proton irradiation of natural abundance Sb at high energy proton sources, i.e., the Isotope Production Facility (IPF) at the Los Alamos Neutron Science Center (LANSCE) at Los Alamos National Laboratory (LANL) and the Brookhaven Linac Isotope Producer (BLIP) at Brookhaven National Laboratory. The LANL team also developed a purified method that provides large quantities of $^{119}$Sb for external use.

One particularly creative aspect of this research campaign is that Kozimor and co-workers adopted an unconventional approach for their radiochemical separation method. They made use of X-ray absorption spectroscopy (XAS) at the Stanford Synchrotron Lightsource (SSRL) to guide efforts to remove Te from Sb. This is apparently the first-time synchrotron spectroscopy has been applied to this area of research. The spectroscopic results were valuable and informed researchers on differences between Te and Sb in aqueous solutions and on solid-state chromatographic supports. The information was used to developed a Te/Sb separation procedure that (1) was compatible with large natSb (25 g) targets, (2) accounted for safety concerns associated with generating large quantities of $^{119m}$Te/$^{119}$Sb, and (3) could be rapidly (∼36 h separation) carried out using remote handling techniques within hot cells.

One of the most interesting discoveries made using this technique is that the Te(IV) was reduced to Te(0) on contact with the column resin. This allowed for more rapid and cleaner separation of the $^{119}$Sb daughter from the $^{119m}$Te parent than was previously possible because the tellurium gets held up on the top of the column as the result of the reduction. The relatively long lifetime of $^{119m}$Te ($t_{1/2} = 4.70(4)$ days) makes this the likely source of $^{119}$Sb that will be transported to hospitals. This is same procedure used for decades to milk $^{99m}$Tc from $^{99}$Mo sources for use as an imaging agent. The potential impact of these results is significant, offering an opportunity to significantly expand efforts to use $^{119}$Sb in targeted Auger therapies to treat disease.

The relatively long lifetime of $^{119m}$Te ($t_{1/2} = 4.70(4)$ days) makes this the likely source of $^{119}$Sb that will be transported to hospitals.

Author Information
E-mail: albrecht-schmitt@chem.fsu.edu.

ORCID ●

Thomas E. Albrecht-Schmitt: 0000-0002-2989-3311

REFERENCES

(1) Brenner, H. Long-term survival rates of cancer patients achieved by the end of the 20th century: a period analysis. Lancet 2002, 360, 1131–1135.

(2) Bennett, K. T.; Bone, S. E.; Akin, A. C.; Birnbaum, E. R.; Blake, A. V.; Brugh, M.; Daly, S. R.; Engle, J. W.; Fassbender, M. E.; Ferrier, M. G.; Kozimor, S. A.; Lilley, L. M.; Martinez, C. A.; Mocko, V.; Nortier, F. M.; Stein, B. W.; Thiemann, S. L.; Vermeulen, C. Large-Scale Production of $^{119m}$Te and $^{119}$Sb for Radiopharmaceutical Applications. ACS Cental Sci. 2019, in press. DOI: 10.1021/acscentsci.8b00869

(3) Francis, J. H. Marie Curie: Radiation as a Medium That Can Cure. Foundations of Ophthalmology 2017, 145–155.

(4) Curry, H. A. Evolution Made to Order: Plant Breeding and Technological Innovation in Twentieth-Century America; University of Chicago Press: Chicago, 2016.

(5) Martland, H. S. The Occurrence of Malignancy in Radio-Active Persons: A General Review of Data Gathered in the Study of the Radium Dial Painters, with Special Reference to the Occurrence of Osteogenic Sarcoma and the Inter Relationship of Certain Blood Diseases. Cancer Res. 1931, 15, 2435–2516.

(6) Sgouros, G. Alpha-particles for targeted therapy. Adv. Drug Delivery Rev. 2008, 60, 1402–1406.

DOI: 10.1021/acscentsci.9b00139
ACS Cent. Sci. 2019, 5, 383–385
(7) Norum, J.; Traasdahl, E. R.; Totth, A.; Nieder, C.; Olsen, J. A. Health economics and Radium-223 (Xofigo®) in the treatment of metastatic Castration-Resistant Prostate Cancer (mCRPC): A case history and a systematic review of the literature. *Global J. Health Sci.* 2015, 8, 1−9.

(8) Serafini, A. N.; Houston, S. J.; Resche, I.; Quick, D. P.; Grund, F. M.; Ell, P. J.; Bertrand, A.; Ahmann, F. R.; Orihuela, E.; Reid, R. H.; Lerski, R. A. Palliation of pain associated with metastatic bone cancer using samarium-153 lexidronam: a double-blind placebo-controlled clinical trial. *J. Clin. Oncol.* 1998, 16, 1574−1581.

(9) Thisgaard, H.; Jensen, M. Production of the Auger emitter $^{119}$Sb for targeted radionuclide therapy using a small PET-cyclotron. *Appl. Radiat. Isot.* 2009, 67, 34−38.