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^{225}Ac/^{213}Bi Generator Based on Millifluidics Controlled Electrodeposition

Los Alamos LDRD Report

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ABSTRACT

Radioisotopes provide both diagnostic tools and therapeutic treatments for cancer and other diseases. In the US, millions of radioisotope doses are given to patients per year. Radiopharmaceutical generators are widely used to provide such short-lived medical radioisotopes in a clinical setting. These generators work by exploiting chemical differences in a parent/daughter isotope relationship. Actinium-225 (half-life 10 d) is used to provide clinically useful amounts of daughter isotopes ^{213}Bi (46 m). An integrated millifluidic ^{225}Ac/^{213}Bi radiopharmaceutical generator device was engineered to produce ^{213}Bi labeled biomolecules. Using recent LANL successes in additive manufacturing of small-scale fluidic devices, a disposable device was developed that integrates three steps for the production of ^{213}Bi labeled antibodies: 1) ^{213}Bi separation from ^{225}Ac parent, 2) ^{213}Bi antibody labeling, and 3) purification of the labelled antibody.

TECHNICAL GOALS

Radioisotopes provide both diagnostic tools and therapeutic treatments for cancer and other diseases [1]. In the US, millions of radiopharmaceutical doses are given per year. Targeted Alpha Therapy (TAT) is an emerging field for the treatment of cancer and other diseases. [2-6] Alpha emitting radionuclides are attached to disease targeting antibodies and deliver a lethal dose of alpha radiation to targeted cells within ~10 cell lengths. This results in a treatment with minimal impact on healthy tissue. Radiopharmaceutical generators are widely used in modern medicine. These generators work by exploiting chemical differences in a parent/daughter isotope relationship, and a longer-lived parent isotope, such as ^{225}Ac, serves as a source of a clinically useful shorter-lived daughter, such as ^{213}Bi, a promising alpha emitter for TAT. [7-14]

Commercial supplies of ^{225}Ac/^{213}Bi are currently under development [15]. Full-scale ^{225}Ac production will enable several hundred therapeutic doses a month. Current ^{225}Ac/^{213}Bi generators, however, cannot provide desirable therapeutic quantities of ^{213}Bi because they rely on ion exchange resins [16], which physically degrade in high radiation fields caused by the immobilized ^{225}Ac parent activity. We thus developed an entirely new generator design approach based on

electroplating to separate ^{213}Bi from the ^{225}Ac parent. Electroplating eliminates immobilization on a polymer skeleton; an electroplating based generator is far more radiation robust and can carry more parent radioactivity, which, in turn, will result in more therapeutic ^{213}Bi batch doses.

SCIENTIFIC APPROACH AND RESULTS

Approach- The approach to a higher ^{213}Bi elution yield is the design of an electroplating mechanism to separate daughter from parent isotope and incorporate such a generator into a small footprint additive manufactured (AM) fluidic system to enable rapid antibody radiolabeling and purification. Bismuth has been reported to spontaneously plate onto nickel metal substrates with greater than 75% plating in 30s at 75°C [17, 18]; this phenomenon is the basis for our generator system. Developing a new generator methodology requires a new form factor for clinical use. Micro- or millifluidics come into consideration. Additive manufacturing provides the ability for iterative design through rapid prototyping, i.e., design prototypes can be rapidly tested and iterated until an optimal design is achieved [19]. The AM technique we used for our radionuclide generator was stereolithography [20] due to the main requirement of having modules watertight.

Results- The overall layout of the millifluidic system developed in this project consists of three different modules; each module has a unique design to fulfill the chemical functionality of the ^{225}Ac/^{213}Bi generator: 1) ^{213}Bi Separation from ^{225}Ac, 2) Bi-DTPA biomolecule labeling, 3) Size Separation. Stereolithography allowed prototypes to be produced in a matter of days, increasing design flexibility. Syringe pumps, valves and a custom control software are used to move solutions through each module. The electrochemical generator was successfully designed using nickel and titanium electrodes. Initial benchtop studies resulted in ^{213}Bi plating yield between 70 and 98 %, with no detectable amount of ^{225}Ac, achieved on Ni plates after 15 minutes. Recovery of ^{213}Bi from the nickel plate was obtained with the application of an outside potential of 2.0 V for 10 minutes in 0.1 M citric acid media of pH 4.0 to 5.5; a recovery yield between 60 and 94 % was achieved. Conditions for antibody labeling were achieved and intial tests were performed. Further work is needed to optimize the labeling. The form factor of the modular system could be optimized to house all modules in one compound apparatus (Fig. 1, Fig. 2).

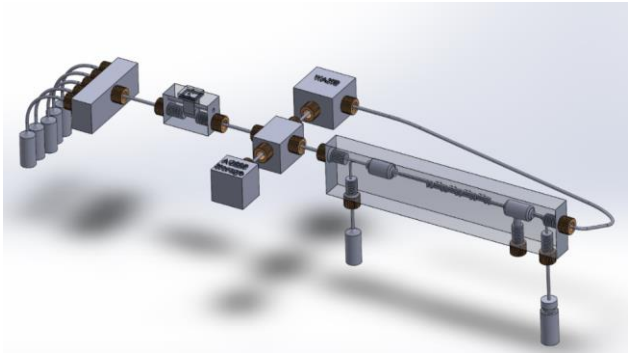

Fig 1: (above) Conceptual 3D rendering of the millifluidic system developed.

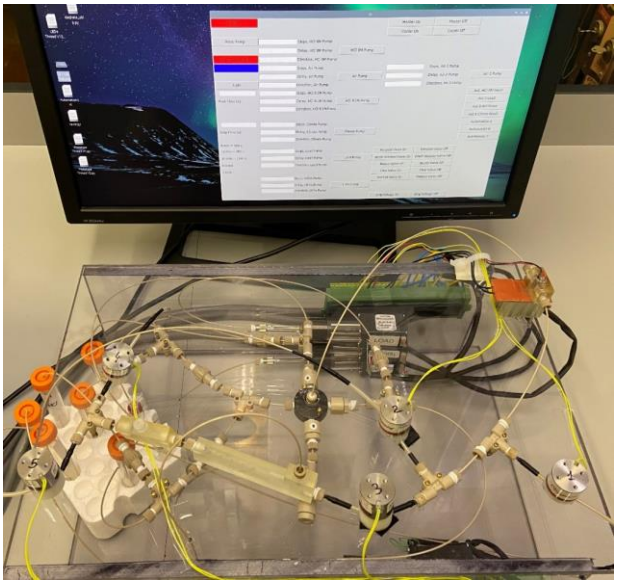

Fig 2: (side) Implementation of the milliflidic ^{225}Ac/ ^{213}Bi generator, Bi-DTPA labeling, and size separation. A custom control interface was developed to transport fluids.

MISSION AGILITY

Results of this project are directly related to the mission of the LANL Isotope Product and the US DOE Isotope Program. More specifically, a new $^{225}Ac/^{213}Bi$ generator concept furthers the utility of TAT isotope ^{225}Ac. The US DOE Isotope Program currently oversees a tri-Lab collaborative effort between LANL, BNL and ORNL with the goal of developing ^{225}Ac bulk production capability. A new, high batch dose $^{225}Ac/^{213}Bi$ generator will synergistically support this effort through a widened application field and enlarged base of potential customers.

TECHNICAL VITALITY

The developed apparatus introduces a novel radionuclide generator. As opposed to state-of-the-art systems that rely on radionuclide sorption on resin or inorganic sorption support, this system uses electroplating as the primary parent/daughter separation mechanism. The radioactivity is deposited on a metal substrate, which results in higher radiation stability. This, in turn, renders the generator more durable and reliable. The electroplating approach can serve as a basis for other nuclide pair generator systems, opening a new direction of radiopharmaceutical generator design.

WORKFORCE DEVELOPMENT

Overall, workforce development was an integral goal and part of this project both in terms of mentoring junior investigators and gaining research experience as scientists. A small team of mostly junior investigators carried out this joined LANL- University of Utah (UU) project: LANL postdoc (1) students (4; of which 3 LANL, 1 UU), technician (1), LANL scientists (2), UU faculty (1). During the course of the project, one individual advanced from Technician to R&D Engineer. A student, who had started out as a post-bachelor student assistant, was hired on as a full-time LANL employee. An undergrad student was hired full time by a different LANL organization, and a radiochemistry postdoc could be hired on by LANL to work on this project.

CONCLUSION

A small footprint, disposable millifluidic device was designed that delivers ^{213}Bi labeled antibodies for clinical application. The device was produced via AM using Form Labs high temperature resin that provides chemical and radiological compatibility. Fluidic channels were printed down to ~1mm diameter. A custom control system is used to transport fluids through each of the core piece of the device which consists of an $^{225}Ac/^{213}Bi$ electrochemical generator for which conditions were defined to provide $^{225}Ac/^{213}Bi$ separation yields of > 90% and ^{213}Bi recovery yields of up to 94%. The device houses three chemistry modules: 1) $^{225}Ac/^{213}Bi$ generator, 2) ^{213}Bi antibody labeling, and 3) final ^{213}Bi antibody purification. The project increased this technology from a TRL of 3, proof of concept, to a TRL of 6, system / subsystem valiation.

ACRONYMS AND DEFINITIONS

DTPA	Diethylenetriamine pentaacetate
LANL	Los Alamos National Laboratory
BNL	Brookhaven National Laboratory
ORNL	Oak Ridge National Laboratory
UU	University of Utah
AM	Additive Manufacturing
TAT	Targeted Alpha Therapy

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