Article

Development of ^{225}Ac Production from Low Isotopic Dilution ^{229}Th

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ABSTRACT: The promise of ^{225}Ac targeted alpha therapies has been on the horizon for the last two decades. TerraPower Isotopes are uniquely suited to produce clinically relevant quantities of ^{225}Ac through the decay of ^{229}Th. Herein, a rapid processing scheme to isolate radionuclidic and radioisotopically pure ^{225}Ac in good yield (98%) produced from ^{229}Th that contains significant quantities of ^{228}Th activity is described. The characterization of each step of the process is presented along with the detailed characterization of the resulting ^{225}Ac isotopic starting material that will support the cancer research and development efforts.
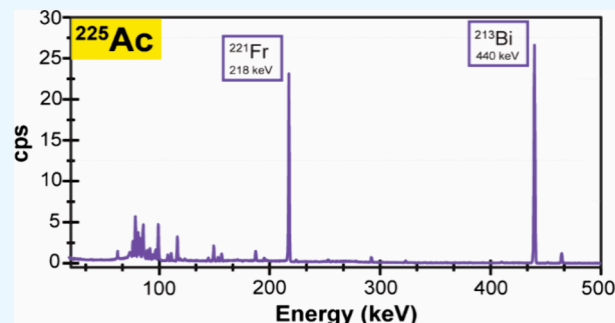
INTRODUCTION

Targeted alpha therapy (TAT) is a promising new avenue for conventional cancer therapies (e.g., γ-irradiation or chemotherapeutics) and has seen preliminary investigation for pathogenic diseases.[1−4] TAT typically couples an α-emitting radionuclide via a chelator (a major point of development) to a cell surface targeting vector, such as an antibody or peptide.[3−9] In biological tissues, α-particles only travel a few cellular diameters (<100 μm). Coupled with a high linear energy transfer (10^2 MeV/μm), TAT can selectively destroy diseased cells with fewer adverse effects than conventional chemotherapies. Of the candidate α-emitters suitable for TAT, ^{225}Ac *and its daughter* ^{213}Bi *present the most promise.*[10−17]

^{225}Ac, in the neptunium decay series, has a half-life of 9.920 days and primarily proceeds through six daughter isotopes, where the most likely decay path produces four α- and two β-particles (Figure 1).[18,19] Early-stage clinical trials and compassionate use cases of ^{225}Ac therapeutics have shown great promise, such as ^{225}Ac-PSMA-617 for prostate cancer or ^{225}Ac-HuM195 mAb for acute myeloid leukemia, among others.[20,21] However, many clinical trials have been stunted by the limited supply of ^{225}Ac, and there have been no FDA phase III trials to date. There are few legacy sources of the parent ^{233}U, that are the most direct and cleanest (in terms of radionuclidic/isotopic purity) route to obtain ^{225}Ac via ^{229}Th ($t_{1/2}$ = 7932 y). Alternatives, such as ^{232}Th spallation via ^{232}Th(p,x)^{225}Ac led by the U.S. Department of Energy (DOE) and more commercially accessible cyclotron methods via ^{226}Ra(p,2n) have been investigated with good production yields.[22−24] However, each suffers from its own challenges, e.g., the ^{227}Ac coproduced from spallation and the need for ^{226}Ra targets in cyclotron methods.[25]
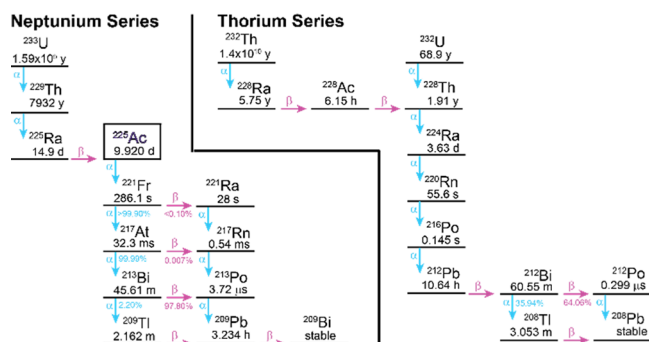
Figure 1. Decay chains of the neptunium series containing ^{225}Ac and thorium series containing ^{228}Th.[18] Half-lives are provided from the NuDAT database.[19] Figure adapted in part with permission from ref 18. Copyright 2005, Elsevier.

To date, there are only three sources of ^{225}Ac used in clinical trials across the Americas, Europe, and Australia: (1) the Joint Research Center (JRC) of the European Commission (Karlsruhe, DE) supplies ~350 mCi annually, (2) Oak Ridge National Laboratory (DOE, ORNL) (TN, USA) supplies ~600 mCi annually, and (3) the Institute of Physics and Power Engineering (IPPE) (Obninsk, RU) supplies an equivalent amount.[18,26−29] All of the ^{225}Ac used in humans thus far has

been sourced from [229]Th. The current world supply cannot meet the demand for large clinical trials or widespread implementation in hospitals. TerraPower Isotopes (TPI) is working with Isotek Systems LLC, a U.S. federal cleanup contractor at ORNL, to recycle [229]Th that would otherwise be irretrievably lost when its radiological parent, [233]U, (that is handled as a waste product) is converted into a disposal-ready form. TPI has access to [229]Th, which is not isotopically diluted with [232]Th relative to other sources. The isotopic composition of most of the TPI [229]Th available includes [232]Th and appreciable quantities of [228]Th with an average composition of 1000:1 molar ratio of [229]Th/[228]Th (Figure 1). This poses technical challenges with radiological containment/shielding: from the equilibrium quantity of [220]Rn gas (the naturally occurring isotope) to the significant dose contribution of the [208]Tl (E_γ = 2614 keV, I_γ = 99.75%).[19] Furthermore, TPI seeks to meet world demand by setting up multiple [229]Th-containing generators in parallel, which necessitated the development of a streamlined processing scheme.

Described herein are the separation scheme and analytical characterization for TPI's production of [225]Ac (Figure 2).
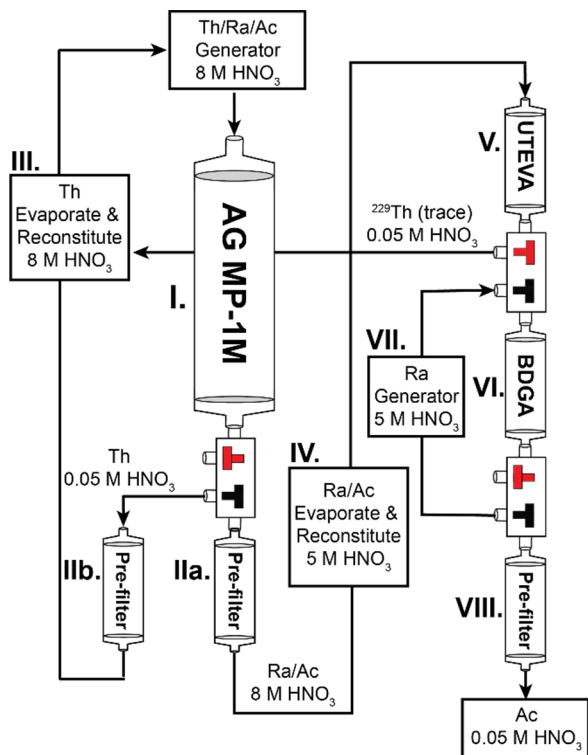
Figure 2. Full processing scheme for isolating [225]Ac. There are three main separation steps: I. Th/Ra/Ac. Separation on AG MP-1M; V. Separation of residual Th on UTEVA; VI. Separation of Ra/Ac on BDGA. No matrix exchanges are included in this process, evaporations are included to manage process volumes, and prefilter columns are included to reduce organic impurities.

Building on the legacy of the DOE, JRC, and Canadian Nuclear Laboratories [225]Ac processing, the main separation is achieved on anion exchange resin.[18,26−31] In step (I), Th is retained on the anion exchange resin AG MP-1M (primarily) as the putative $[\text{Th(NO}_3)_6]^{2-}$ anion in 8 M HNO_3. Ra^{II} and Ac^{III} do not adsorb under this condition and pass through a prefilter resin (IIa) in the load and wash fractions. Th^{IV} is recovered by elution with 0.05 M HNO_3 passing through a

second prefilter resin (IIb). Explicit prefilter steps are added to reduce organics and coloration associated with the AGMP-1M. Owing to the process volume, the Ac^{III} and Ra^{II} fractions are then brought to a soft dryness and reconstituted in 5 M HNO_3 (IV). The Ac^{III}/Ra^{II} separation is achieved through an initial UTEVA (V) column to remove any residual Th^{IV}. The UTEVA load and wash fractions are passed directly onto a DGA-branched (BDGA) column (VI). Ac^{III} is retained on BDGA in 5 M HNO_3 where the Ra^{II} is eluted through in the load and wash fractions and reserved for later Ac^{III} in-growth and elution (VII). Ac^{III} is eluted from the BDGA in 0.05 M HNO_3 and through a prefilter resin (VIII) to remove any residual organics. Affinity constants for these resins are well reported.[32−34] Experimental details, such as the resin bed and mobile phase volumes, can be found in the Experimental Section. The process reported herein was conducted on [229]Th cows of ~1 μCi (37 kBq). However, in full production, this process will be scaled to 100s of mCi of [225]Ac.

The general operational flexibility of this process arising from both the chemical and mechanical components distinguishes it from other reports.[24−27] Every separation is achieved in HNO_3, and this lowers processing time associated with volume reductions, matrix exchanges, and resuspensions. Optimization/minimization of all process conditions resin BV without the use of polishing columns cuts hours to days from the process time (on scale). Running the UTEVA/(B)DGA as a column stack in the process minimizes transfer losses. Adding prefilter resin throughout removes color (organics) associated with resin decomposition. The process is equipped with several bypass valves to ameliorate backpressure issues and enable flow to be reversed across all major separation steps. Key metrics for success of this separation scheme include (1) no [228/229]Th^{IV} detectable in the Ra^{II} fractions going into the Ra^{II} generator (VII), (2) neither Th nor Ra detected in the [225]Ac BDGA fractions (VIII), and (3) good yield of [225]Ac through the process.

RESULTS AND DISCUSSION

The purity of all fractions was tracked throughout the process by HPGe measurements. Daughters from the [228]Th present an opportunity for process verification through daughters such as [224]Ra··· →···[212]Pb. Namely, if there is a substantial quantity of either [228]Th or [224]Ra, the presence of [212]Pb ($t_{1/2}$ = 10.6 h, E_γ = 238 keV, I_γ = 43.3%) is detected. The main γ-lines used for [225]Ac quantitation include daughters with amenable half-lives and high branching ratios [213]Bi ($t_{1/2}$ = 45.61 m, E_γ = 440 keV, I_γ = 26.1%) and [221]Fr ($t_{1/2}$ = 4.9 m, E_γ = 218 keV, I_γ = 11.6%). Secular equilibrium is achieved in >6 h, such that the activities of these daughters are approximately equal to the [225]Ac activity. Example summary tables with measured activities of [221]Fr, [213]Bi, [229]Th, and [225]Ra are in Tables S1−S5.

A summary of the most significant fractions (with the largest activities) is found in Figure 3. These normalized γ-spectra were measured 1 day post-elution to ensure (1) [224]Ra daughters would be detectable if present in the sample and (2) secular equilibrium has been reached with the [221]Fr and [213]Bi. The starting [229]Th stock that was processed is ~1 μCi (37 kBq). [225]Ra follows the expected path coming through the AG MP-1M load and wash, where [229]Th and [228]Th daughters are detected only in the elution step. [225]Ra (40 keV) is detected in all of the expected fractions including the BDGA load and wash fractions (that form IV in Figure 2) and are free
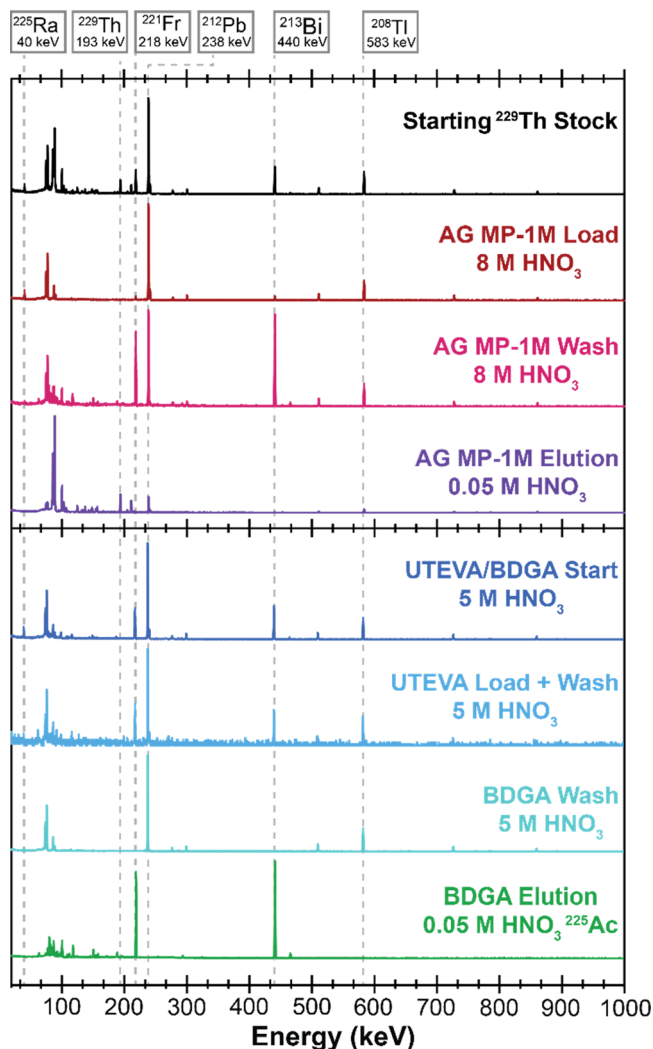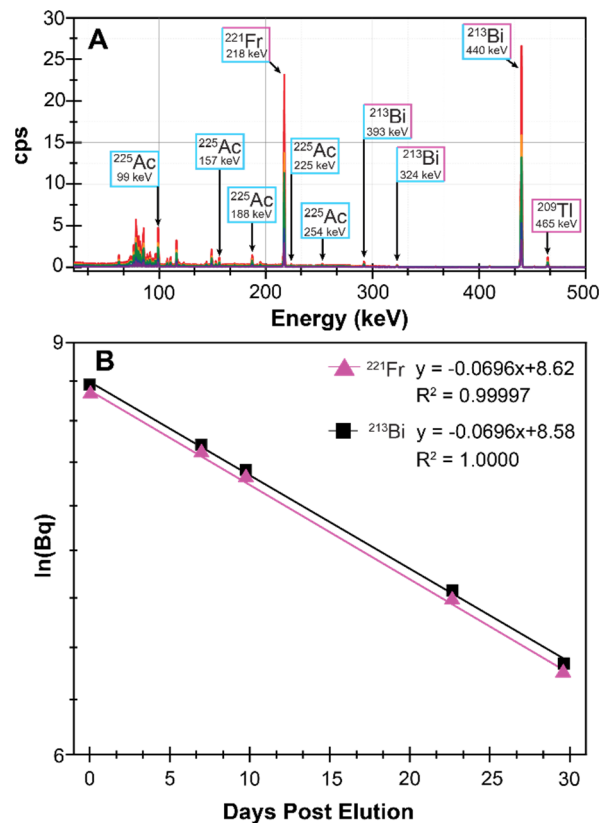
Figure 3. HPGe γ-spectra for each step of the process post prefilter, the intensities are in counts per second (cps) normalized to the most intense peak in each spectrum. Important γ-lines associated with the purity of the process are annotated with gray lines.

Figure 4. (A) γ-spectra of the BDGA elution fraction containing ^{225}A were measured 0 days (red), 7 days (orange), 10 days (green), 23 days (blue), and 30 days (purple) post elution. Spectral assignments are provided for the major ^{225}Ac and daughter peaks, pure α (blue), pure β (pink), and mixed α/β (pink/blue). (B) Semilog plot of the corresponding activities (Bq) for the major ^{221}Fr (pink triangles) and ^{213}Bi (black squares). The slopes of the linear regressions represent the λ value for ^{225}Ac found in eqs 1 and 2.

from ^{229}Th, meeting the first requirement metric. More critically, the ^{212}Pb (238 keV) and ^{208}Tl (583 keV) lines are detected in all fractions *except* the elution of BDGA containing the ^{225}Ac. This meets the second metric: product ^{225}Ac being free from other radiometal impurities.

The purity of ^{225}Ac was assessed in Figure 4A where a single γ-spectroscopy sample was analyzed over 30 days. Only peaks associated with ^{225}Ac, and its daughters, were observed and annotated accordingly. Further, tracking the ^{221}Fr and ^{213}Bi peaks used for quantitation confirmed the radiochemical purity of the product material via the semilog plot in Figure 4B that was fit using a natural logarithm form of the first-order solution to a first-order Bateman equation (eq 1), representing ^{225}Ac exponential decay, where A_t is the activity at the time of the measurement in Bq, A_0 is the starting activity of the parent in Bq, and λ is described in eq 2, where $t_{1/2}$ is the half-life of the parent:

$$\ln(A_t) = \ln(A_0) - \lambda t \tag{1}$$

$$\lambda = \frac{\ln(2)}{t_{1/2}} \tag{2}$$

This yielded an excellent agreement between the calculated $t_{1/2}$ for ^{225}Ac = 9.959 d and the reported half-life of 9.92 d.[16] These were calculated using the slopes from the linear fits (Figure 4B) as λ (0.0696 for both the ^{221}Fr and ^{213}Bi fits with $R^2 \sim 1$) using eq 2. This provides confidence and credibility that the ^{225}Ac obtained through this process on the μCi scale is free from ^{229}Th/^{224}Ra daughters, essential for fitness in clinical use. The purity of the resulting ^{225}Ac was covalidated by α-spectrometry (Figure S2, bottom) that supports the findings in the γ-spec. The α-spectra of our purified ^{225}Ac was compared against the parent $^{228/229}$Th isotopes, no peaks were observed that would indicate parent isotopes were present in the product.

^{225}Ac is an excellent isotope for the treatment of many cancer types, of broad interest to the TAT community. TPI has developed a streamlined, highly scalable production route described herein. ^{225}Ac can be obtained with high radionuclidic purity, free from ^{229}Th. The process met key metrics outlined in the introduction including (1) no Th^{IV} was detectable in the Ra^{II} fractions going into the Ra^{II} generator (Figure 2, VII), (2) no Th^{IV} nor Ra^{II} was detected in the ^{225}Ac^{III} BDGA fractions (Figure 2, VIII), and (3) the process had an excellent process yield of 98% ± 5%. This work is based on the ORNL and JRC Karlsruhe processes. However, the following are key deviations that produced excellent product purity in fewer steps. The main Th/Ra/Ac separation on AG MP-1M is reliant on an

oversized column relative to the amount of Th being loaded, such that no Th was observed in the elution of the UTEVA column. This removes the need for multiple stages of anion exchange; instead a highly efficient, small UTEVA column "polishes" any residual Th[IV]. There are no time-consuming matrix exchanges with limited volume reductions in the process. We optimized the process in nitric acid across all steps that removed the need to conduct multiple evaporations with either HCl and/or HNO_3. The [229]Th cows can be readily readjusted from 0.05 M HNO_3 to 8 M HNO_3 for the next process evolution again, dramatically reducing the process time. Finally, this process is highly scalable and can be conducted in less than a week processing time.

■ EXPERIMENTAL SECTION

General Considerations. CAUTION! [232]Th, [229]Th, and [228]Th are radioactive isotopes that, without proper handling, present a serious threat to human health owing to their α-, β-, and γ-radiation. The work presented herein was conducted in facilities specially equipped to handle these materials. Parent [233]U material was provided by the United States DOE and initial purification of the [229]Th from the parent material was performed by Isotek Systems, LLC. All solutions were prepared with ultrapure water (18.2 MΩ/cm resistivity; Millipore Super-Q Plus Water Purification System), and all the experiments were conducted at room temperature; chemicals were of analytical reagent grade. HNO_3 was Ultratrace, 67−70% from Spectrum Chemicals. Anion exchange resin was obtained from BioRad (AG MP-1M, 50−100 mesh, Cl⁻ form) and was suspended in water, and the fines were decanted 10 times prior to use. Extraction resins were purchased from Eichrom and included UTEVA (Uranium und TEtraValent Actinides, denoting a diamyl, amylphosphonate resin; 100−150 mesh) prepacked 2 mL gravity columns, BDGA (50−100 mesh) prepacked 2 mL cartridges, and prefilter resin (100−150 μm). All columns were purchased from BGB Analytik and made from polypropylene; frits were made from polyethylene. Fittings and stopcocks were obtained from Qosina and made from ethylene tetrafluoroethylene and polypropylene, respectively. Solutions were pumped using a Watson-Marlow 120 cased pump fit with Marprene Thermoplastic elastomer (TPE) tubing (0.5 mm ID, 1.6 mm wall thickness).

AG MP-1M Separation. Prewashed AG MP-1M resin 50−100 mesh (3 mL) was loaded into a BGB column (12.8 × 60 mm) and fit with a 16−20 μm frit. The resin was conditioned at 100 mL/h with 3 × 3 bed volumes (BV) of the following: 8 M HNO_3, H_2O, 8 M HNO_3. Two prefilter columns were prepared by charging a BGB column (12.8 mm × 60 mm) and fit with a 16−20 μm frit with 3 mL of dry resin. Each column was conditioned the same as AG MP-1M. [229]Th (~1 μCi) at secular equilibrium was loaded at 60 mL/h and fractions were collected in 2 BV of each wash in 8 M HNO_3 or elution with 0.05 M HNO_3 matrix. The activity of [229]Th in the resulting fractions was quantified by employing γ-spectroscopy. The load and wash fractions were combined in a 100 mL Teflon beaker and brought to a soft dryness by heating.

UTEVA/BDGA Separations. UTEVA 100−150 μm prepacked 2 mL gravity feed column was conditioned with 3 × 3 BV of the following: H_2O, 5 M HNO_3, H_2O, and 5 M HNO_3. The BDGA 50−100 μm 2 mL prepacked cartridge and prefilter column (prepared the same as above) were

conditioned with the same matrix exchanges; however, the solutions were pumped at 40 mL/h. The material isolated from the AG MP-1M resulted in no visible residue, so the beaker was rinsed with 5 × 1 mL of 5 M HNO_3 into the gravity feed UTEVA column. The resin was washed further with 3 × 3 BV of 5 M HNO_3—load and wash fractions were sampled for γ-spectroscopy and immediately pumped onto the BDGA column. Fractions were collected across 3 wash steps in 5 M HNO_3 (to remove the Ra[II]) and 4 elution steps in 0.05 M HNO_3 (to isolate the [225]Ac). Each fraction was sampled for γ-spectroscopy.

Gamma Spectroscopy. Gamma characterization was performed using an Ortec Ametek system comprised of two coaxial HPGe detectors model GEM80P4-95, coupled with DSpec jr 2.0 multichannel analyzers, and operated under GammaVision spectrum analysis software version 8. The gamma system was calibrated using the common multinuclide standard from Eckert and Ziegler (product number 8504). The standard consists of [241]Am, [109]Cd, [57]Co, [139]Ce, [203]Hg, [113]Sn, ^{137}Cs, [44]Mn, [88]Y, [65]Zn, and [60]Co. Samples were counted for 600 or 3600 s depending on the activity and the dead time of the detector was kept below 10%. MDAs for each isotope are listed in Tables S1−S5. The energy calibration used for all gamma spectra followed the polynomial in eq 3. The full calibration report may be found in Figure S1 and Table S6:

$$E = -2.0491E^{-8*}C^2 + 0.322^*C + 0.193188 \qquad (3)$$

Alpha Spectroscopy. Alpha characterization samples were prepared by direct deposition on a 19 mm stainless steel disc brought to dryness on a hot plate. Product [225]Ac was compared to standards of [228]Th and [229]Th purchased from Eckert and Ziegler. Measurements were performed with an Ortec AMETEK/ORTEC Inc., with 450 mm^2 ULTRA-AS ion-implanted silicon detectors, and spectra were analyzed using AlphaVision software. Energy and efficiency calibration was performed by using a certified standard of mix alpha emitters of Am-241, Pu-239, Cm-244, and Np-237 from Eckert and Ziegler. The efficiency at the counted shelf was determined to be equal to 10.1 ± 0.18% over a gain of 4.878 ± 0.064 keV/Ch. Resultant α-spectra can be found in Figure S2.

■ ASSOCIATED CONTENT

ⓈⒾ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c01769.

Activities of [221]Fr, [213]Bi, and [229]Th in μCi, and [225]Ra in net cps, γ-spec data, calibration files, and the resulting α-spec (PDF)

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Notes

The authors declare no competing financial interest.

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