Development of Diagnostic Procedures Based on Alpha Spectroscopy for the Investigation of Radiopharmaceuticals *In Vitro*

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Background

Radiopharmaceuticals have been used since the 1940s and have widespread therapeutic applications. In the past two decades, targeted cancer treatments involving radiopharmaceuticals have gained in popularity. Targeted Alpha Therapy (TAT) uses alpha emitting radionuclides, such as Ac-225, coupled to tumor selective carrier molecules to target the affected cells at a close range.

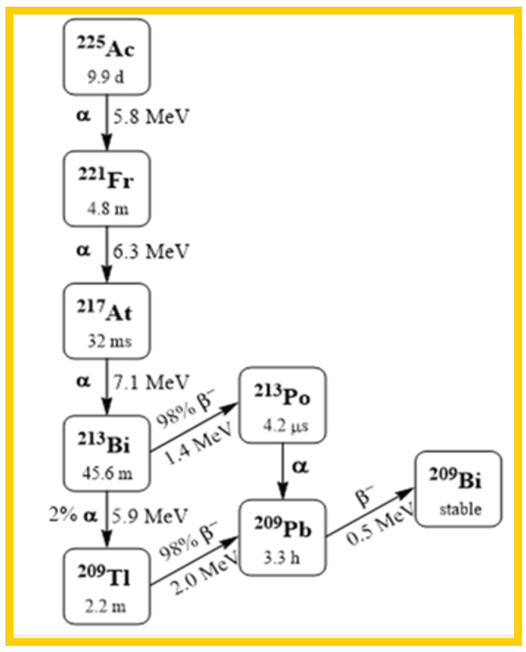


Fig.1: Decay chain of Ac-225.

Motivation

Alpha detectors are typically operated under vacuum due to the short range of alpha particles in air, making them unsuitable to use for biological samples. The goal of this project is to design an alpha detector that is made specifically to measure low activity biological samples in air. This would make it possible to better understand the biodistribution of the daughter products in TAT. Ac-225 emits 4 alpha particles through its decay chain to stable Bi-209, and the leaking of these particles from the target cell may have adverse effects to the body. It Is often assumed that the daughter products are retained in the cell overtime. This assumption can be tested by evaluating the distribution of daughter products *in vitro* using alpha spectroscopy with tumor cell lines.

Alpha Detector Design

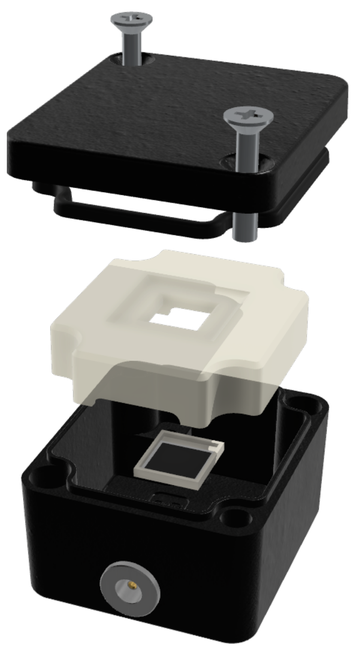


Fig.2: 3D model of detector box.

A detector prototype was constructed using a 10 mm x 10 mm PIN diode attached to a 3D printed holder. When constructing a sample holder, the short range of alpha particles had to be considered in order to minimize energy loss. The holder secures and seals the diode in an aluminum box which helps shield the diode from external factors and creates a safe space for the samples to be placed. A frame was 3D printed to match the diode dimensions and adhered to polyethylene terephthalate (PET) film. The appropriate thickness for PET film was chosen to be in the 0.9-13 μm range. The sample will then be directly on the PET film which is in direct contact with the PIN diode, minimizing the distance the alpha particle travels before reaching the detector.

Ac-225 Measurement

A 1 μL sample of 100 Bq Ac-225 was used for initial measurements with the detector prototype and a sample holder with 0.9 μm PET foil. An energy calibration was performed, and multiple measurements of the sample were taken with varying run times.

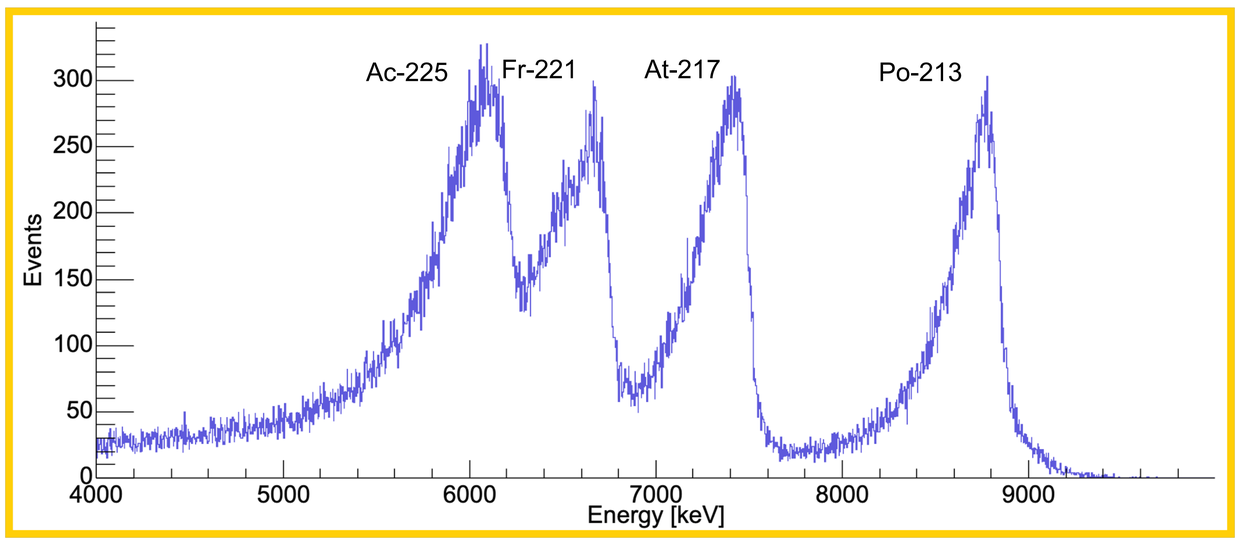
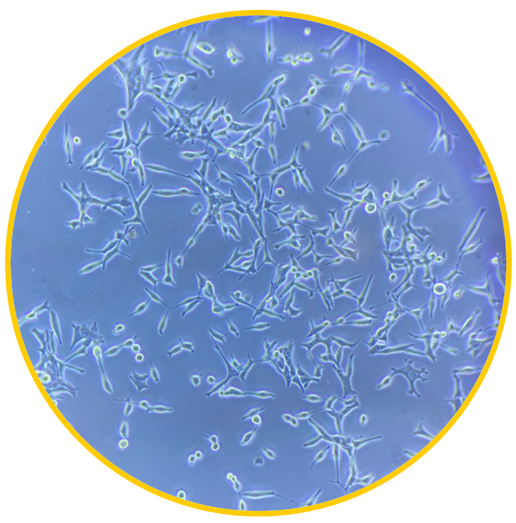


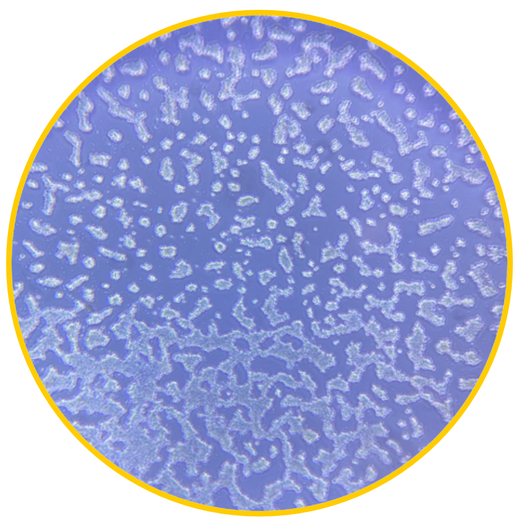
Fig.3: Alpha spectrum of Ac-225 sample collected over a 2-day RT.

Cell Lines



LNCaP

- Prostate cancer epithelial cells
- Target: Prostate Specific Membrane Antigen (PSMA)
- Targeting Vector: PSMA-617



AR42J

- Pancreatic tumor cells
- Target: Somatostatin Receptor 2 (SSTR2)
- Targeting Vector: TATE

Cell Uptake

The AR42J cells were incubated with [225Ac]Ac-CROWN-TATE tracer doses of 10, 1, or 0.1 kBq/mL for 1 or 3 hours. A blocking agent control was included for the 1 kBq/mL dose with 1 hour incubation and confirmed the binding specificity of [225Ac]Ac-CROWN-TATE to SSTR2 on AR42J cells. Uptake percentage was determined using the activity in counts per minute (CPM) inside the cell obtained via gamma counter after the incubation period.

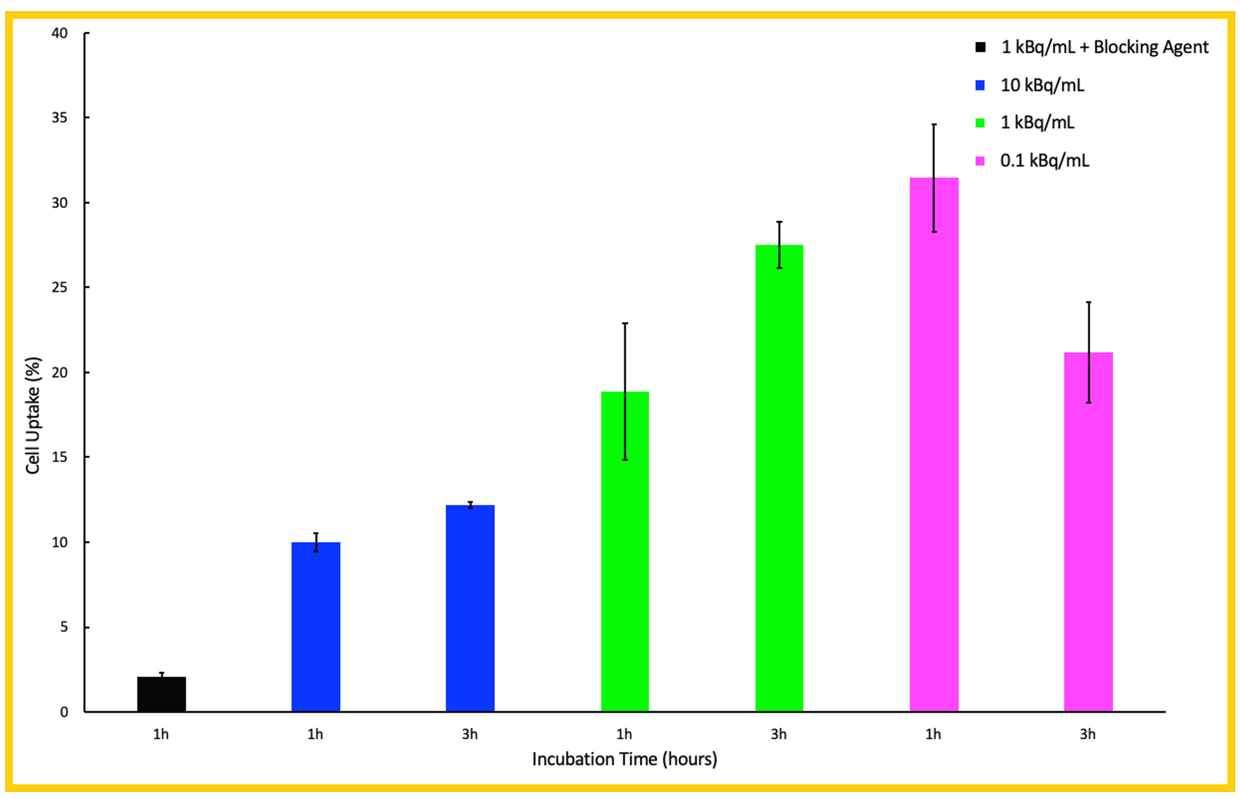


Fig.4: [225Ac]Ac-CROWN-TATE uptake percentage into AR42J cells.

Next Steps

- Trial cell seedings directly on sample holders for future cell uptake studies
  - Assessing the alpha detector's efficiency with biological samples and determining a detection limit
    - Performing cell uptake studies with LNCaP and AR42J cells with activity measured with the alpha detector

Discovery, accelerated