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Recent developments in high- and low-energy particle beam-based production of actinoids and lanthanoids at TRIUMF

by Paul Schaffer (TRIUMF)

Number of participants: 12 persons in 40/S2-C01 - Salle Curie (CERN) + 11 people connected through Zoom

- Paul started by a disclosure as he is a full-time employee of TRIUMF and he is compensated by ARTMS as Chief Technology Officer. He is a listed inventor on patents in technology licensed to ARTMS. This presentation will include mention of solid target technology related to ARTMS' product line. To avoid bias, the advantages and disadvantages of alternative isotope production approaches will be discussed, when appropriate.
- The presentation was divided into 3 parts
    - 1) Background: TRIUMF, Infrastructure, and Capabilities
    - 2) Discussion: Isotope Production Research (A Cyclotron Perspective); Radiopharmaceutical Design and Development
    - 3) Summary, Conclusions
- **1) Background: TRIUMF, Infrastructure, and Capabilities**
    - TRIUMF
        - Founded in 1968 by 3 universities (the University of British Columbia, Simon Fraser University, and the University of Victoria), TRIUMF has evolved into a multidisciplinary facility owned and operated by a consortium of Canadian universities from coast to coast
        - ~600 staff and students
    - **6 (soon to be 7) cyclotrons + 2 linear accelerators on site**
    - **Energy range from 13 MeV** (25 microA) **to 520 MeV** (350 microA)
    - Activities
        - Isotope production
        - Radiochemistry
            - Purification
            - Chelate development
            - In vitro testing

        - In vivo testing
        - UBC (University of British Columbia) Centre for Comparative Medicine
    - Proton Therapy
    - Bio-BetaNMR
    - Other drivers: ARIEL and ISAC
- **Life sciences at TRIUMF => Focuses on advancing accelerator-based technology for the development of isotopes that can improve life**
    - Applied ion beams
    - Nuclear chemistry
    - Applied isotopes
- TRIUMF capabilities
    - Accelerator Development and Operations
    - Accelerator Target Development
    - Isotope Production
    - Radiopharmaceutical Production
- TRIUMF partnerships
    - Radiopharmaceutical Production
    - (Pre)Clinical Studies
    - Imaging and Detector Development

- **2) Discussion: Isotope Production Research (A Cyclotron Perspective); Radiopharmaceutical Design and Development**
    - **500 MeV Isotope Production (Isotope Production Facility) => TRIUMF's IPF (500 MeV Isotope Production: Th232)**
        - Simultaneous irradiation of 12 targets (max 8 mm each)
        - Continuously receives beam ~7 months/year (450-480 MeV, 60-150 μA)
        - Th232 produces 2 different 225Ac products
            - Directly-produced 227,225Ac
            - Generator-produced 225Ac (which has higher radionuclidic purity and reduced 227Ac content)
        - Gamma spectroscopy was used to measure the target's radioactive inventory => 47 nuclides quantified, resulting in 38 cross section measurements

- Separation of 227,225Ac from remaining Th and spallation/fission products: ion exchange + extraction chromatography
- Repeating final process step produces 225Ac
- How much Ac-225 can we produce? => TRIUMF's Actinium production focuses on supporting internal research and collaborations with external partners
    - Total Actinium yield per target: up to 220 MBq
    - To improve the Actinium Yield
        - Increase target material
        - Increase irradiation dose
        - Shorten the cool-down time
    - Thorium-232 targets for BWXT Medical, Inc. (producing higher yields of Ac-225 for clinical trial use)
        - Dose: 25,000 µAh
        - Cool down time: 1 day,
        - Thicker targets planned for the near future
- After Thorium spallation, which other radiometals can we utilize?
    - Pb212 (from Th228) or U230
    - Th227 or Bi213
- Production and SPECT Imaging of 225Ac and 226Ac => Key Question: Where do Ac and daughters reside?
- 226Ac phantom SPECT Imaging => Goal: quantify optimal protocols for our preclinical scanner to conduct 226Ac imaging
- **Summary: 226Ac phantom SPECT imaging**
    - **HEUHR 158 keV images have the best quantitative accuracy and higher contrast recovery**
    - **For in vivo imaging, high resolvability and quantitative accuracy is important, so the HEUHR collimator is most appropriate**

- **Chelate and radiopharmaceutical development**
    - Designing chelators capable of binding emerging isotopes of clinical importance
        - Commercially-available chelates may not exhibit chemical behaviour needed for widespread use, on-site formulation of radiopharmaceuticals (temperature, pH, concentration)
        - High-denticity chelator for large metals

        - Understand selectivity for various isotopes
        - Enable kit-like formulation
        - Enable multi-isotope incorporation (i.e. theranostic applications)
    - Trica vs. Crown
    - New chelators for therapeutical isotopes: “Crown”
        - Crown: a macrocyclic chelate for therapeutic isotopes: Ac3+, Bi3+, Lu3+, Tb3+
        - Labeling: quantitative, fast, ambient temperature, physiological pH
        - Simple, hydrophilic, comparable with DOTA chemistry
        - Crown: improves apparent molar activity => Less peptide with the same amount of activity, less chance to saturate the receptor
    - **Summary: 226Ac in vivo SPECT imaging**
        - **First in vivo quantitative SPECT images of 226Ac**
        - **Explored the theranostic potential of 226Ac SPECT imaging**
        - **Future work will evaluate pharmacokinetics of matched 225Ac/226Ac preclinical radiopharmaceuticals**
        - **Demonstrates personalized dosimetry can start at preclinical stages**
- **Key challenges and future directions**
    - Maintenance shutdowns => Production gap is emerging as a key risk for clinical application
    - Old infrastructure
        - Objective: replace, enhance functionality of BL1A
        - Next step: 2025 CFI Infrastructure Fund; application submitted for consideration
            - Under review
            - $13M budget ($8M from CFI + provincial matching)
        - NFRF-Transformation: Rare Isotopes to Transform Cancer Therapy => $23.7 mil over 6 years
- **<24 MeV Isotope Production**
    - Emergence of radiometals assisted by technology advancements
    - Radiometals by hospital-based cyclotron
        - Technetium, Gallium, Copper, Zirconium

- New Infrastructure: Institute for Advanced Medical Isotopes (IAMI) => New >$70M facility

- **3) Summary, Conclusions**

  - **Direct, cyclotron-production of many radiometals is paving the way for a robust, decentralized supply system for isotopes of emerging clinical importance**
  - **Promising clinical results for treating late-stage cancers is driving demand for both beta- and alpha- emitting isotopes for use in TRT**
  - **ISOL-produced isotopes can be used for preclinical TRT, as shown with [225/226Ac]Tb-crown-TATE in neuroendocrine tumour-bearing mice**
  - **Large accelerator facilities, such as TRIUMF (and PSI!) can serve to innovate new isotopes, and new technologies by applying their accelerator infrastructure, along with their multidisciplinary expertise to help understanding life at the molecular level**

Q&A session / discussion outcome

- The impact of shutdowns was discussed in a bit more details.
- In the future, they will have a dedicated cyclotron to supply the isotopes for the clinics.
- Paul mentioned that Gallium is what will be needed in the future for prostate cancer treatment.
- Following a question about the production of Actinium in the world, Paul answered that a solution is looking also at the low-energy production and we need a community effort to supply enough Actinium for routine treatments.
- The redundancy was discussed and Paul answered that if we can demonstrate clinical benefits, then you have strong case to have more suppliers and provide more redundancy.
- Concerning the primary beam, instead of protons, why not using Helium3 (it would have much higher yield of stability)? Paul answered that he was not aware of anything on this for TRIUMF.
- What is the difference between Thorium or Uranium? Paul answered that the yield is higher on Thorium.
- What is the project of electron acceleration? Paul answered that the medical isotope target station has been designed and we should hear some results in the the future. The ARIEL electron linac should come in ~ 5 years.

Alessandro, Elias, Michele, Thierry (and Paul)