Production and applications of very high specific activity Sn-117m and labeled chelates/molecules

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Objectives:
Cardiovascular diseases represent a leading cause of death and, specifically, a ruptured vulnerable plaque (VP) accounts for about 70% of fatal acute myocardial infarctions and/or sudden death [1]. Despite this, there are no available methods to both image (monitor) and treat this problem. Recently, Sn-117m labeled annexin has found successful application in pre-clinical and clinical studies for this purpose. Biological labeling demands high specific activity (>1000 Ci/g) that can only be produced with accelerators. We employed the Cd-116(α,3n)Sn-117m reaction and a novel chemical separation/purification method to produce the radioisotope which was subsequently chelated to aminobenzyl-DOTA and conjugated to annexin V-128 for these *in-vivo* studies. Promising initial results of both imaging and therapeutic modalities are emerging.

Methods:
Sn-117m is a 14 day half-life gamma (~159 keV) and conversion electron (~130 keV) isotope that has been used for bone pain palliation studies and more recently has also found application in investigative efforts to image and treat VP [2]. We employed the Cd-116(α,3n)Sn-117m production reaction with the 47 MeV alpha beam available at the University of Washington Medical Center MC50 cyclotron and an electroplated Cd-116 solid target. Resulting yields were confirmed to be high (~0.15 mCi/μAh) [3] with minimal undesirable by-products. Based on early work by Meares [4] at UC Davis, an ion exchange column method was used to isolate the Sn-117m resulting in a very pure high specific activity (~20,000 Ci/g) product. The Sn-117m was attached to a bifunctional chelating agent (aminobenzyl-DOTA) using a microwave reactor at elevated temperatures and then purified using HPLC. Conjugation of the chelate to a biological molecule (annexin V-128) was accomplished by preparing the isothiocyanate version of the chelate and then reacting it with lysine residues on the annexin for 90 mins at 37°C – see Fig.1. Several analytical methods (cell binding, electrophoresis, gel permeation chromatography) were used to evaluate the cGMP [Sn-117m]-DOTA-annexin that was produced.

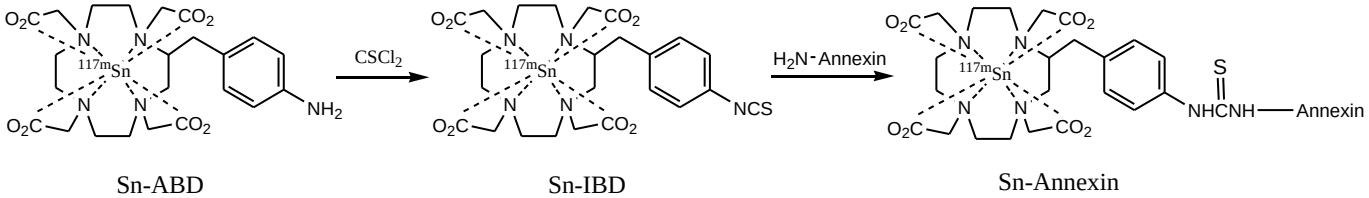

Figure 1. Production of [Sn-117m]-DOTA-annexin

Results: PAGE determined that the product was >95% monomer; cell binding results were typically pK=20-24. Overall chelation yields were ~95% and ~40% for conjugation to the annexin. This product was injected in ApoE mice and a therapeutic effect observed at very low doses (~1.7 μCi - equivalent to 3-5 mCi in humans) [5,6]. Statistically significant data were obtained showing that apoptotic bodies and macrophages decreased while smooth muscle cells and collagen increased in the cardiac brachiocephalic arteries and the sinotubular junction where VP was observed to occur. The dose dependent results obtained are indicative of plaque stabilization, inflammatory reduction and a positive therapeutic outcome. Early human studies also indicate that imaging with as low as 3 mCi may be possible.

Conclusions: Very high specific activity Sn-117m has been produced and used to label annexin under cGMP to study vulnerable plaque in animals and humans. Evidence for imaging and positive therapeutic effect has been observed with very low systemic doses (3 mCi in human; 1.7 μCi in mice).

References: [1] Langer HF et al, (2008) J Am Col Cardiol Vol 52 No1, 1-12. [2] Srivastava SC, (2012) Semin Nucl Med Vol 42, 151-163. [3] Qaim SM and Dohler H, (1984) *Int J Appl Radiat Isot Vol.35 No.7*, 645-650. [4] Meares C, private comm. [5] Virmani R, TCT2012 ('Innovations' session): "Simultaneous Localization and Treatment of Vulnerable Plaque by Tin-117m Conversion Electrons: First-in-Human Results", (Oct 22, 2012). [6] Gonzales G, (2012) World J Nucl Med Vol 11, 152.