

Manufacturing and integrated medical imaging of high specific activity [Sn-117m]-annexin in cardiovascular disease

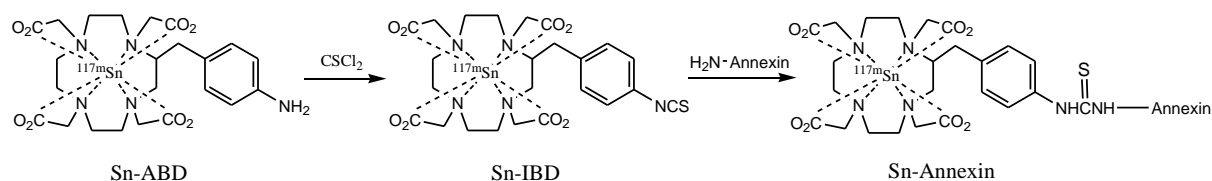
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Background: Cardiovascular diseases represent a leading cause of death and, specifically, a ruptured coronary vulnerable plaque (VP) accounts for about 70% of fatal acute myocardial infarctions and/or sudden death and a high incidence of stroke in unstable carotid plaque. Despite this, there are no available methods that can both image (monitor) and treat these problems. 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($\alpha,3n$)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 integrated imaging and therapeutic modalities are emerging.

Methodology: Sn-117m is a 14 day half-life gamma (~159 keV) and conversion electron (~130 keV) isotope used for bone pain palliation studies and now also in investigative efforts to image and treat VP. We employed the Cd-116($\alpha,3n$)Sn-117m production reaction and an ion exchange column method 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) 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 reacting it with lysine residues on the annexin:



Results: 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). 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. Ultra-sound, gamma (planar and SPECT) and CT *in-vivo* data were taken along with optical, autoradiography and histology data from excised carotid plaque tissue. These imaging results are still being analysed but are indicative of selective uptake of the Sn-annexin in cardiovascular VP and other inflammation sites.

Conclusions: Very high specific activity Sn-117m has been produced and used to label annexin under cGMP to study vulnerable plaque and unstable 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).