Targeting of Vulnerable [atherosclerotic] Plaque using [tin-117m]-DOTA-ANNEXIN

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Abstract

ABSTRACT BODY:

Objectives : Tin-117m emits mono-energetic conversion electrons (range ~290 µm) and an ideal (86%, 159 keV) imaging photon. We report on a tin-117m labeled targeting molecule that demonstrates efficacy in imaging and treating vulnerable plaque.

Methods : Annexin V, found on the inner cell membrane, specifically binds to phosphatidylserine (PS). When cells undergo apoptosis, the PS is exposed for binding. The targeting molecule we have developed for vulnerable plaque (VP) imaging and therapy is [tin-117m]-DOTA-annexin (TA). Pre-clinical ApoE-/- mouse therapy trials were undertaken using systemic doses of 1.0 µCi, 1.7 µCi and 3.4 µCi/25 g mouse. Clinical imaging trials for safety (500 µCi) were completed and the Phase 2 (γ/SPECT imaging-3 mCi) study in human carotid endarterectomy subjects is underway.

Results : The pre-clinical data show statistically significant therapeutic effects at these doses: increased cap thickness and reduced size of the necrotic core, 60d after TA administration, suggesting plaque stabilization. The human equivalent of the 1.7 µCi dose corresponds with ~3 mCi used in the clinical study where the systemically injected TA is seen to bind to components of VP. Additionally, in vivo imaging of human aortic aneurysms has been achieved. The cGMP prepared TA has been administered without any adverse events.

Conclusions : The clinical studies performed to date have provided histology as a comparison and measure of TA binding and localization. Human imaging studies are ongoing. A measure of plaque stabilization in the latest trial is also underway.

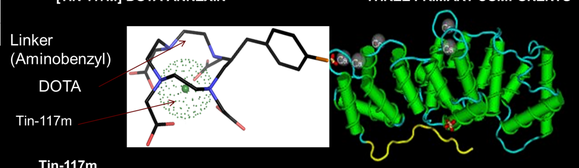
Goals and Rationale

- Localize vulnerable atherosclerotic plaque
  - Lesions with:
    - Cap thickness ≤ 65 uM
    - Large lakes of lipid
    - Containing numerous activated macrophages & foam cells
- Treat vulnerable plaque with conversion electrons
  - Activated macrophages & foam cells undergo either necrosis or apoptosis
  - Necrosis
    - Causes loss of integrity of cell membrane
      - Noxious substances released into surrounding tissue, **increasing inflammation**
  - Apoptosis
    - Organized, programmed cell destruction
      - Noxious substances packaged in 'apoptosomes' for phagocytosis by adjacent calls
      - **No increase in inflammation**

Why Tin-117m Annexin?

- Annexin binds to cells expressing phosphatidylserine [PS] on the outer leaflet of the cell membrane
  - Severely stressed cells
  - Cells which have initiated apoptosis
- Annexin bound to PS provides the 'eat me' signal to phagocytic cells
- The combination of severely stressed cells and permeability of the lesion to radiolabeled annexin allows the tin-117m annexin to bind to macrophages in the lesion
- HYPOTHESIS:
  - Sn-117m conversion electrons would cause the stressed macrophages to undergo apoptosis instead of necrosis, decreasing inflammation in the lesion.

[TIN-117M]-DOTA-ANNEXIN **THREE PRIMARY COMPONENTS**



Tin-117m
- Imaging photon 159 keV (86% abundant)
  Decay – Isomeric Transition
  Conversion electron has short path over relevant biological range
- 14 day half-life

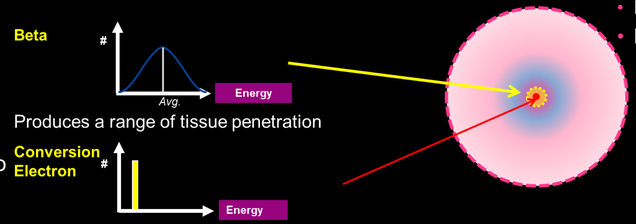
Aminobenzyl DOTA
- Securely holds the Tin-117m

Annexin V
- Naturally occurring human protein
- Annexin V binds to phosphatidylserine expressed on the outer leaflet of cell membranes of apoptotic and highly stressed cells

[Tin-117m]-DOTA-Annexin
- Localizes in vulnerable plaque
- Treats without damaging surrounding tissue

TIN-117M HAS UNIQUE CAPABILITIES

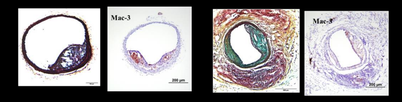
RADIATION ENERGY

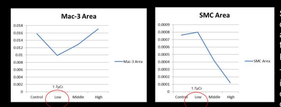


	Tin-117m	Alpha Particles[1]	Beta Particles[2]
Range in tissue (µm)	290	40-90	50-5000+

[1]ALPHARADIN; [2]METASTRON & QUADRAMET

APO-E MOUSE THERAPY STUDY

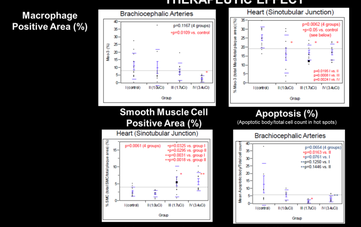




Sn-117m Annexin decreased macrophages and increased SMC cells in the lesion at a dose of 1.7 µCi

Toxicity studies showed no indication of toxicity based on histologic assessment of the liver and kidney.

APO-E -/- MOUSE THERAPY STUDY: STATISTICALLY SIGNIFICANT THERAPEUTIC EFFECT

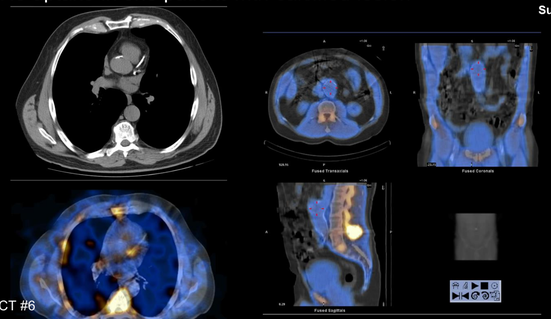


"…suggest rapid vulnerable plaque stabilization" - R. Virmani

HUMAN STUDY TO IMAGE VULNERABLE PLAQUE IN CAROTID ARTERIES - CONFIRM WITH HISTOLOGY OF EXCISED TISSUE

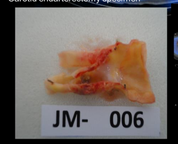
- Planar imaging in first 5 human studies did not image carotid plaque.
- SPECT/CT images on next 4 subjects demonstrated:
  - Focal uptake in 3 subjects with histologically confirmed carotid VP
  - No uptake in one patient with calcified lesion

Subject #6

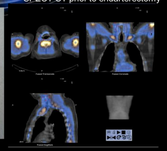


SUBJECT #6

Carotid endarterectomy specimen



SPECT CT prior to endarterectomy

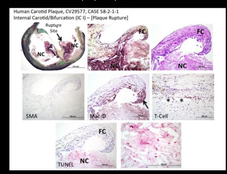


Subject had a ruptured TCFA on histology

Subject had AAA

SUBJECT #6 Histology

- Histology: Image stained by Movat pentachrome is shown in the upper left panel – the arrow marks the site of plaque rupture



Conclusion

- Apo e-/- mouse data suggests a single dose of ^{117m}Sn-Annexin reduces inflammation in vulnerable atheroma
- SPECT-CT of human subjects undergoing carotid endarterectomy demonstrates targeting of ^{117m}Sn-Annexin to the lesion site.
- Further studies are planned to determine if ^{117m}Sn-Annexin can passivate vulnerable plaque in human subjects.

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