Vulnerable Plaque Opportunities

Simultaneous Localization and Treatment of Vulnerable Plaque by Tin-117m Conversion Electrons: First-in-Human Results

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CARDIOVASCULAR RESEARCH FOUNDATION
a passion for innovation

AMERICAN COLLEGE OF CARDIOLOGY

Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship

- Consulting Fees

Company

- Abbott Vascular
- 480 Medical / Arsenal Medical
- Atrium Medical Corporation
- Biosensors International
- GlaxoSmithKline
- CBard/Lutonix
- Medtronic AVE
- Terumo Corporation
- W.L.Gore

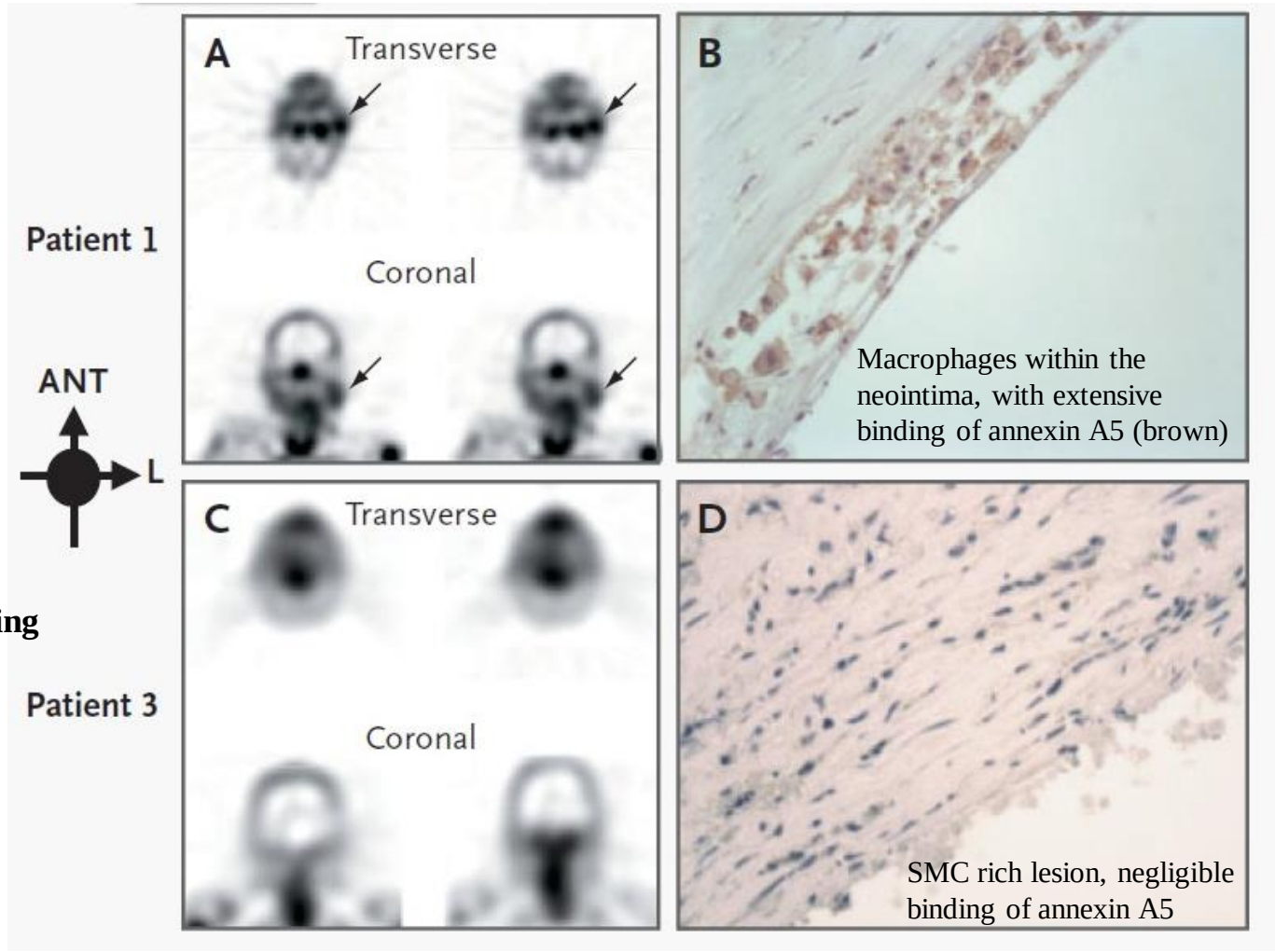
Noninvasive Detection of Plaque Instability with Use of Radiolabeled Annexin A5 in Patients with Carotid Artery Atherosclerosis

Patient 1:
TIA 3 days before imaging

Uptake of radiolabeled annexin A5 only in the culprit lesion (arrows)

Patient 3:
TIA 3 months before imaging

No evidence of annexin A5 uptake

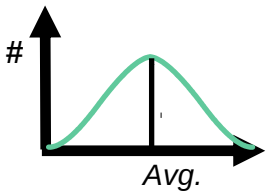


SPECT **Histology (Endarterectomy)**

Narula J, et al. N Engl J Med 2004; 350: 1472-3.

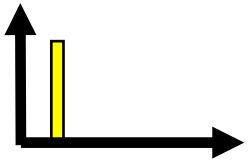
Tin-117m Has Unique Capabilities

Beta

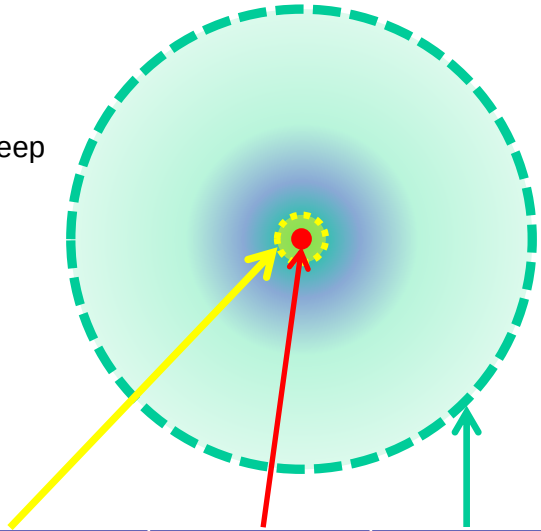


Produces a range of tissue penetration, some deep

Conversion Electron



Penetrates a set distance *(discrete energy)*

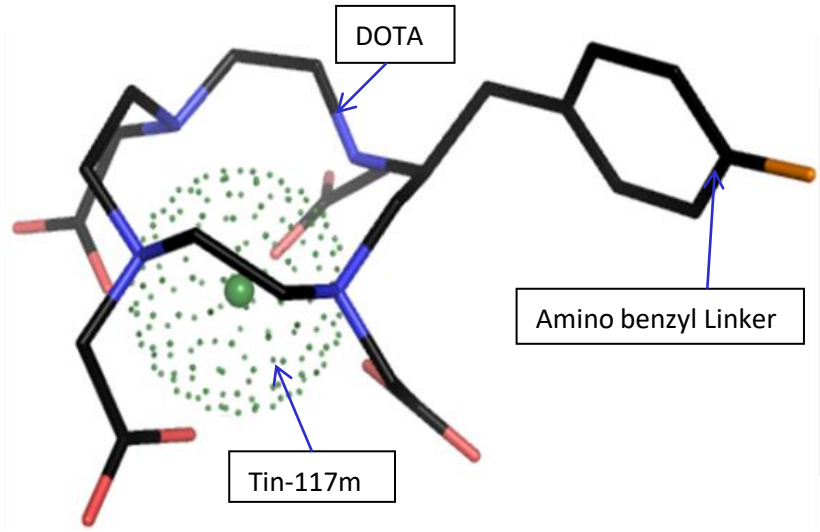


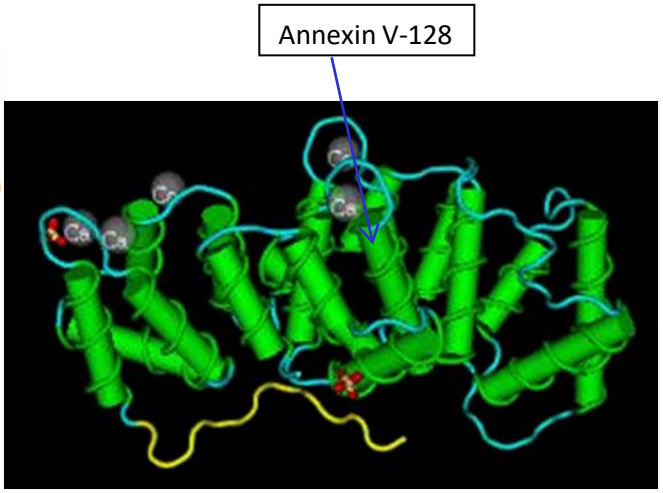
	Tin-117m	Alpha Particles[1]	Beta Particles[2]
Range in tissue (µm)	**290**	**40-90**	**50-5000+**
Shielding needed during administration	**No**	**No**	**Yes**

[1]ALPHARADIN; [2]METASTRON & QUADRAMET

- Conversion electrons (C.E.) 140 KeV discrete energy for therapy have a 290 µm range
  1) Lower external radiation
  2) Easier handling and reduced hospitalization containment
  3) C.E. have been proven to induce apoptosis
- Half-life of 14 days is consistent with treatment requirements
  1) Logistic flexibility
  2) Cell division cycles and therapy dosing
- Gamma ray (159 KeV) similar to Tc-99m (140 KeV) allowing for existing standard gamma camera imaging & techniques

The Product is Comprised of a Radioisotope, Tin-117m, That is Held within a DOTA Molecule Linked to a Targeting Molecule, Annexin V





Tin-117m

- Therapeutic conversion electron has strong ionization effect over relevant biological range (<300 µm)
- 14 day half-life is ideal for therapy
- High specific activity suitable for labeling proteins and antibodies
- Imaging compatible with existing SPECT gamma cameras

Annexin V

- Naturally occurring human protein
- Annexin V binds to specific cell membrane chemicals that are expressed in apoptotic macrophages

Amino benzyl DOTA

- Securely holds the Tin-117m
- Links Tin-117m to annexin

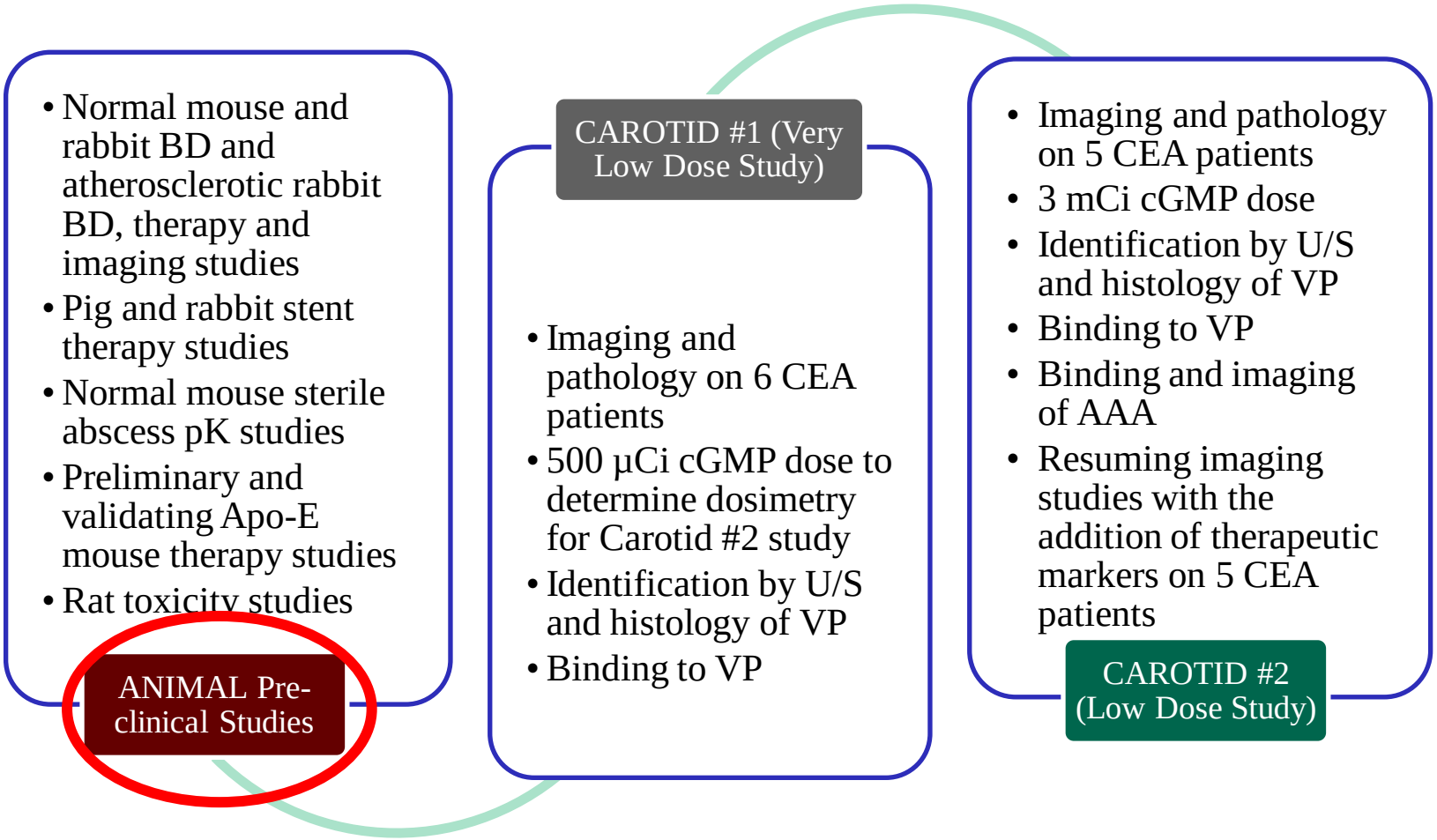
Therapeutic Application of Tin-117m-DOTA-Annexin

Tin-117m-DOTA-Annexin Addresses the Therapeutic Unmet Needs of Vulnerable Plaque

- ✓ Non-invasive
- ✓ An IV systemic injection provides localized vulnerable plaque therapy
- ✓ Targets and treats vulnerable plaque inflammation in the necrotic core
- ✓ Treats vulnerable plaque without damaging the surrounding tissue
- ✓ Half-life allows for one month of therapy with a single injection
- ✓ Therapeutic outcome can be measured with imaging using the same product

PRE-CLINICAL AND CLINICAL STUDIES

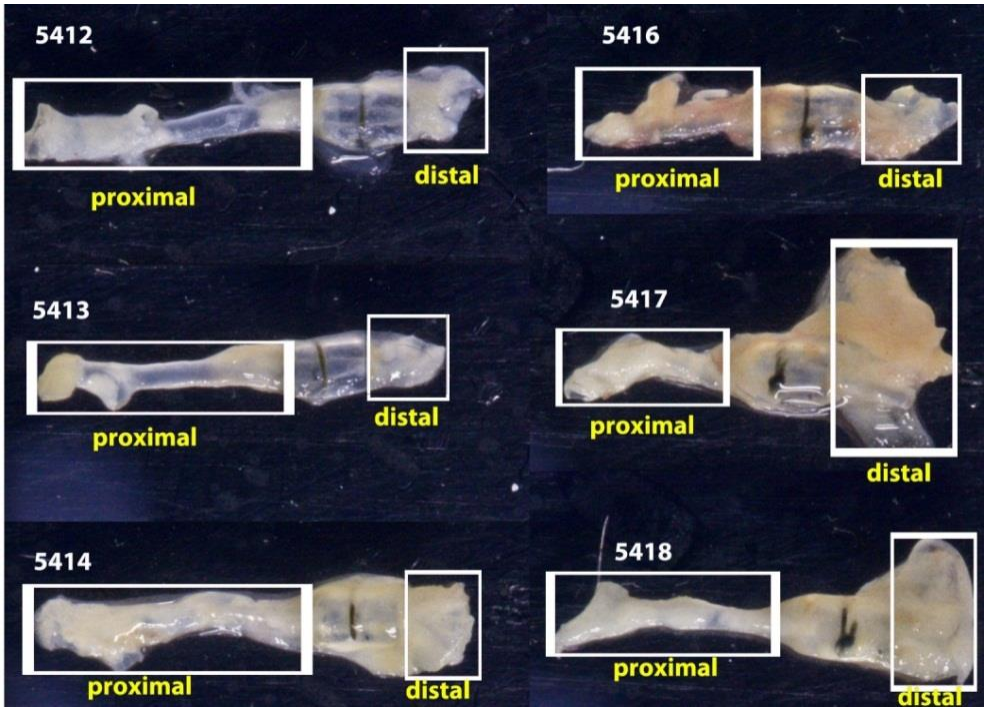
ANIMAL PRE-CLINICAL STUDIES COMPLETED AND HUMAN CLINICAL STUDIES - COMPLETED AND ONGOING



AAA = abdominal aortic aneurysm, BD = biodistribution, CEA = carotid endarterectomy; VP = vulnerable plaque, U/S = ultra sound

PRELIMINARY APO-E MOUSE THERAPY STUDY

HISTOLOGY STATISTICALLY SIGNIFICANT THERAPEUTIC EFFECT AND CONFIRMS THIS IS A GOOD REPRODUCIBLE ATHEROSCLEROTIC ANIMAL MODEL

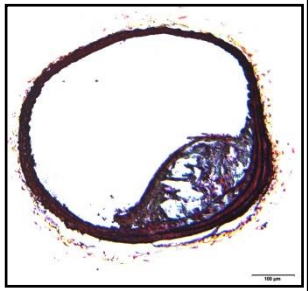


- Dose ranging study to determine if tin-117m/annexin has a therapeutic effect
- 26 Apo-E mice with carotid cast, fed on high fat diet for 10 weeks and injected with saline (control), low (1.7 µCi), medium (16.7 µCi) or high (80~83 µCi) doses then continued feeding high fat diet for 4 weeks

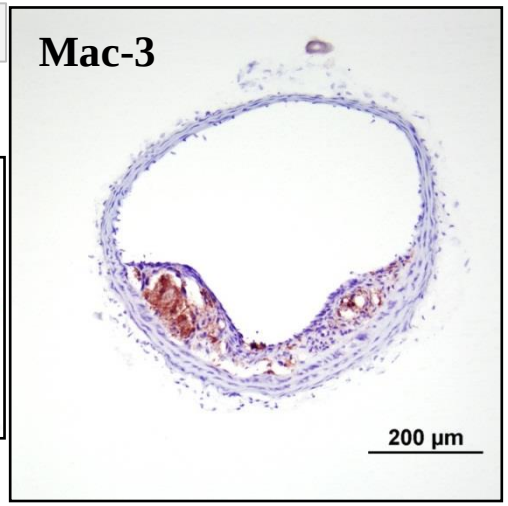
PRELIMINARY APO-E MOUSE THERAPY STUDY

CONTROL MAC-3 VS. LOW DOSE (1.7 µCi) MAC-3

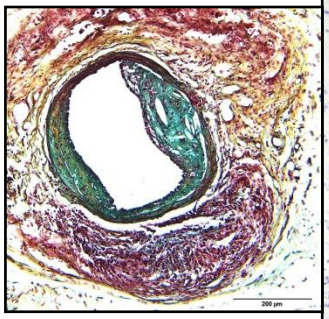
Control



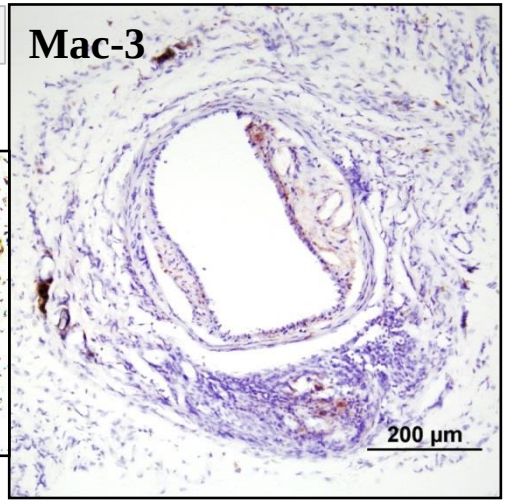
Mac-3

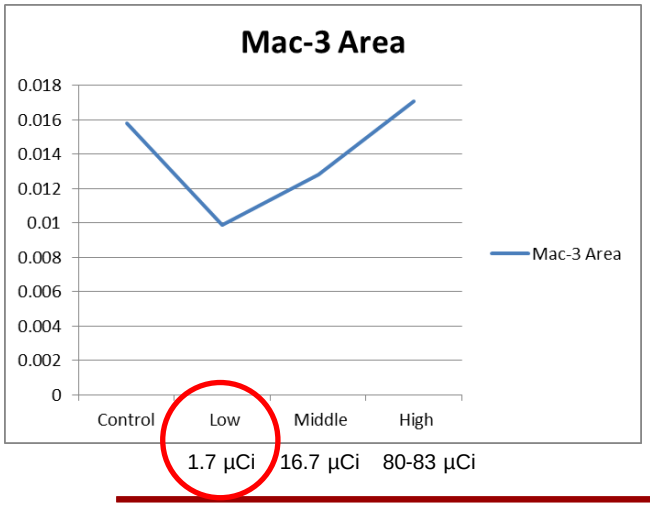


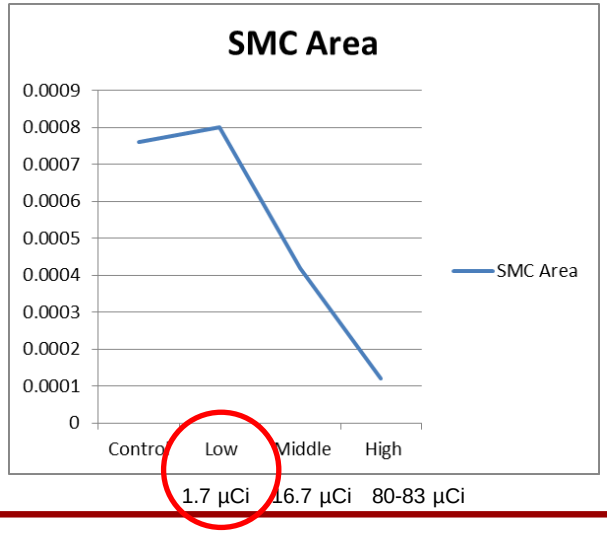
Low Dose



Mac-3



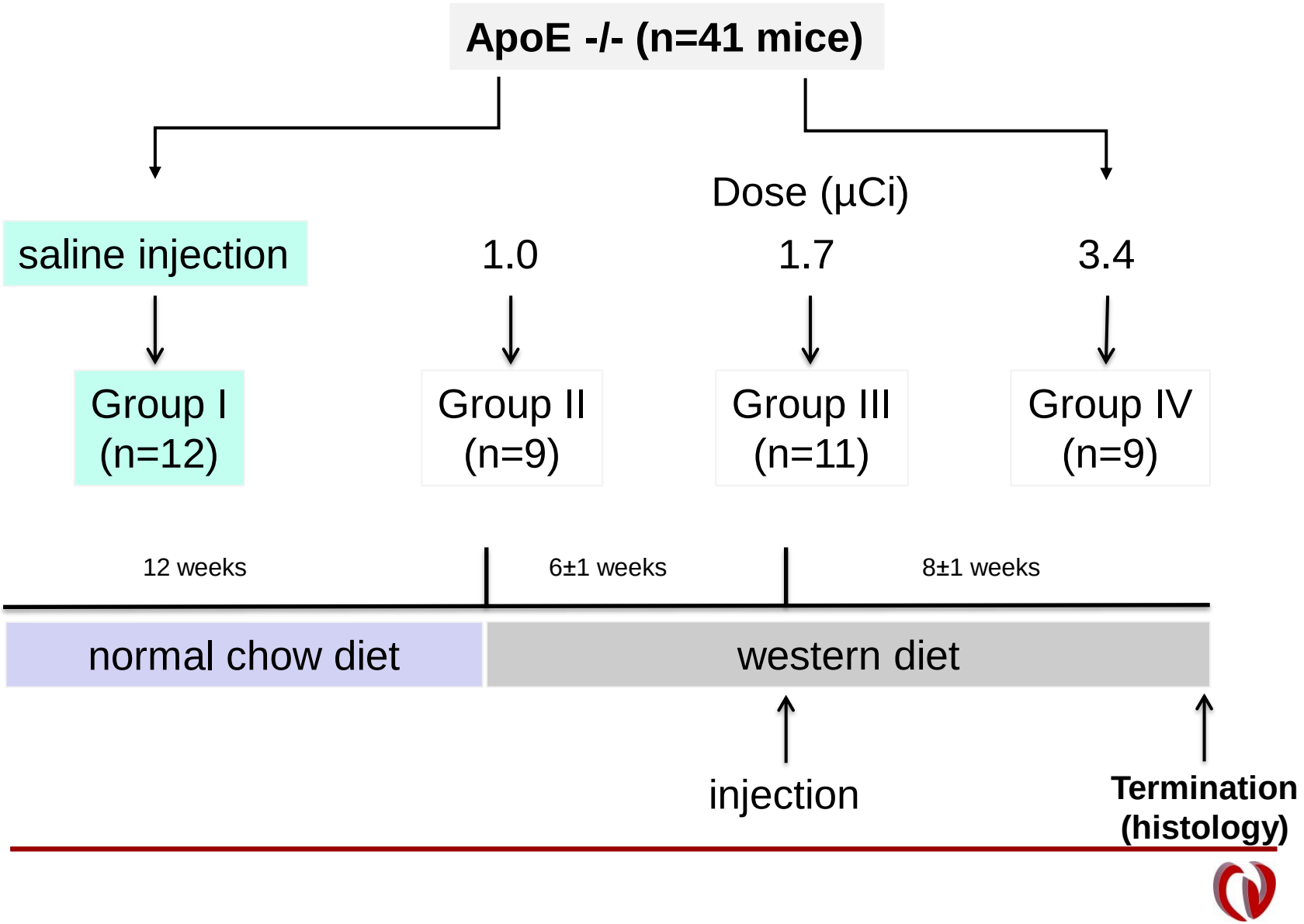




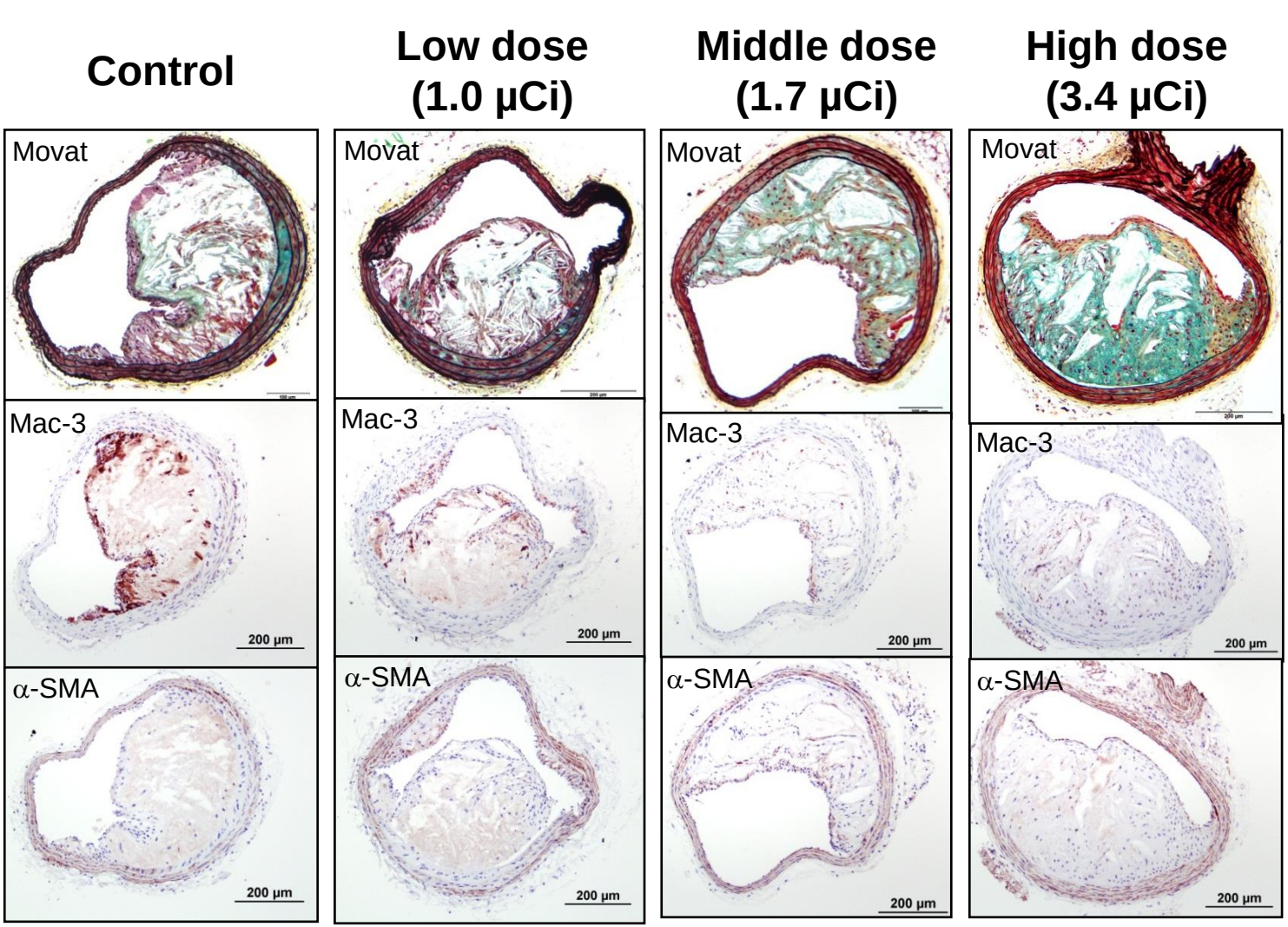
- Histology showed reduced macrophage and increased SMC expressions at low (1.7 µCi) group.
- In addition, rat toxicity studies showed no indication of toxicity based on blood samples and histologic assessment of the liver and kidney.

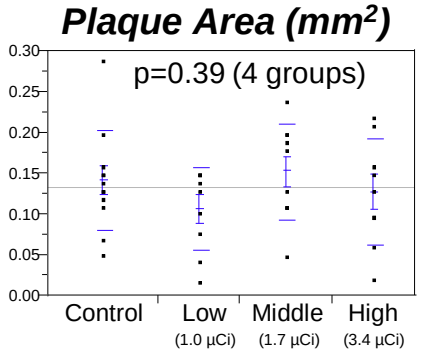
Overall Study Scheme:

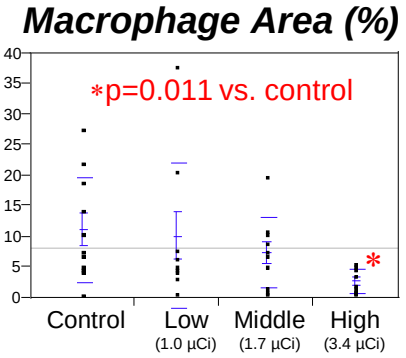
Tin-117m-Annexin V: the 2nd ApoE Mouse Study

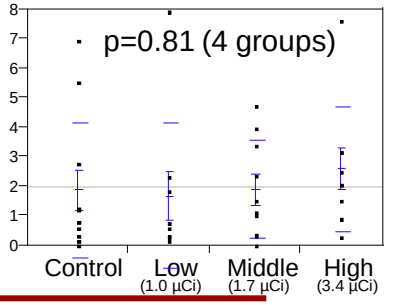


Macrophage and Smooth Muscle Cell Expression in the Brachiocephalic Arteries: the 2nd ApoE Mouse Study

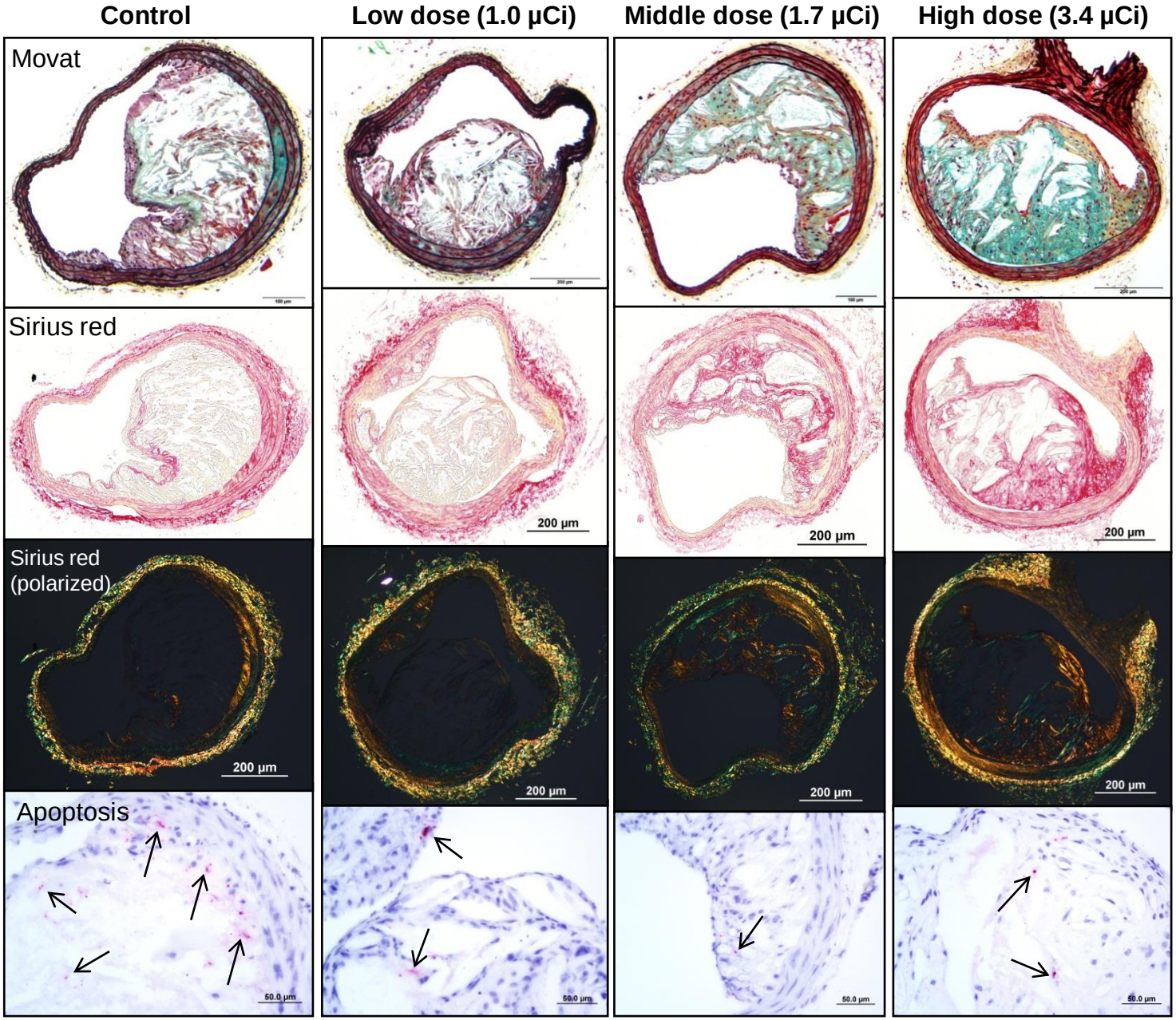




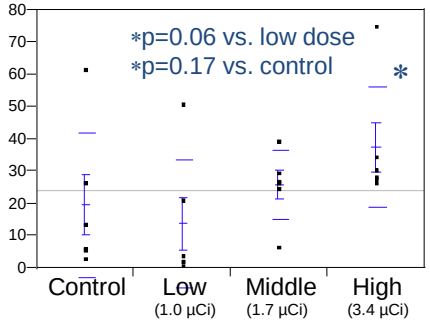




Collagen (Sirius Red Staining) and Apoptosis in the Brachiocephalic Arteries: the 2nd ApoE Mouse Study

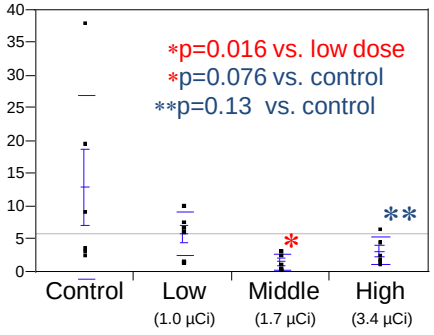


Collagen (%)



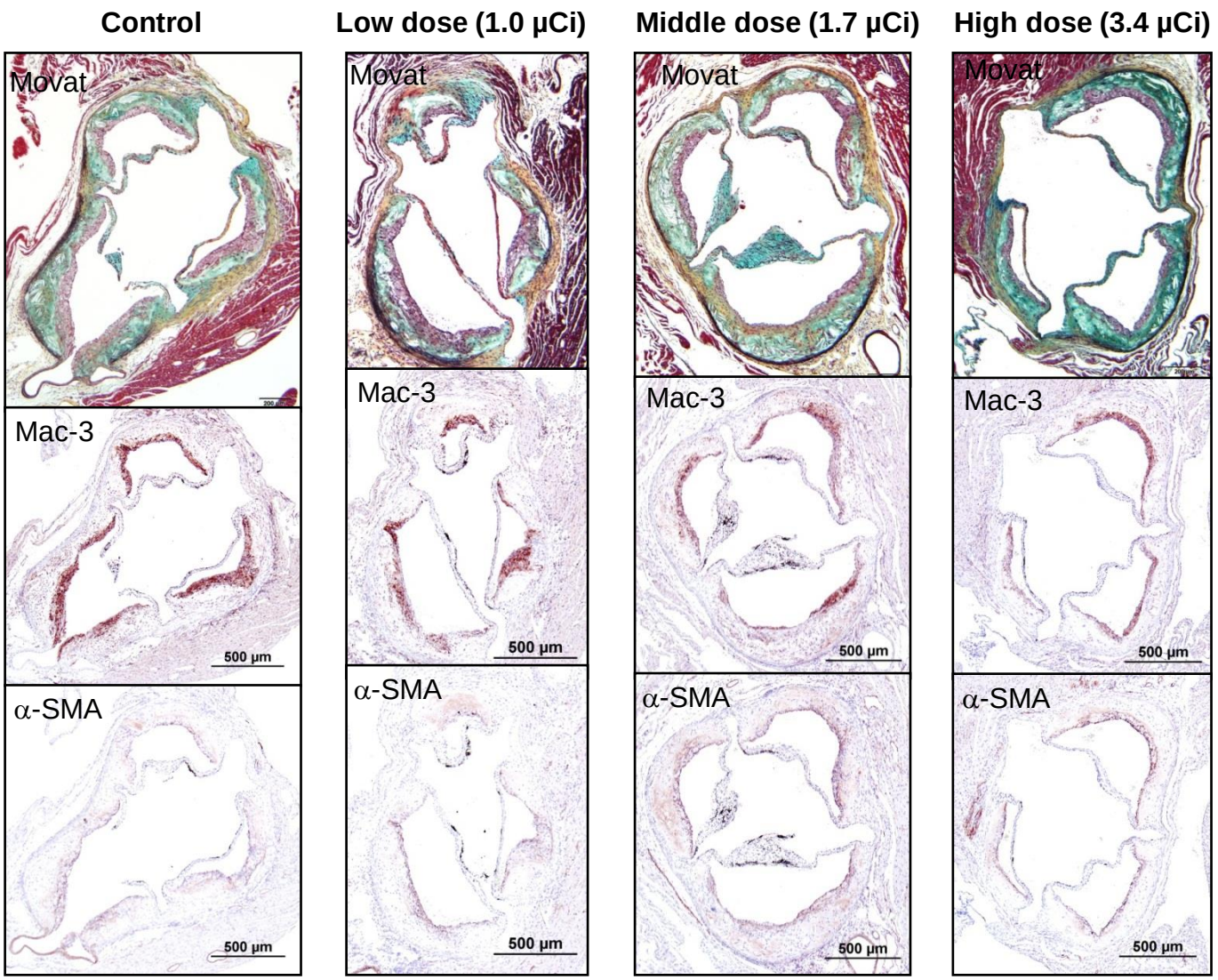
Apoptosis (%)

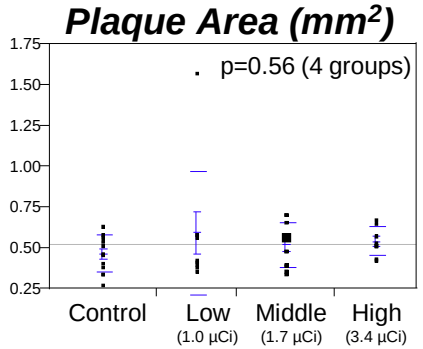
(Apoptotic body/total cell count in hot spots)

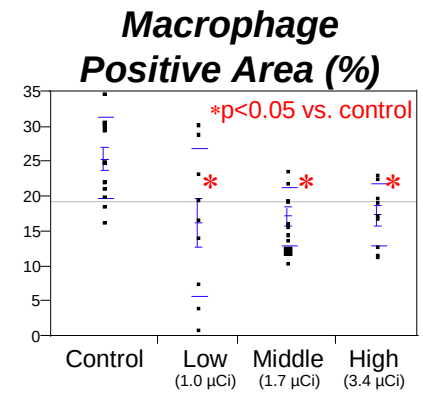


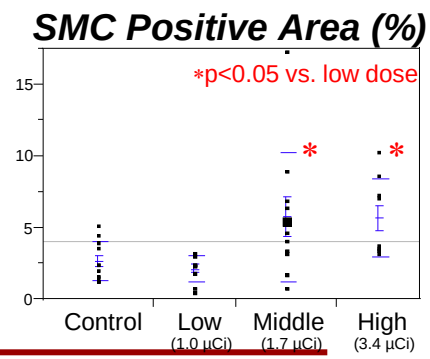
Sirius red and apoptosis staining were performed in selected mice. (n=24; 6 from each group)

Macrophage and Smooth Muscle Cell Expression in Sinotubular Junction: the 2nd ApoE Mouse Study

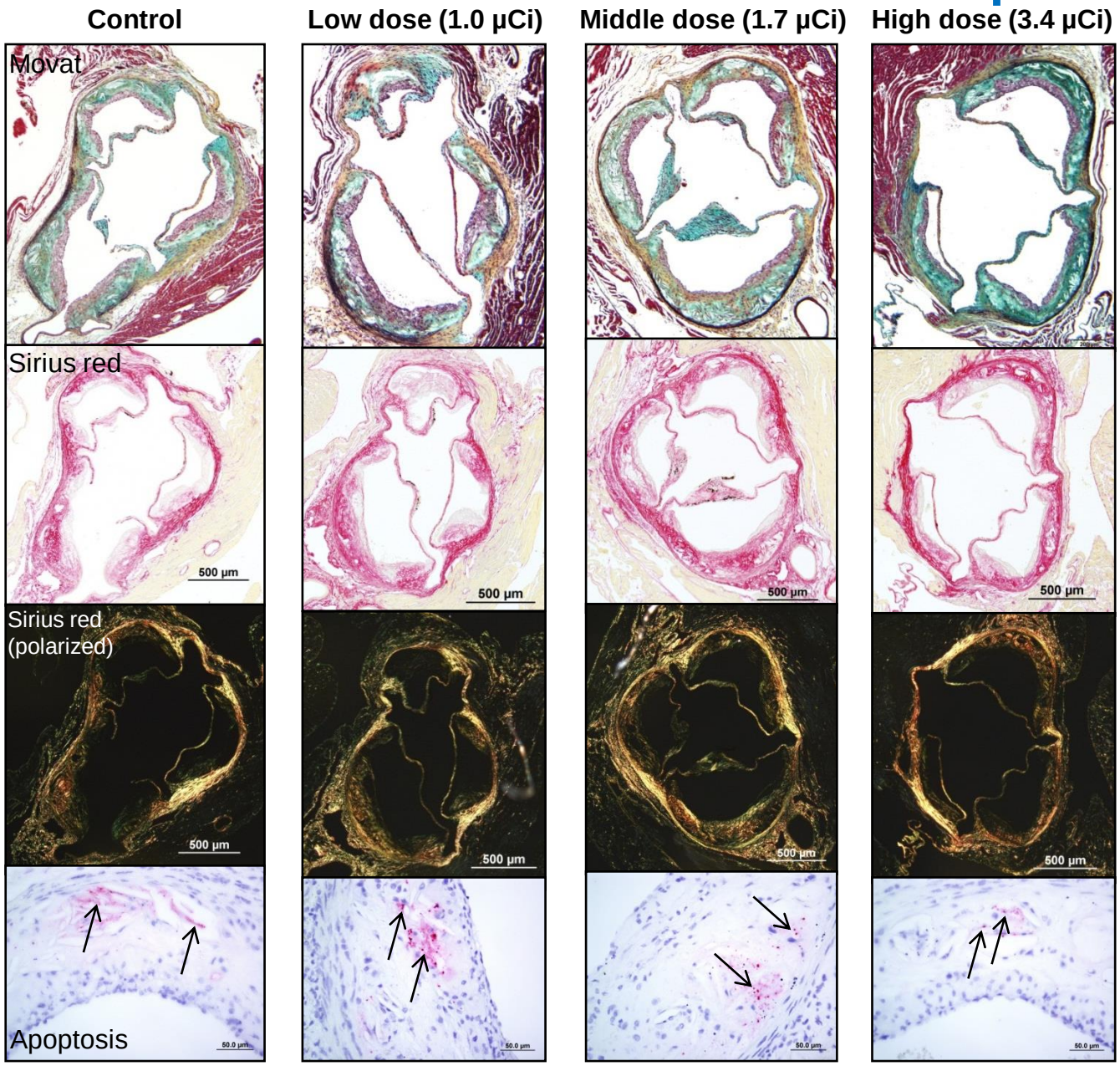


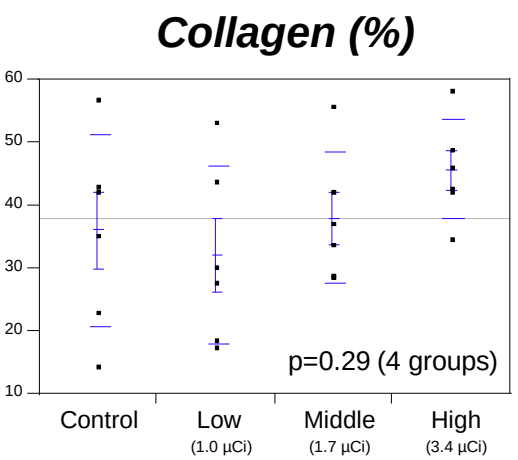


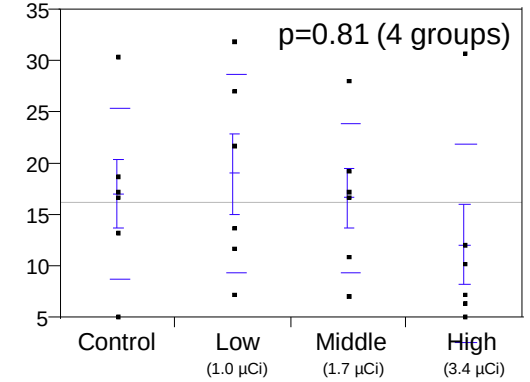




Collagen (Sirius Red Staining) and Apoptosis in Sinotubular Junction: the 2nd ApoE Mouse Study







Sirius red and apoptosis staining were performed in selected mice. (n=24; 6 from each group)

PRE-CLINICAL AND CLINICAL STUDIES

ANIMAL PRE-CLINICAL STUDIES COMPLETED AND HUMAN CLINICAL STUDIES - COMPLETED AND ONGOING

- Normal mouse and rabbit BD and atherosclerotic rabbit BD, therapy and imaging studies
- Pig and rabbit stent therapy studies
- Normal mouse sterile abscess pK studies
- Preliminary and validating Apo-E mouse therapy studies
- Rat toxicity studies

ANIMAL Pre-clinical Studies

CAROTID #1 (Very Low Dose Study)

- Imaging and pathology on 6 CEA patients
- 500 µCi cGMP dose to determine dosimetry for Carotid #2 study
- Identification by U/S and histology of VP
- Binding to VP

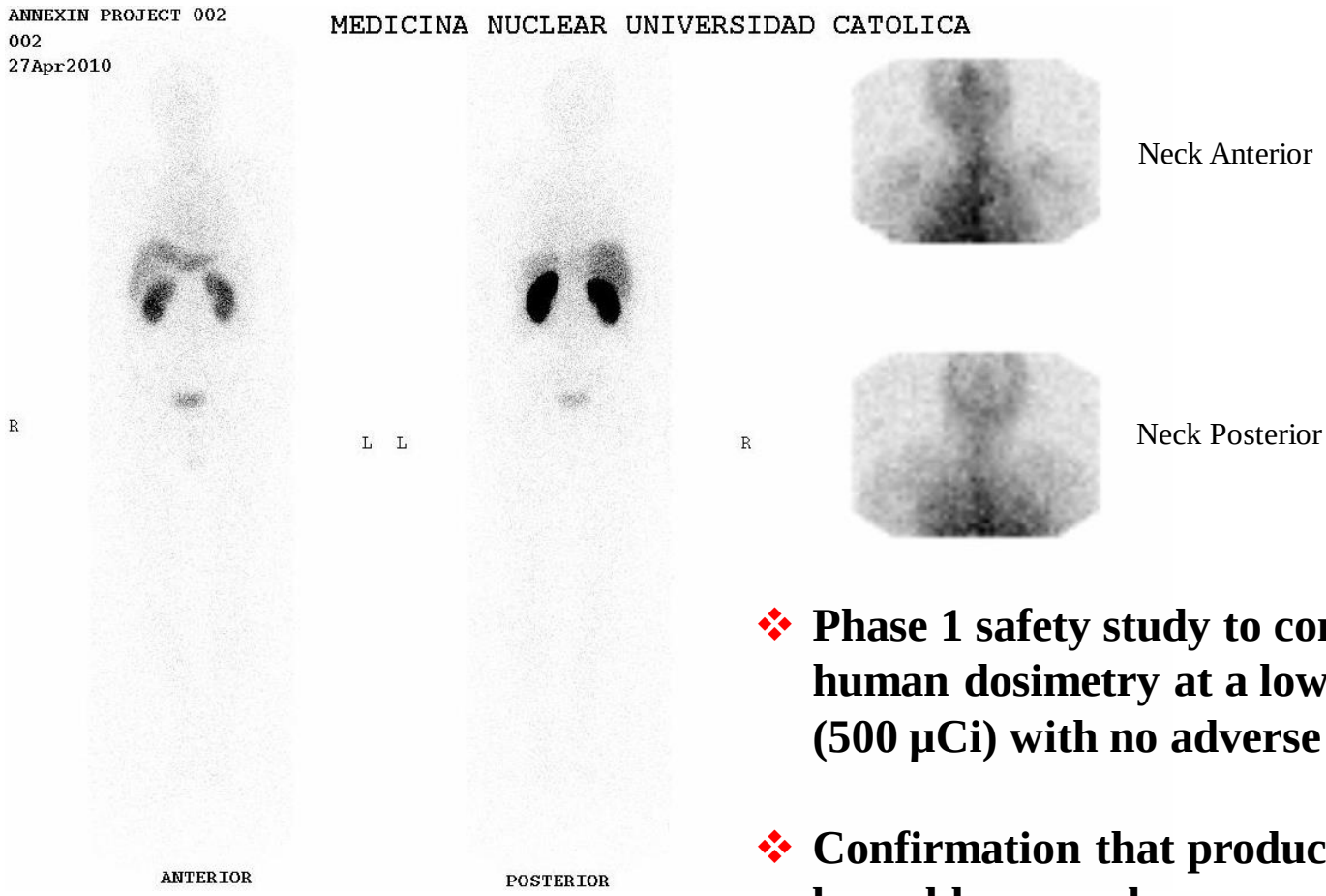
- Imaging and pathology on 5 CEA patients
- 3 mCi cGMP dose
- Identification by U/S and histology of VP
- Binding to VP
- Binding and imaging of AAA
- Resuming imaging studies with the addition of therapeutic markers on 5 CEA patients

CAROTID #2 (Low Dose Study)

CAROTID #1 HUMAN CLINICAL STUDY

(Very Low Dose Study)

Identified VP and Bound to VP

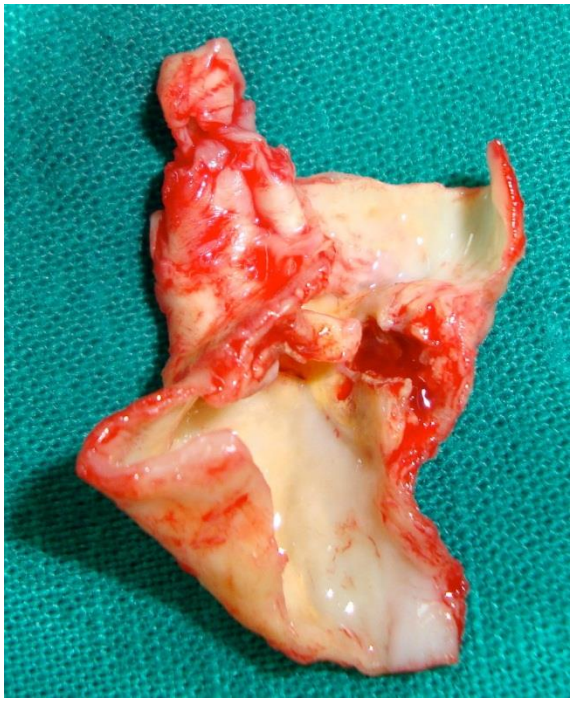


- **Phase 1 safety study to complete human dosimetry at a low dose (500 µCi) with no adverse effects**
- **Confirmation that product bound human plaque**

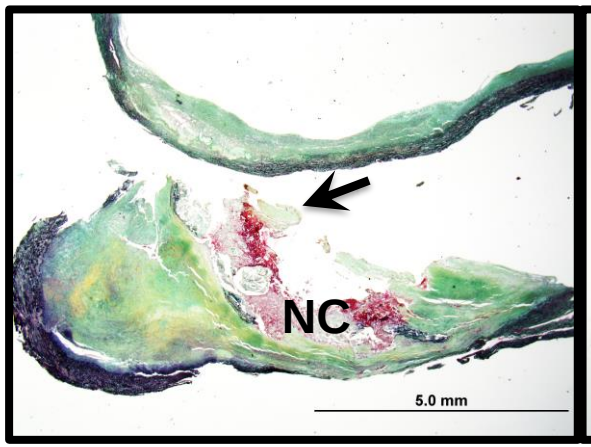
CAROTID #1 HUMAN CLINICAL STUDY

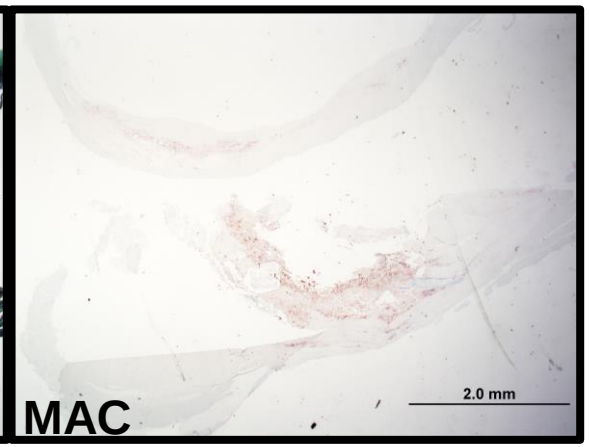
(Very Low Dose Study)

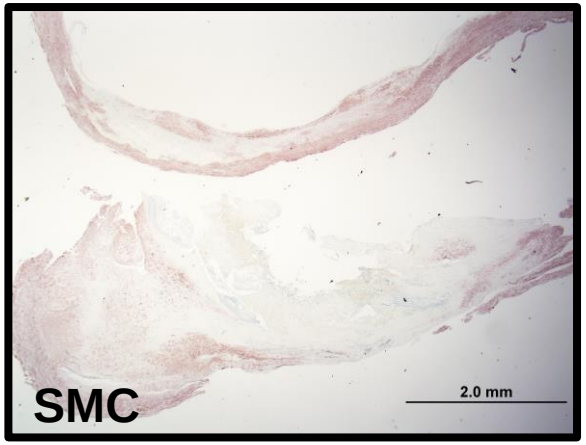
Histology has shown that patients had vulnerable/ruptured plaques
The tagged annexin specifically identified in the region of the VP



Tissue tagged with enough activity to count, but not to image.







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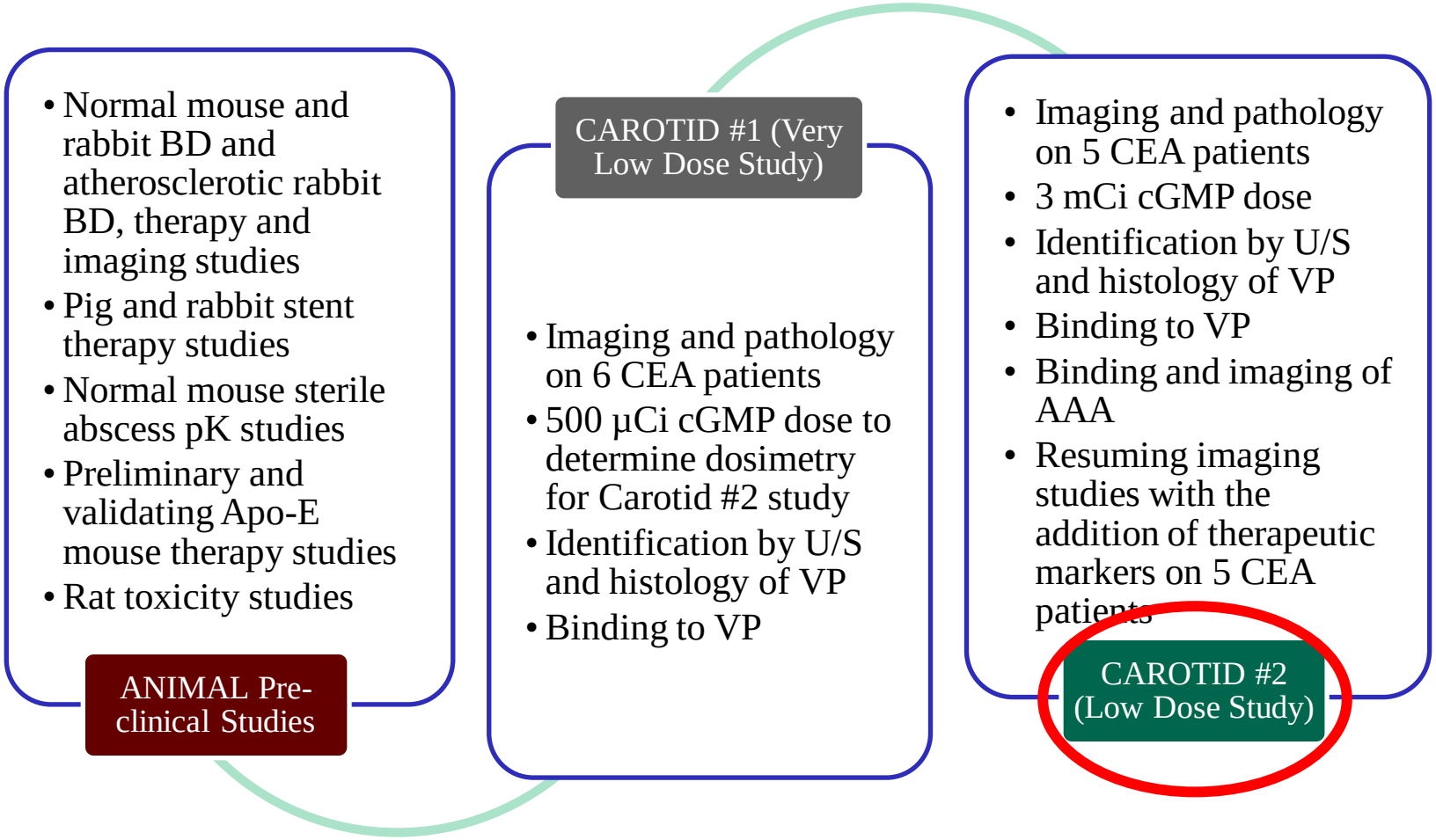


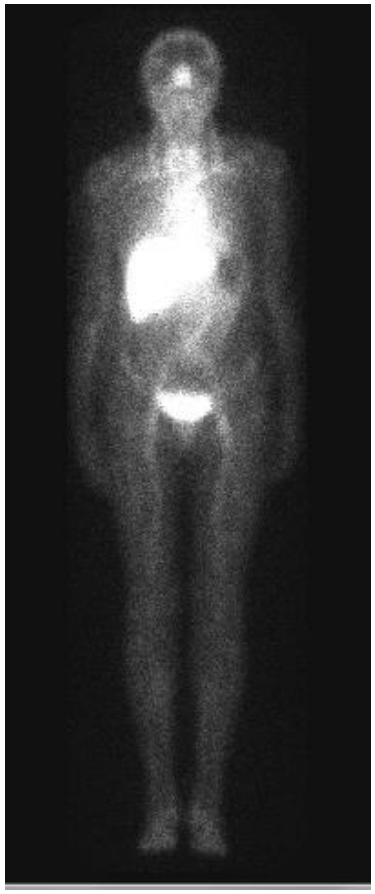
CAROTID #2 HUMAN CLINICAL STUDY

(Low Dose Study)

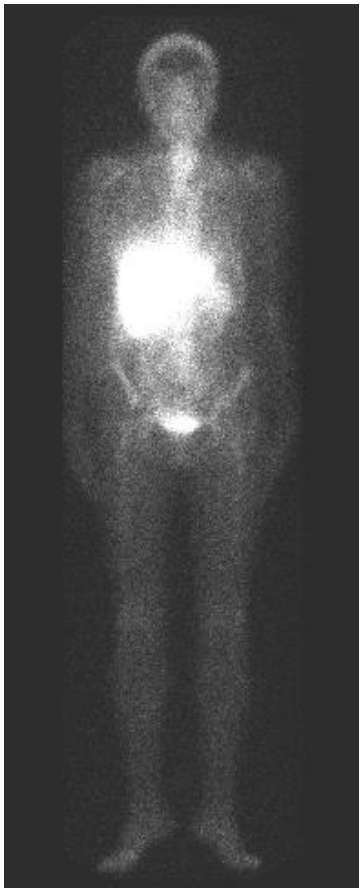
Three of first 5 subjects showed tagging of carotid plaque, but not enough to image.

Subject 5

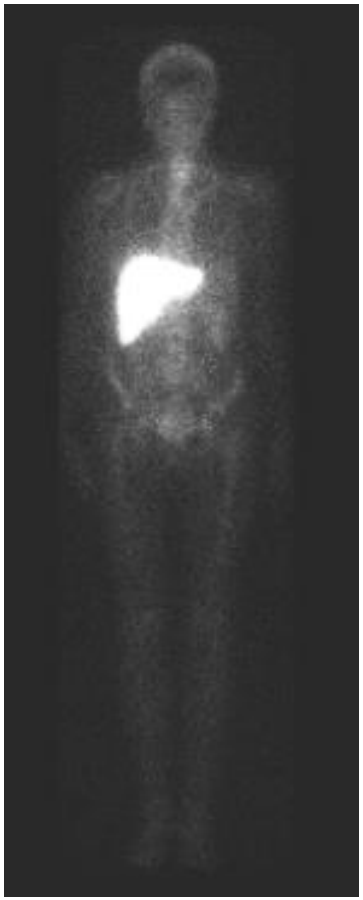
1 Hr. Anterior



24 Hr. Anterior



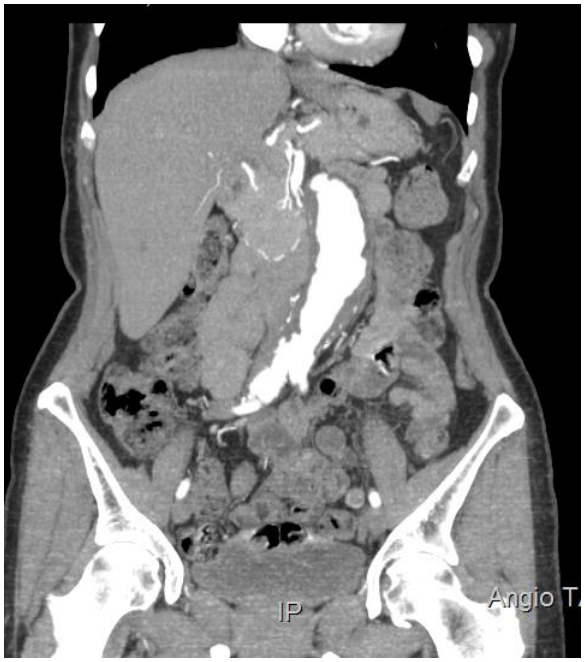
24 Hr. Whole Body

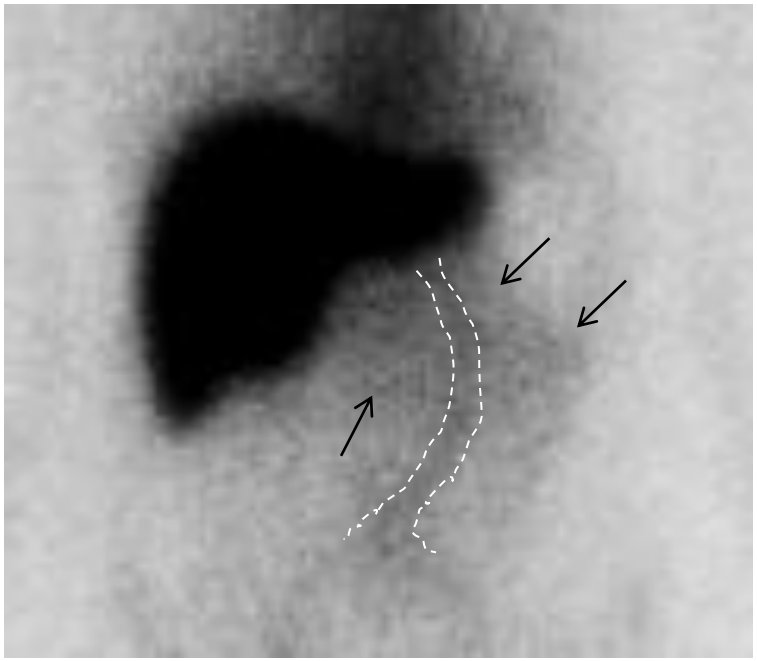


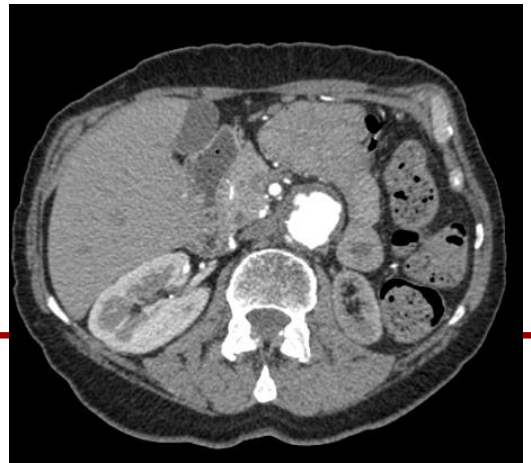
CAROTID #2 HUMAN CLINICAL STUDY

(Low Dose Study)

"THE DARKER AREA IN THE ANEURYSM IS THE LUMEN, THE HAZE AROUND IT IS THE INFLAMMATION INDUCED BY CLOT IN THE ANEURYSM." – H. WILLIAM STRAUSS, MD





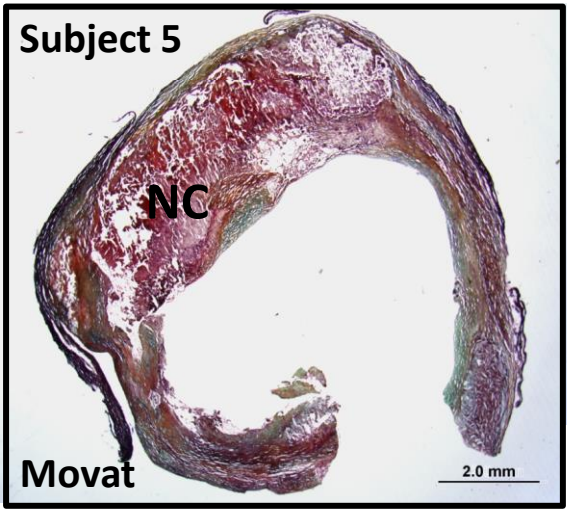


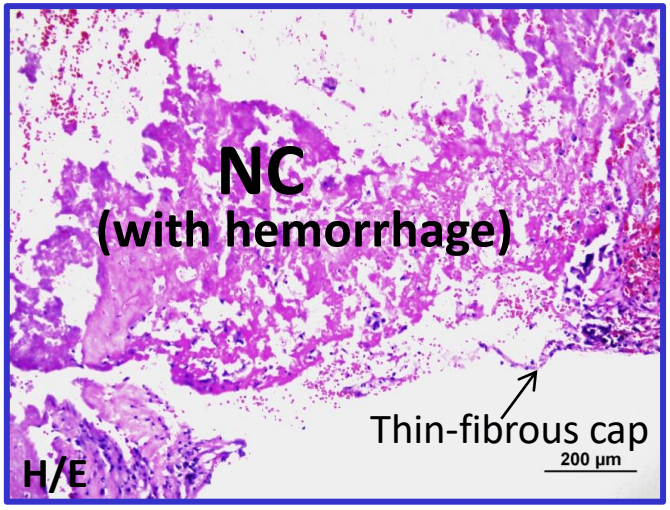
- Imaged an aortic aneurysm

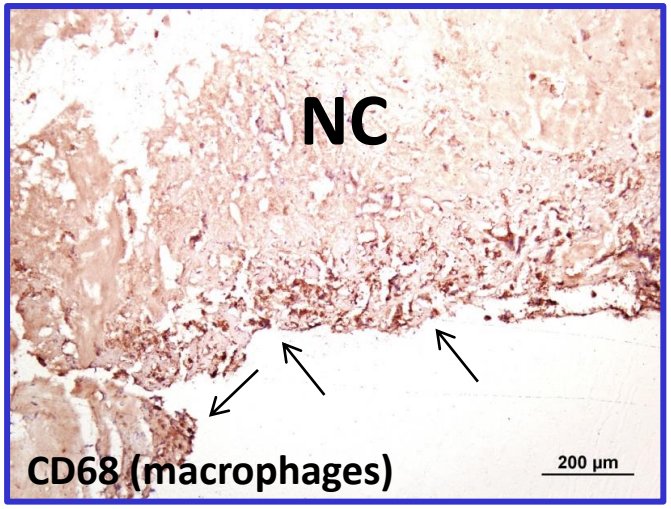
CAROTID #2 HUMAN CLINICAL STUDY

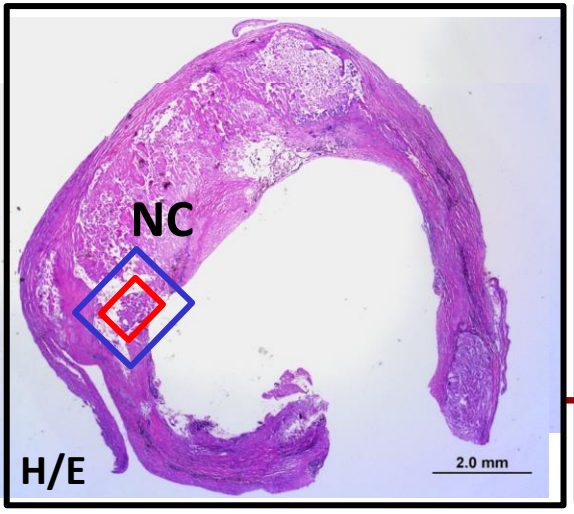
(Low Dose Study)

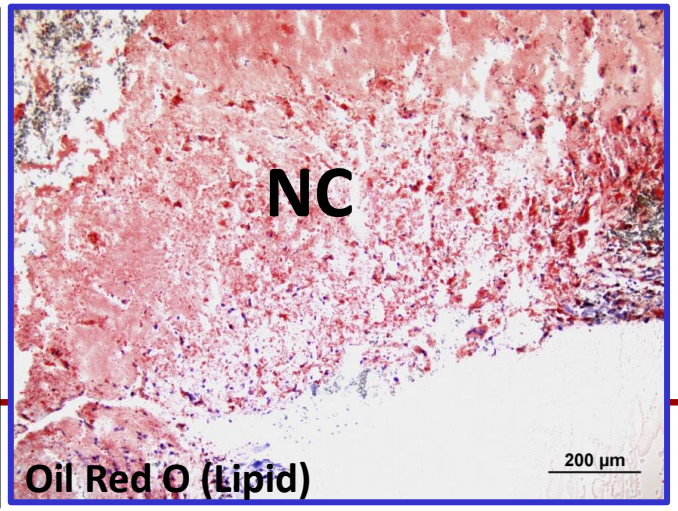
Two of 5 patients had vulnerable/ruptured plaque confirmed on histology containing excessive macrophages, lipid, and apoptotic bodies in the region of the necrotic core.

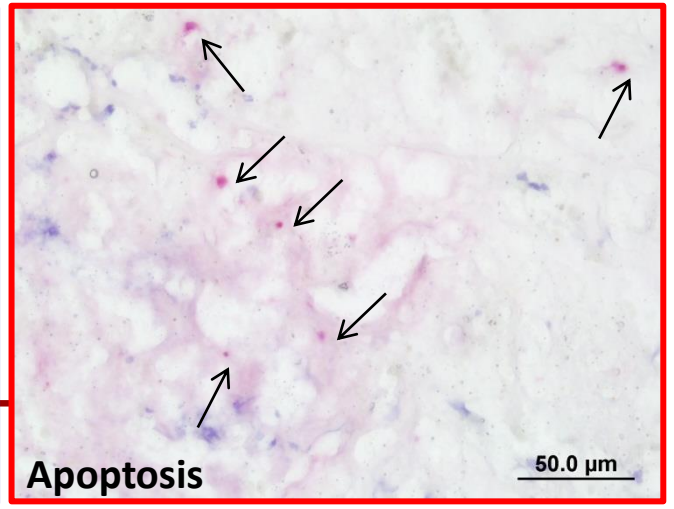












Summary

Simultaneous Localization and Treatment of Vulnerable Plaque by Tin-117m Conversion Electrons

- Tin-117m can be detected by existing gamma cameras / SPECT imaging and its therapeutic conversion electron has strong ionization effect over relevant biological range, while annexin V binds to specific cell membrane chemicals that are expressed in apoptotic macrophages.

- Injection of Tin-117 labeled annexin is associated with reduced expression of macrophages and greater expression of smooth muscle cells with greater collagen content and less apoptotic bodies in brachiocephalic arteries and sinotubular junction in a murine model of atherosclerosis.

- The first human carotid study with a very low dose (500 µCi) injection showed the tagged annexin in carotid arteries where histology confirmed the presence of vulnerable/ruptured plaques. No adverse effects were observed.

- The second human carotid study with a low dose (3 mCi) injection showed tagging of carotid plaques in 3 of 5 subjects where histology demonstrated the presence of vulnerable plaques in 2 subjects. Abdominal aortic aneurysm was also imaged by SPECT.

- A systemic injection of Tin-117m-DOTA-Annexin has a potential therapeutic effect in stabilizing vulnerable atherosclerotic plaques that can be measured by imaging modalities. The therapeutic utility of this agent should be confirmed by further human clinical studies.

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