

# Regional Therapy for the Atherosclerotic Plaque:

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# Focal and Regional Therapy for Vulnerable Plaque

- Balloon Angioplasty Plaque Sealing
- Stent Design Considerations
- Drug-eluting Stents (DES)
- Bioabsorbable Stents
- Photo Dynamic Therapy (PDT)
- Sonotherapy
- Cryotherapy

# Photodynamic Therapy

## The Dental Approach Regional Therapy



Please no stents



Post PDT

# Photodynamic Therapy

## *What are the “treatment imperatives” ...*

- PDT involves the interaction of a photosensitizing drug, light and tissue oxygen.
- Photosensitizing agents, many of which are porphyrins or chemicals can be given locally or systemically.
- The timing of light delivery is crucial for achieving the biological response.
- PDT generates free radicals, which exerts its cytotoxic effect at the site of the light irradiation, results in changes in proteins and lipids.

# Who Involves in PDT for atherosclerosis

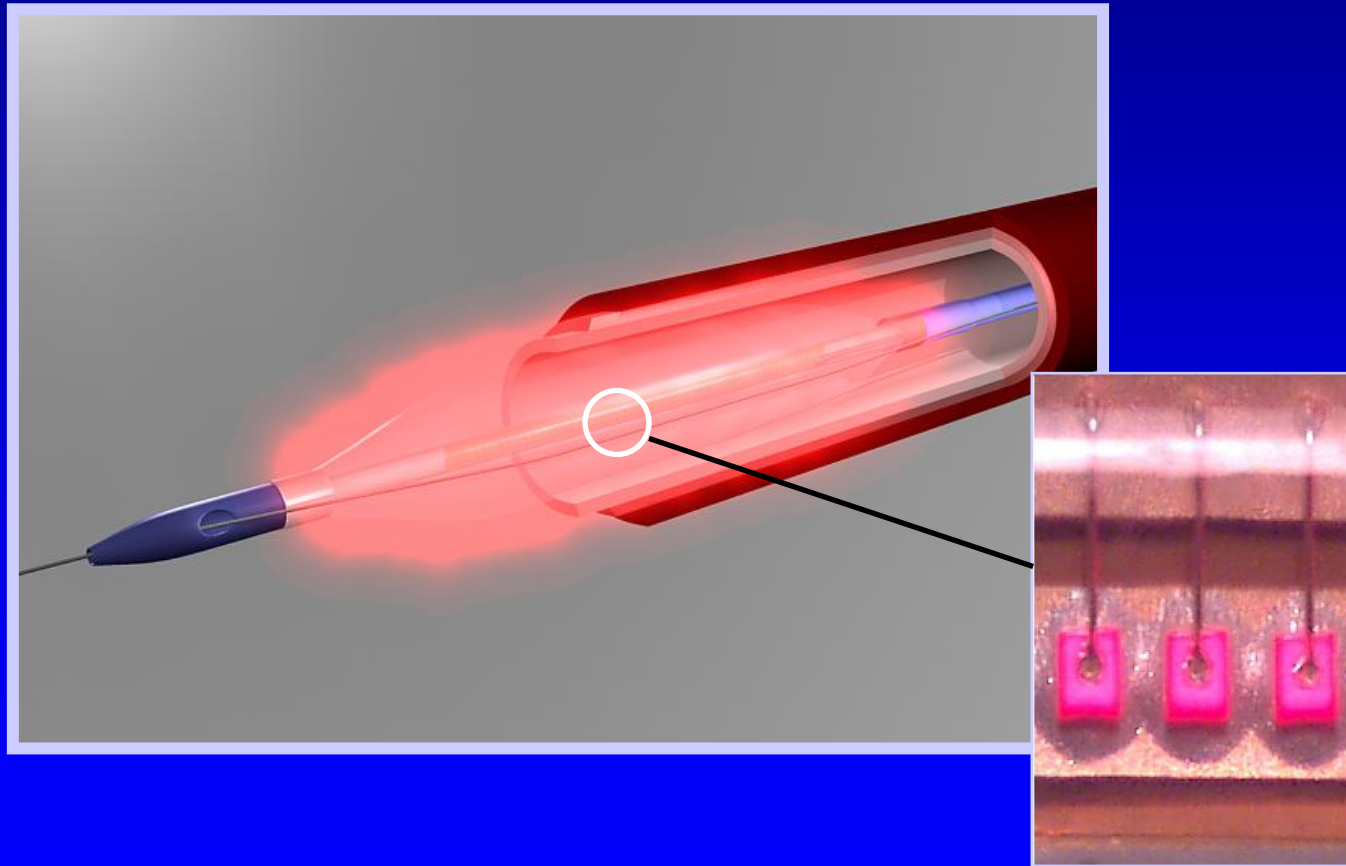
- Pharmacyclics      Antrin      Clinical
- Mirvant/Guidant      MV 0611      Preclinical
- Light Sciences      LS11      Preclinical

# Photoreactive agent: LS11

- Amphiphilic molecule - water soluble
- Not metabolized
- Strong fluorescence at 675 nm
- Minimal skin photosensitivity in man
- LS11 is approved in Japan for oncology use
- Phase 2 cancer and retinal trials ongoing

# Light Infusion Technology™

LS11 activated with endovascular LED  
– no need for laser

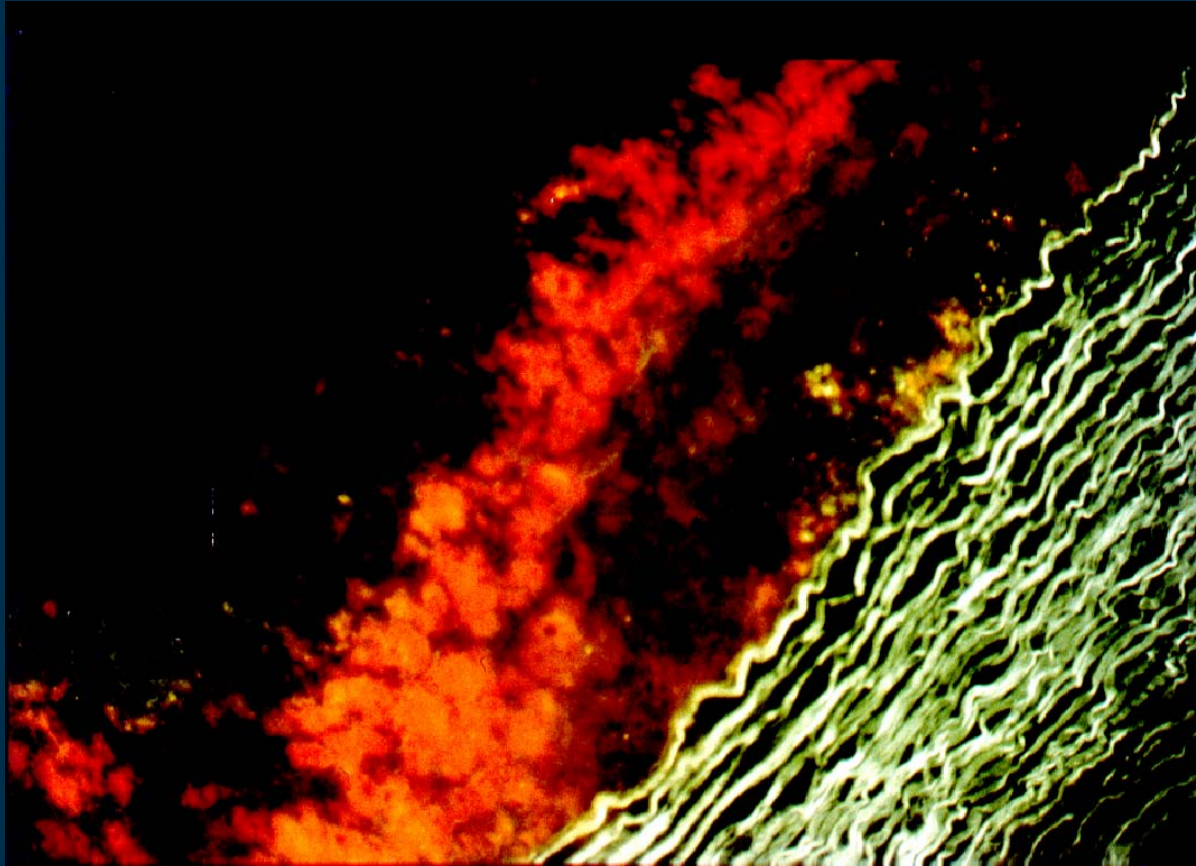


# Properties Specific to LS11

- Ultra-short interval between drug delivery and light activation
  - Activation 5-10 mins after infusion
- Low light dose required
  - Short procedure time with brief blood-flow occlusion for light activation
- Systemic safety in man
- Selective accumulation in atherosclerotic plaque<sup>1,2</sup>



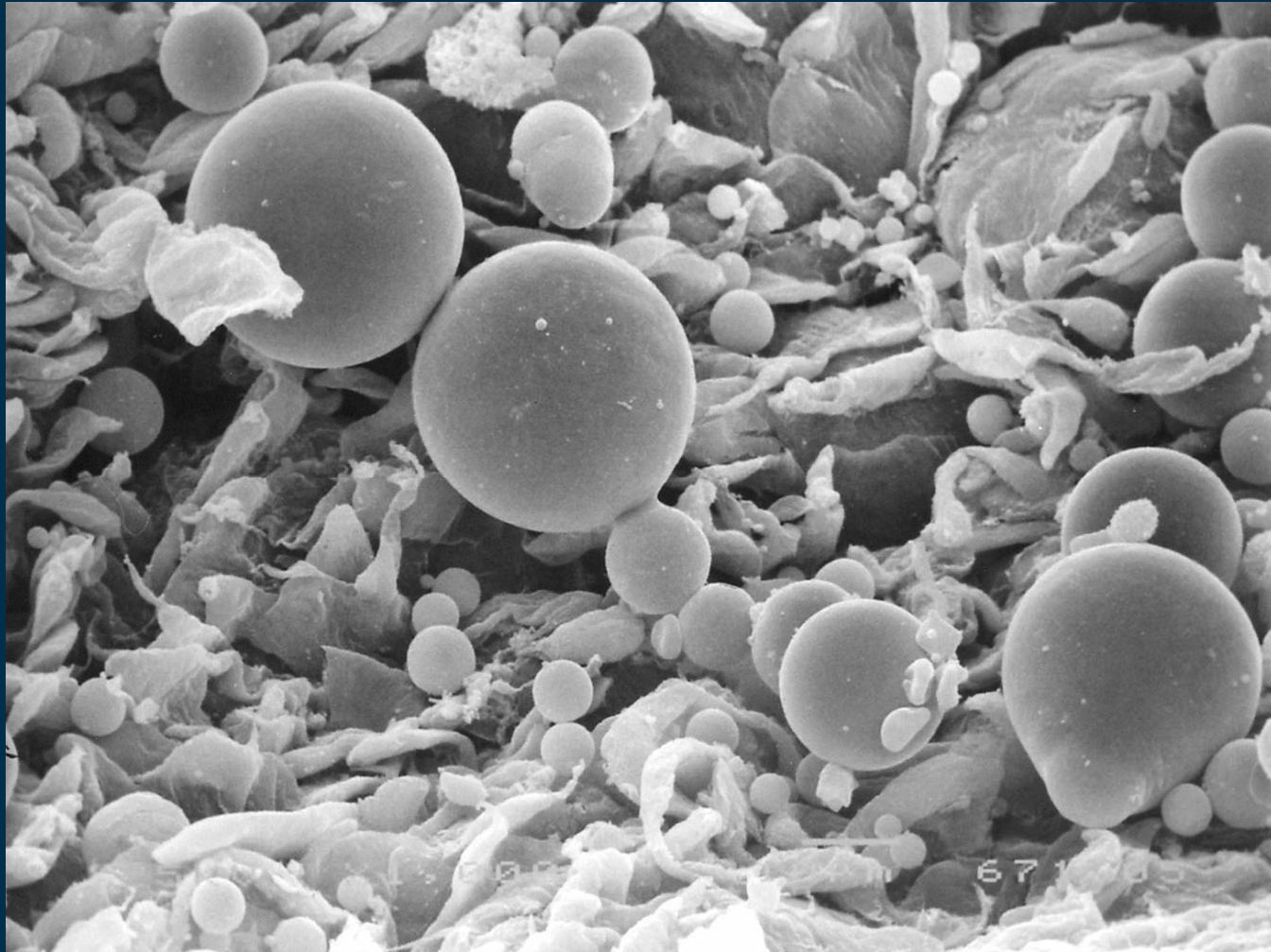
# Selective Plaque Accumulation



LS<sub>11</sub> revealed in atherosclerotic plaque in rabbit aorta using  
fluorescence microscopy

*Image through courtesy of Dr K Aizawa, Tokyo Medical University*

# Photo-atherolysis?



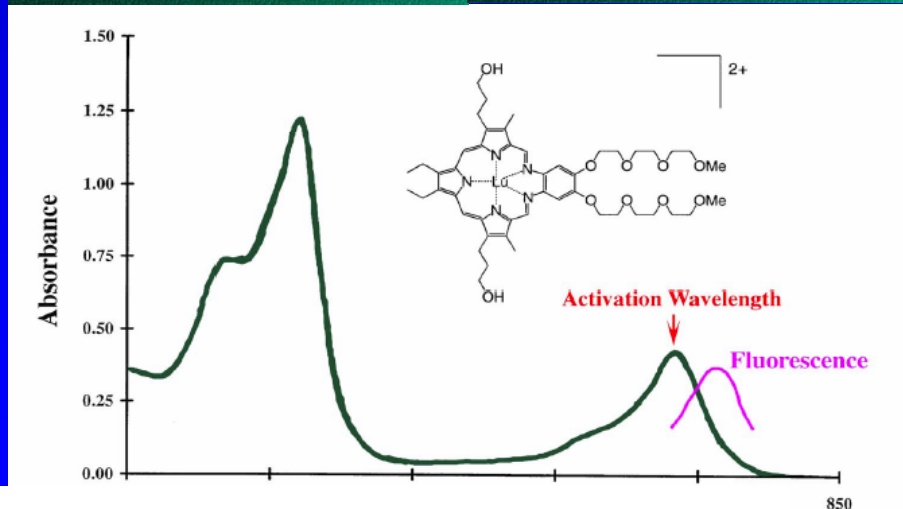
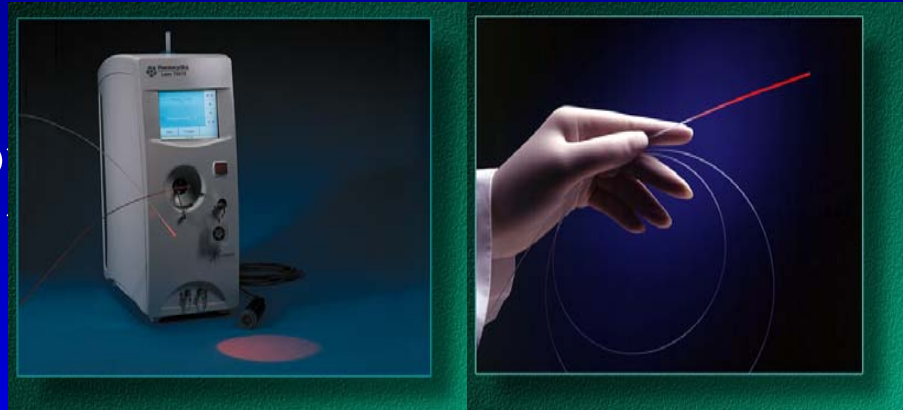
Dissociation of plaque lipid after LS<sub>11</sub> PDT treatment

(Saito T et al. Tokyo, J)

# Motexafin Lutetium (MLu) Phototherapy

*A novel experimental therapy  
being tested for the treatment of atherosclerosis*

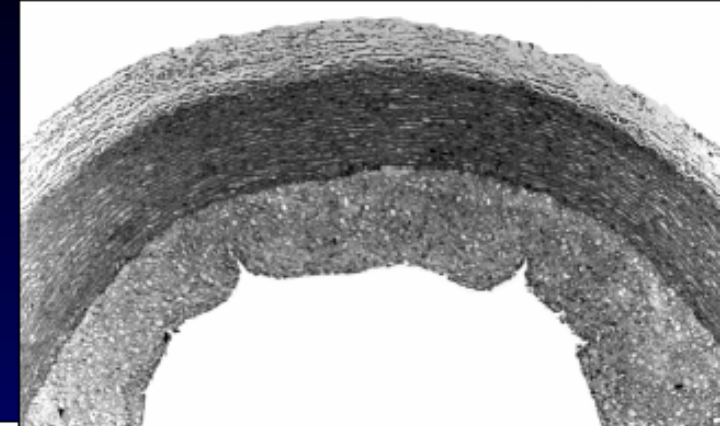
- Expanded porphyrin (motexafin lutetium, Antrin<sup>®</sup>)
- Excited by red light that penetrates tissue and blood
- Water soluble, synthetic
- Enhanced binding to LDL
- Localizes in atheroma
- Short plasma half life



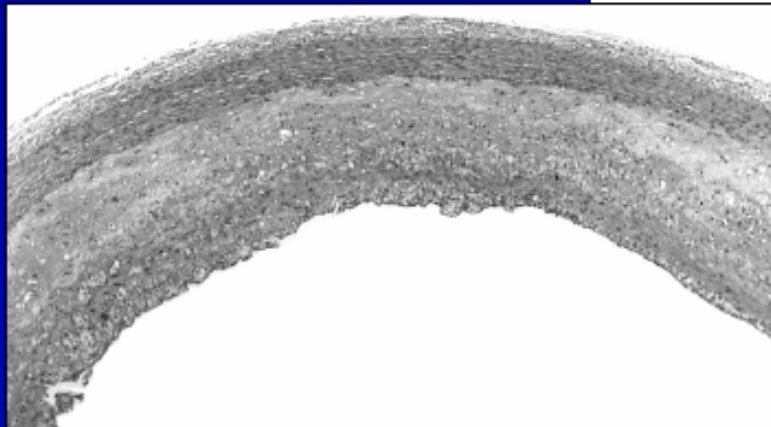
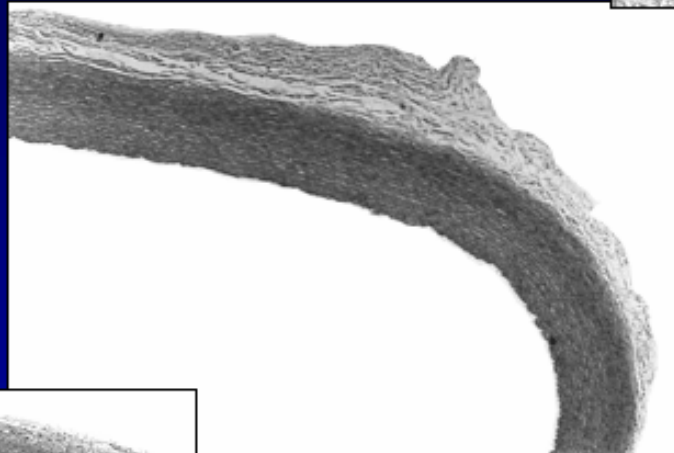
Far red light ~730 nm light treatment 941 sec to achieve 400 J/cm

# Histology

## *Hyperlipidemic Rabbit Model*



Above



Below

### Treatment Site

*Mean % plaque area @ 2 weeks:*

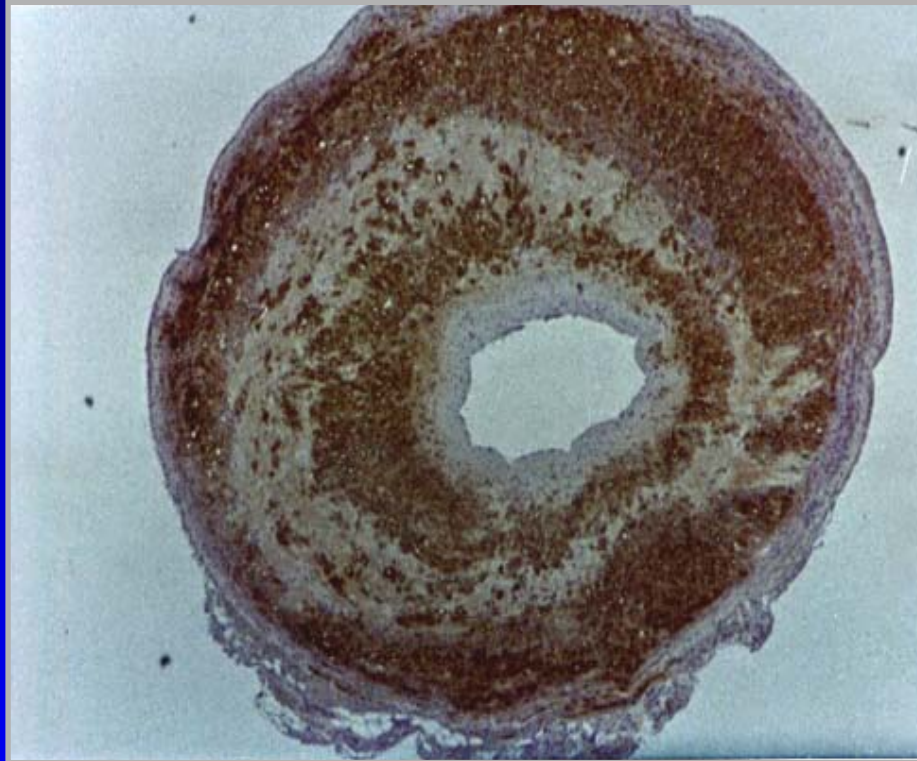
Control (36) 82%

PDT (40) 73%

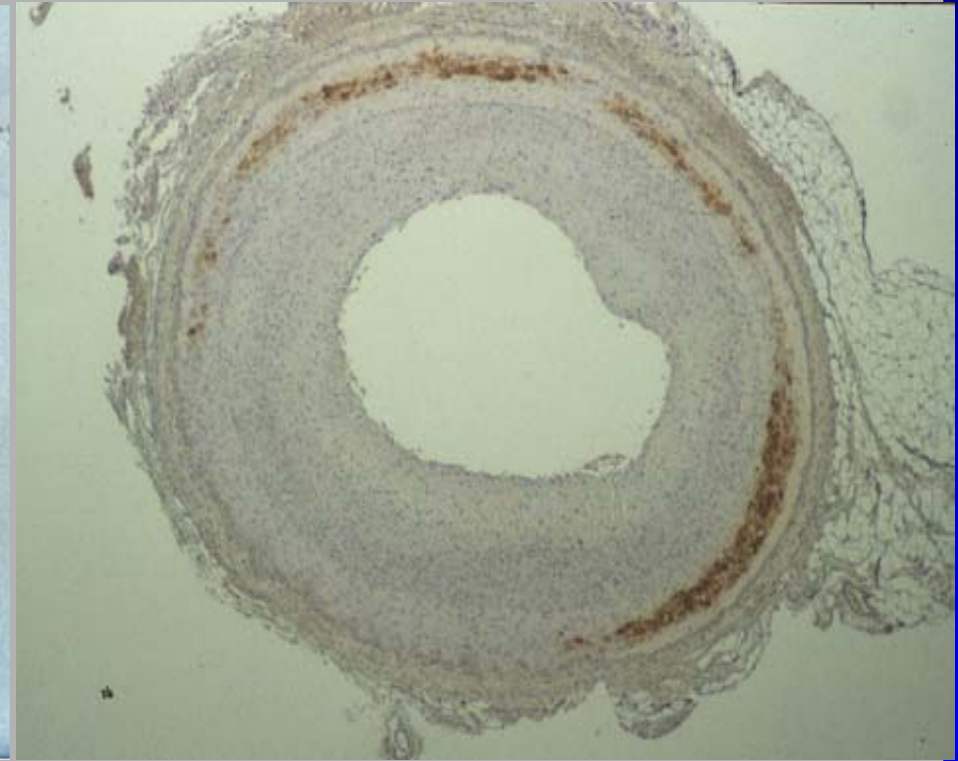
$p < 0.001$

# MLu Phototherapy: *Effect on Macrophages*

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**Control**



**Treated**

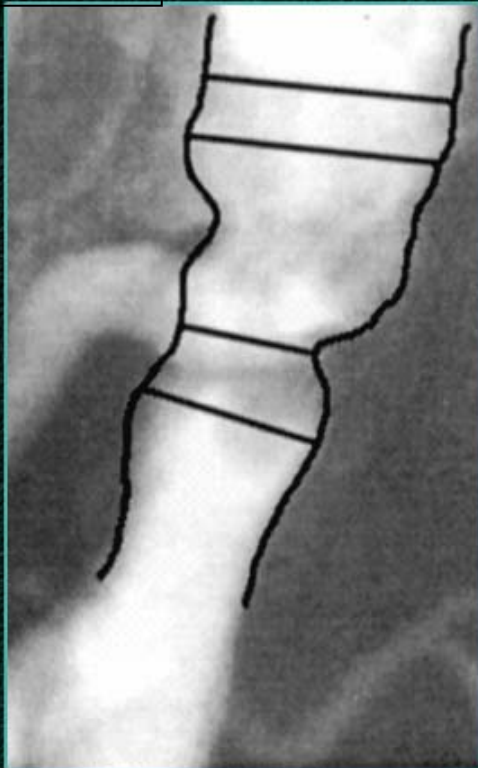
Immunoperoxidase staining with RAM11

Hayase M, et al. *Cardiovascular Res.*  
2001;49:449-55

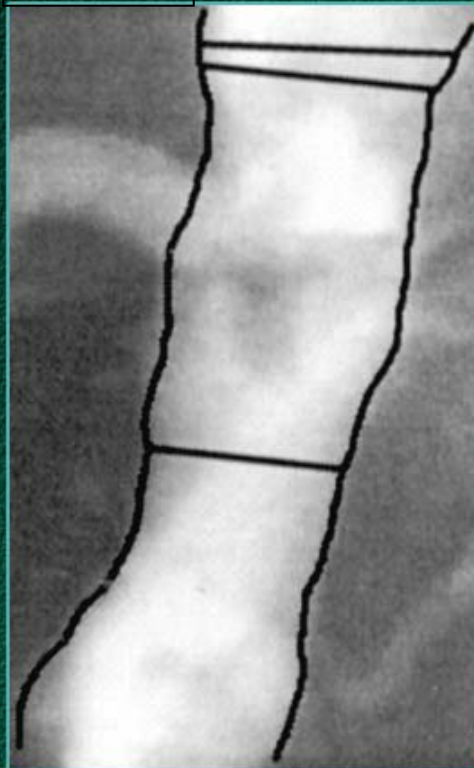
# Motexafin Lutetium Phototherapy

## *Peripheral Arterial Disease: Angiogram Results*

*Day 0*



*Day 28*



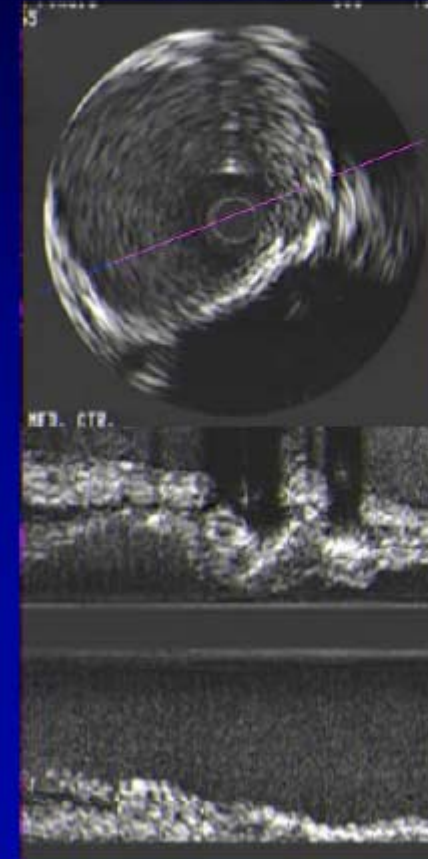
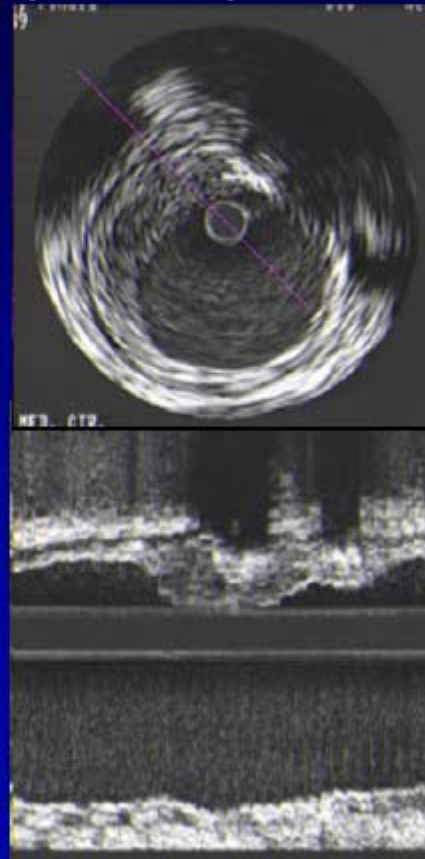
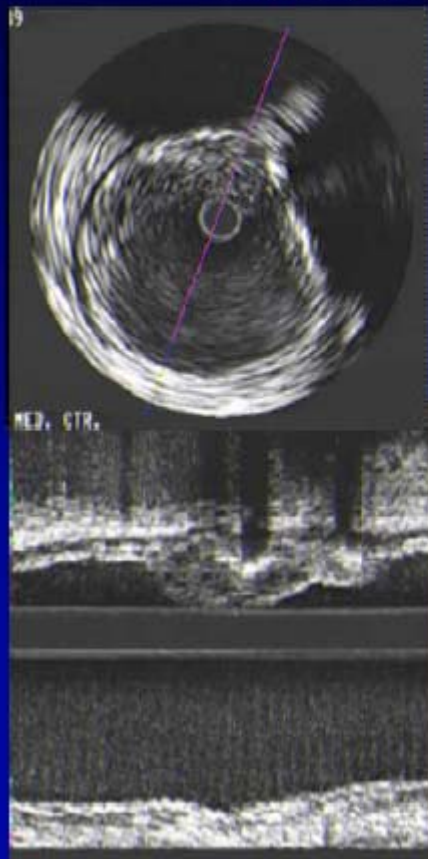
Quantitative  
Angiography  
Demonstrates 50%  
Improvement in  
Luminal Diameter

# Photoangioplasty for Human Peripheral Atherosclerosis Results of a Phase I Trial of PDT with Motexafin Lutetium (Antrin)

## Non Critical Lesion - Peripheral Antrin Study

BASELINE (No PTA)

6 Mo FUP



# Phase 1 PAD Study Summary and Conclusions

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- Motexafin lutetium phototherapy was well tolerated with no adverse vascular responses seen at 28 days following treatment
- No evidence of deleterious effects on treated arterial segments
- A potential role for motexafin lutetium phototherapy in the treatment of atherosclerosis is supported by angiography, IVUS, ABI and clinical outcome measures

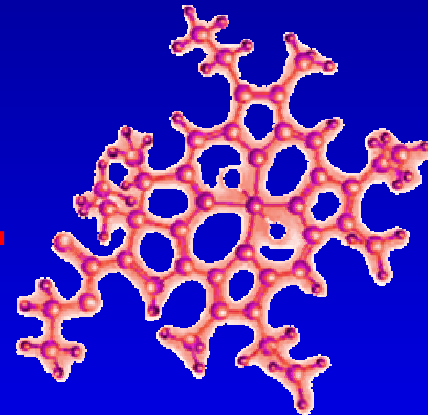


# MIRVANT PROGRAM

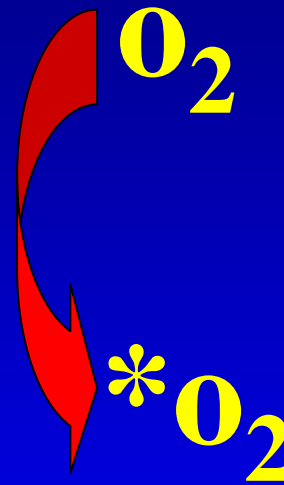


**Miravant  
Light Catheter**

+



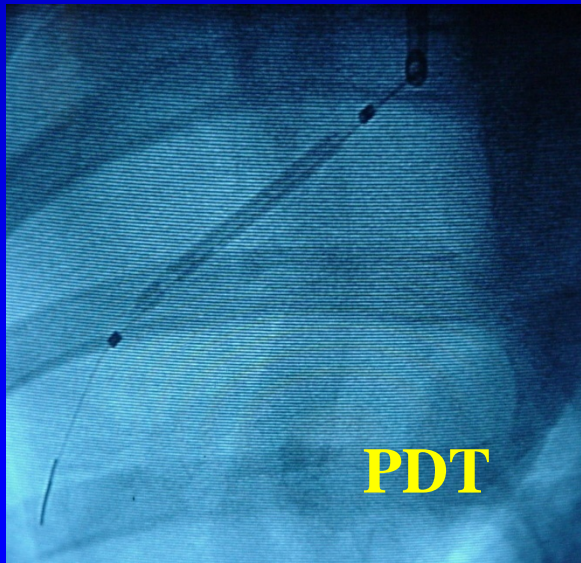
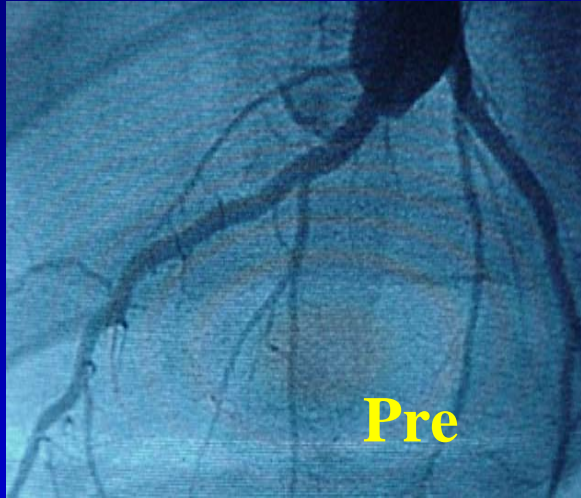
**Miravant  
Photosensitizer  
Compound  
(MV0611)**



**Cell  
Depletion**

**Biological  
Response**

# Coronary Artery PhotoPoint PDT Procedure

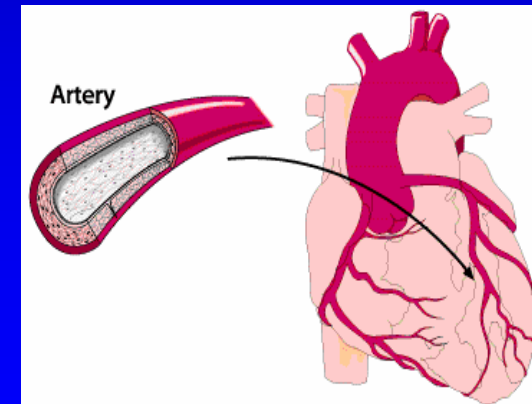


PDT zone to prevent geographic miss

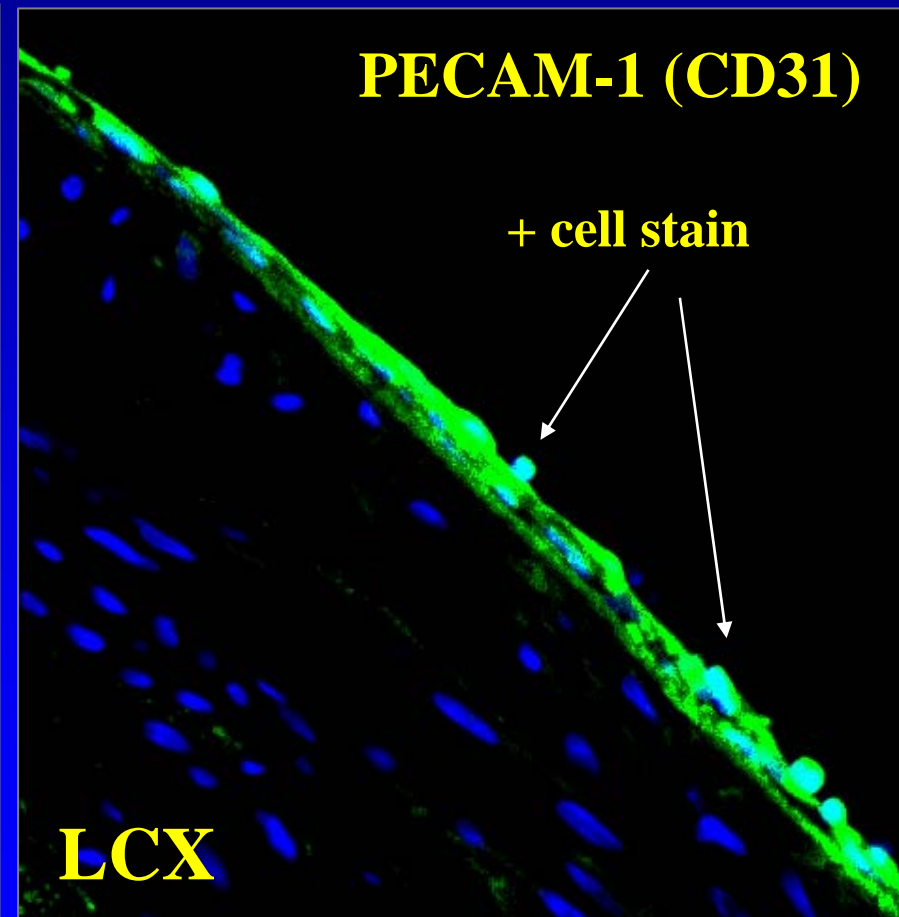
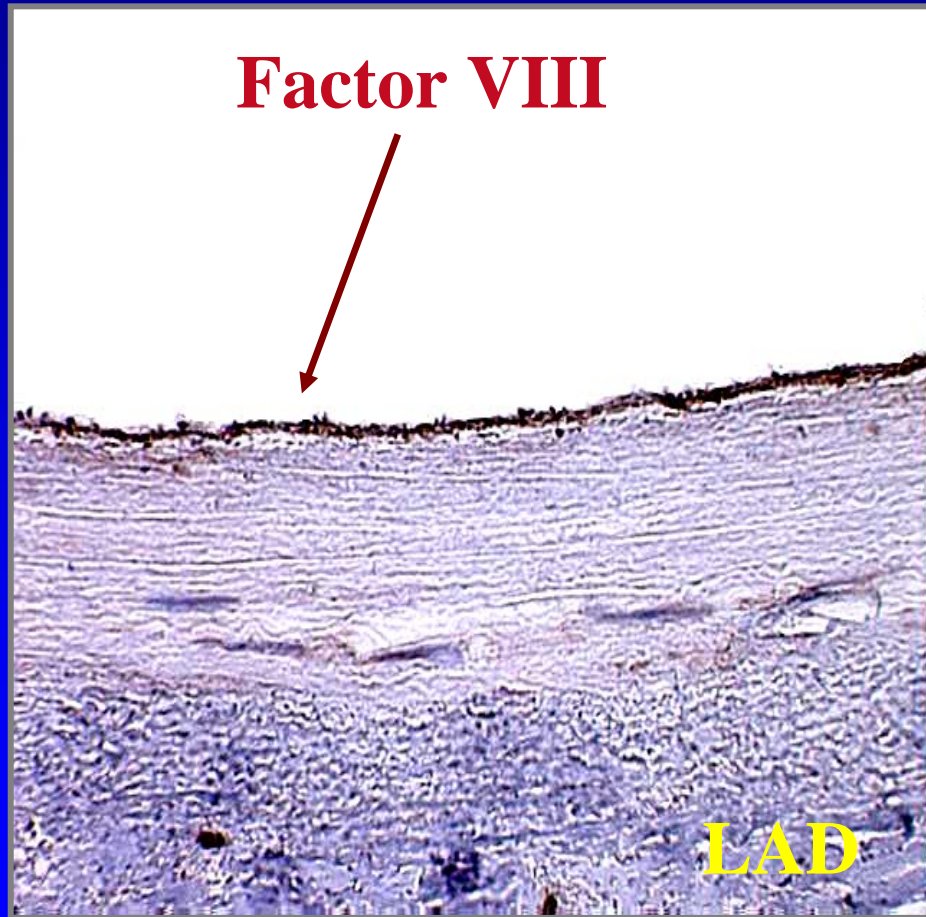
PTCA Balloon (2cm)

Artery

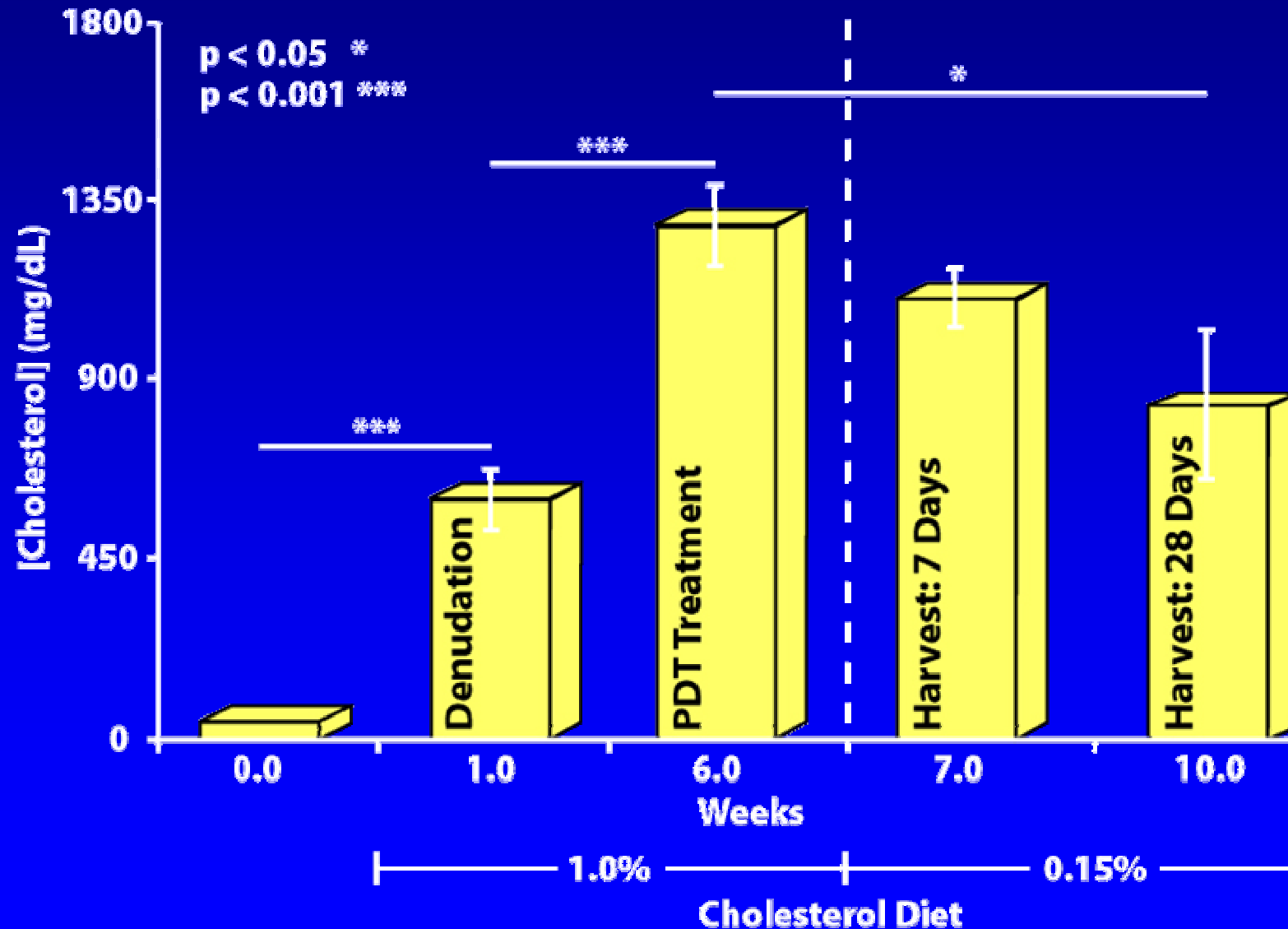
Light Device (3cm)



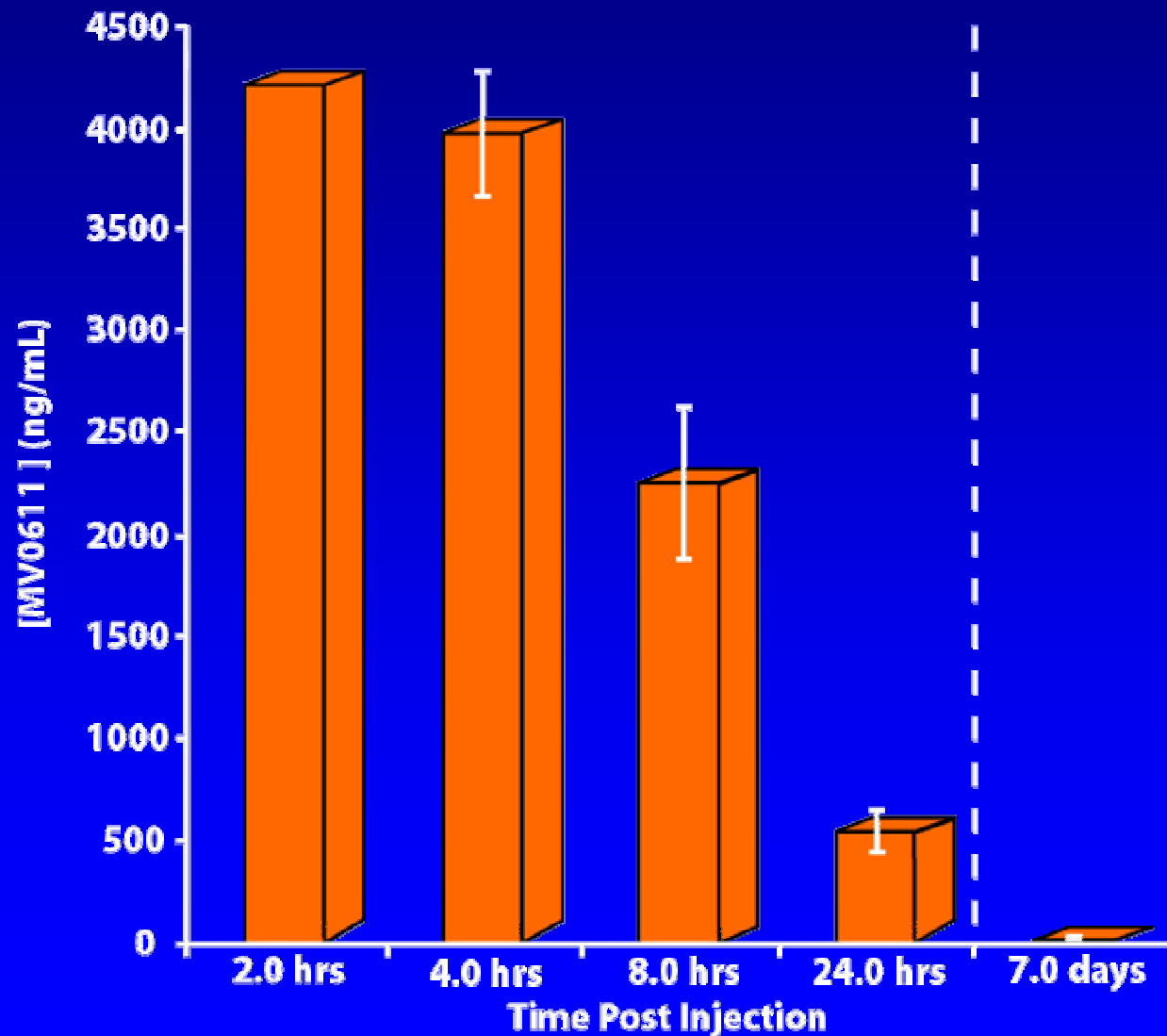
# Re-endothelialization @ 14 Days after Intracoronary PhotoPoint + Angioplasty



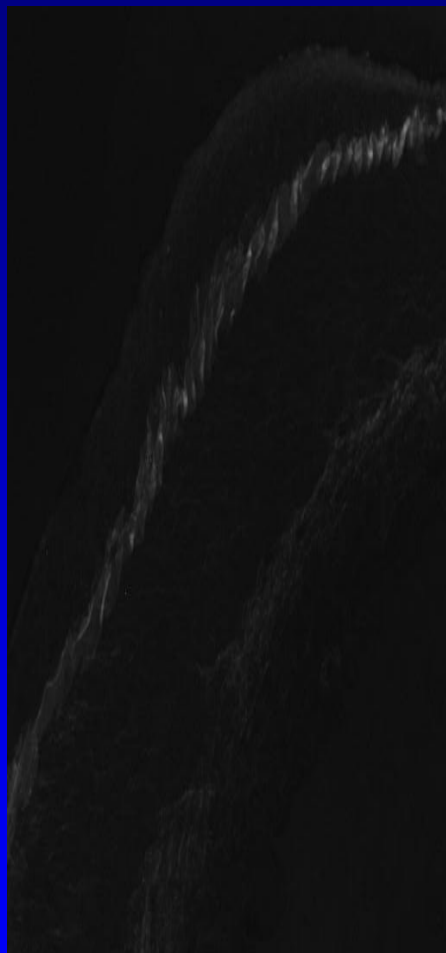
# Plasma Cholesterol Values in Hypercholesterolemic Rabbits



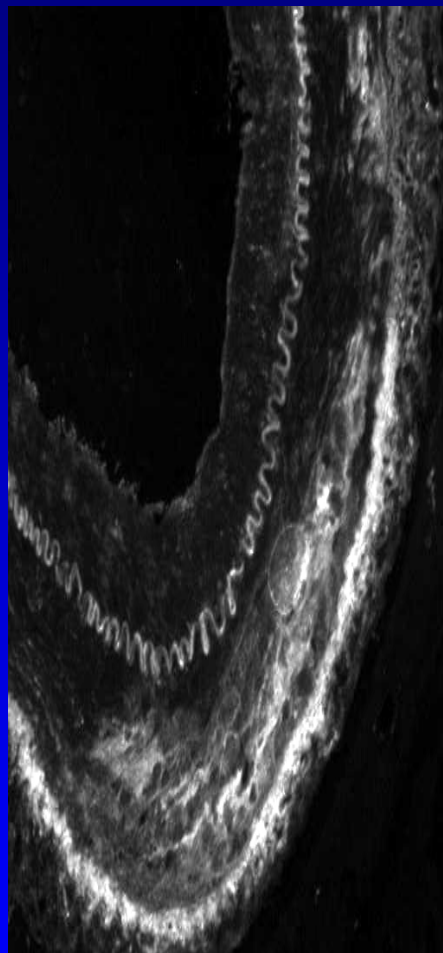
# Plasma MV0611 Concentration in Hypercholesterolemic Rabbits



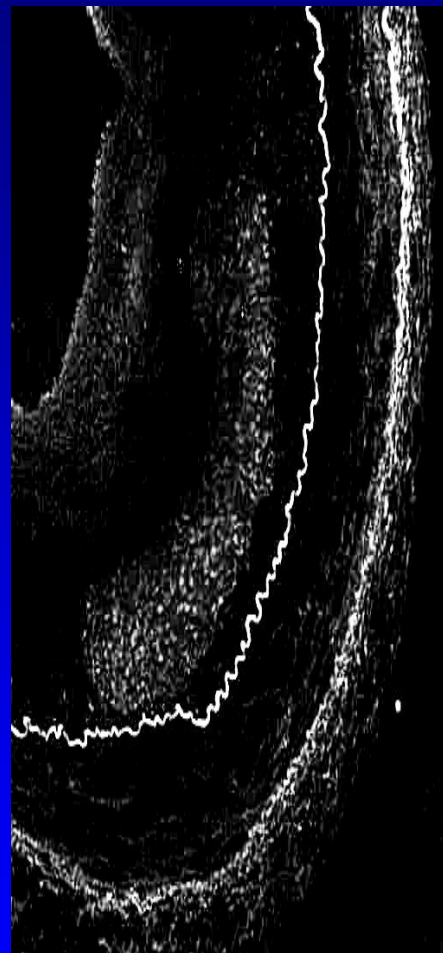
# Tissue Distribution of MV0611



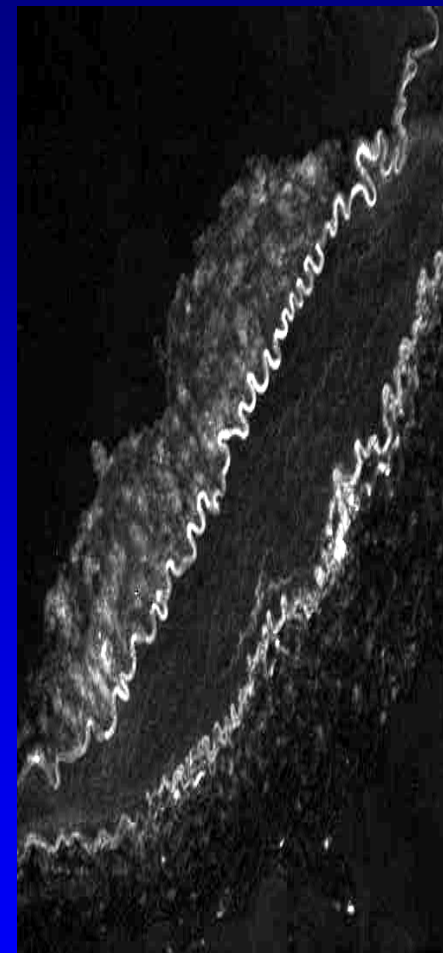
Control



4 hours



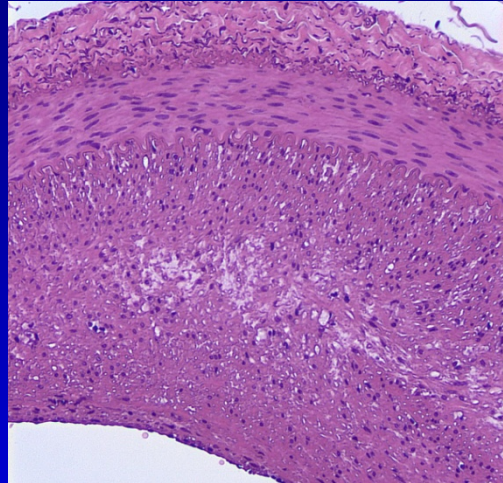
8 hours



24 hours

**Autofluorescent Drug Localized in Plaques**

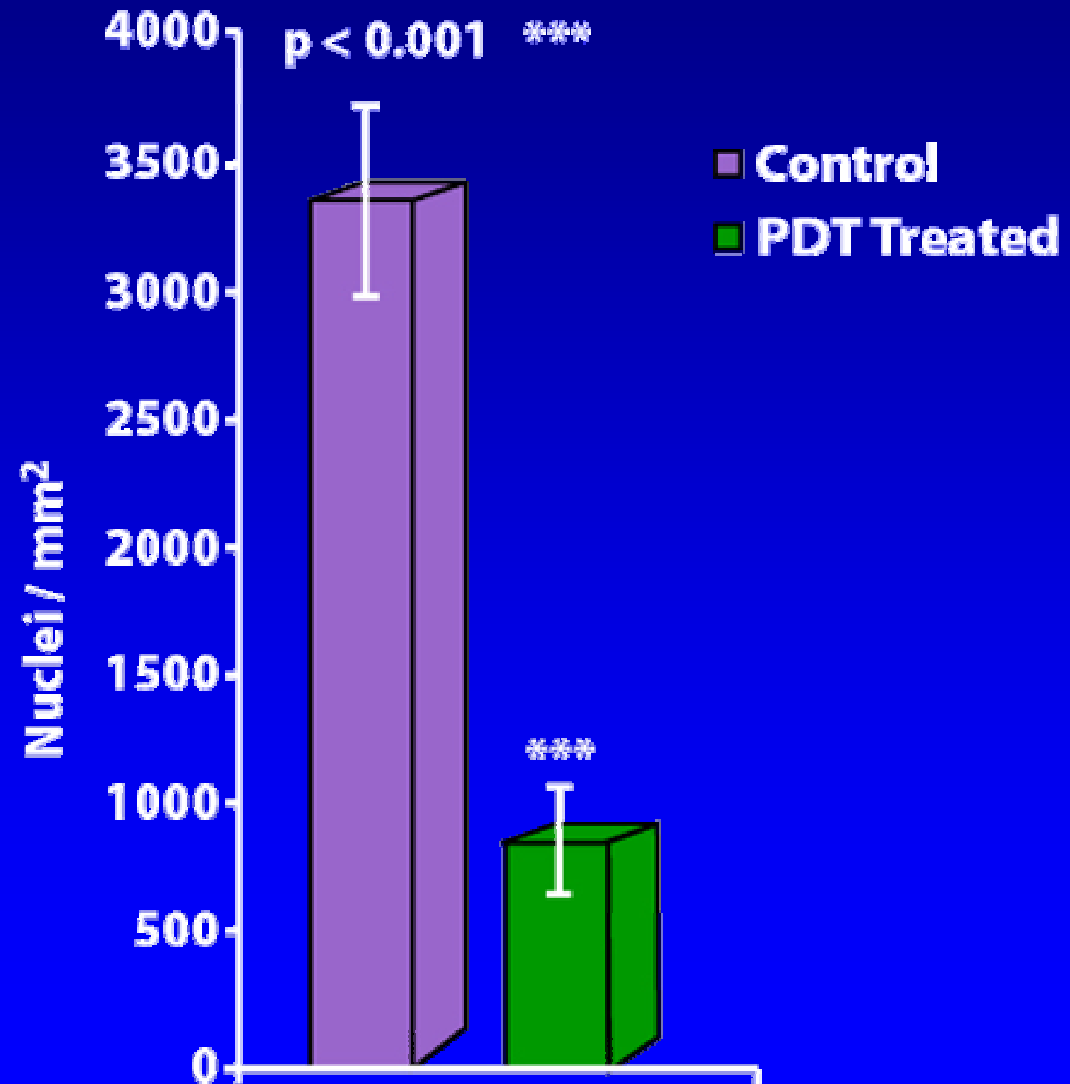
# Effect of PhotoPoint PDT on Plaque Nuclei (8.0 Hours Drug Incubation)



Control

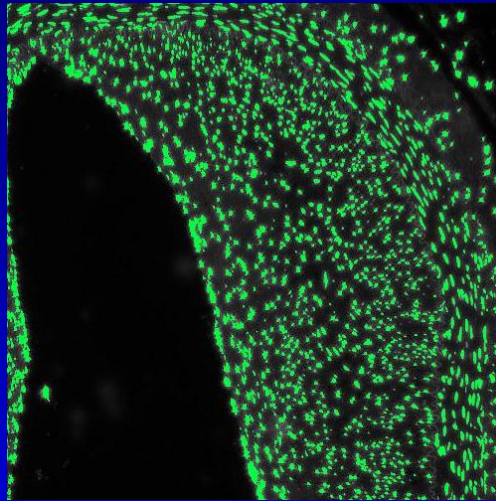


PDT Treated

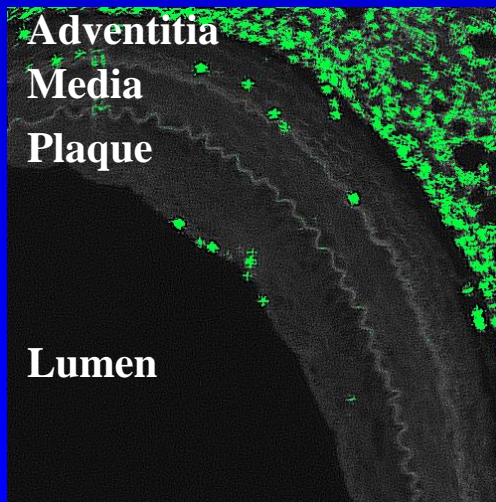


# Targeted Reduction of Nuclei

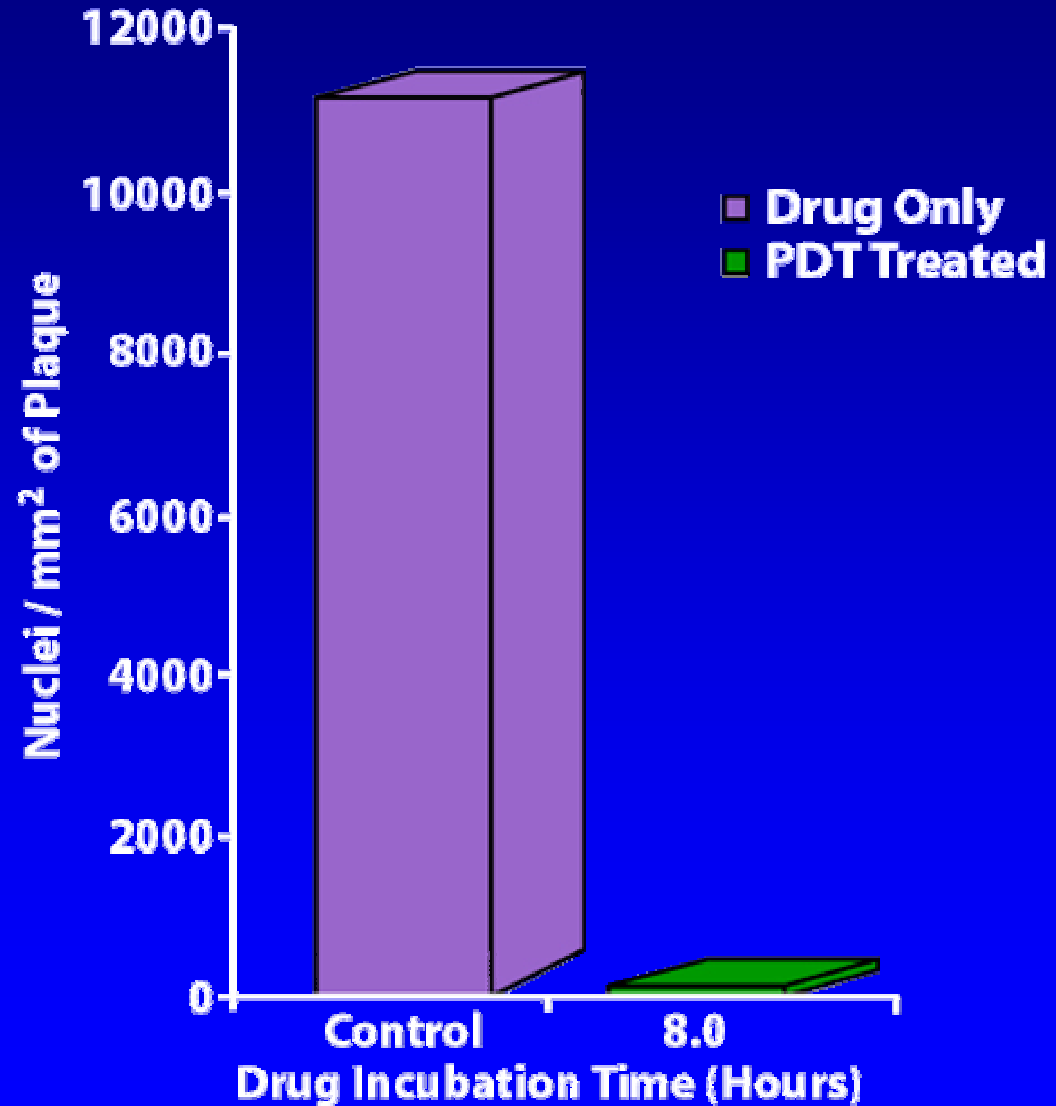
## DAPI Nuclear Stain



Control

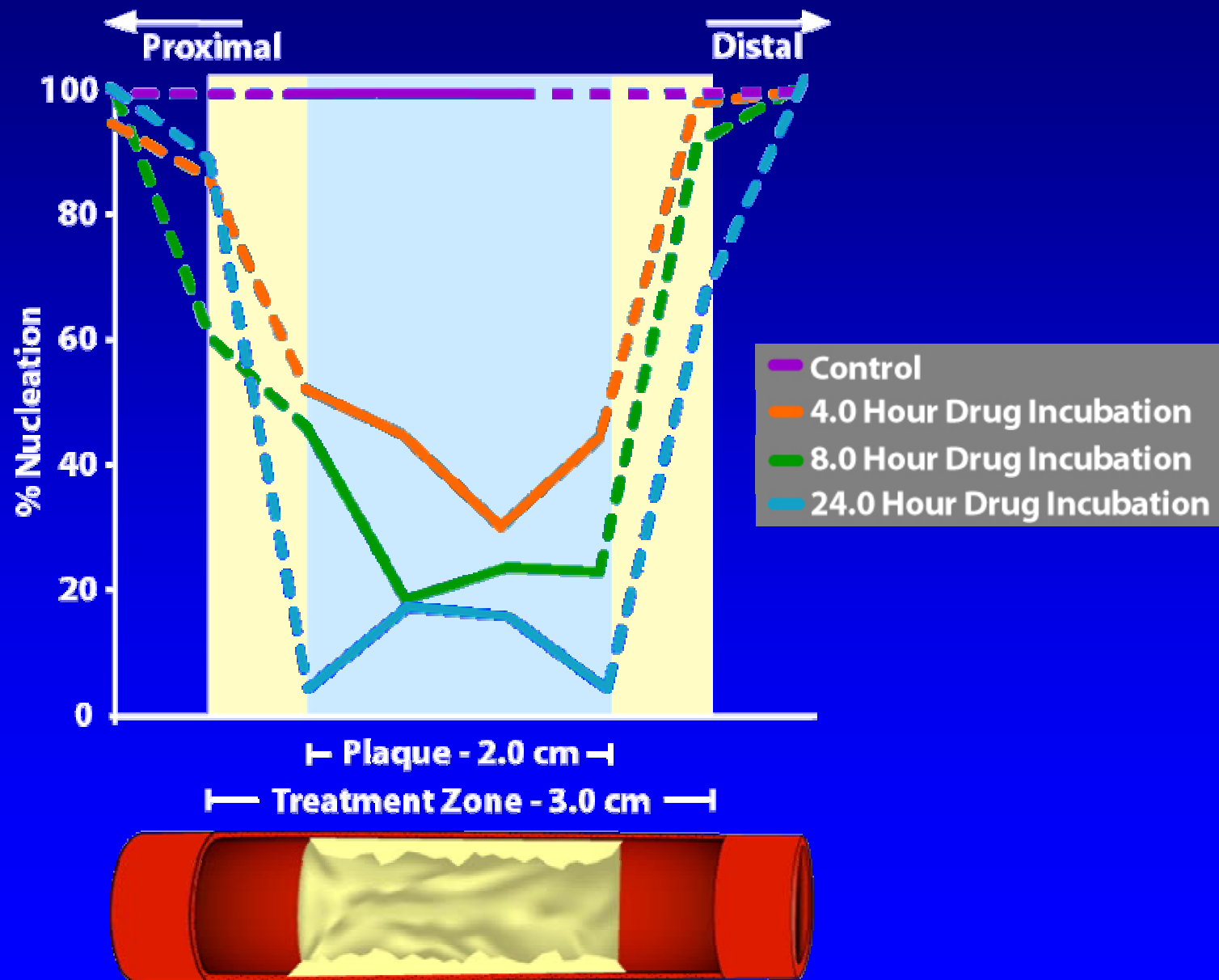


PDT Treated

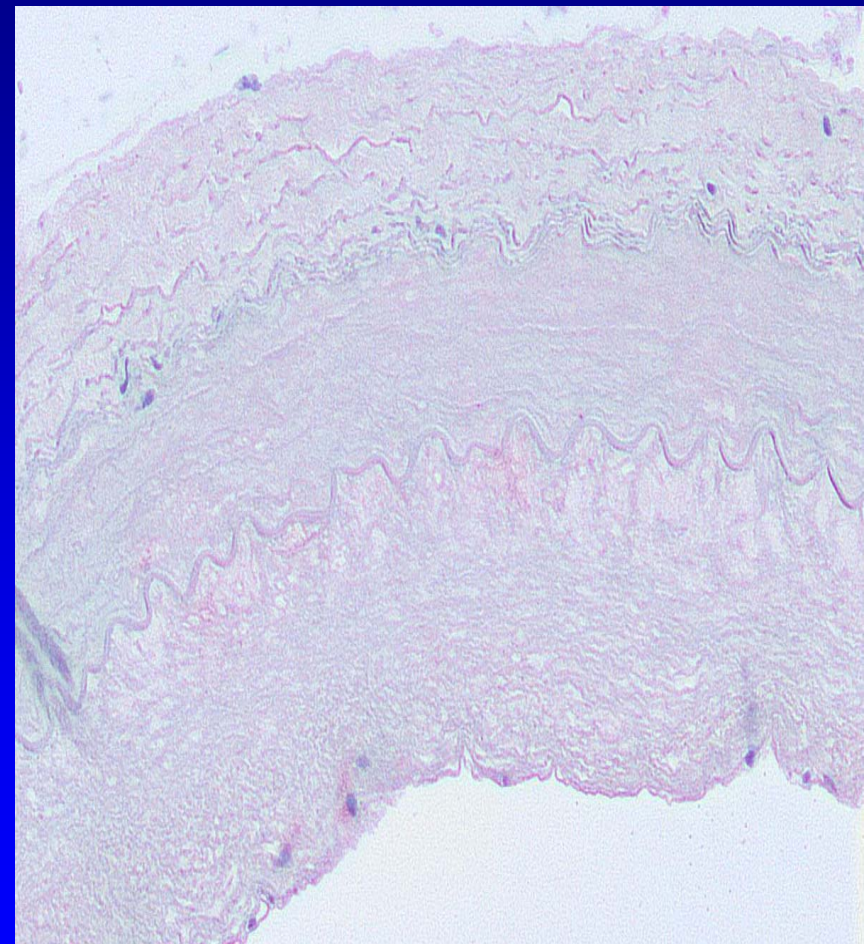
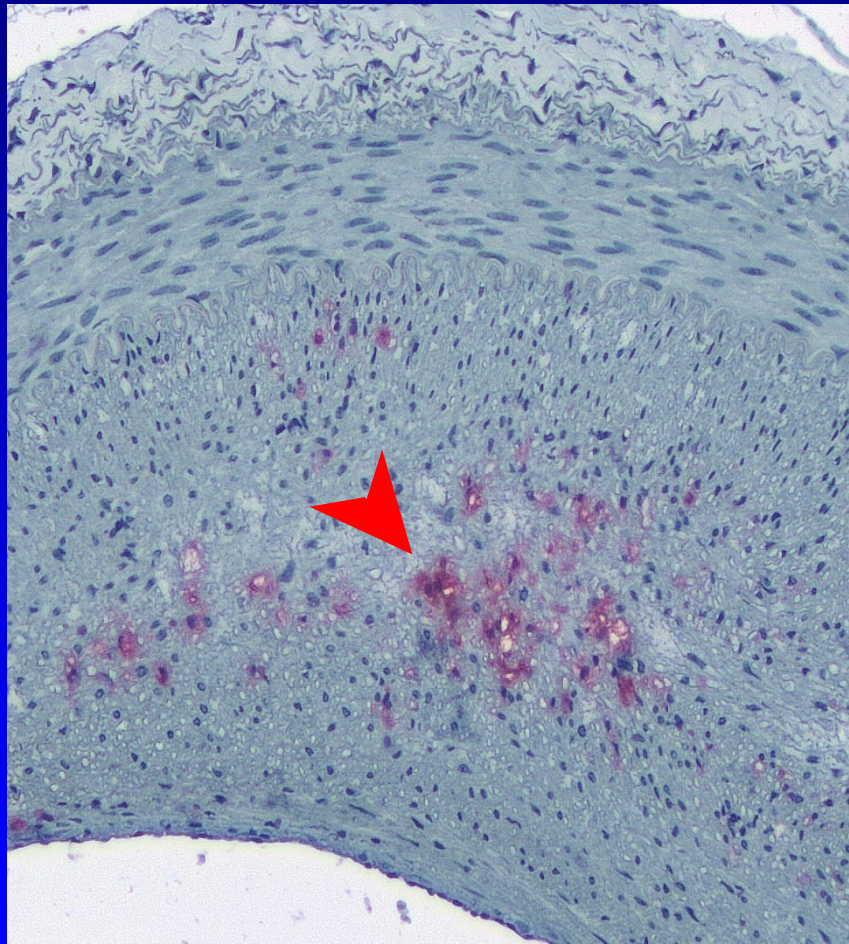




# Effect of PDT on Entire Plaque Lengths

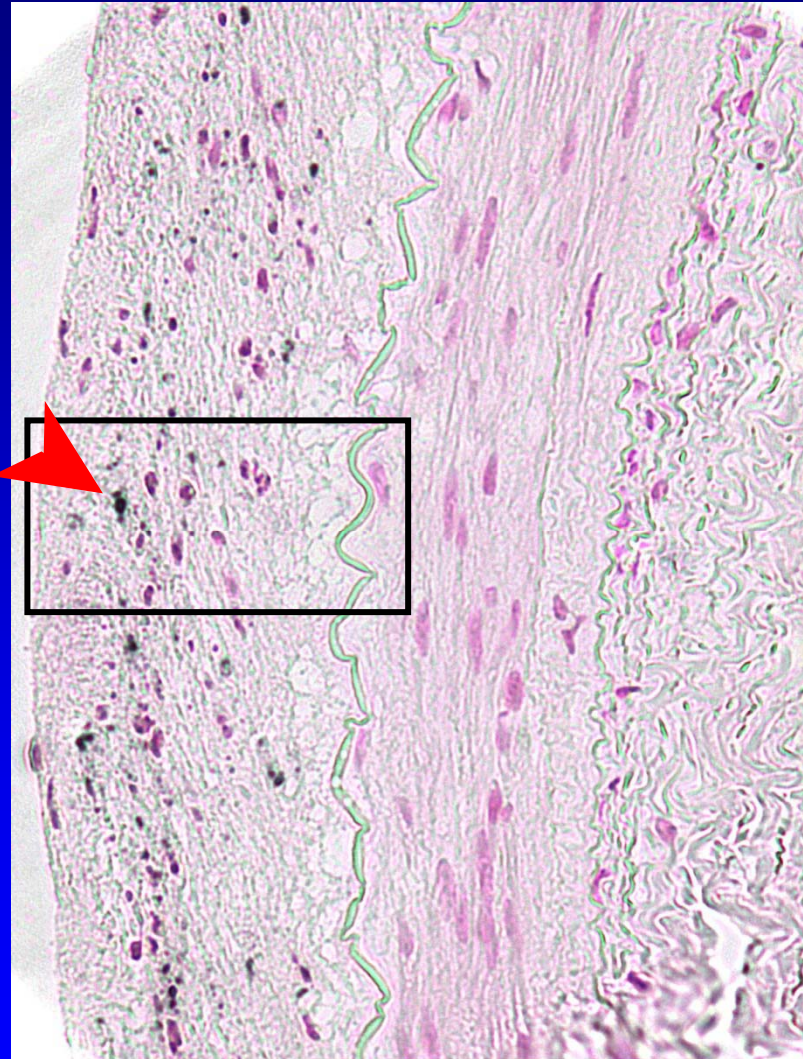
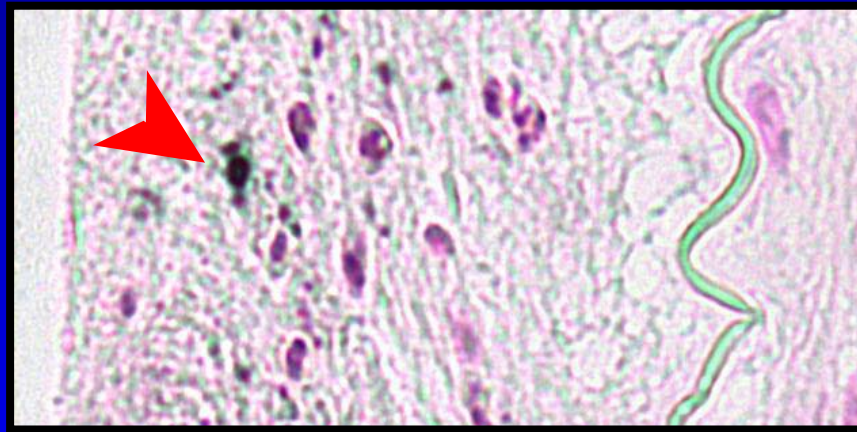


# PDT Induced Loss of 'Foam' Cell Macrophages



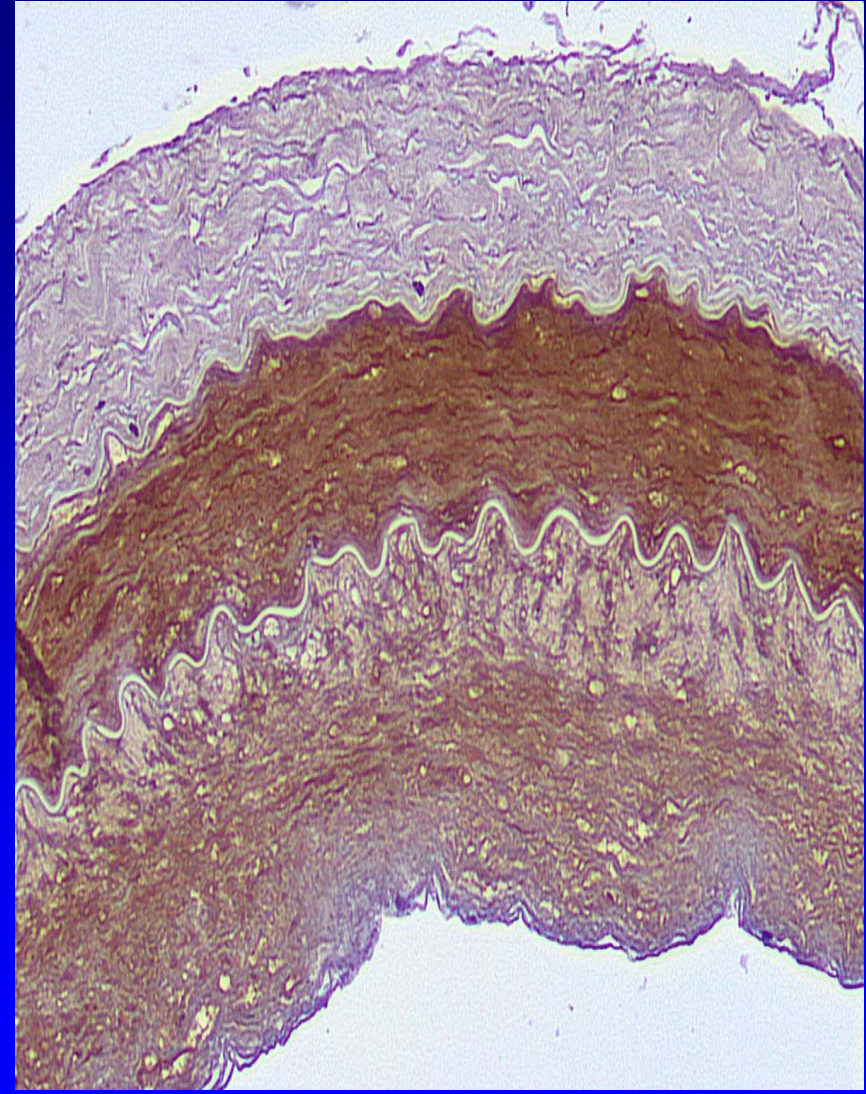
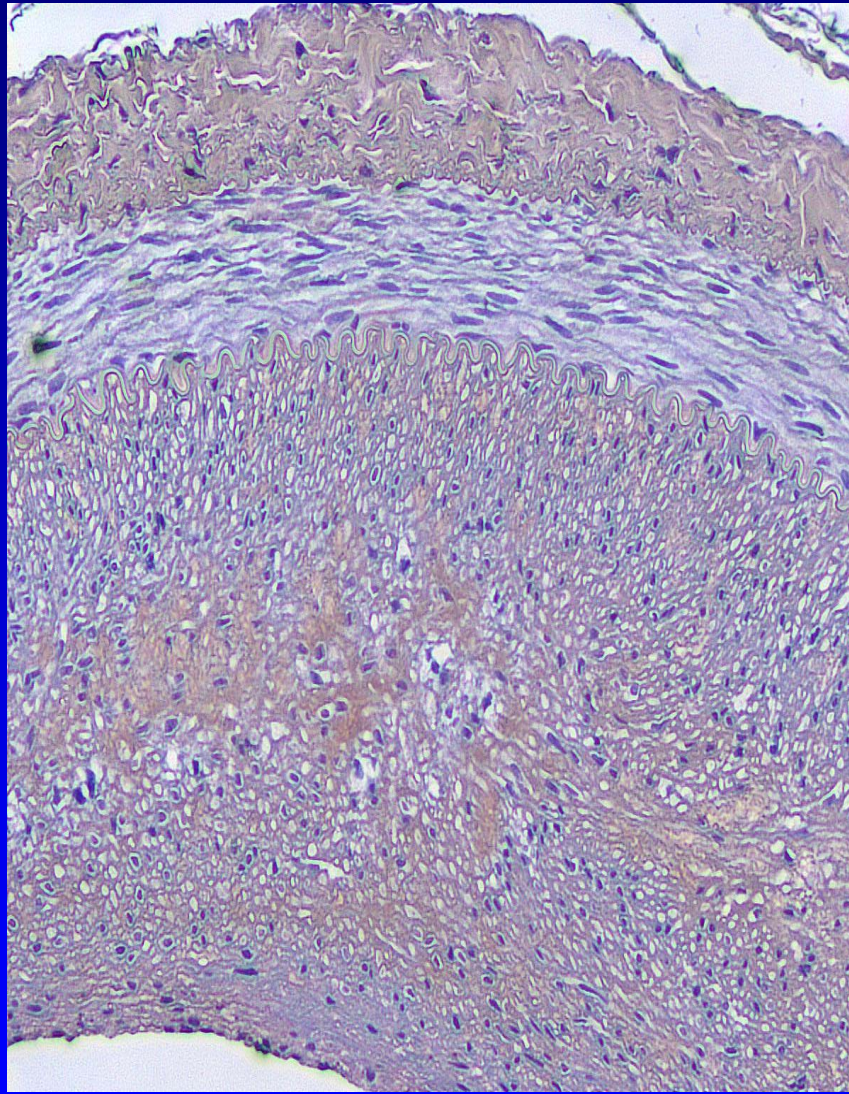
**Complete Elimination of Macrophages**

# DNA Fragmentation (TUNEL)



**Apoptosis of Atherosclerotic Plaque Cells *In Situ***

# Increased P53 Expression



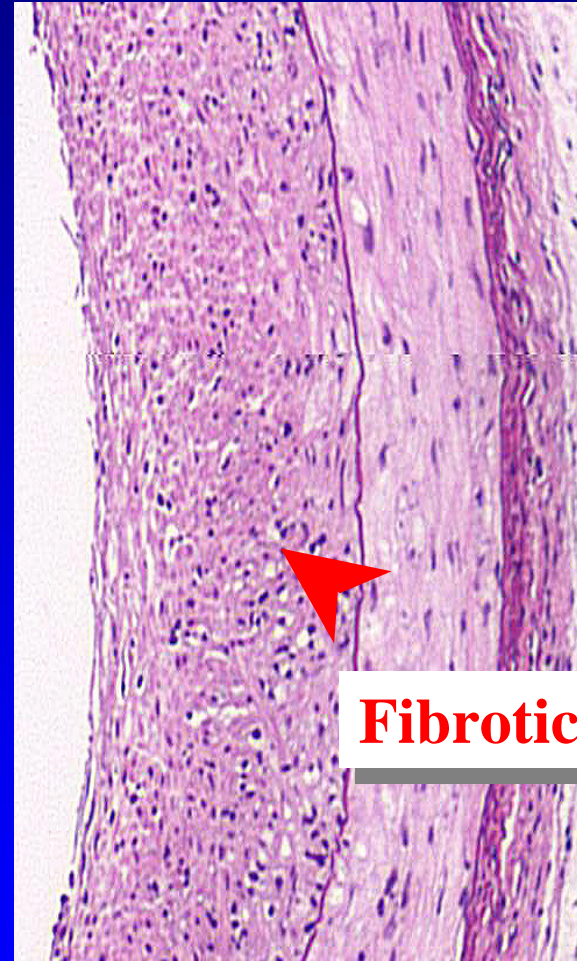
**PDT Induction of Cellular Apoptosis**

# PDT Eliminates Macrophages, Lipid and Induces Plaque Fibrosis



**Macrophages**

**Sham Control**



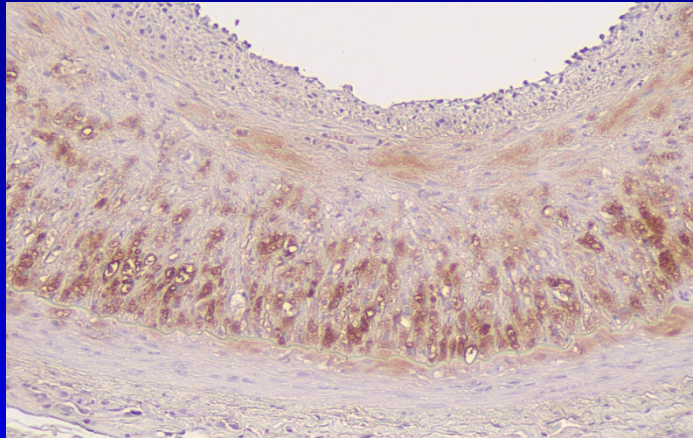
**Fibrotic Region**

**PDT Treated**

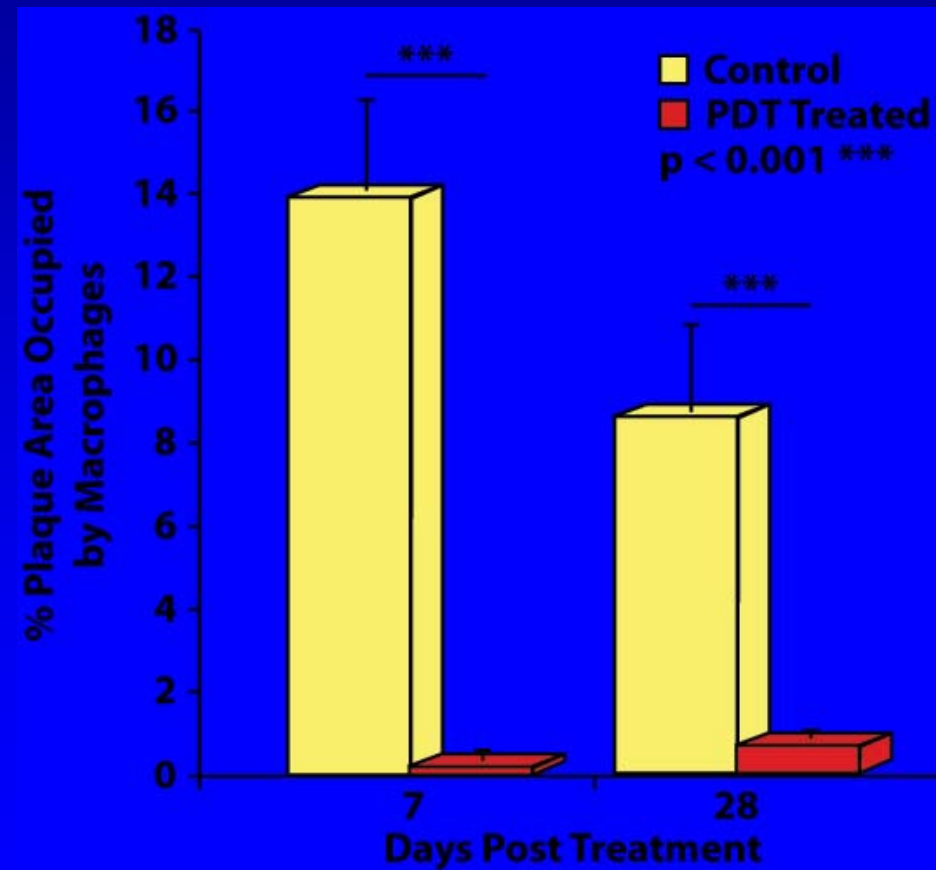
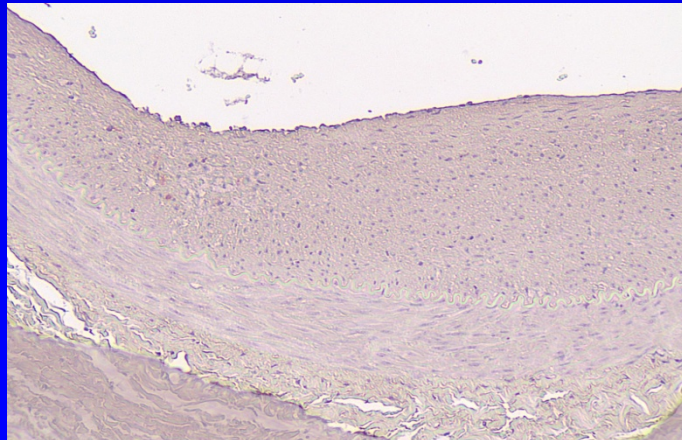
**28 Days Post Treatment**

# Effect of PDT on Plaque Macrophage Content

Sham Control @ 28d

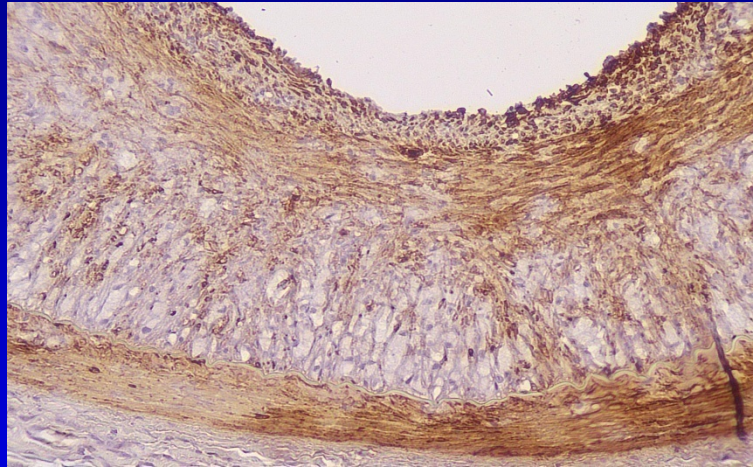


PDT Treated @ 28d

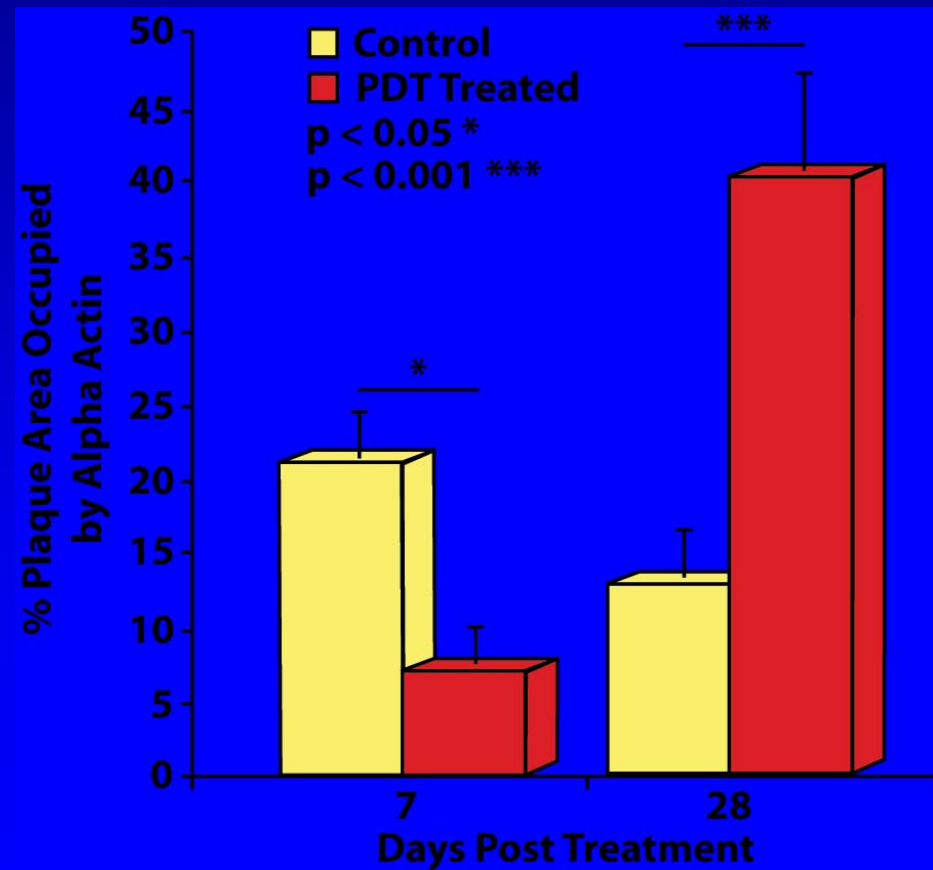
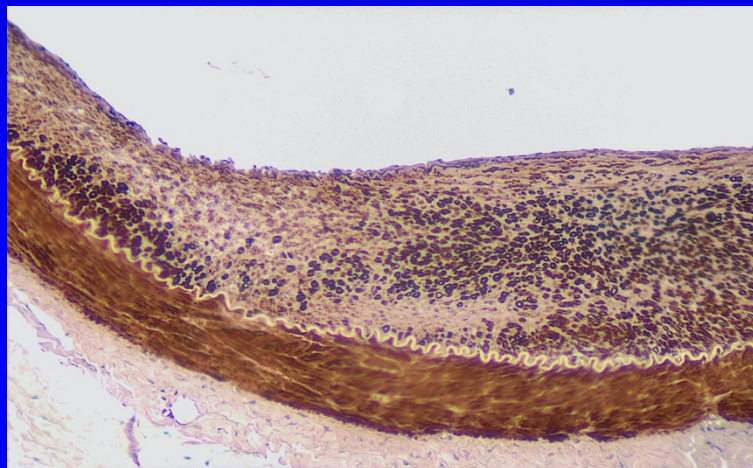


# Effect of PDT on Plaque Smooth Muscle Alpha Actin Content

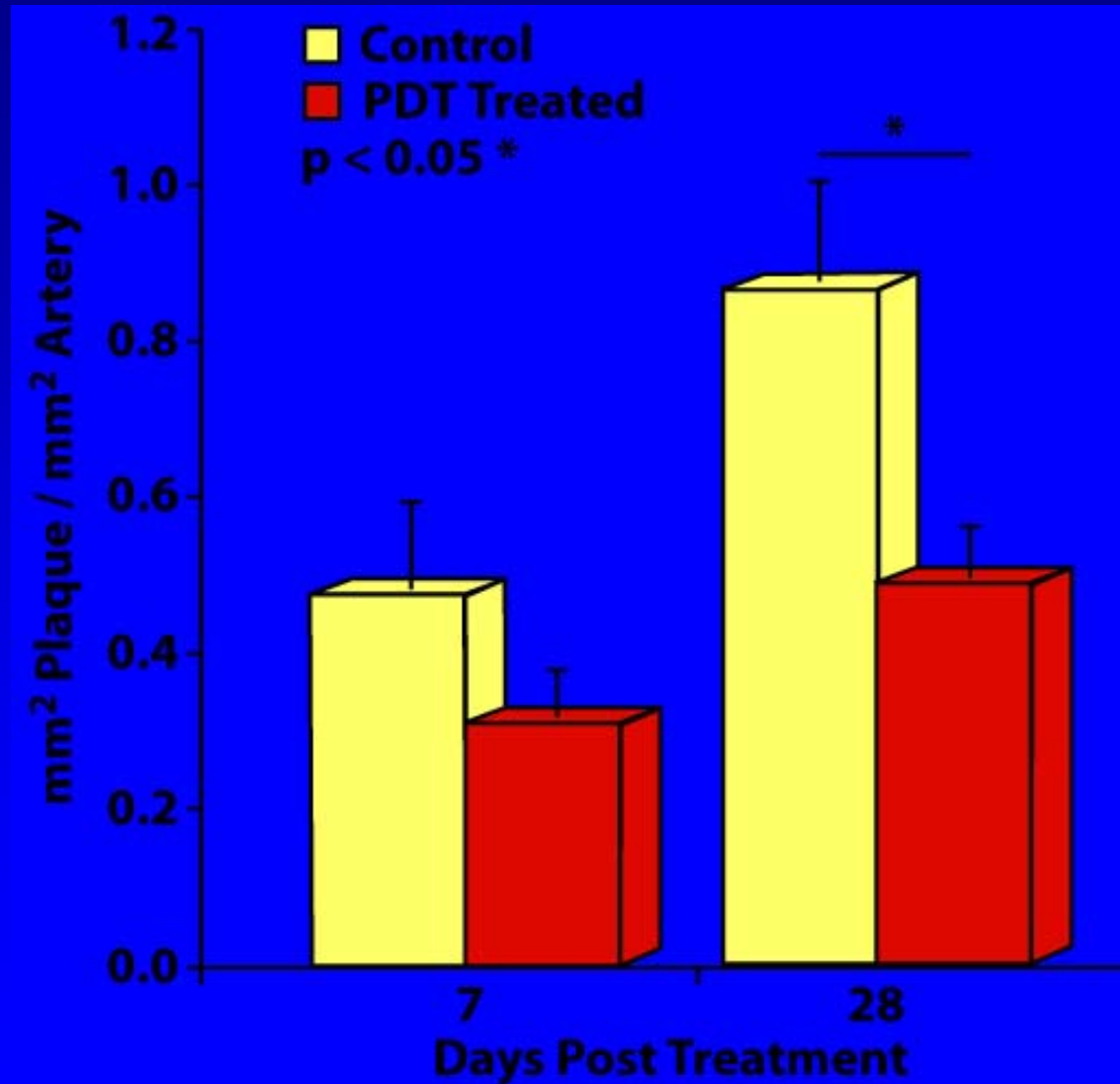
Sham Control@ 28d



PDT @ 28d



# PDT-Induced Reduction in Plaque Area





# **Summary**

**PDT reduces plaque cell number**

**Apoptotic elimination macrophages is maintained at 28 days and limits disease progression**

**Repopulation of plaques with smooth muscle cells is predictive of plaque stabilization**

**At 28 days PDT causes plaque regression**

**No evidence of inflammation, thrombosis or aneurysm formation**