Diesel Exhaust and Atherosclerotic Plaque Stability R01 ES13434

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Specific Aim 1: To determine whether acute and/or chronic exposure to diesel exhaust in a unique exposure chamber 1. induces oxidative stress, 2. increases plasma cytokines and 3. contributes to the progression and destabilization of advanced atherosclerotic lesions in the innominate arteries of older apolipoprotein E deficient mice. We will also determine whether diesel exhaust exposure causes 4. changes in cardiovascular function (heart rate variability, blood pressure, and ECG) and 5. NO mediated dilation

Apolipoprotein E Deficient Mice

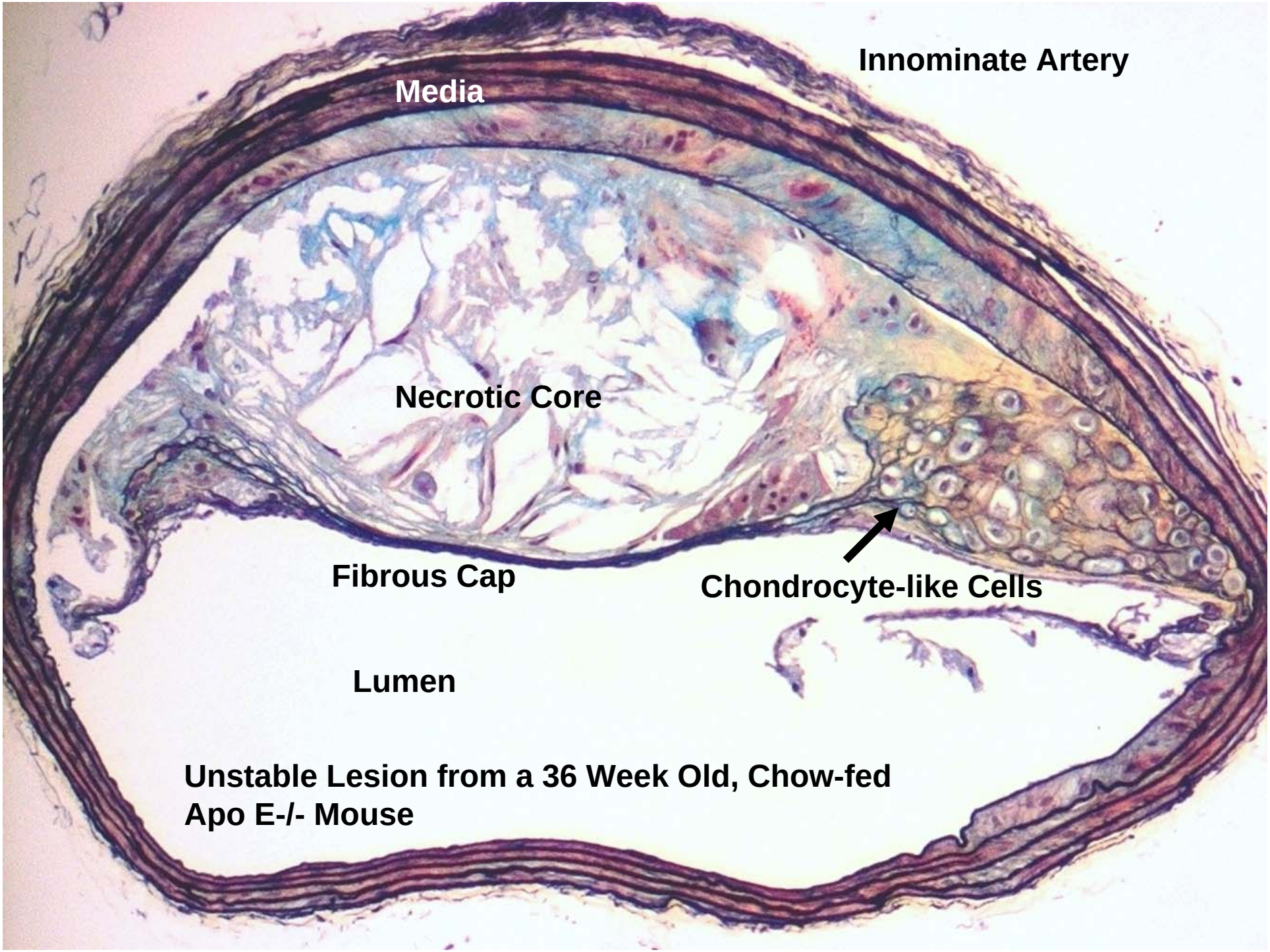
- Plump, A.S., Smith, J.D., Hayek, T., Aalto-Setala, K., Walsh, A., Verstuyft, J.G., Rubin, E.M., and Breslow, J.L. 1992. Severe hypercholesterolemia and atherosclerosis in apolipoprotein E-deficient mice created by homologous recombination in ES cells. *Cell* 71:343-353.

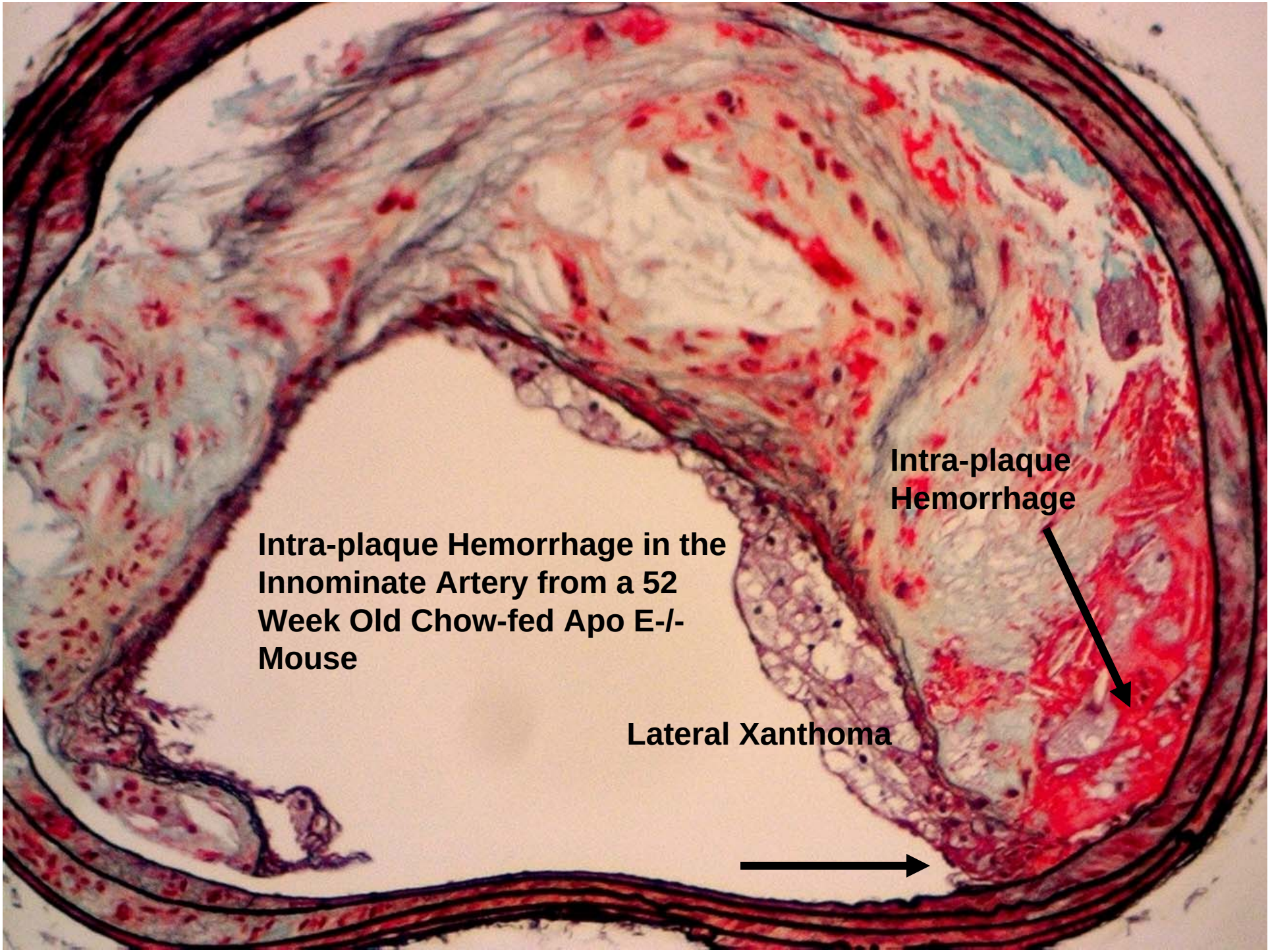
- Zhang, S.H., Reddick, R.L., Piedrahita, J.A., and Maeda, N. 1992. Spontaneous hypercholesterolemia and arterial lesions in mice lacking apolipoprotein E. *Science* 258:468-471.

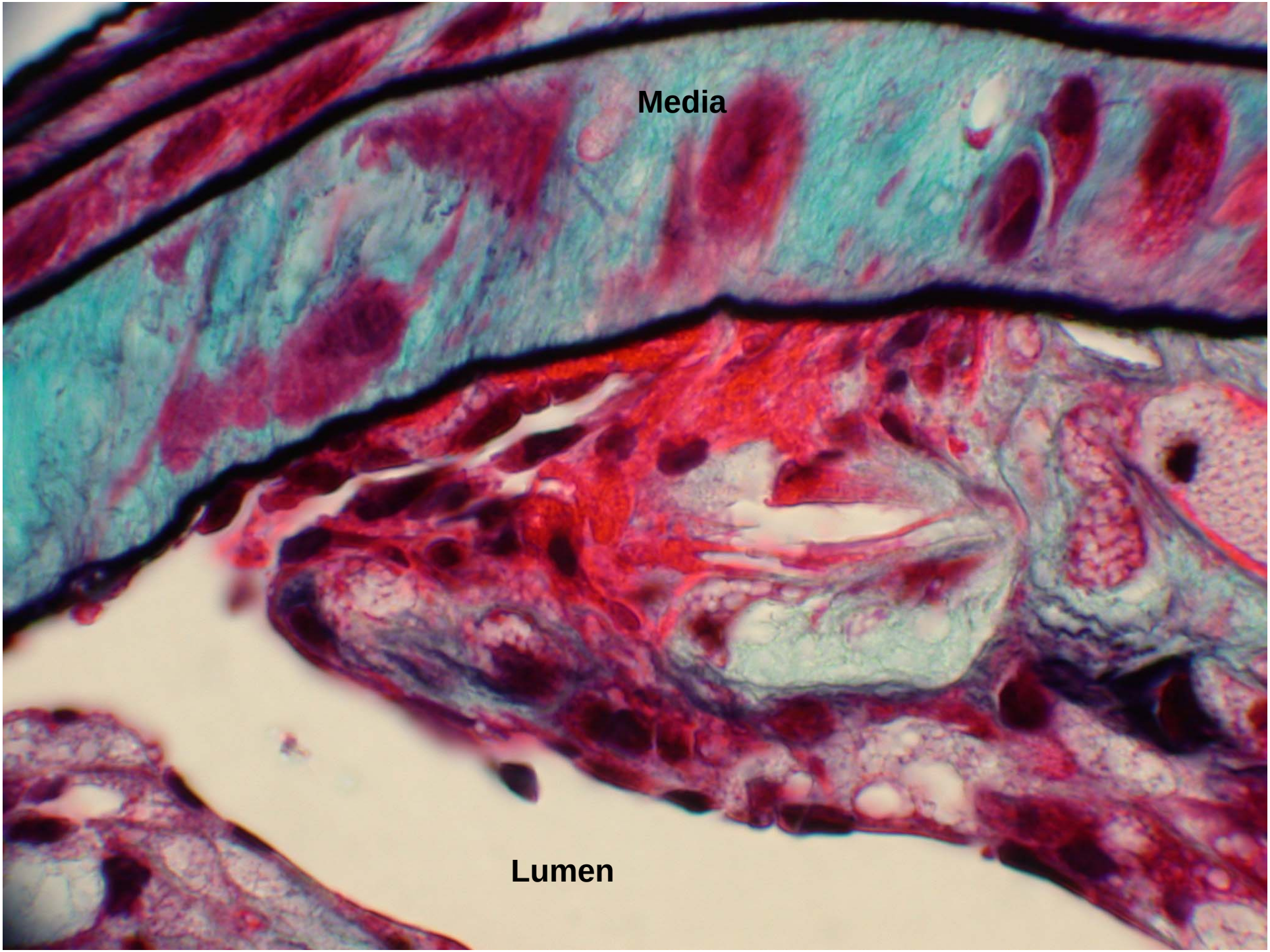

Ascending and Descending Aorta and Branches
of the Cerebral Arteries in the Apo E-/- Mouse
Innominate Artery

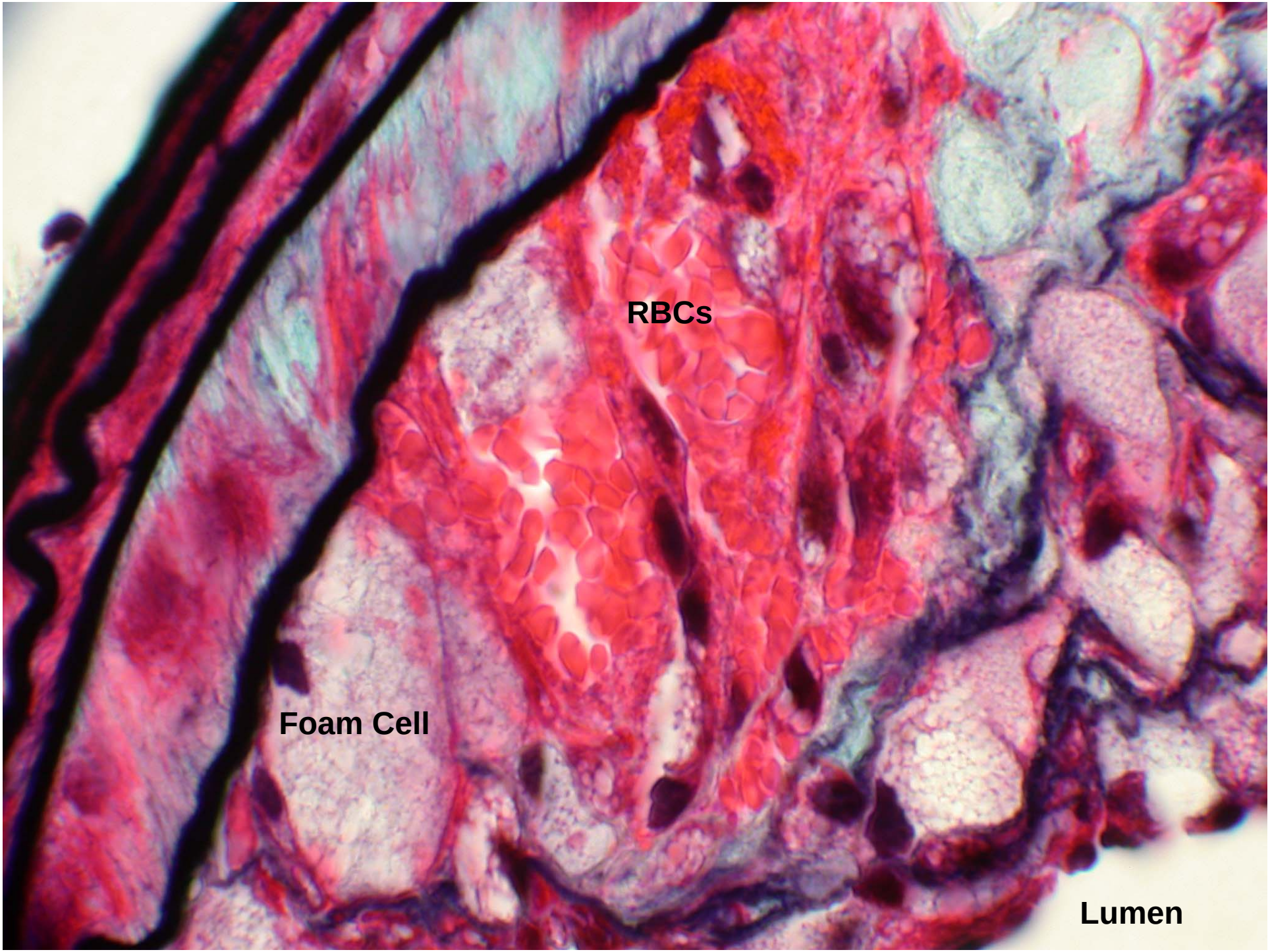
Characteristics of Unstable Plaques

- Large Necrotic Core
- Thin Fibrous Cap
- Rupture/Fissure at Lateral Margins
- Intra-plaque Hemorrhage
- Thrombosis
- Calcification

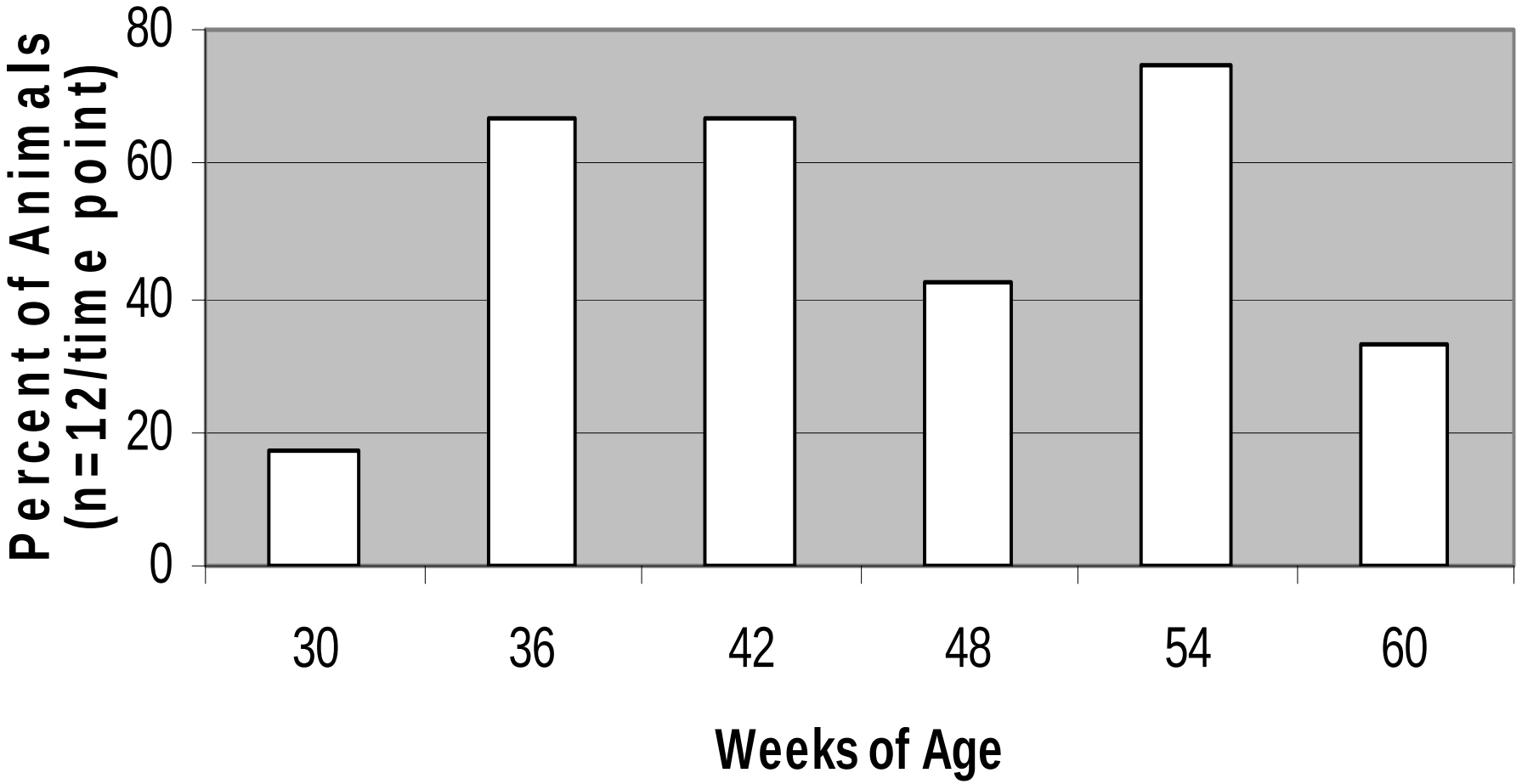

Innominate Artery
Media
Necrotic Core
Fibrous Cap
Chondrocyte-like Cells
Lumen
Unstable Lesion from a 36 Week Old, Chow-fed
Apo E-/- Mouse


Intra-plaque Hemorrhage in the Innominate Artery from a 52 Week Old Chow-fed Apo E-/- Mouse
Intra-plaque Hemorrhage
Lateral Xanthoma


Media
Lumen


RBCs
Foam Cell
Lumen

Frequency of Hemorrhage in Atherosclerotic Lesions in the Innominate Artery of Older Apo E-/- Mice



Subaim 1A. To determine whether acute exposure to diesel exhaust stimulates the progression of advanced atherosclerotic lesions and contributes to measures of plaque instability in older apo E-/- mice with established lesions.

Exposure to: 100 ug/m3	**6 hours – 1 day**	**6 hours- 3 days**	**6 hours – 5 days**
Sacrifices – time post last exposure	1 day	1 day	1 day
	3 days	3 days	3 days
	2 weeks	2 weeks	2 weeks
Exposure to: 200 ug/m3	**1 day**	**3 days**	**5 days**
Sacrifices – time post last exposure	1 day	1 day	1 day
	3 days	3 days	3 days
	2 weeks	2 weeks	2 weeks
Exposure to: 400 ug/m3	**1 day**	**3 days**	**5 days**
Sacrifices – time post last exposure	1 day	1 day	1 day
	3 days	3 days	3 days
	2 weeks	2 weeks	2 weeks

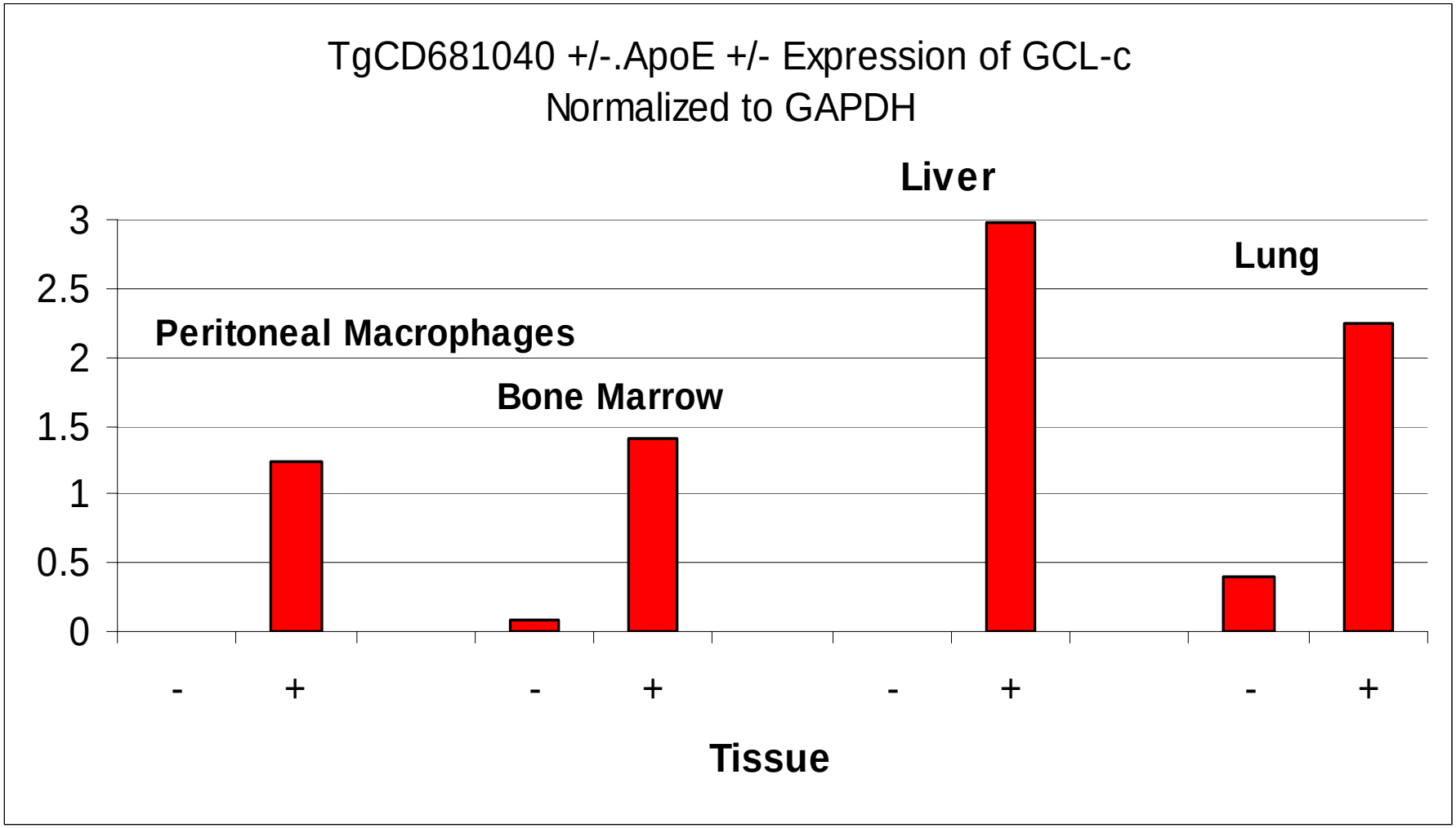
Time Course and Dose Response for Acute Exposure to Diesel Exhaust

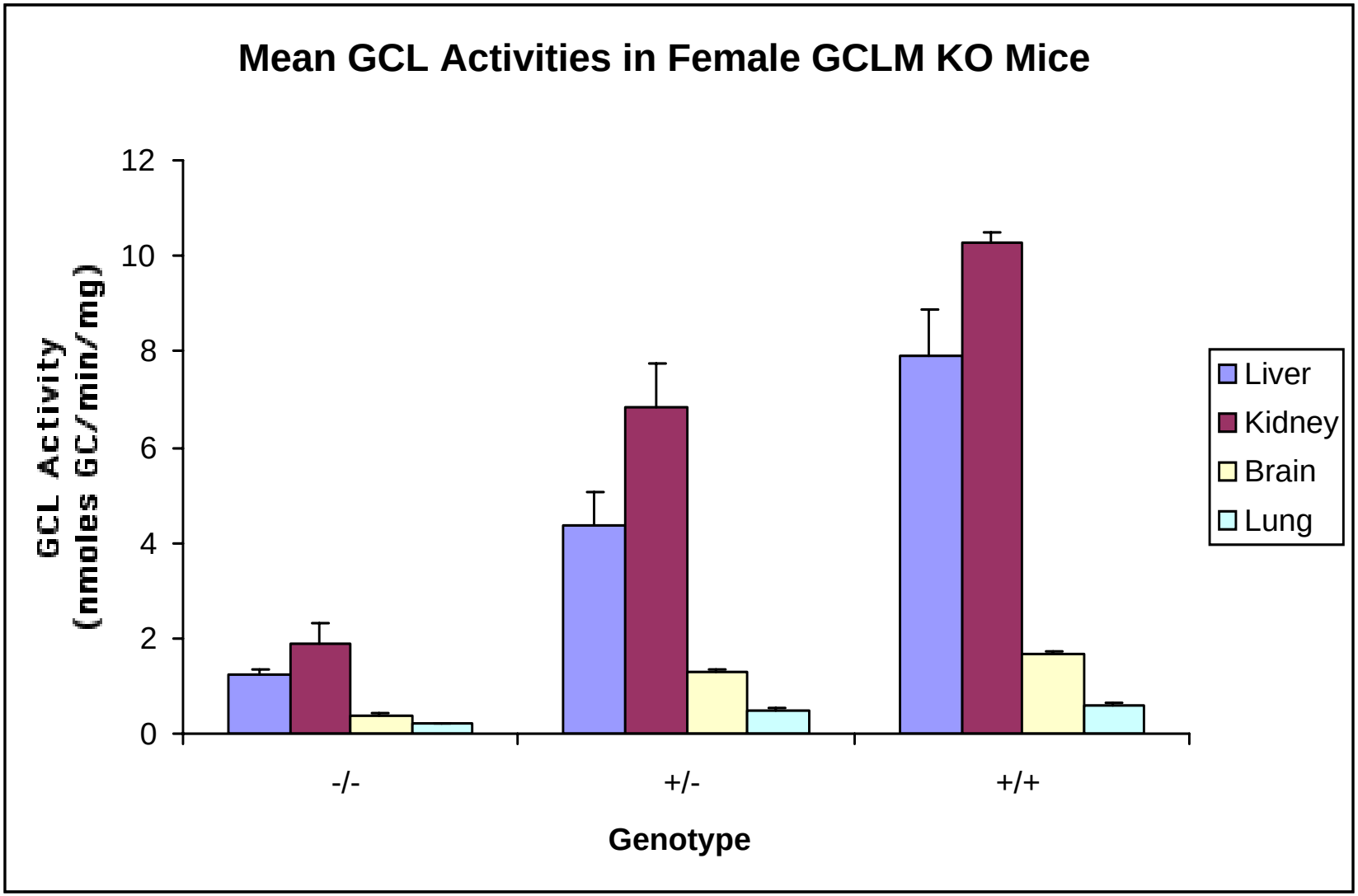
Subaim 1B. To determine whether sub-chronic exposure to diesel exhaust stimulates the progression of advanced atherosclerotic lesions and contributes to measures of plaque instability in older apo E-/- mice with established lesions.

Exposure to: 100 ug/m3	**5 days/wk for 4 weeks**	**5 days/wk for 8 weeks**
Sacrifices – time post last exposure	1 day	1 day
	3 days	3 days
	2 weeks	2 weeks
Exposure to: 200 ug/m3	**5 days/wk for 4 weeks**	**5 days/wk for 8 weeks**
Sacrifices – time post last exposure	1 day	1 day
	3 days	3 days
	2 weeks	2 weeks
Exposure to: 400 ug/m3	**5 days/wk for 4 weeks**	**5 days/wk for 8 weeks**
Sacrifices – time post last exposure	1 day	1 day
	3 days	3 days
	2 weeks	2 weeks

Time Course and Dose Response for Sub-Chronic Exposure to Diesel Exhaust

Specific Aim 2: To determine whether acute and/or chronic exposure to diesel exhaust induce comparable systemic cytokine responses and progression and destabilization of advanced atherosclerotic lesions in the innominate arteries, and changes in cardiovascular function and NO mediated dilation, in apolipoprotein E deficient mice that have increased or decreased capacities for producing the main endogenous antioxidant, **glutathione**.


TgCD681040 +/-.ApoE +/- Expression of GCL-c
Normalized to GAPDH
Liver
Lung
Peritoneal Macrophages
Bone Marrow
3
2.5
2
1.5
1
0.5
0
- + - + - + - +
Tissue


Mean GCL Activities in Female GCLM KO Mice
GCL Activity (nmoles GC/min/mg)
12
10
8
6
4
2
0
-/-
+/-
+/+
Genotype
Liver
Kidney
Brain
Lung