Targeting novel lipids for developing new diabetic and cardiovascular drugs

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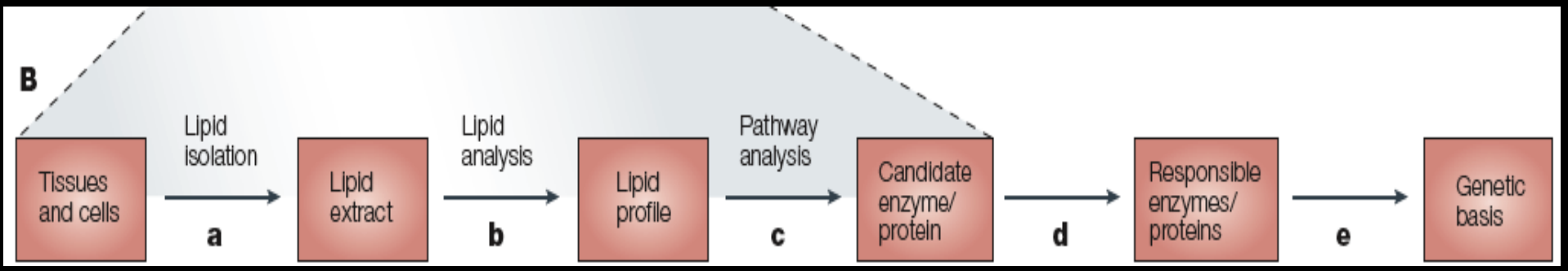
LIPODOMICS

DNA → RNA → Protein → Metabolites

GENOMICS	PROTEOMICS	METABOLOMICS

LIPIDS

LIPIDOMICS



Wenk MR. Nat Rev Drug Discov 2005, 4:594-610.

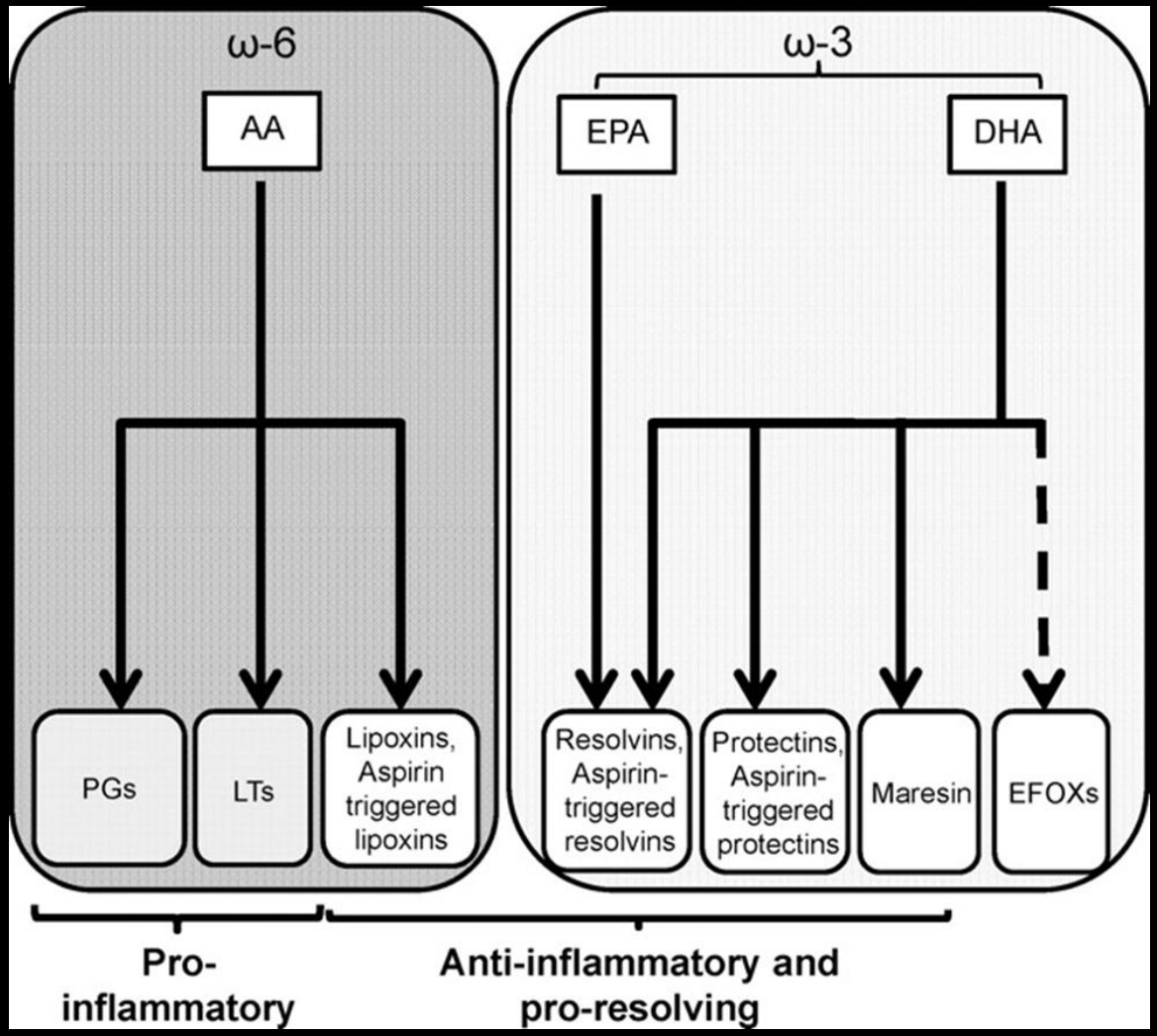
Fatty Acyls [FA]

Subclasses

http://www.lipidmaps.org/data/classification/LM_classification_exp.php?category=1

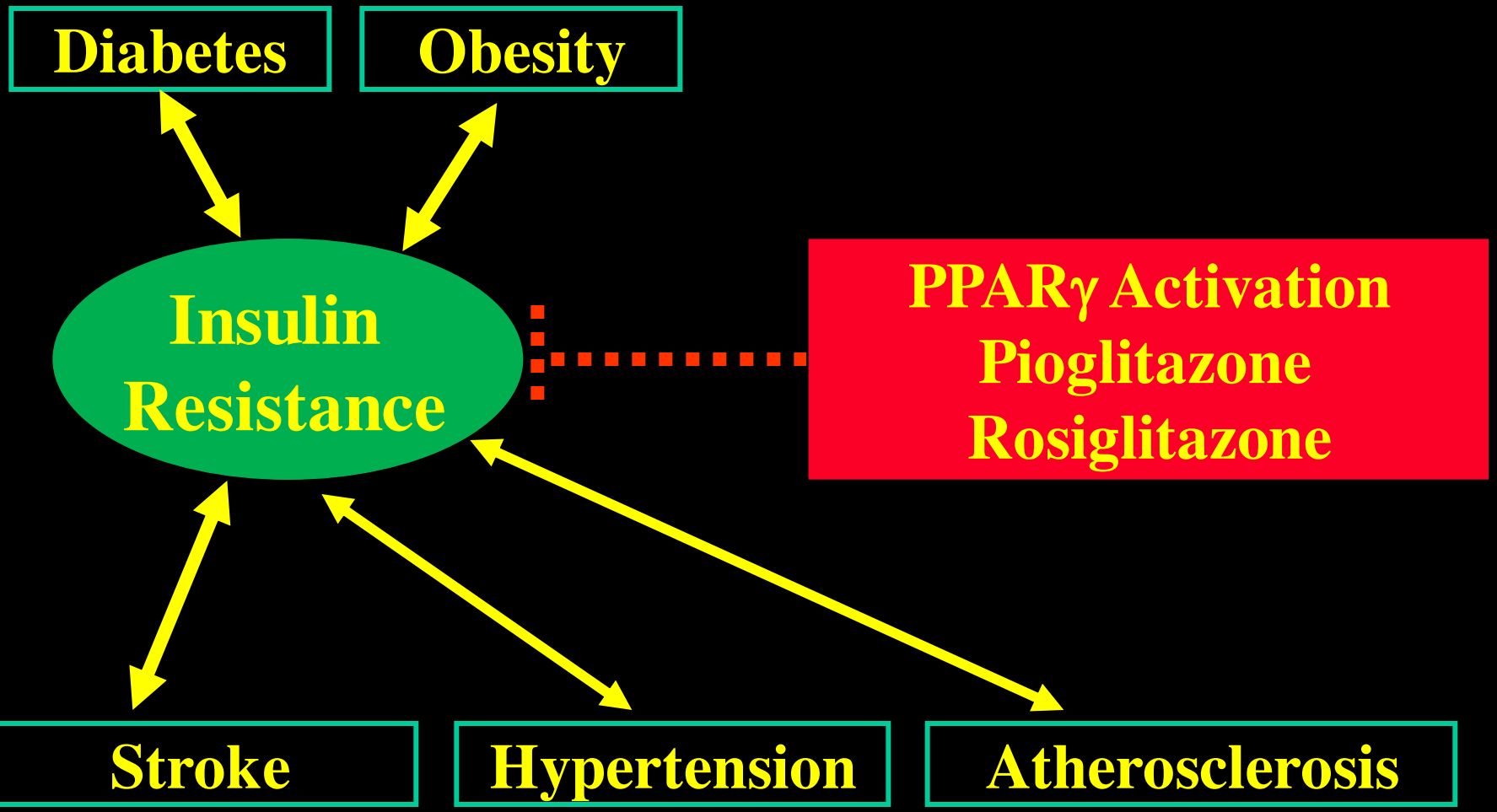
Fatty Acids and Conjugates [FA01]
- **Straight chain fatty acids [FA0101]**
- **Methyl branched fatty acids [FA0102]**
- **Unsaturated fatty acids [FA0103]**
- **Hydroperoxy fatty acids [FA0104]**
- **Hydroxy fatty acids [FA0105]**
- **Oxo fatty acids [FA0106]**
- **Epoxy fatty acids [FA0107]**
- **Methoxy fatty acids [FA0108]**
- **Halogenated fatty acids [FA0109]**
- **Amino fatty acids [FA0110]**
- **Cyano fatty acids [FA0111]**
- **Nitro fatty acids [FA0112]**
- **Thia fatty acids [FA0113]**
- **Carbocyclic fatty acids [FA0114]**
- **Heterocyclic fatty acids [FA0115]**
- **Mycolic acids [FA0116]**
- **Dicarboxylic acids [FA0117]**

Formation of bioactive lipid mediators



Maskrey B H et al. Arterioscler Thromb Vasc Biol 2011;31:1001-1006

PPAR-γ : A Transcription Factor Linking Obesity, Diabetes, Hypertension, Atherosclerosis and Stroke



Nissen Meta-analysis

Table 4. Rates of Myocardial Infarction and Death from Cardiovascular Causes.

Study	Rosiglitazone Group	Control Group	Odds Ratio (95% CI)	P Value
	no. of events/total no. (%)			
Myocardial infarction				
Small trials combined	44/10,285 (0.43)	22/6106 (0.36)	1.45 (0.88–2.39)	0.15
DREAM	15/2,635 (0.57)	9/2634 (0.34)	1.65 (0.74–3.68)	0.22
ADOPT	27/1,456 (1.85)	41/2895 (1.42)	1.33 (0.80–2.21)	0.27
Overall			1.43 (1.03–1.98)	0.03
Death from cardiovascular causes				
Small trials combined	25/6,845 (0.36)	7/3980 (0.18)	2.40 (1.17–4.91)	0.02
DREAM	12/2,635 (0.46)	10/2634 (0.38)	1.20 (0.52–2.78)	0.67
ADOPT	2/1,456 (0.14)	5/2895 (0.17)	0.80 (0.17–3.86)	0.78
Overall			1.64 (0.98–2.74)	0.06

N Engl J Med. 2007 Jun 14;356(24):2457-71. Epub 2007 May 21.

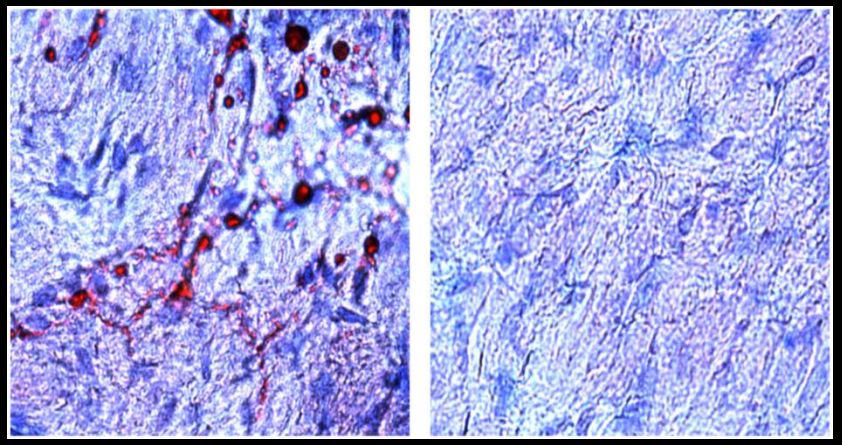
Because of the increased CV risk

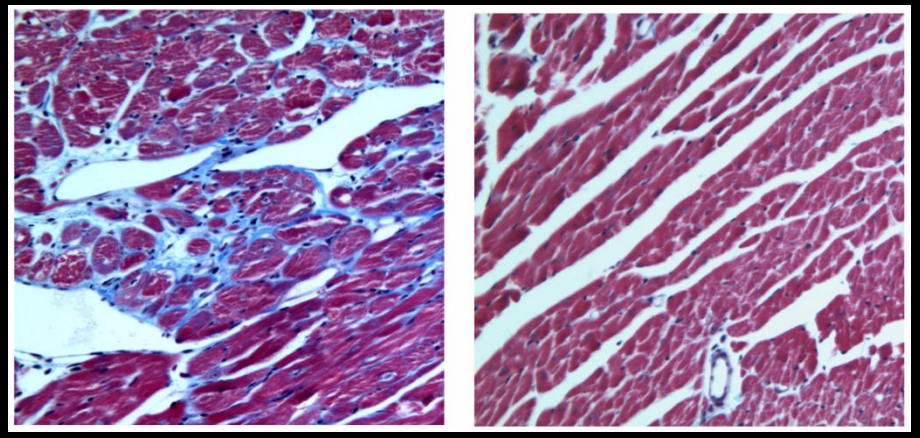
EMA (European Medicines Agency) recommended in September 2010 that Avandia was suspended from the European market.

Avandia will be pulled from retail pharmacy shelves on November 18, 2011, FDA announced on May 24, 2011. Only certified doctors will be allowed to prescribe the drug, and only to patients who've been informed of the risks and who will fill their prescriptions by mail order through specific pharmacies.

Potential Mechanisms?

- Cardiomyocytes?
- Vascular System?
- Lipid Metabolism?
- Off-targets?





Cheng et al, 2004, Nature Medicine

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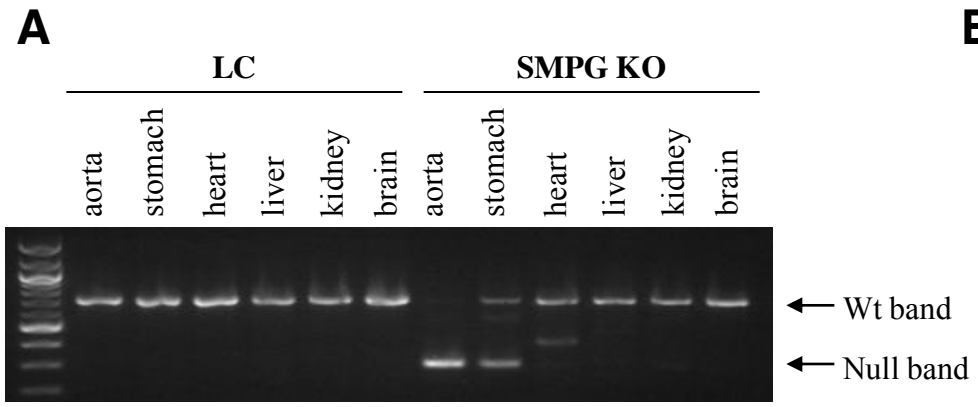
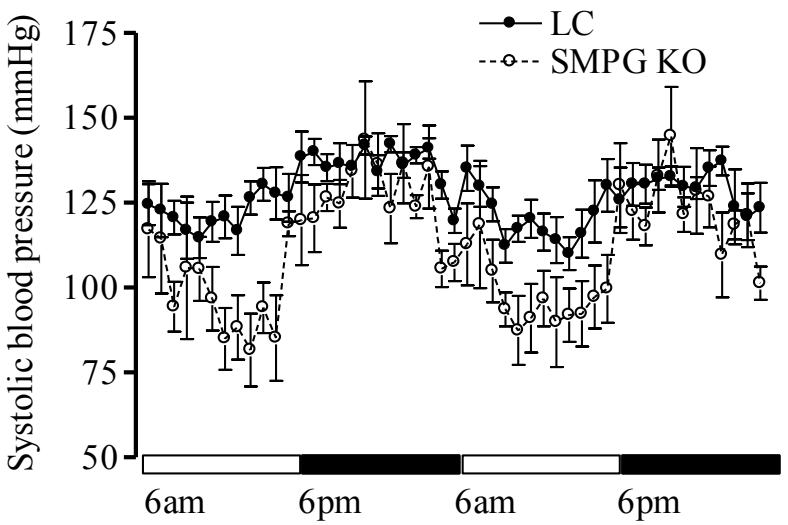
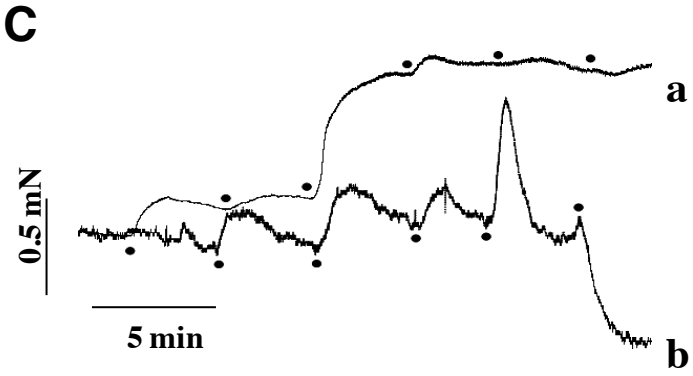
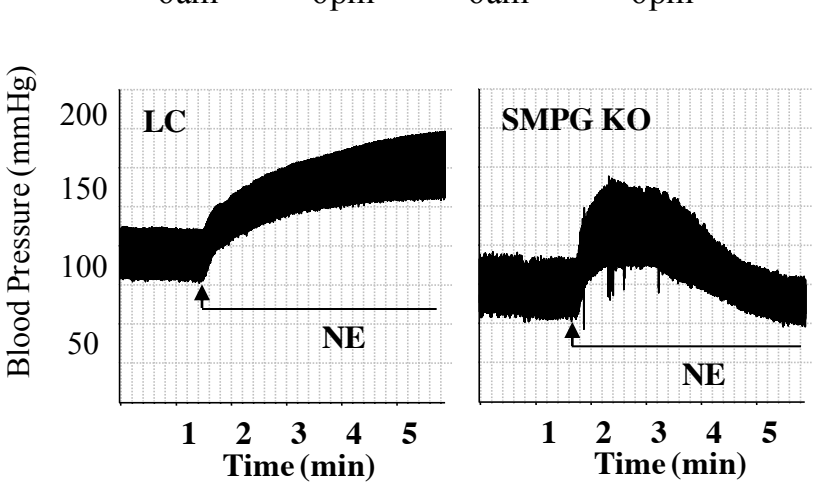
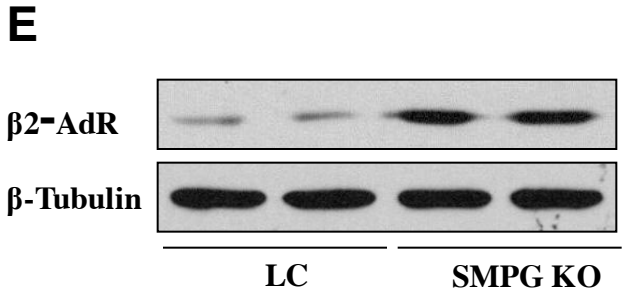
SMC-selective PPARγ deletion leads to hypotension











Chang *et al.*, Circulation 2009 119:2161-9.

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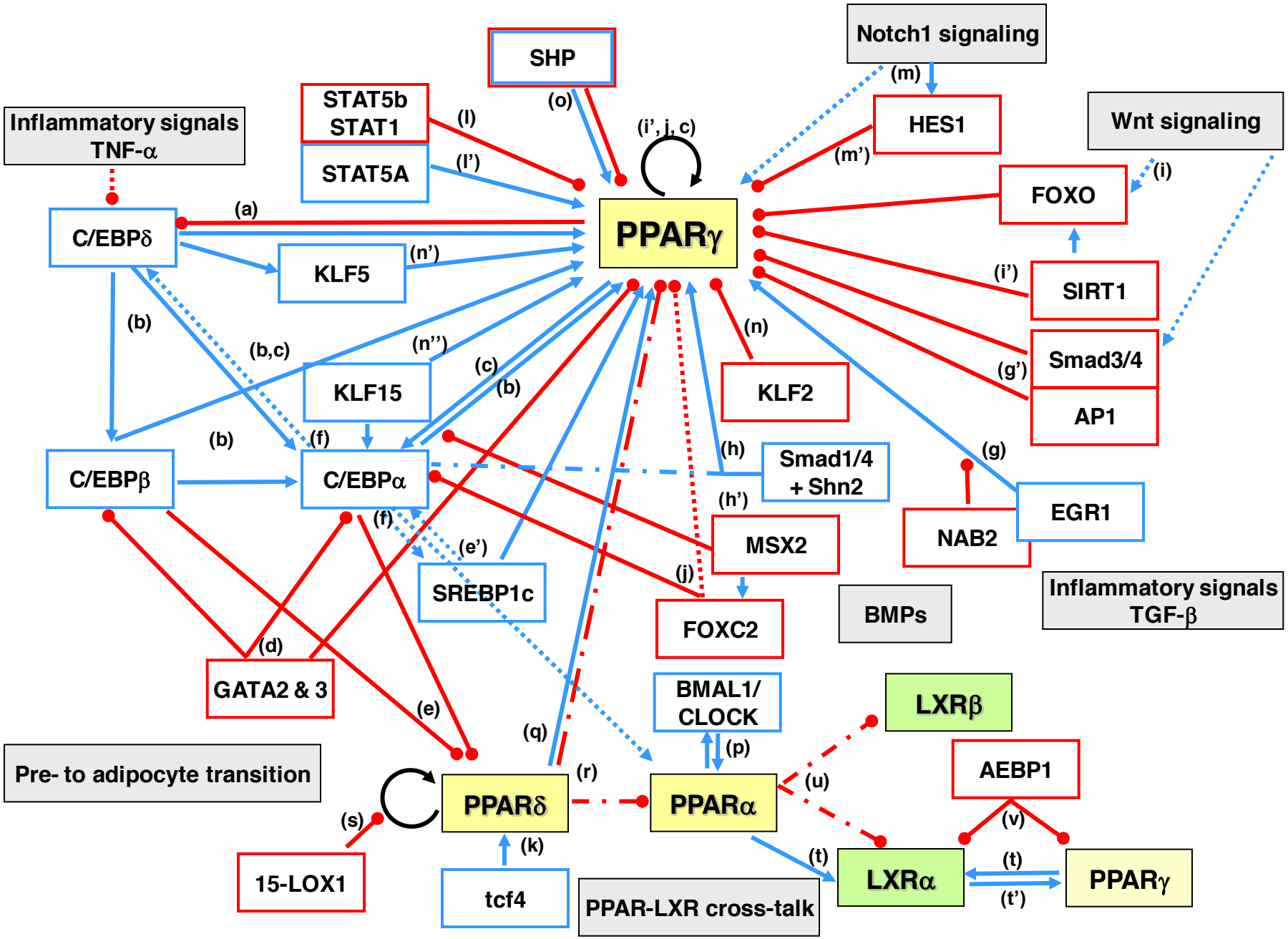

Current Atherosclerosis Reports 2007, 9:230–237

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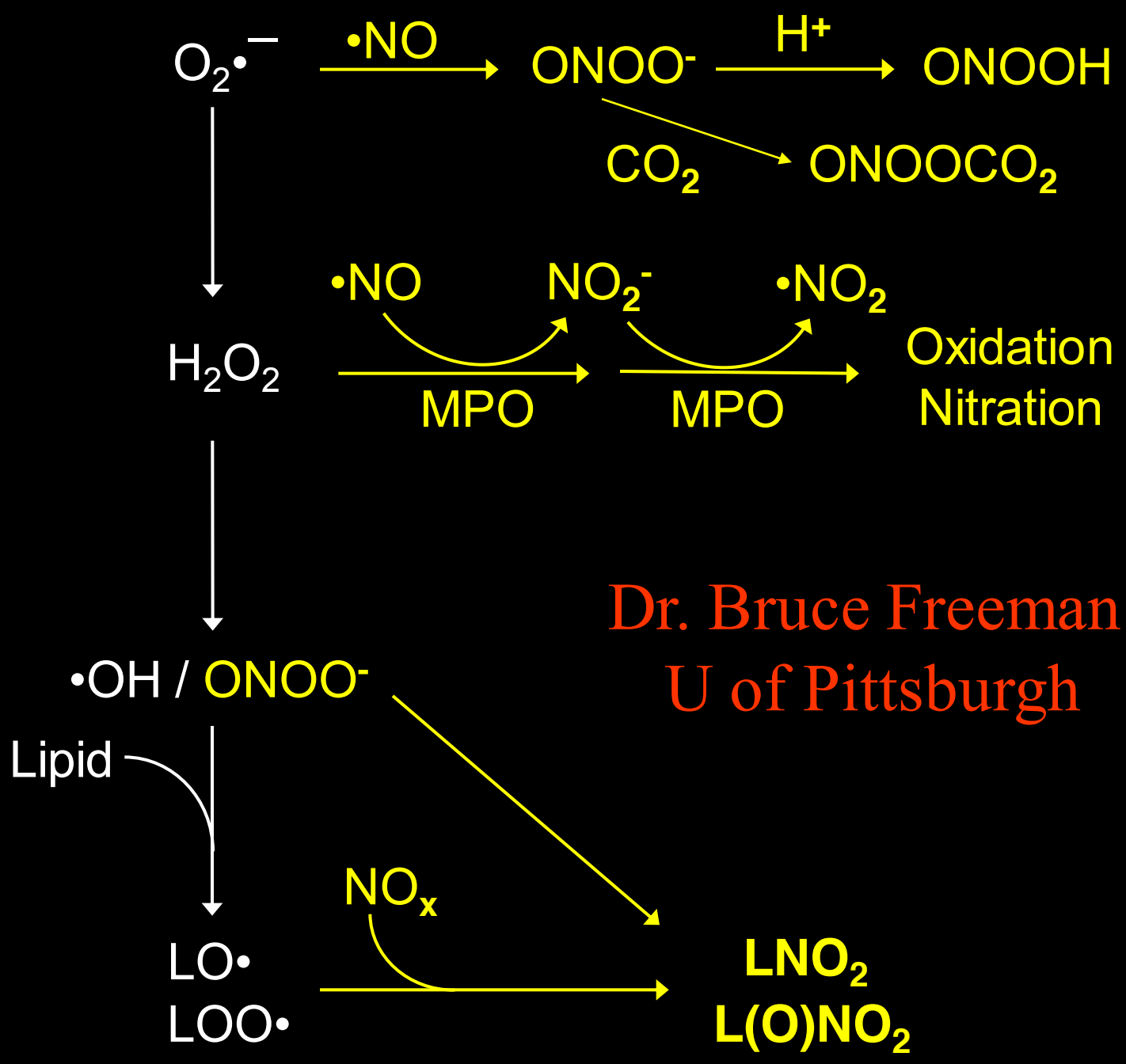
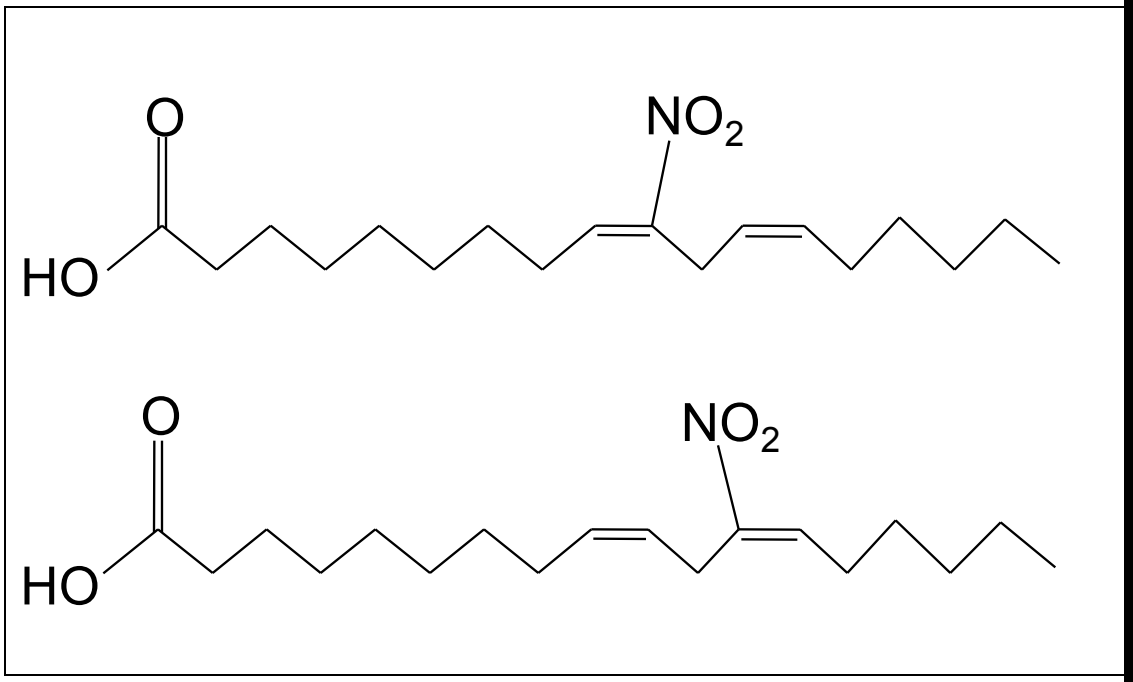


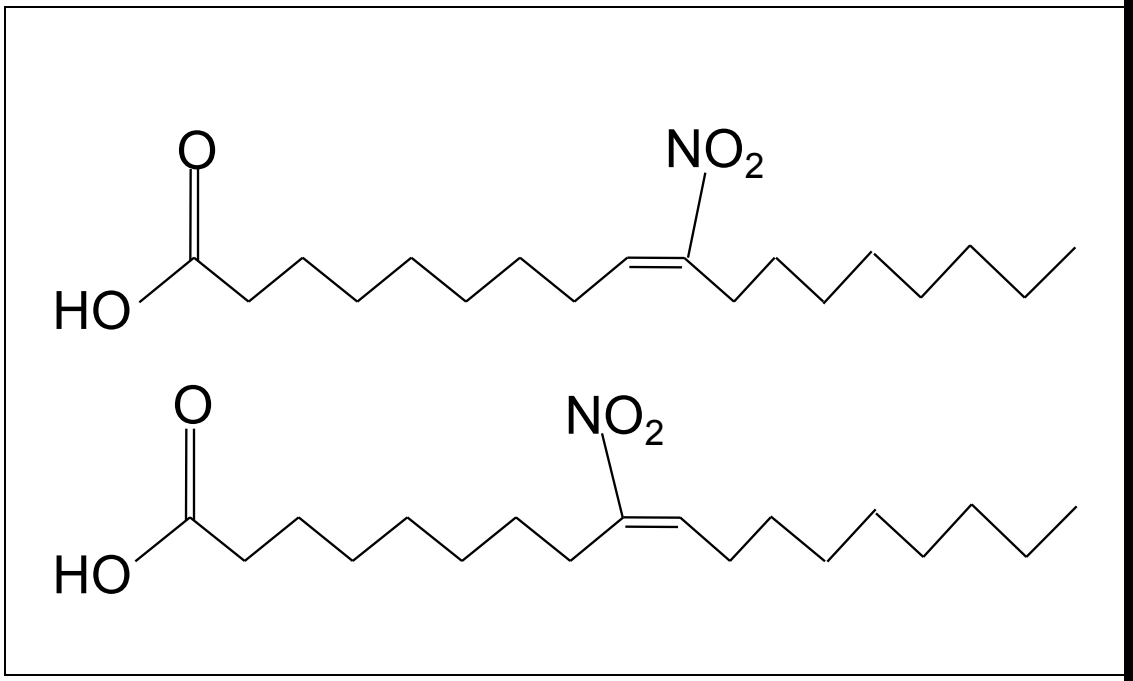
Dr. Bruce Freeman
U of Pittsburgh



LNO_2

C-10 isomer
10-octadeca-9,12-dienoic acid

C-12 isomer
12-octadeca-9,12-dienoic acid

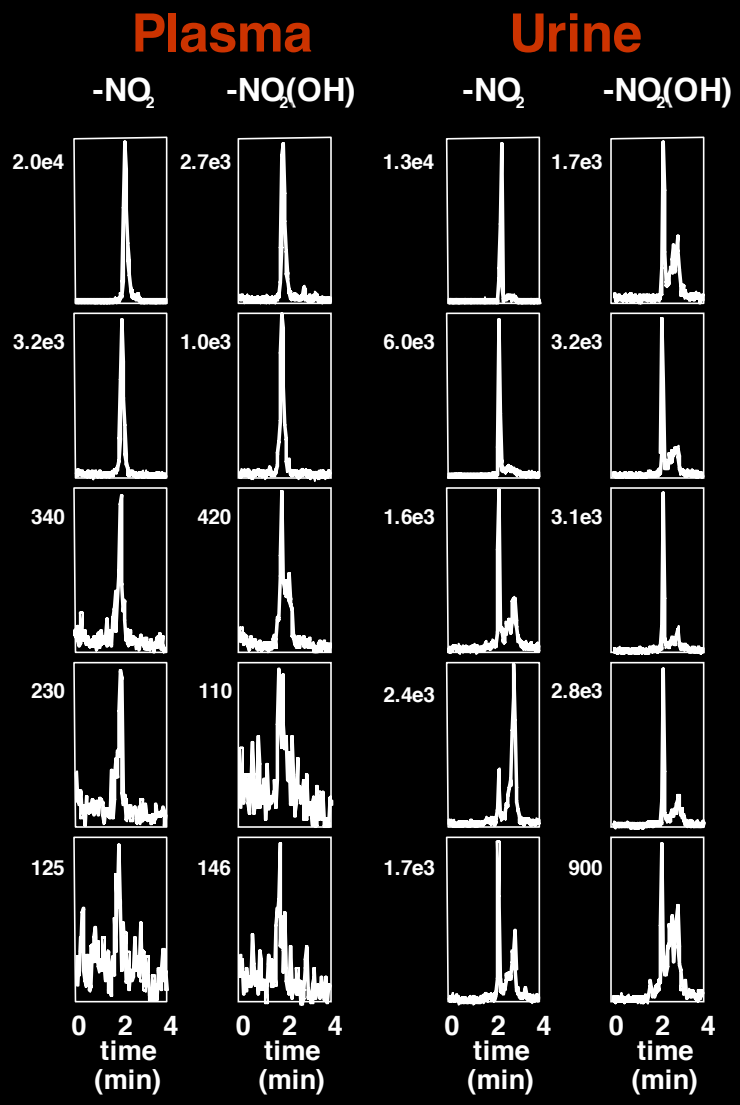


$OA\text{-}NO_2$

C-10 isomer

C-9 isomer

Nitrated Lipid Species in Plasma and Urine



Oleic acid (18:1)

Linoleic acid (18:2)

Linolenic acid (18:3)

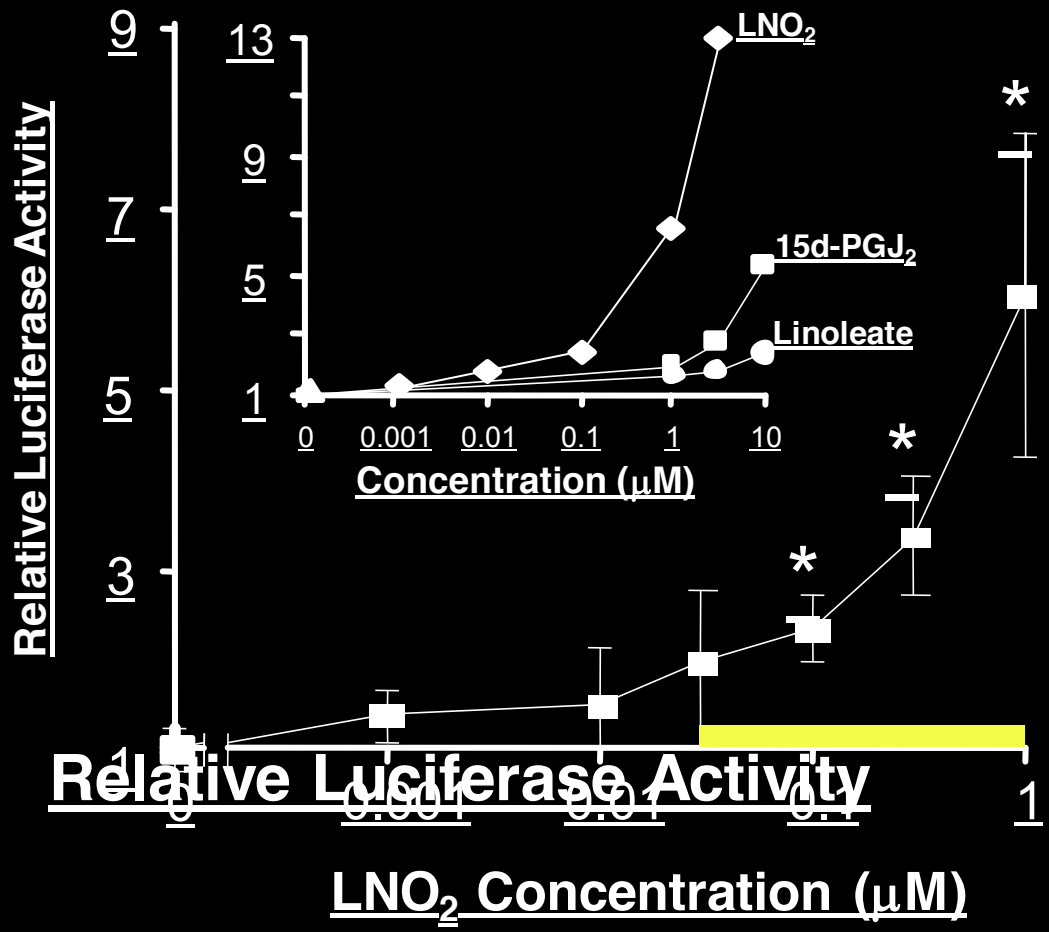
Arachidonic acid (20:4)

Docosahexaenoic acid (22:6)

Baker et al., *J Biol Chem* 2005

PPARγ Ligand Activity of LNO_2

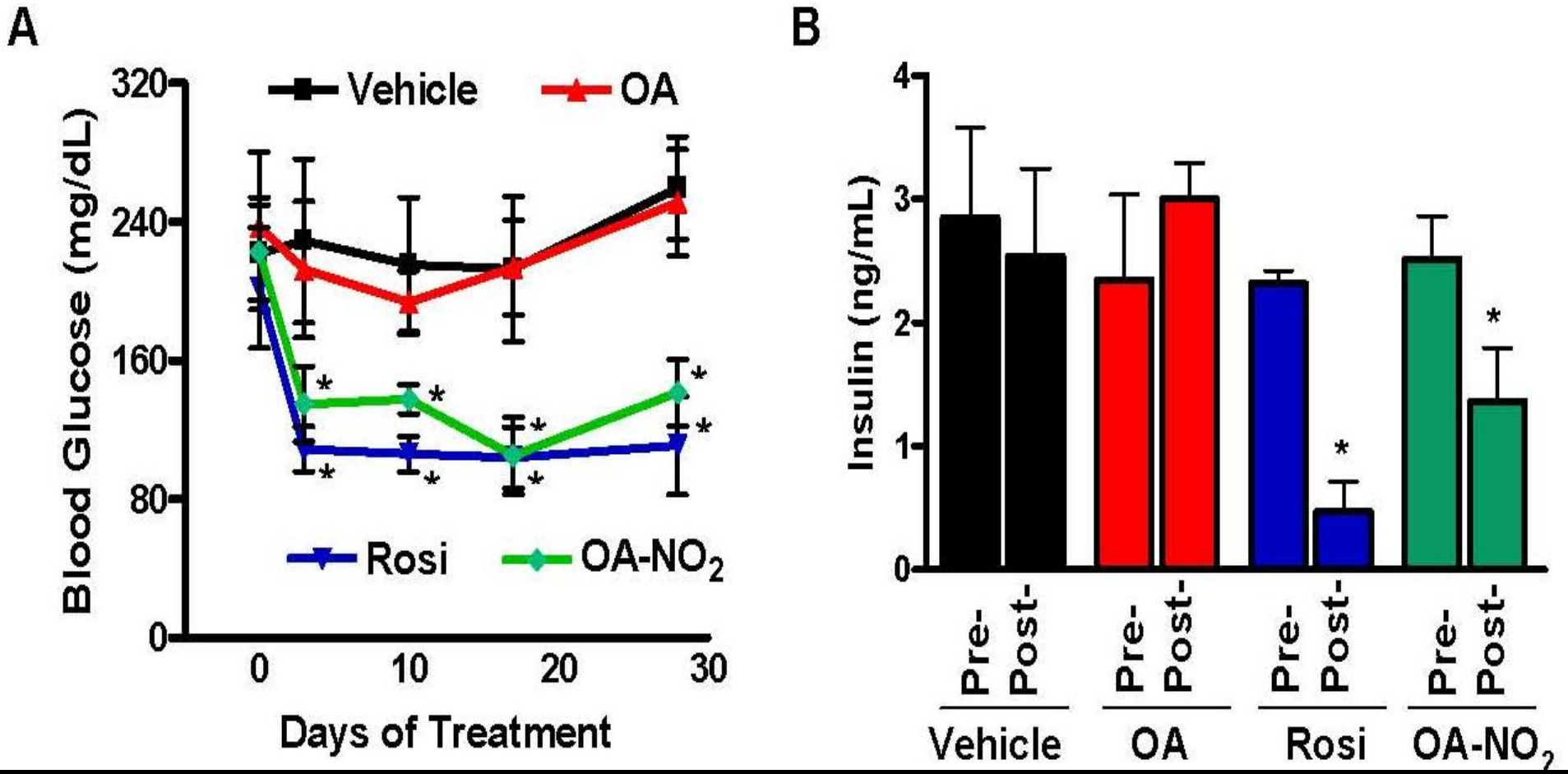
Dose Response and Comparison with 15-deoxy-PGJ_2



Species	Ki (nM)
Linoleate	> 1500
15d-PGJ_2	> 800
Rosiglitazone	53
Nitrolinoleate	133

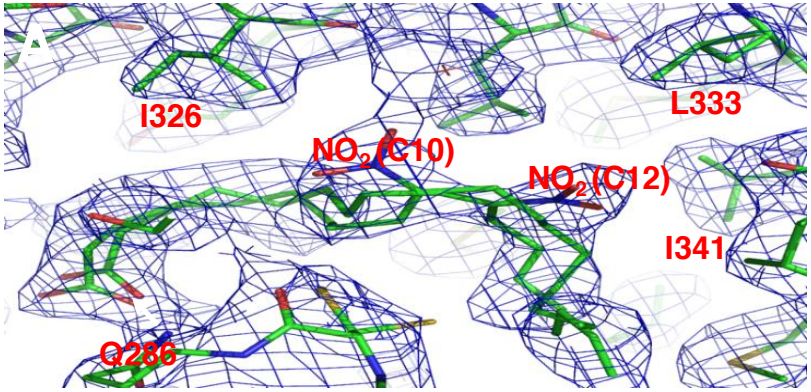
PNAS 2005, 102:2340-5

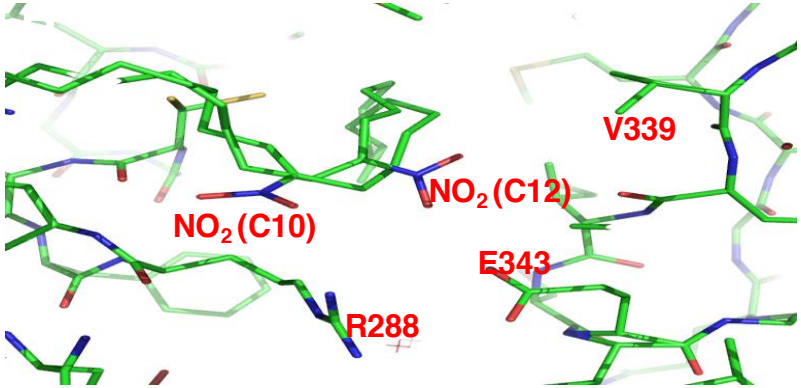
NO_2-FA normalizes hyperglycemia in diabetic mice but is different from TZD Rosiglitazone

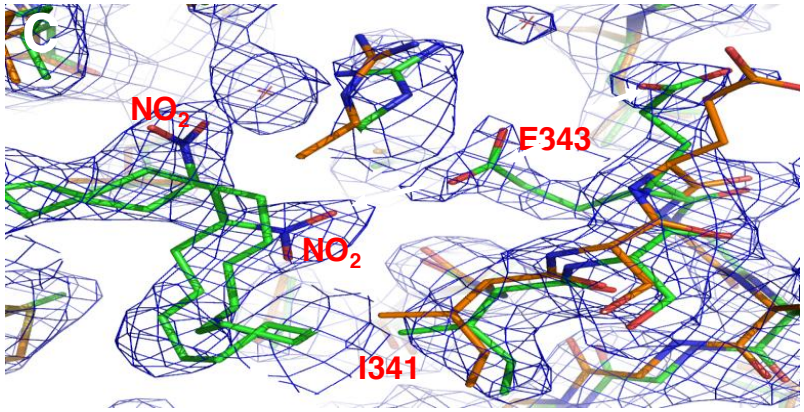


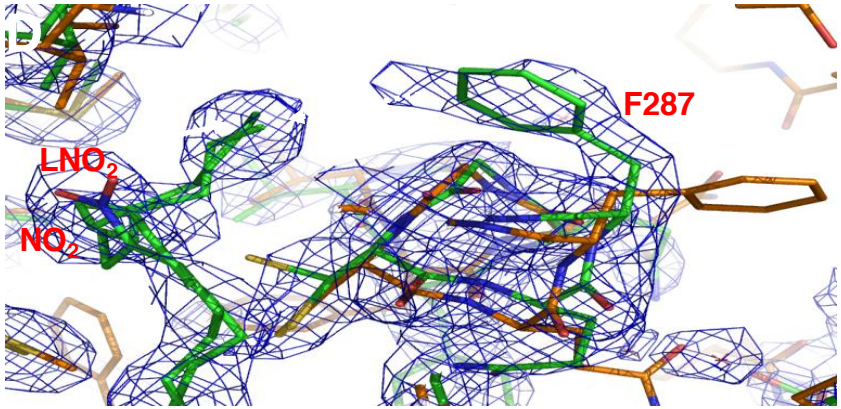
Schopfer et al., 2010 J Biol Chem. 285:12321-12333

Ligand Binding Pocket of PPARγ and the binding mode of LNO_2



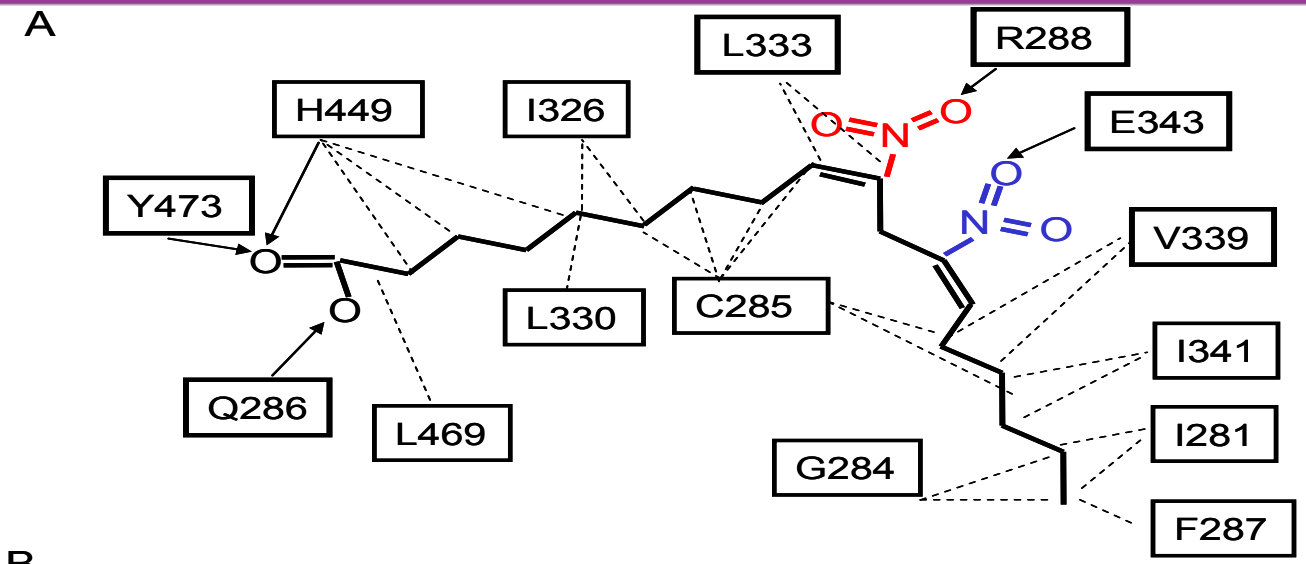


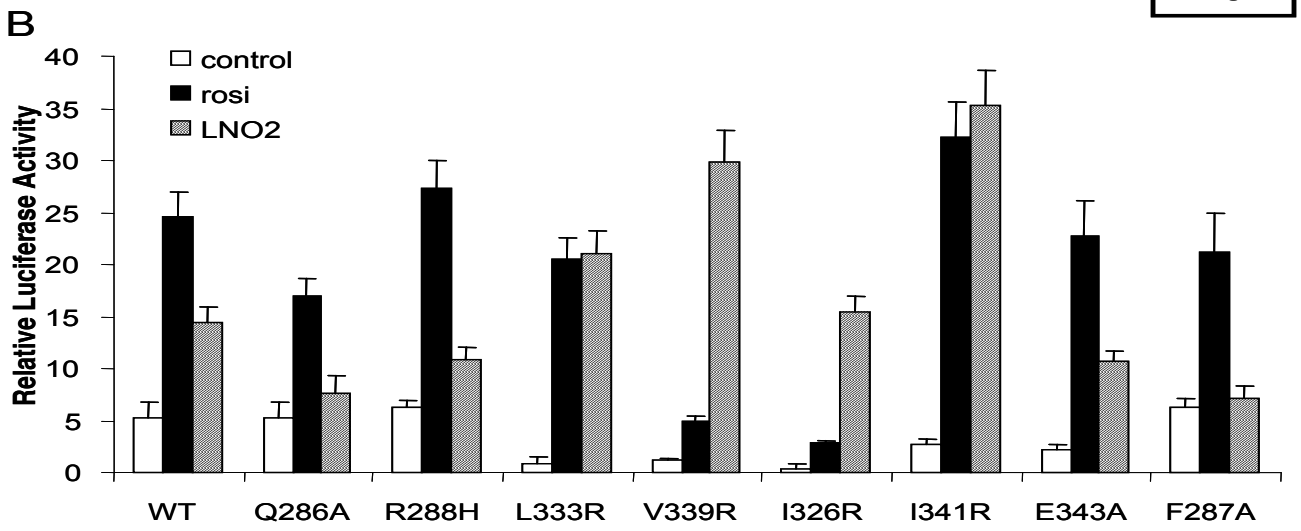




Li et al., *Nat Struct Mol Biol.* 2008, 15:865-7

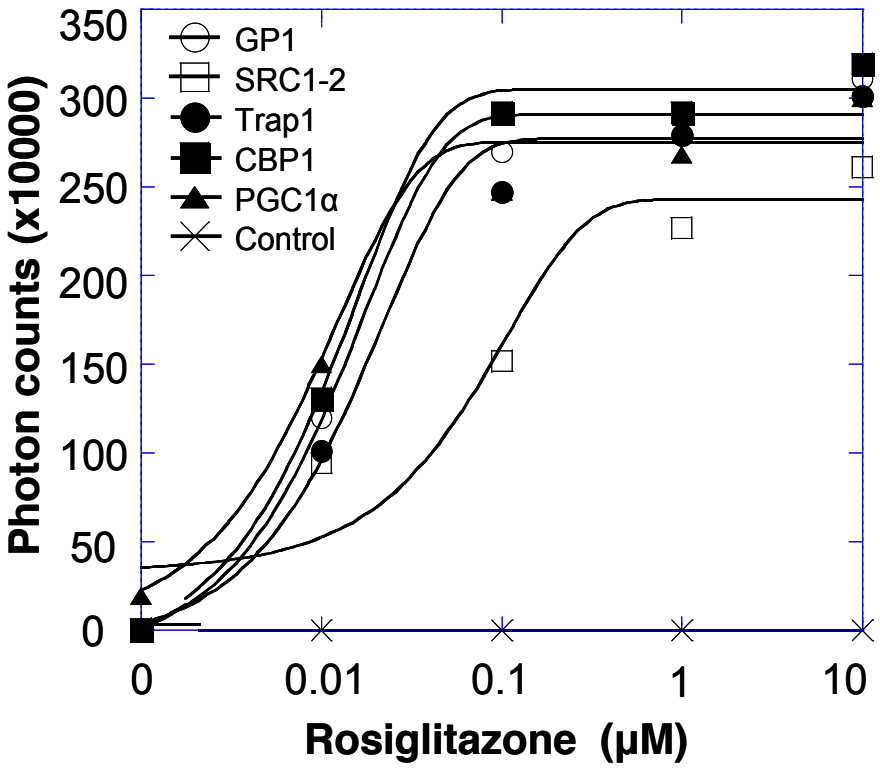
Functional correlation of the LNO_2/PPARγ interactions

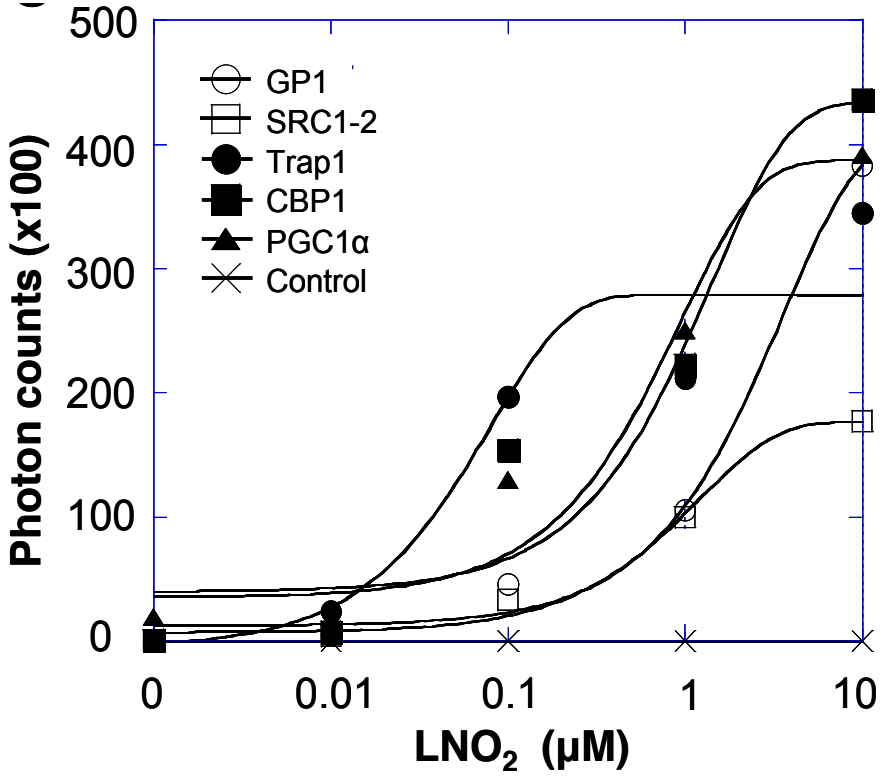




Li et al., Nat Struct Mol Biol. 2008, 15:865-7

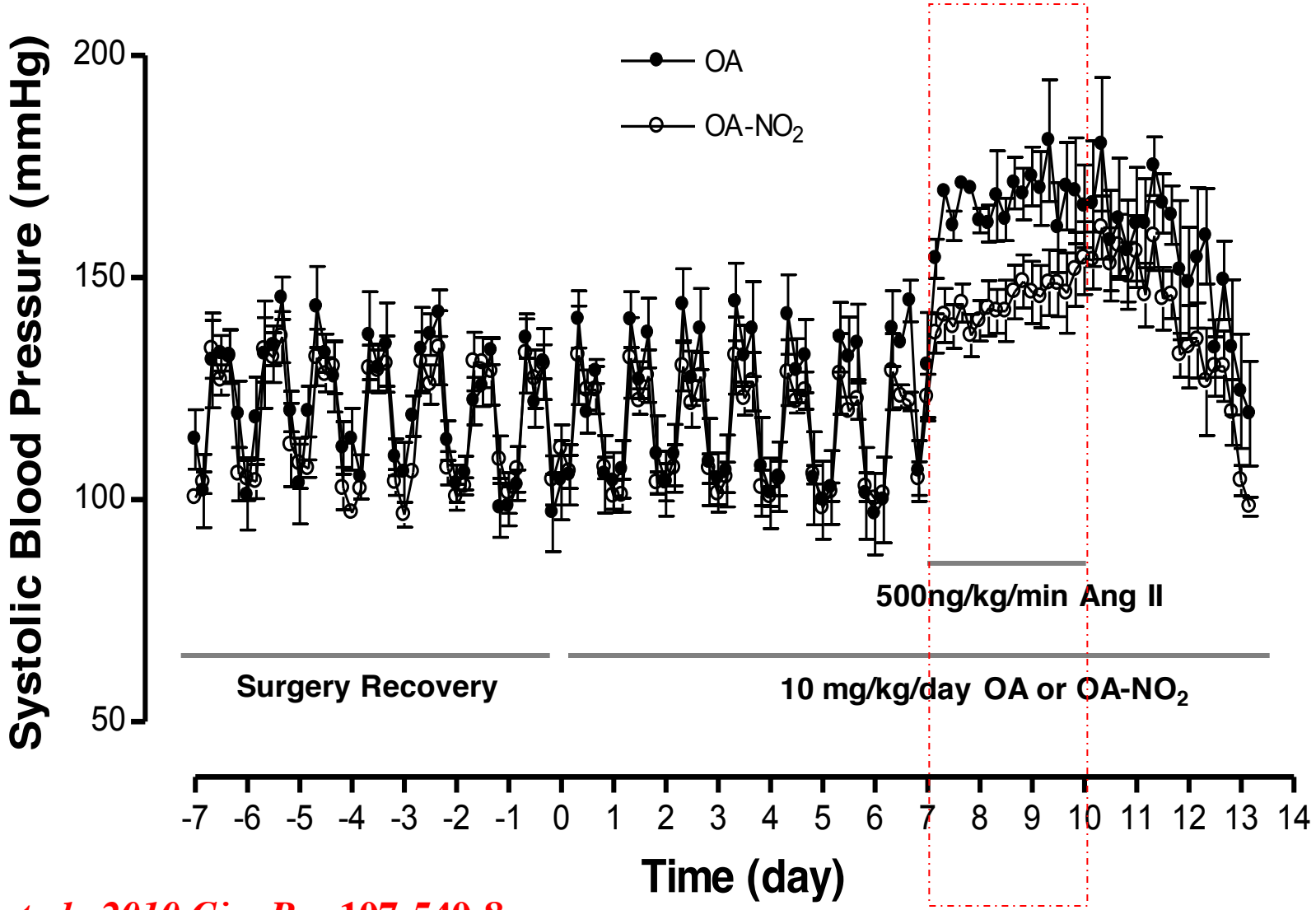
NO_2-FA-activated PPARγ recruits different co-regulators compared to TZD rosiglitazone





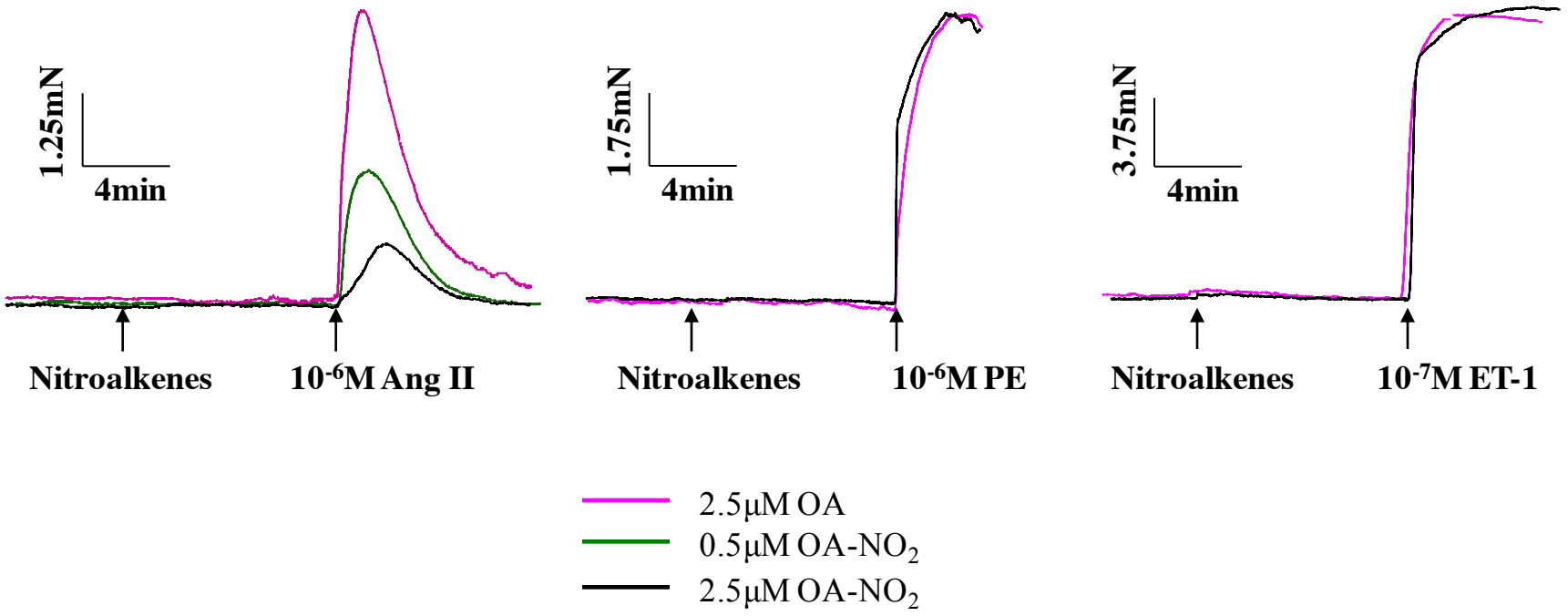
Schopfer et al., 2010 J Biol Chem. 285:12321-12333

Nitrated fatty acid inhibits Ang II-induced hypertension using the radiotelemetry system-derived blood pressure measurement



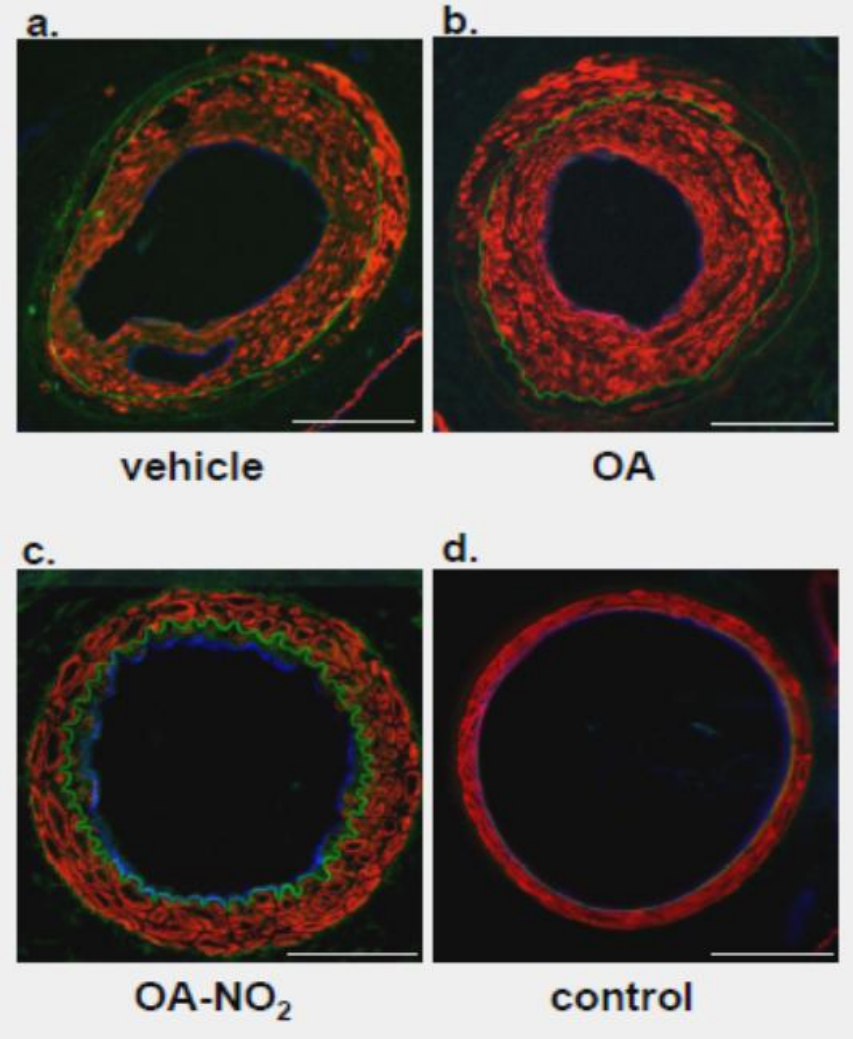
Zhang et al., 2010 Circ Res **107:540-8**

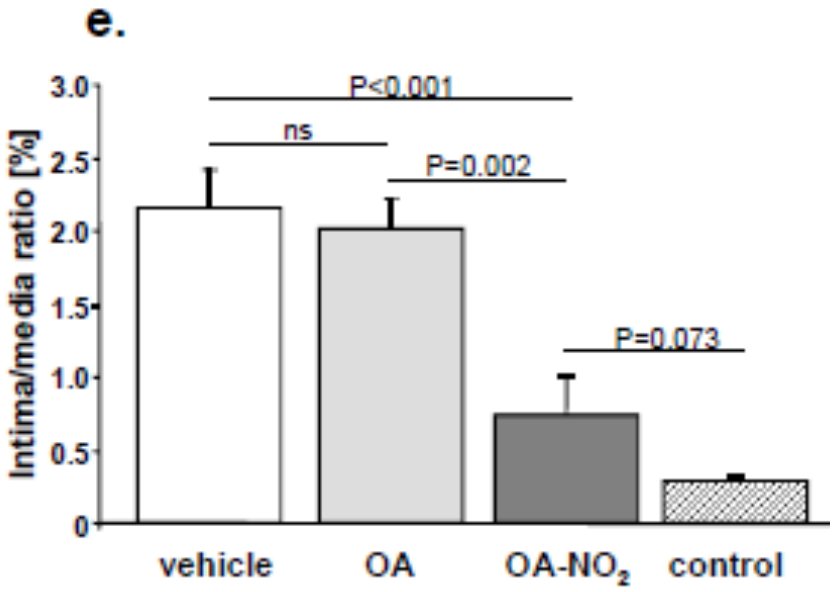
Nitro-oleic acid inhibits Ang II-mediated vessel contraction



Zhang et al., 2010 Circ Res **107:540-8**

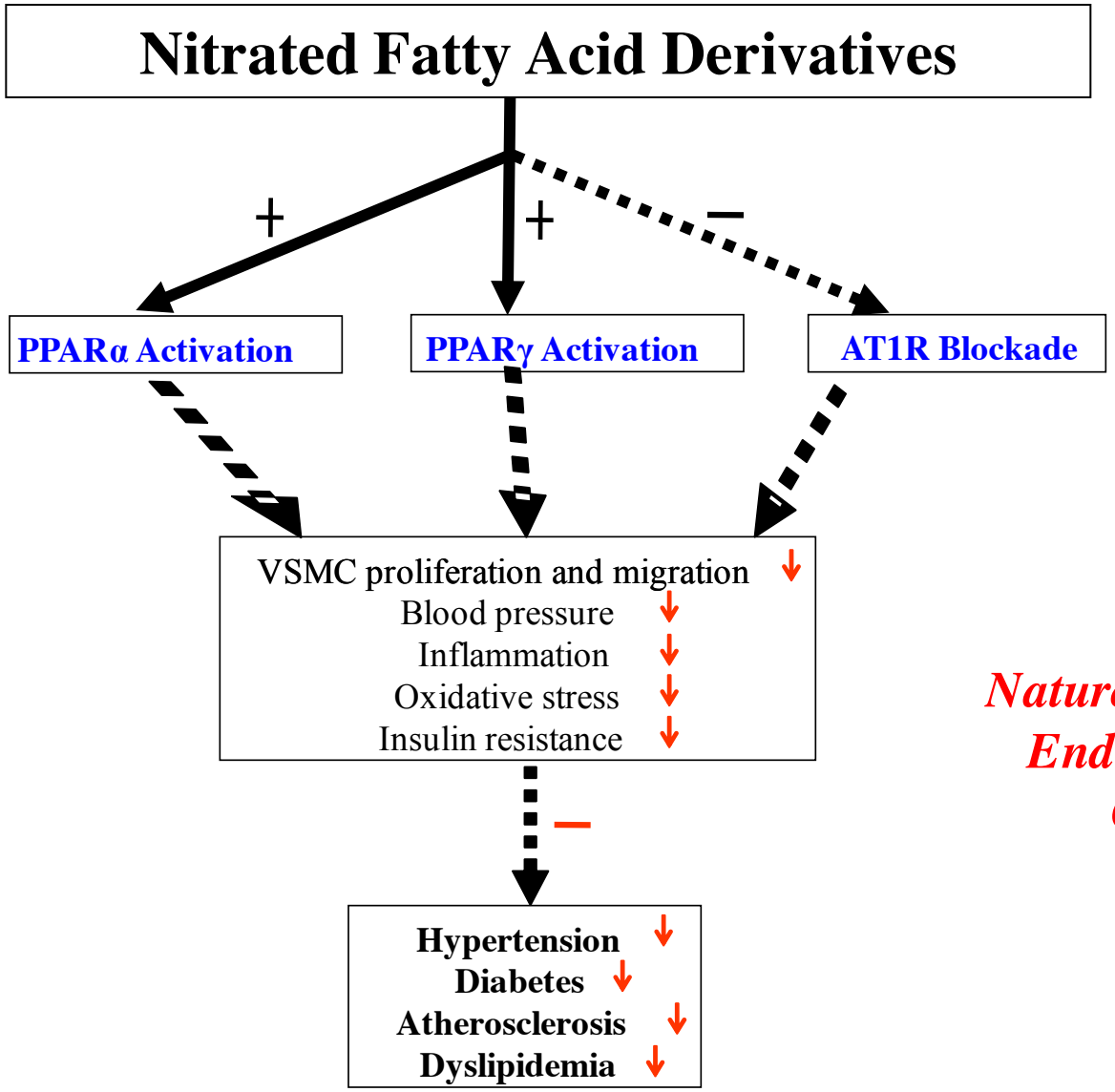
NO_2-FA Inhibits Vascular Lesion Formation





Cole MP, 2010 Circ Res. 105:965-972

Discovery of Nitro-Fatty Acids and Related Studies in Diabetes and CVD



PNAS 2005, 102:2340-5
JBC 2005, 280:42464-75
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Nature Struct Mol Biol 2008,15:865-7
Endocrinology 2008, 149:4086-94
Circ Res 2009,105:965-72
JBC 2010,285:12321-33
Circ Res 2010, 107:540-8