

# ***Oxidized lipids, Intestine, Inflammation, and artery wall metabolism.***

*SoCal Persian American Medical Association*

***Continued Medical Education, February 25, 2017***

*Mohamad Navab*  
*UCLA Cardiology*

# ***Overview:***

- Lipid oxidation***
- Inflammation***
- HDL mimetic peptides***
- Intestine genes***
- Microbiome***

<sup>+</sup>**Immune**<sup>-</sup>  
**System**

The diagram features a central pink text 'CVD'. Four white arrows point towards this central node from the corners. Each arrow originates from a seesaw. The top-left seesaw is labeled '+ Immune System -' in green. The top-right seesaw is labeled '+ Artery wall -' in yellow. The bottom-left seesaw is labeled '+ Blood lipids -' in yellow. The bottom-right seesaw is labeled '+ Coagulation -' in pink. Each seesaw consists of a horizontal line with a small triangle underneath it, representing a fulcrum.

<sup>+</sup>**Artery wall**<sup>-</sup>

**CVD**

<sup>+</sup>**Blood lipids**<sup>-</sup>

<sup>+</sup>**Coagulation**<sup>-</sup>

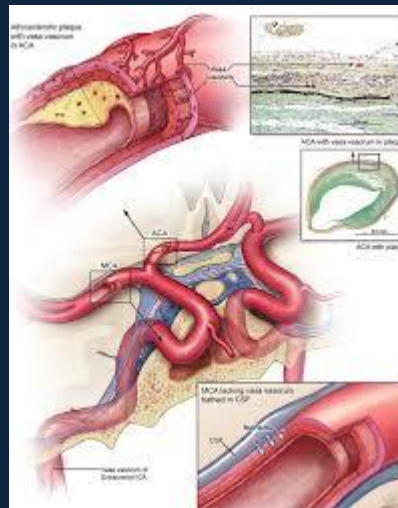
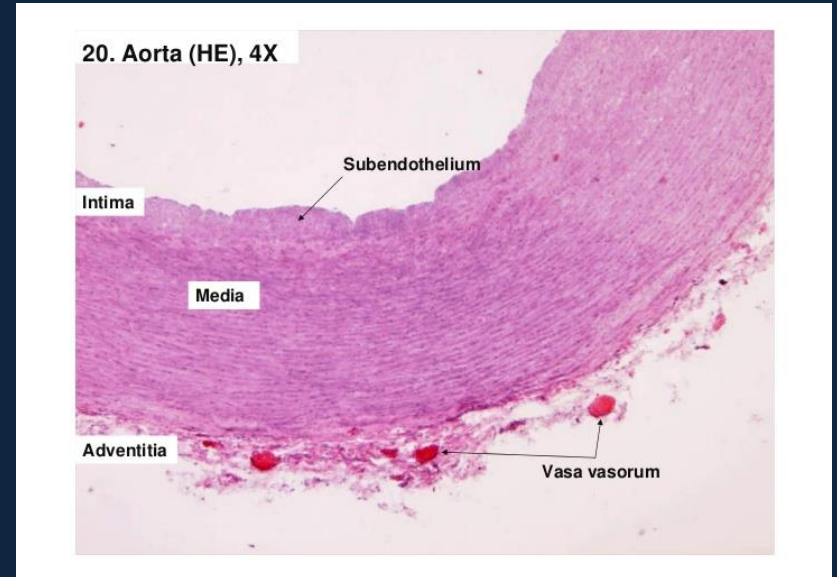
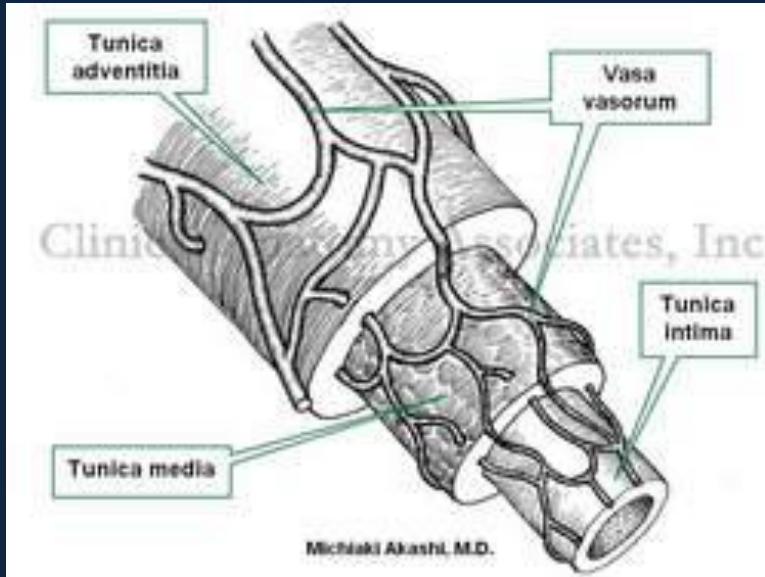
# Arteriosclerosis,

atherosclerosis

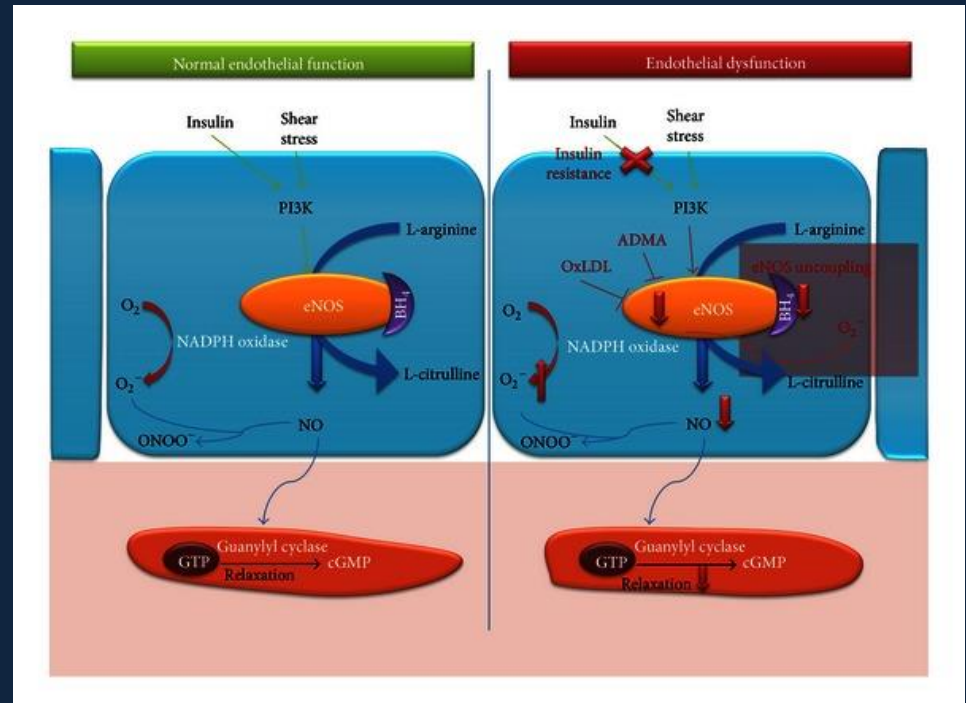
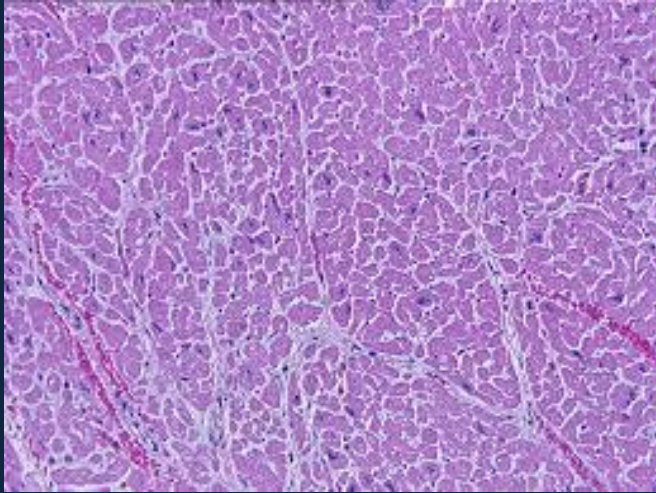


# atherosclerosis

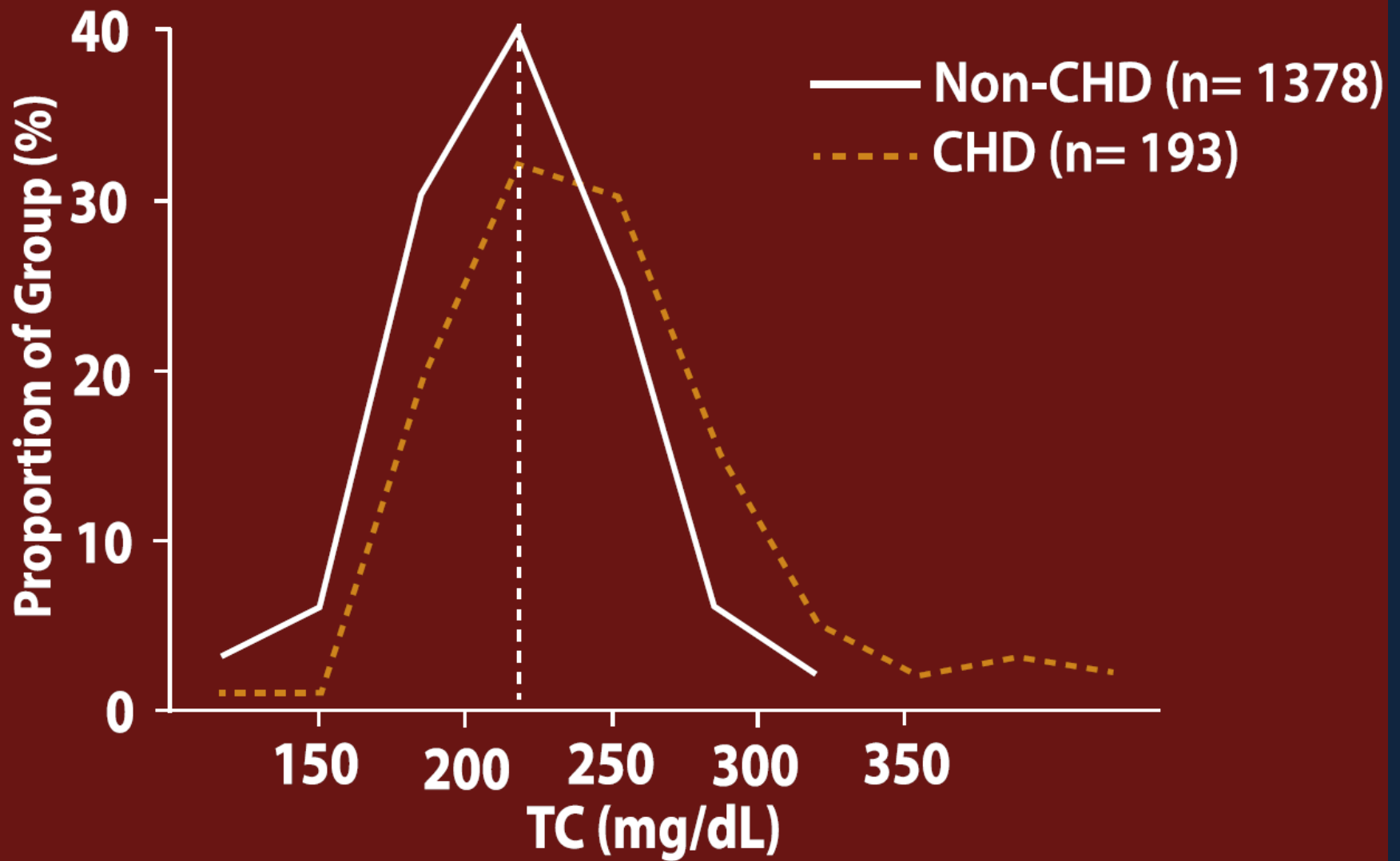
# Vasa vasorum



# Cardiac myocyte capillaries

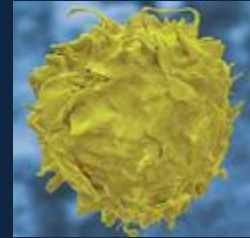
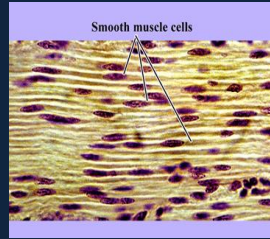
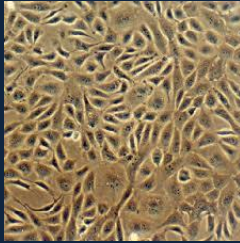
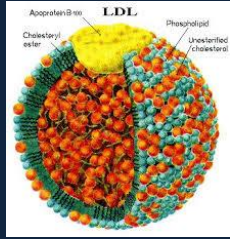


***1950s, Framingham***



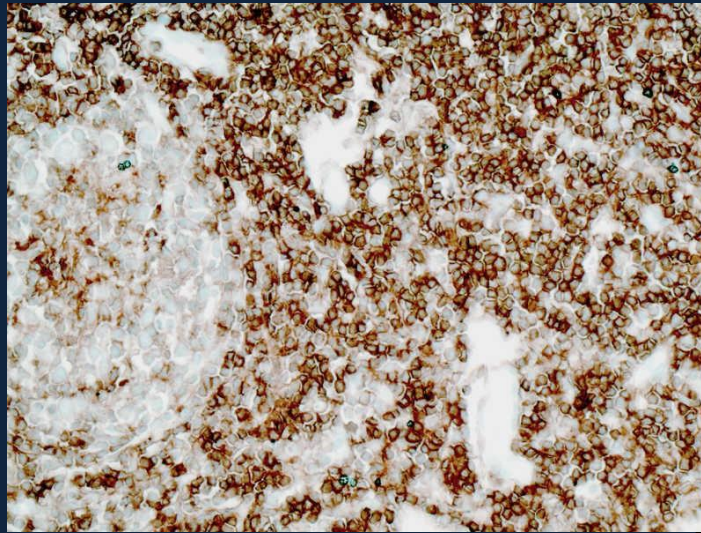


*1970s,*



*LDL, on EC, SMC, Monocyte-Mφ*

*Toxic*



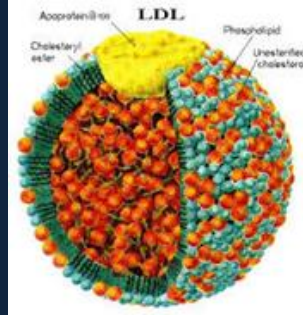
*HDL, OK, even rescued*

*1950s, Framingham*

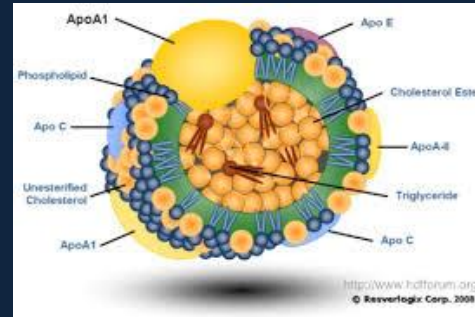
*1970s,*

*LDL, on EC, SMC, Monocyte-M $\phi$*

*Toxic*

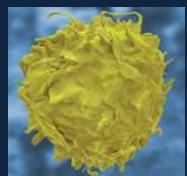
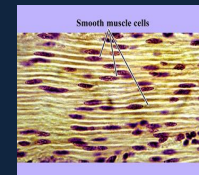
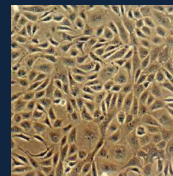


+



*+ HDL, rescued*

*Oxidized-LDL*



*1950s, Framingham*

*1970s,*

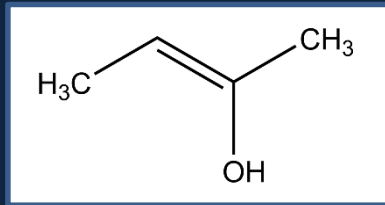
*LDL, on EC, SMC, Monocyte-M $\phi$   
Toxic*

*HDL, OK, even rescued*

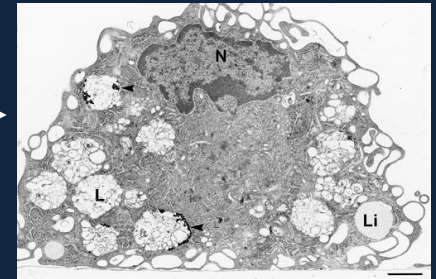
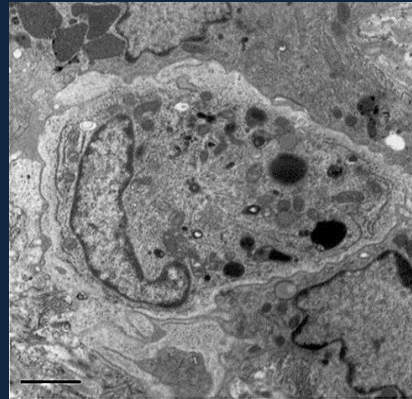
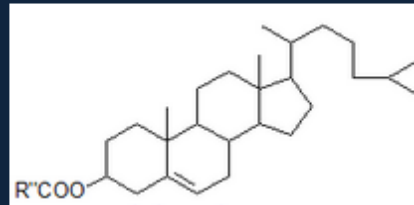
***Oxidized LDL***

Malondialdehyde alteration of low density lipoproteins leads to cholesteryl ester accumulation in human monocyte-macrophages.

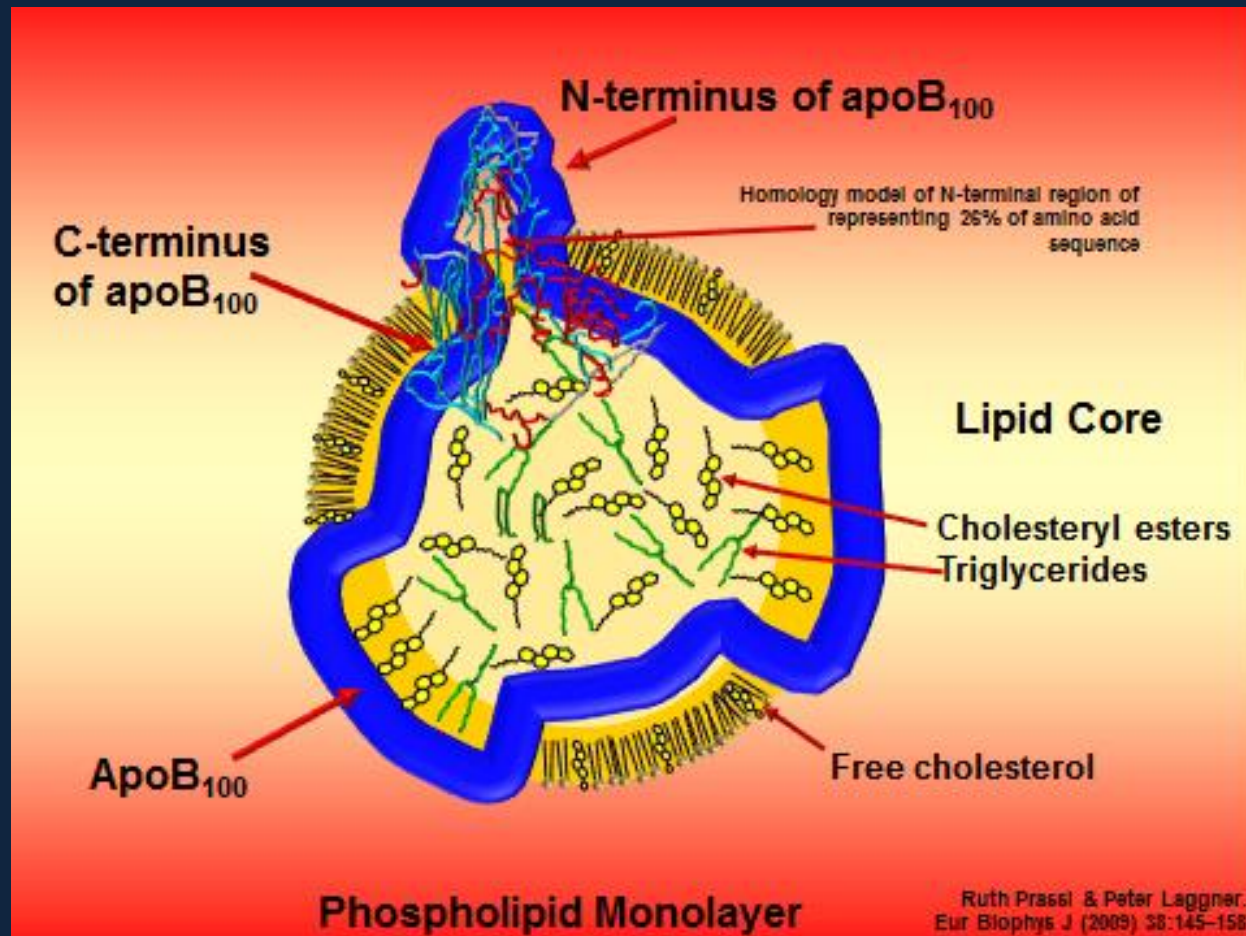
**Fogelman AM, Shechter I, Seager J, Hokom M, Child JS, Edwards PA. Proc Natl Acad Sci U S A. 1980 Apr;77(4):2214-8.**



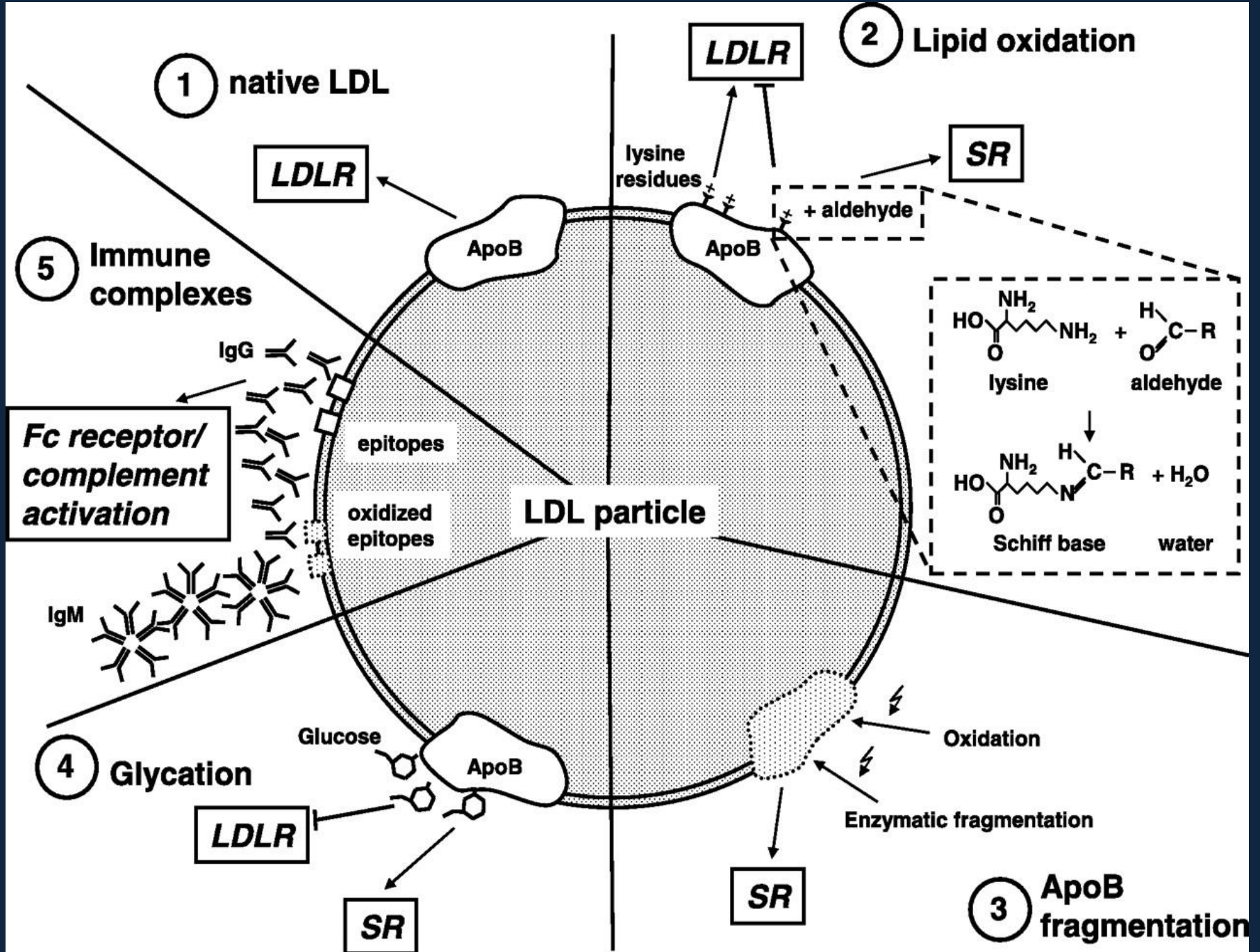
**+ LDL** →



# UCSD group, Cleveland Clinic group: Protein modification of LDL

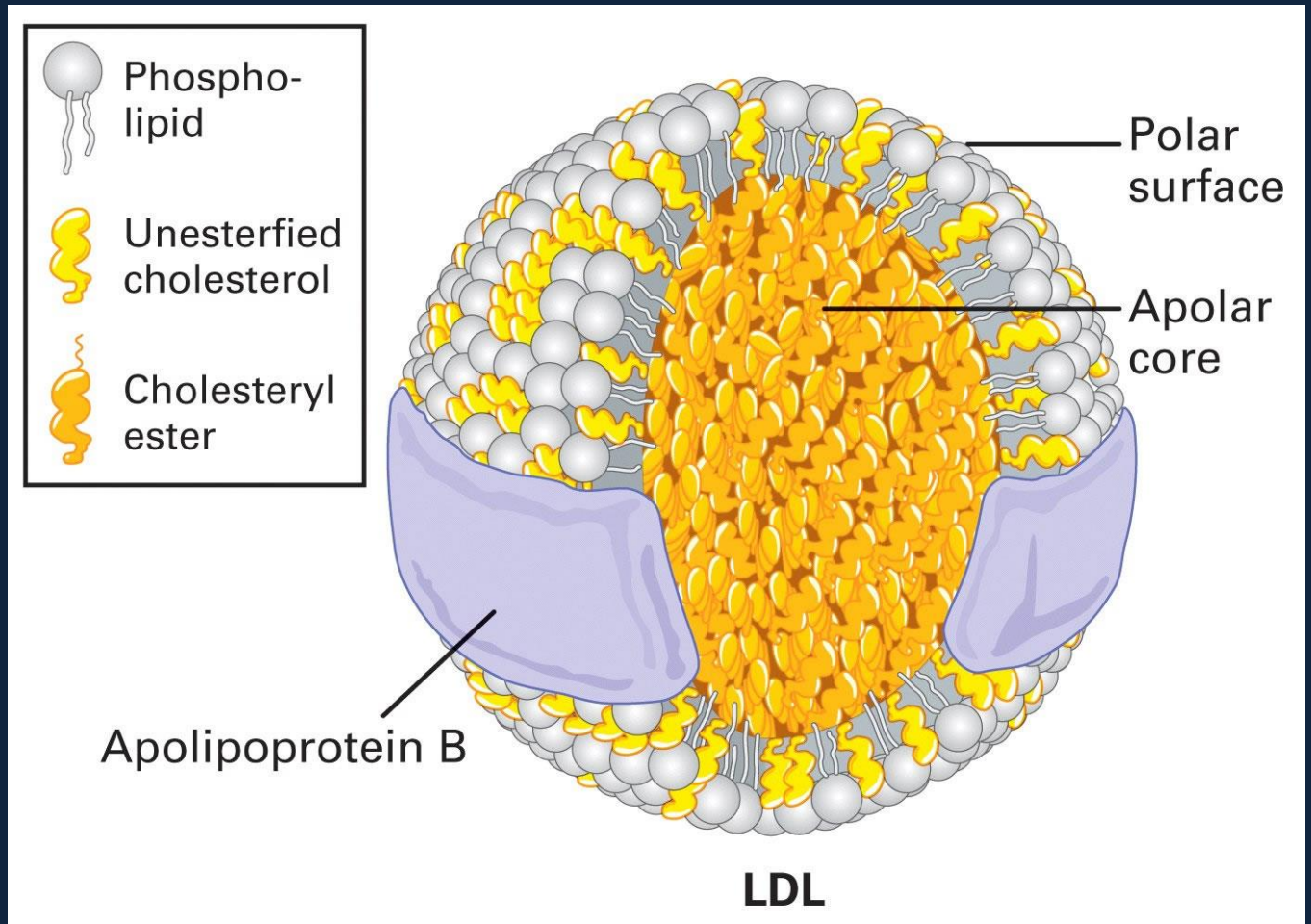


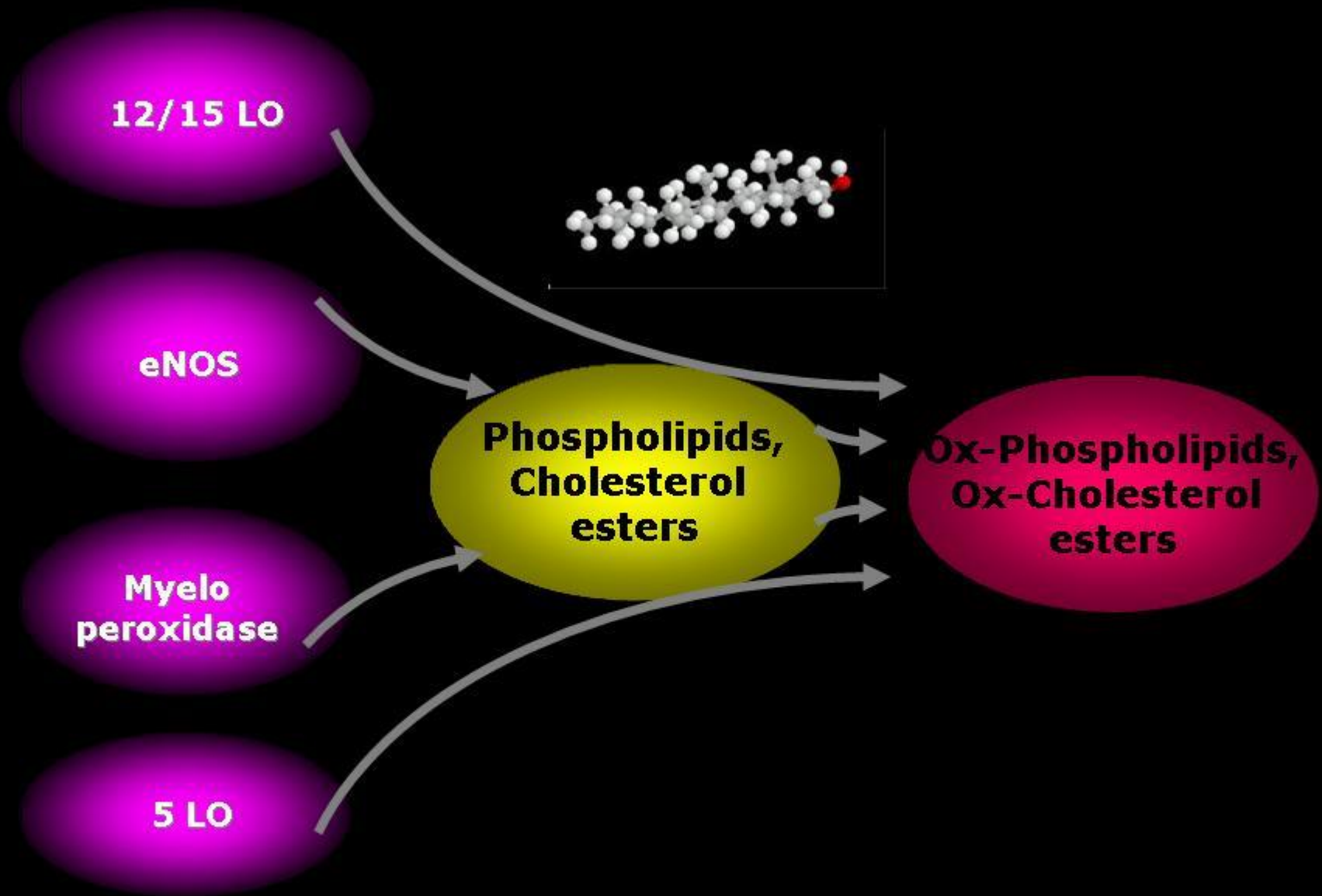




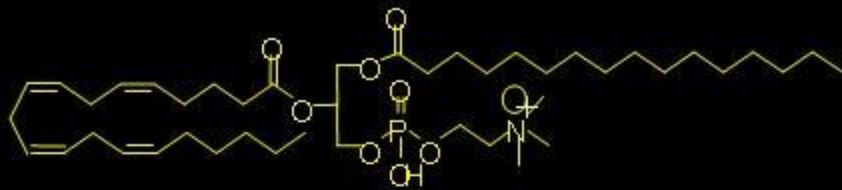
# UCLA group

## Lipid modification of LDL









## Oxidized phospholipids

Andrew D. Watson

N Engl J Med. 2005



Lipids

HPETE

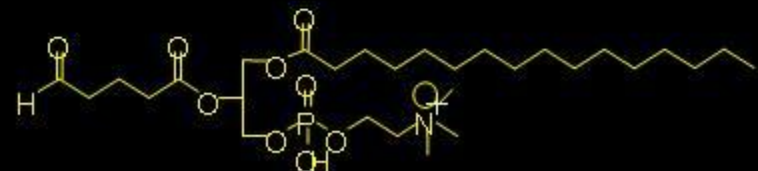
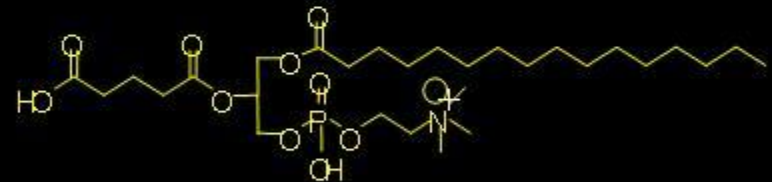
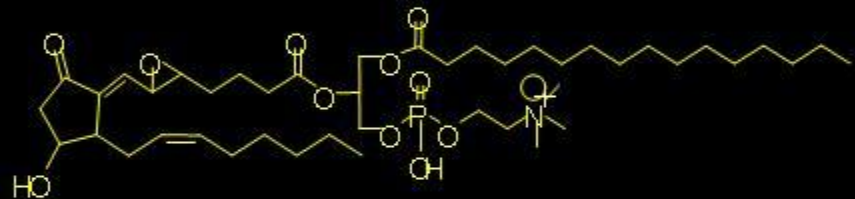
HPODE

ROS

Oxidized  
Lipids

↑ PEIPC, POVPC,  
PGPC, oxy sterols

plaque



*Unlike Framingham data*

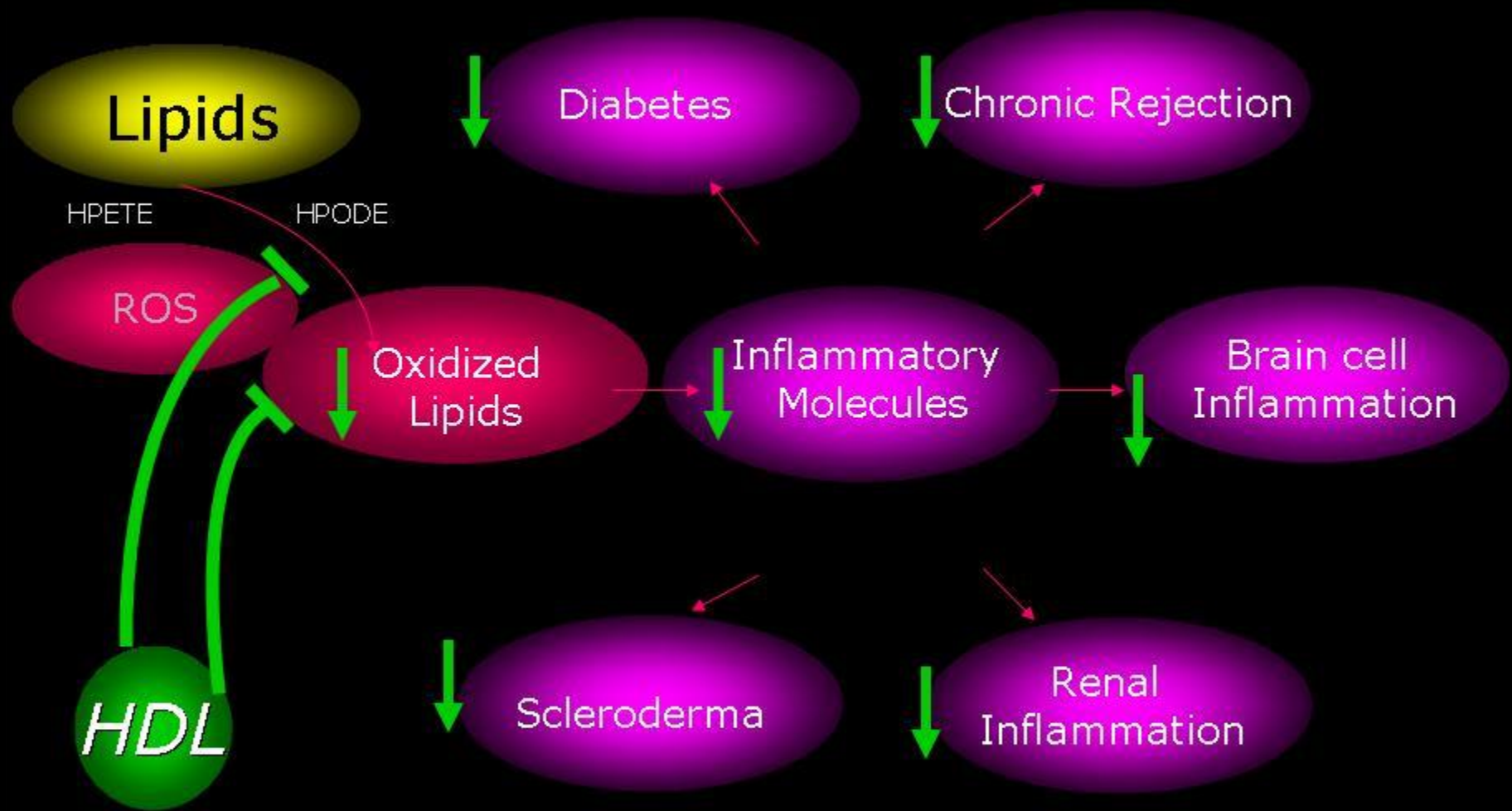
*1980s, some PTs with High HDL-C: events;  
Some with Low HDL, were fine.*

*1995 JCI, HDL function  
(composition, structure, Quality), LA Times.*

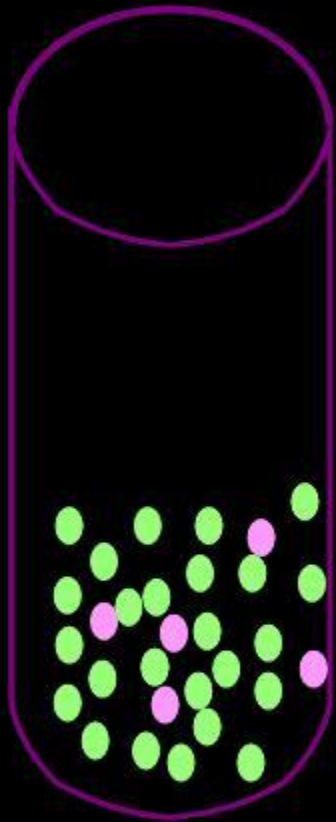
*New, and protective HDL*

*Old and non working HDL.*

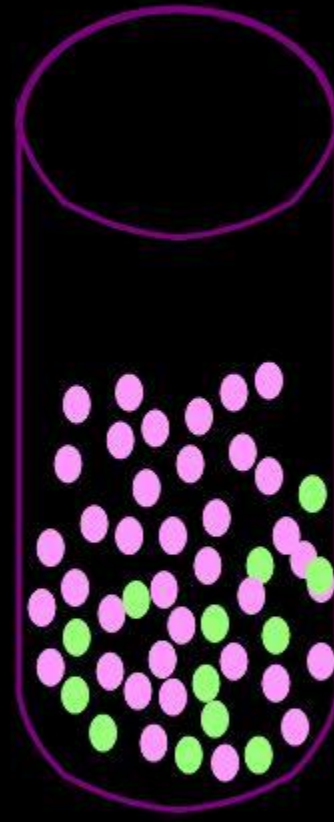
# HDL Anti inflammatory Properties



Anti inflammatory  
HDL



Pro inflammatory  
HDL



# *Properties of LDL and HDL*

*Small dense LDL*

*Non protective HDL*

*Unlike Framingham data*

*1980s, High HDL-C, events; Low HDL, OK*

*1995 JCI, HDL function*

*(composition, structure, Quality), LA Times*

***No worries about low HDL-C***

*Lower your LDL*

*Smart life style, proven therapy (if needed)*

***We do not have meds to improve HDL function.***

***Torcetrapib, Anacetrapib, ... Niacin...***



*We do not have meds to improve HDL function.*

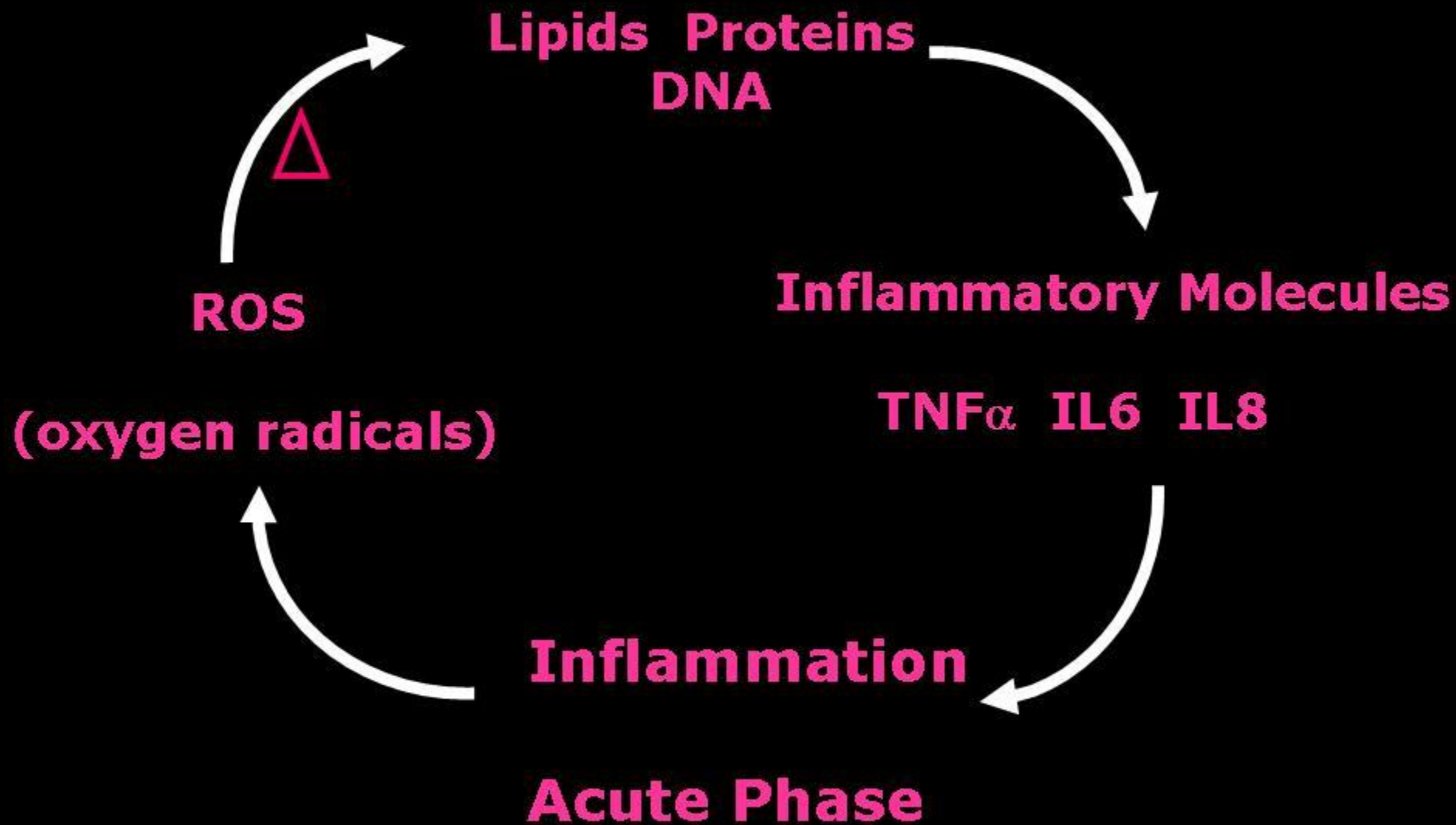
*Torcetrapib, Anacetrapib, ... Niacin...*

***We have good meds to reduce LDL:***

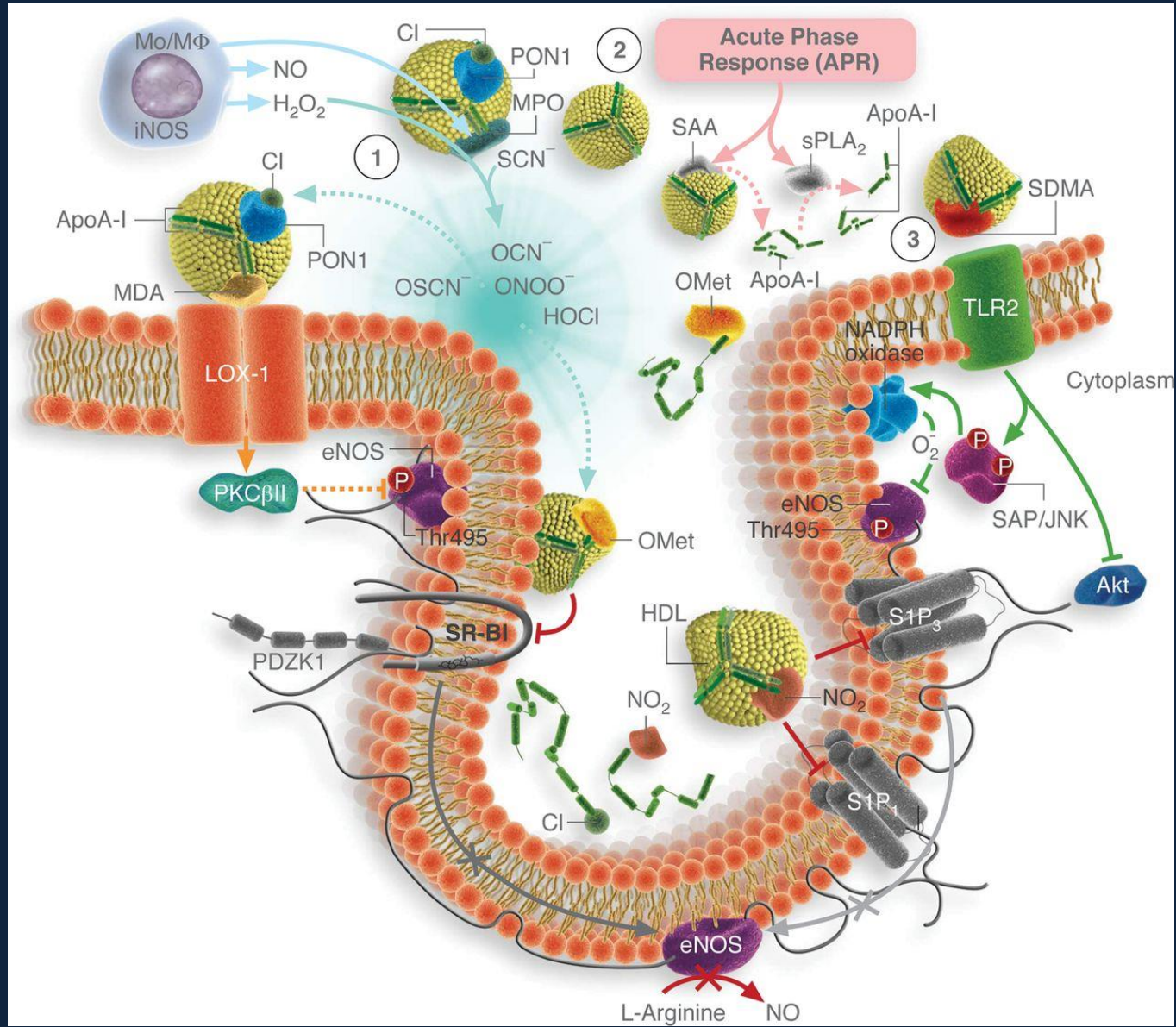
***-Statins***

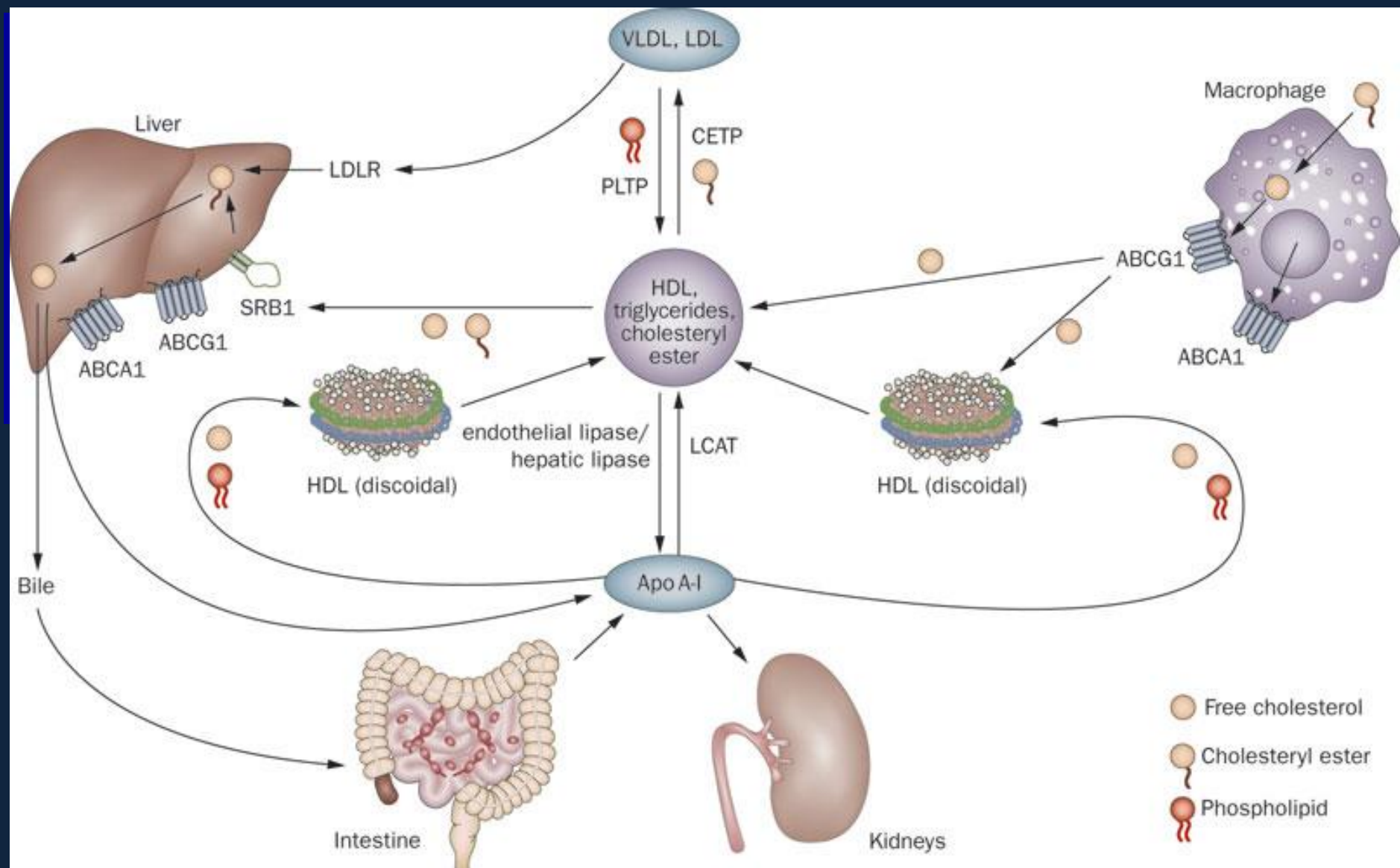
***-Ezetimibe, Vytorin***

***-PCSK9 inhibitors, alirocumab..***



# *In many disorders HDL is dysfunctional*





Anti-inflammatory and antioxidant properties of HDLs are impaired in type 2 diabetes.

**Morgantini C**, Natali A, Boldrini B, Imaizumi S, **Navab M**, Fogelman AM, Ferrannini E, Reddy ST.

Diabetes. 2011 Oct;60(10):2617-23. doi: 10.2337/db11-0378. Epub 2011 Aug 18.

Proinflammatory high-density lipoprotein results from oxidized lipid mediators in the pathogenesis of both idiopathic and associated types of pulmonary arterial hypertension.

**Ross DJ**, Hough G, Hama S, Aboulhosen J, Belperio JA, Sagggar R, Van Lenten BJ, Ardehali A, Eghbali M, Reddy S, Fogelman AM, **Navab M**.

Pulm Circ. 2015 Dec;5(4):640-8. doi: 10.1086/683695.

Heart failure is associated with impaired anti-inflammatory and antioxidant properties of high-density lipoproteins.

**Kim JB**, Hama S, Hough G, **Navab M**, Fogelman AM, Maclellan WR, Horwich TB, Fonarow GC.

Am J Cardiol. 2013 Dec 1;112(11):1770-7. doi: 10.1016/j.amjcard.2013.07.045.



**Proinflammatory high-density lipoprotein as a biomarker for atherosclerosis in patients with systemic lupus erythematosus and rheumatoid arthritis.**

McMahon M<sup>1</sup>, Grossman J, FitzGerald J, Dahlin-Lee E, Wallace DJ, Thong BY, Badsha H, Kalunian K, Charles C, Navab M, Fogelman AM, Hahn BH.

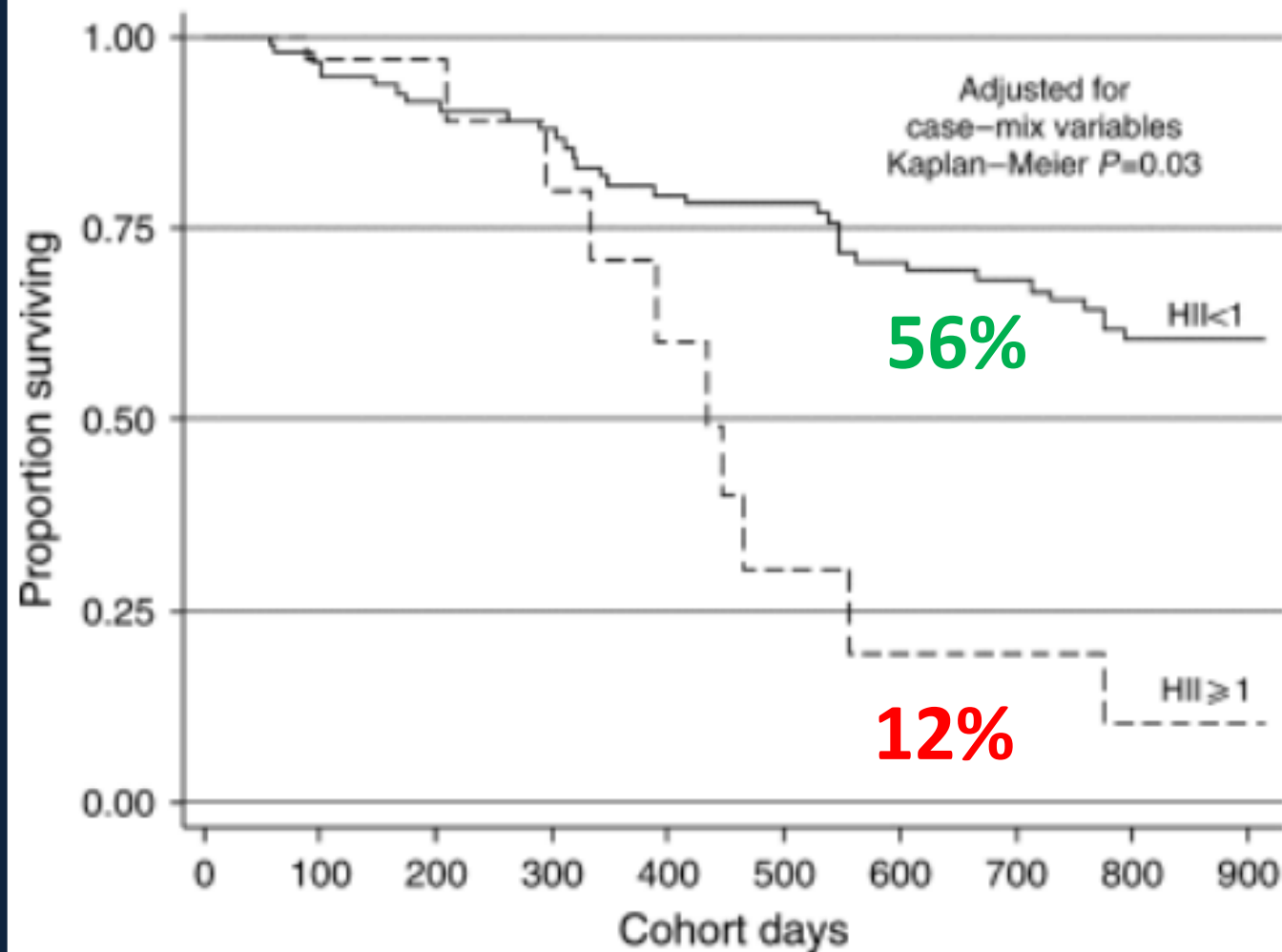
[HIV-1 infected patients with suppressed plasma viremia on treatment have pro-inflammatory HDL.](#)

**Kelesidis T**, **Yang OO**, **Currier JS**, **Navab K**, **Fogelman AM**, **Navab M**.  
Lipids Health Dis. 2011 Feb 23;10:35. doi: 10.1186/1476-511X-10-35.

189 MHD PTs

Low HDL Inflammatory  
Index

High HDL Inflammatory  
Index



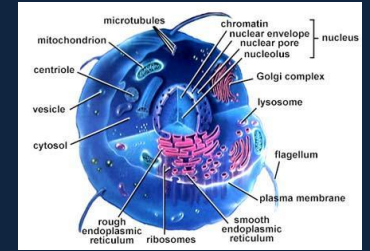
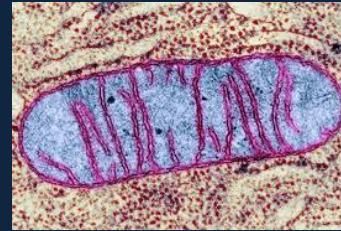
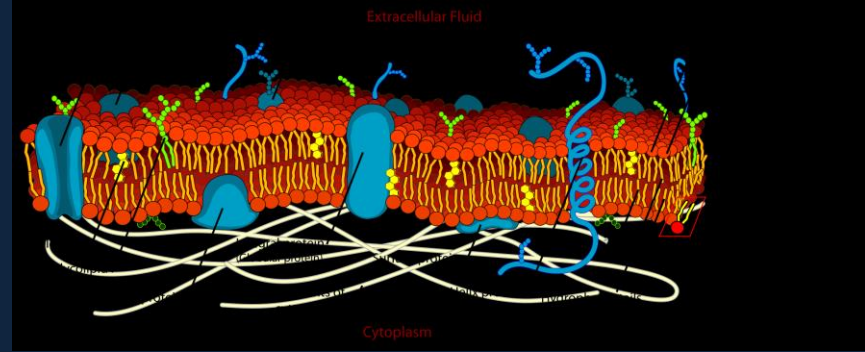
Kalantarzadeh et al. 2007

# LDL

# HDL

# Cell membrane and components

# Mitochondria ...

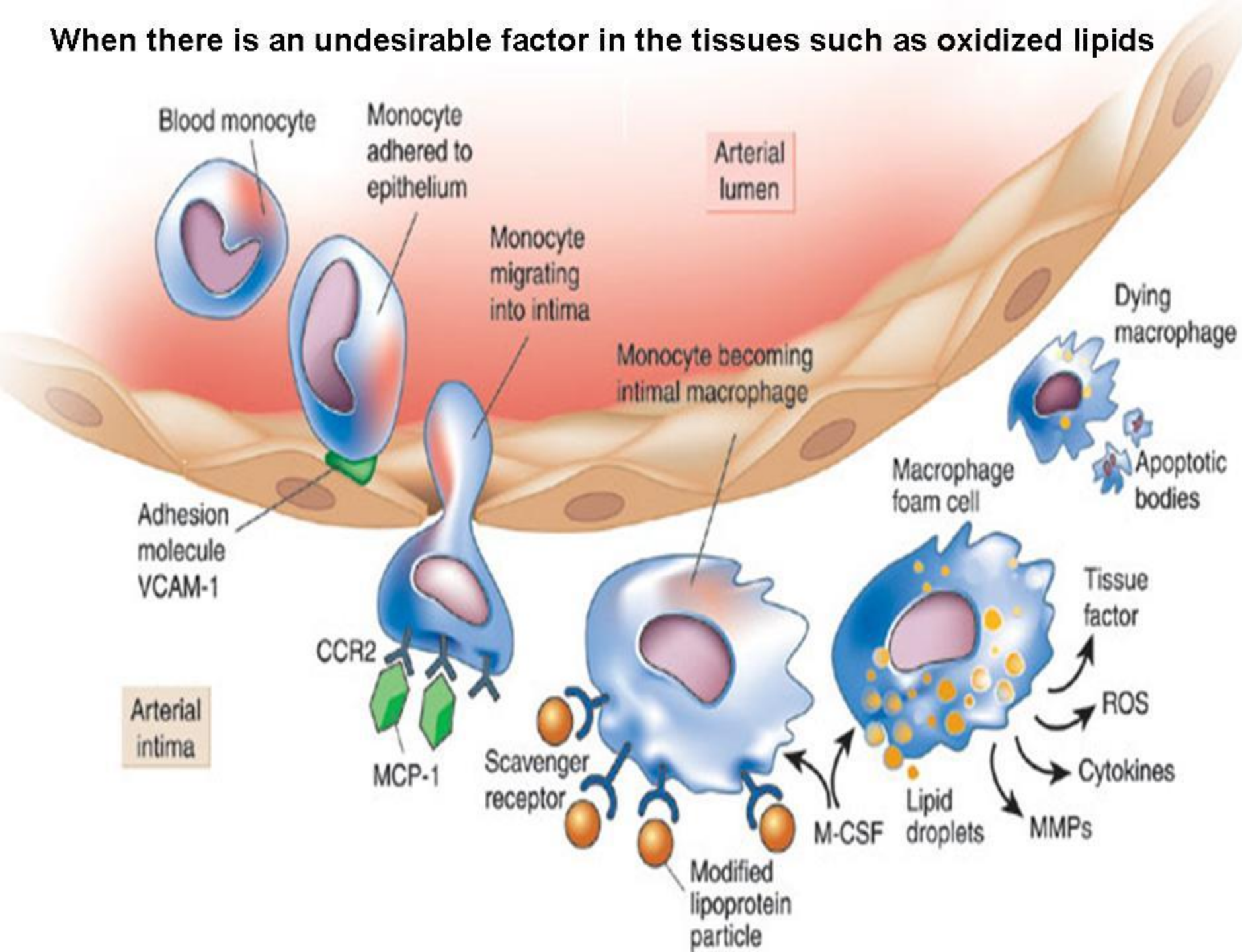


# The entire immune system..





When there is an undesirable factor in the tissues such as oxidized lipids



The same way that we bring food,  
oils and fats  
to our home



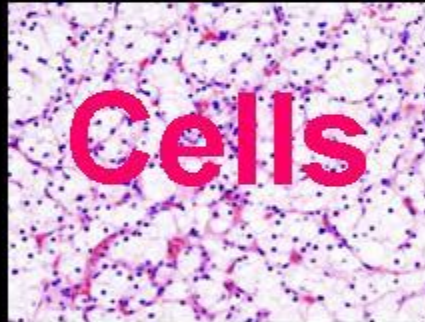
And we allow the waste  
to be taken away



LDL



Lipids



Toxic  
waste

HDL

For your patients  
Easy way to remember the  
bad cholesterol

LDL

Makes you

Lousy

Lazy



HDL

Makes you

Happy

Healthy

High







Lipid Metabolism and Transport	Hemostasis	Immune Response	Metal Binding	Vitamin Transport
ApoA-I, ApoA-II ApoA-V, ApoD ApoE, ApoF ApoC-I, ApoC-II ApoC-III, ApoC-IV ApoO, Apo(a) LCAT, PLTP, CETP PAFAH, SAA4 Pon1, Pon3 Albumin, Transthyretin ApoM, ApoB ApoL-I	Fibrinogen $\alpha$ Fibrinogen $\beta$ Fibrinogen $\gamma$ ApoH $\alpha$ -2 macroglobulin	Platelet basic prot. Vitronectin Haptoglobin rel. prot. Ac-muramoyl amidase Ig $\alpha$ -1 chain C Ig $\gamma$ -1 chain C Ig $\kappa$ -1 chain C Ig $\lambda$ -1 chain C AMBP, AZGP1 Serpine G1 Platelet factor 4 ApoL-I	HB $\alpha$ , HB $\beta$ Ceruloplasmin Hemopexin Serotransferrin His-rich glycoprot. AMBP	Aafamin Vit. D bind. prot. Retinol bind. prot.
ApoA-IV $\alpha$ -1-acid glycoprot. 1 $\alpha$ -1-acid glycoprot. 2 SAA1/2	Prothrombin Kininogen Kallistatin	ApoA-IV LPS-binding protein $\alpha$ -2 antiplasmin	$\alpha$ -1 anti-trypsin Serum amyloid P ITIH4 $\alpha$ -1 anti-chymo. Fibronectin $\alpha$ -2 HS glycoprot.	Acute Phase Response/ Inflammation
	Anti-thrombin III Plasminogen Serpine G1 Serpine D1 Kallikrein	$\alpha$ -2 antiplasmin	Prenyl-Cys-oxid. $\alpha$ -1 anti-trypsin Hep. cofactor 2 ITIH4, ITIH1, ITIH2 $\alpha$ -1 antichymo. Serpine F1, AMBP	Proteolysis/ Inhibition
ApoJ	Comp. C9	Comp. 1S, Comp. C2 Comp. 4B, Comp. B Comp. H, Comp. C3 ApoJ		Complement

**Table 5** Broad range of lipid species isolable from HDL

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Dihydroceramide  
Ceramide  
Monohexosylceramide  
Dihexosylceramide  
Trihexosylceramide  
GM3 ganglioside  
Sphingomyelin  
Sphingosine-1-phosphate  
Phosphatidylcholine  
Alkylphosphatidylcholine  
Alkenylphosphatidylcholine (plasmalogen)  
Lysophosphatidylcholine  
Lysoalkylphosphatidylcholine (lysoplatelet activating factor)  
Phosphatidylethanolamine  
Alkylphosphatidylethanolamine  
Alkenylphosphatidylethanolamine (plasmalogen)  
Lysophosphatidylethanolamine  
Phosphatidylinositol  
Lysophosphatidylinositol  
Phosphatidylserine  
Phosphatidylglycerol  
Bis(monoacylglycero)phosphate  
Cholesterol ester  
Cholesterol  
Diacylglycerol  
Triacylglycerol



The diagram consists of three circles arranged in a triangle, connected by white lines. The top circle is yellow and contains the text 'Particle - Structure - Metabolism'. The bottom-left circle is purple and contains the text 'Proteome'. The bottom-right circle is blue and contains the text 'Lipidome'. In the center of the triangle, the text 'HDL Functionality' is written in blue. The background is a solid dark blue.

**Particle**  
**- Structure**  
**- Metabolism**

**HDL**  
**Functionality**

**Proteome**

**Lipidome**

*2000*

*Making the good cholesterol better*

## ApoA-1 mimetic peptides.

2F      Ac-D-W-L-K-A-F-Y-D-K-V-A-E-K-L-K-E-A-F-NH<sub>2</sub>

3F      Ac-D-W-L-K-A-F-Y-D-K-V-A-E-K-L-K-E-A-F-NH<sub>2</sub>

→ 4F      Ac-D-W-F-K-A-F-Y-D-K-V-F-E-K-L-K-E-A-F-NH<sub>2</sub>

5F      Ac-D-W-F-K-A-F-Y-D-K-V-F-E-K-L-K-E-F-F-NH<sub>2</sub>

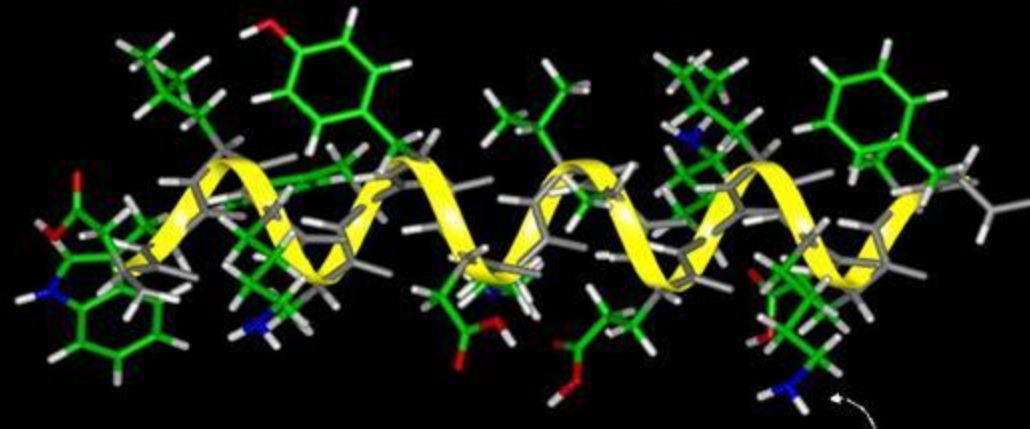
6F      Ac-D-W-L-K-A-F-Y-D-K-V-A-E-K-L-K-E-A-F-NH<sub>2</sub>

7F      Ac-D-W-L-K-A-F-Y-D-K-V-A-E-K-L-K-E-A-F-NH<sub>2</sub>

*Circulation 2003*

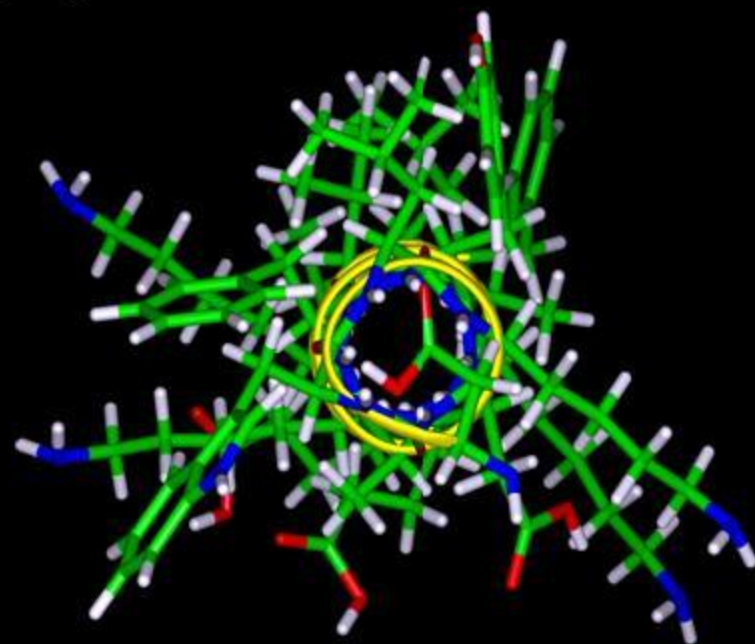
# *Apo A-I Peptide Mimetic*

Hydrophobic face

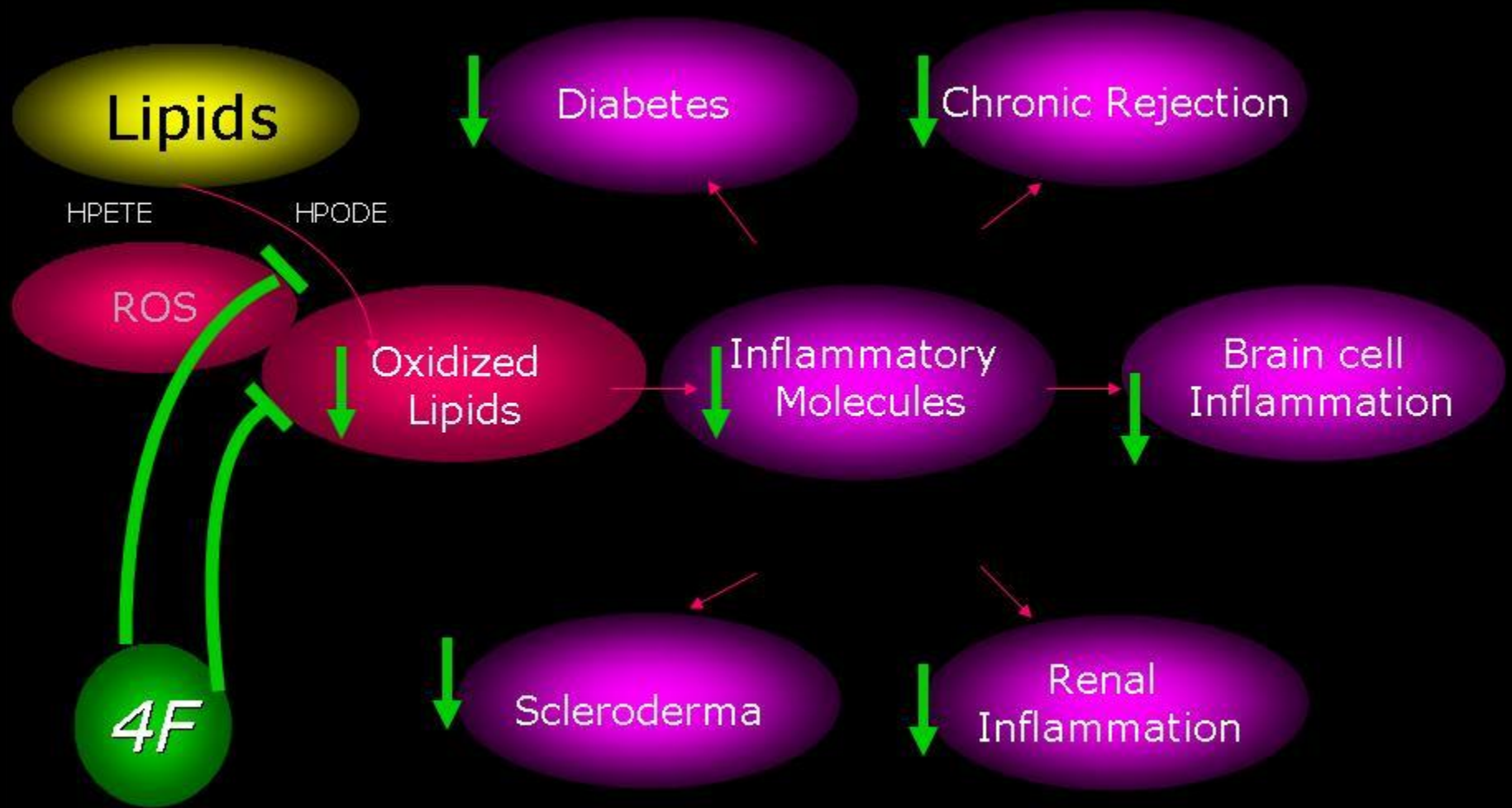


Hydrophilic face

Amino group



# 4F Anti inflammatory Properties



Micheal Jackson

Has extremely high affinity for  
oxidized lipids  
( $K_d$   $1 \times 10^{-5}$  and  $10^{-6}$ )



# Reduced complications

Atherosclerotic lesions in mice, Circulation 2001

Diabetes mouse model , Diabetes 200

Lupus, Betty Tsao

Prevented influenza virus vascular inflammation, Circulation 200

Treatment with apolipoprotein A-1 mimetic peptide reduces lupus-like manifestations in a murine lupus model of accelerated atherosclerosis.

Woo JM, Lin Z, **Navab** M, Van Dyck C, Trejo-Lopez Y, Woo KM, Li H, Castellani LW, Wang X, Iikuni N, Rullo OJ, Wu H, La Cava A, Fogelman AM, Lusis AJ, **Tsao** BP.

Arthritis Res Ther. 2010;12(3):R93. doi: 10.1186/ar3020. Epub 2010 May 18.

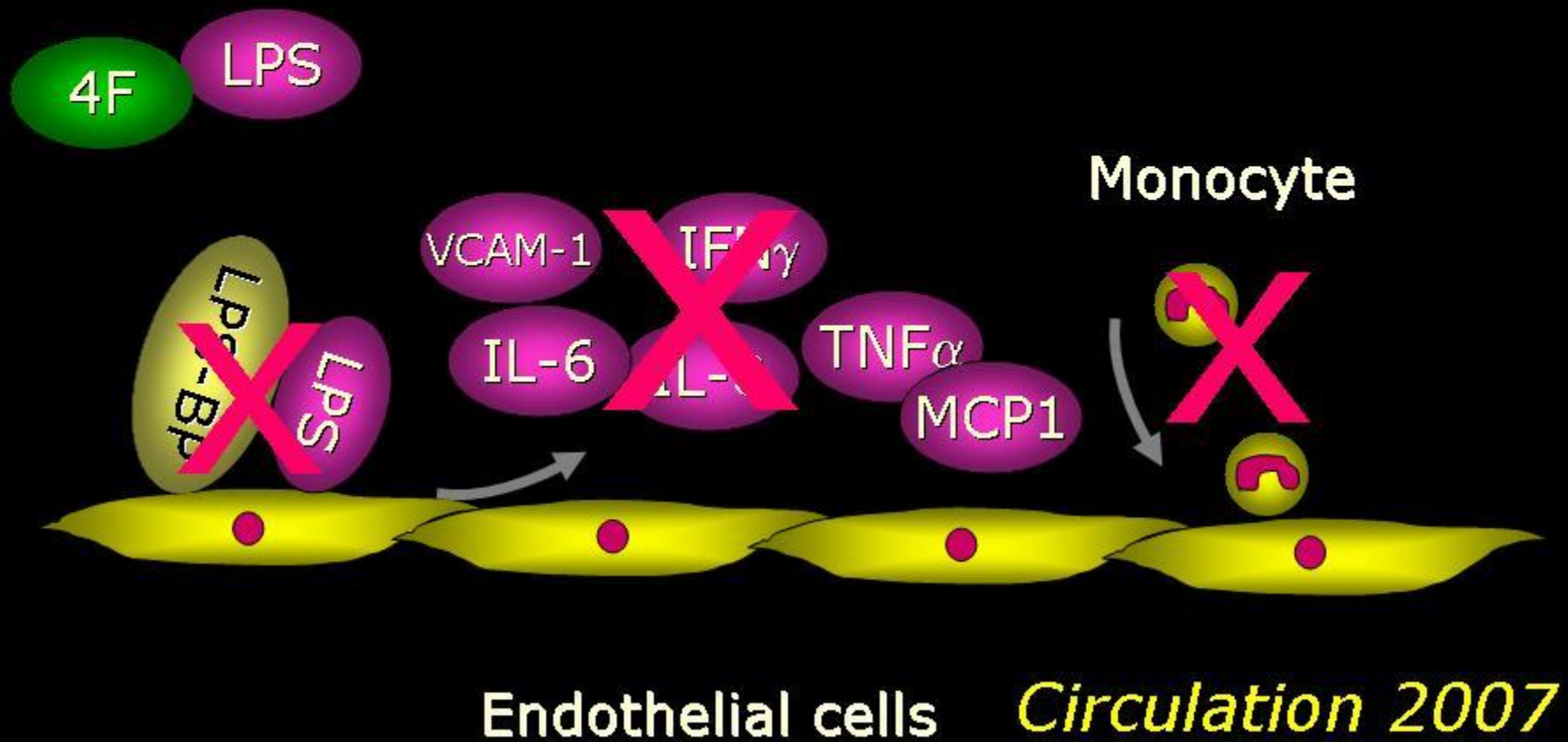
Amelioration of nephropathy with apoA-1 mimetic peptide in apoE-deficient mice.

Vaziri ND, **Kim** HJ, Moradi H, Farmand F, **Navab** K, **Navab** M, Hama S, Fogelman AM, Quiroz Y, Rodriguez-Iturbe B.

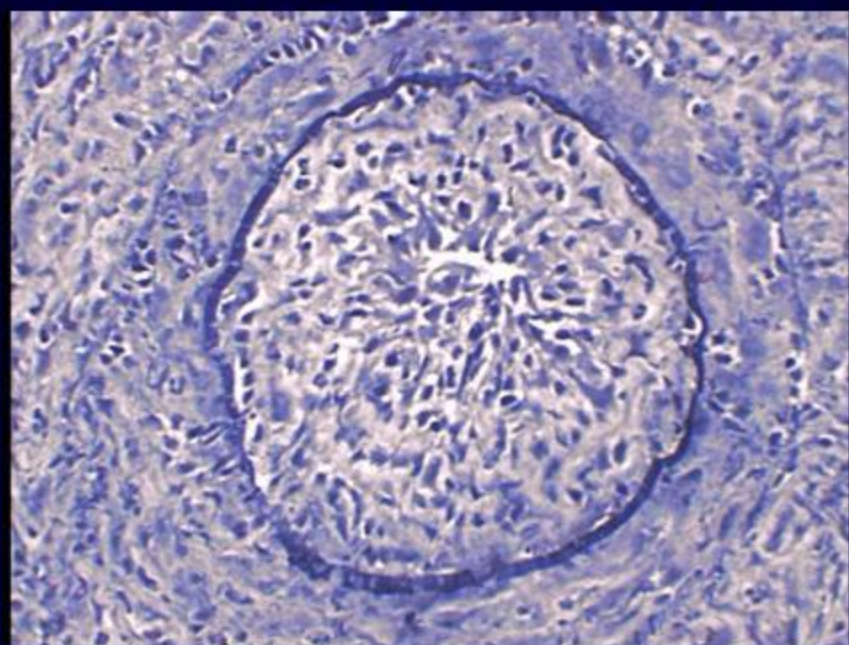
Nephrol Dial Transplant. 2010 Nov;25(11):3525-34. doi: 10.1093/ndt/gfq274. Epub

# Infection, Inflammation

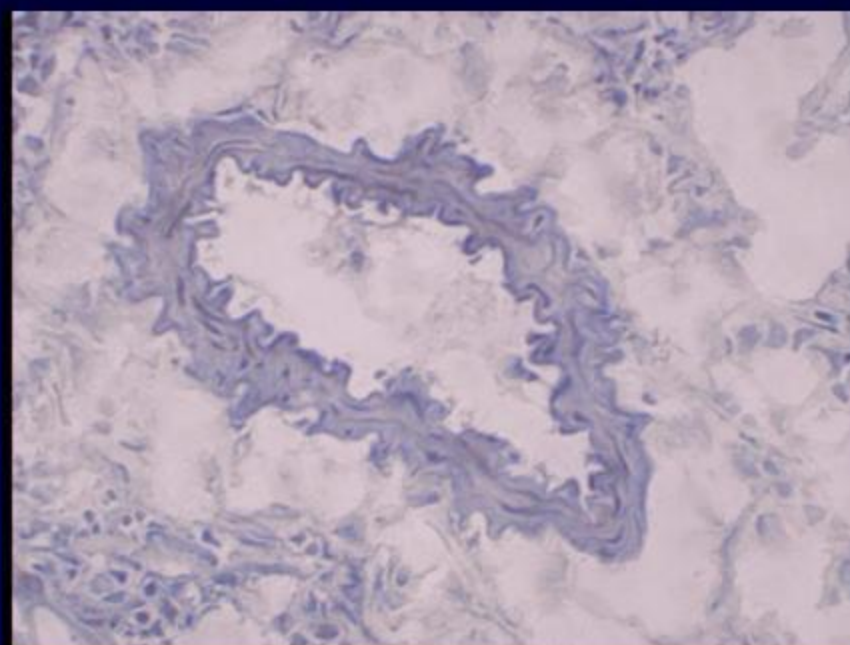
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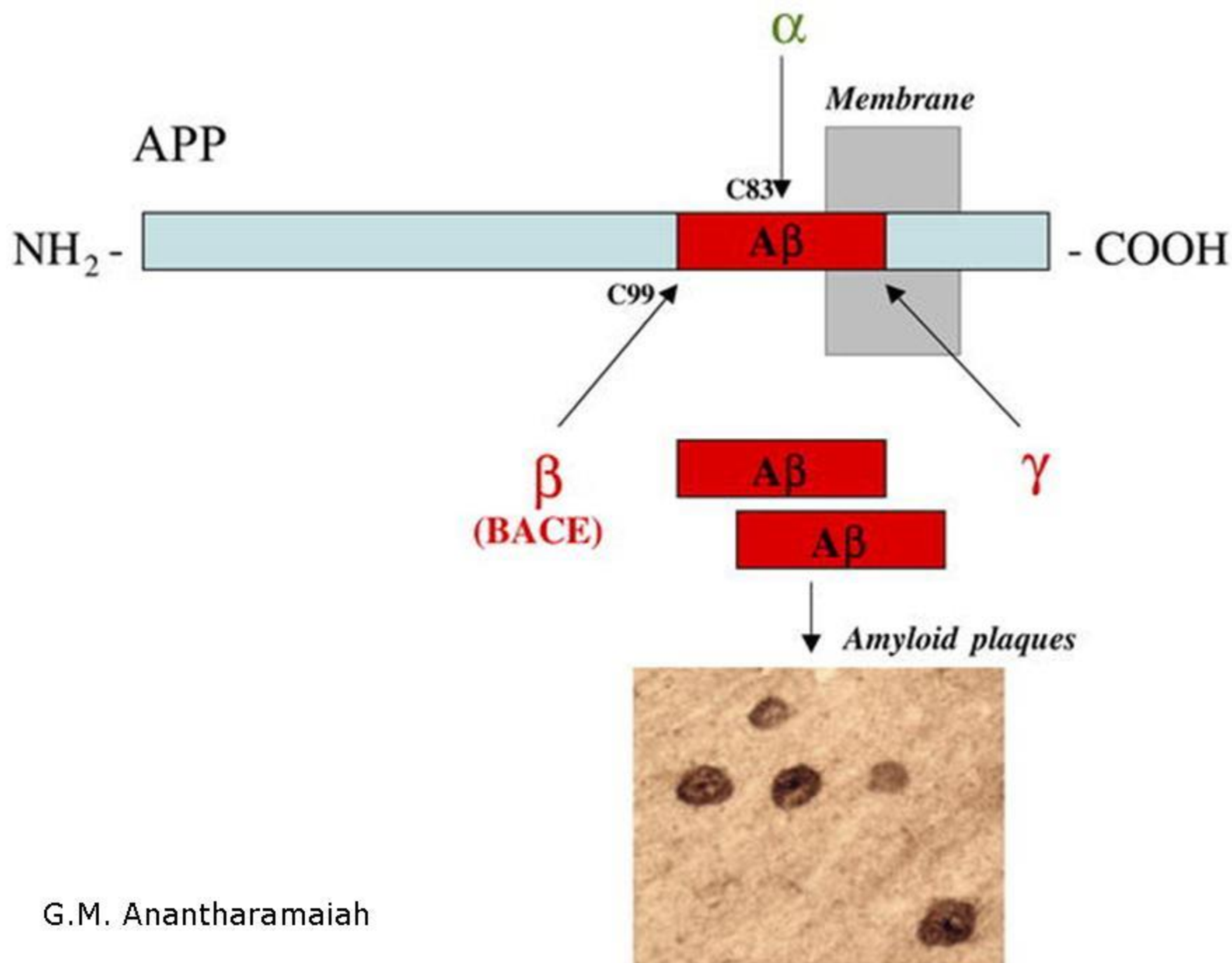
# 4F Dramatically Reduces Cardiac Allograft Vasculopathy



PBS Control



4F Treated





# Plaques in the brain

control



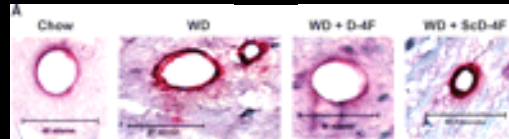
+Peptide



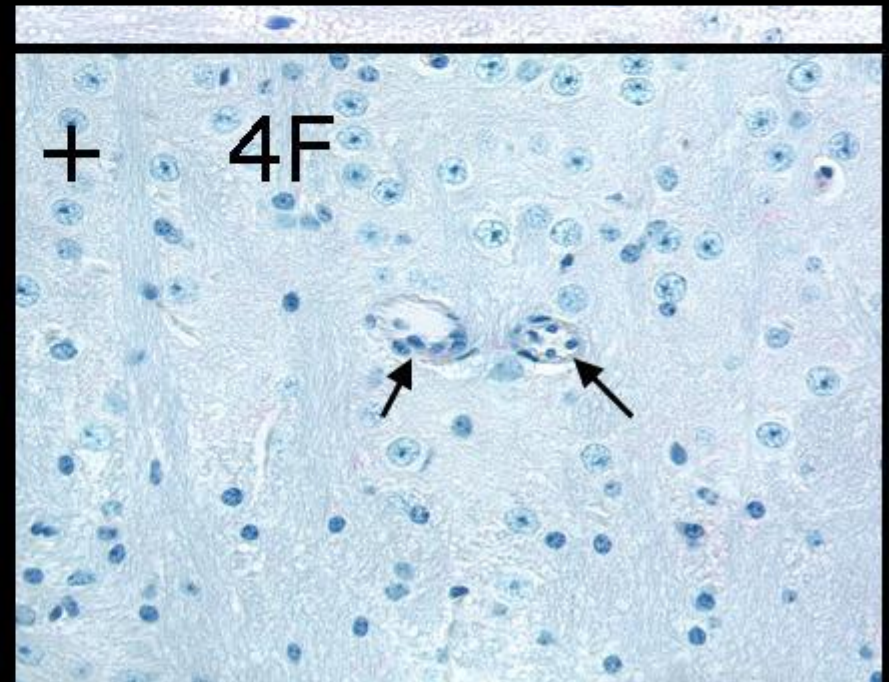
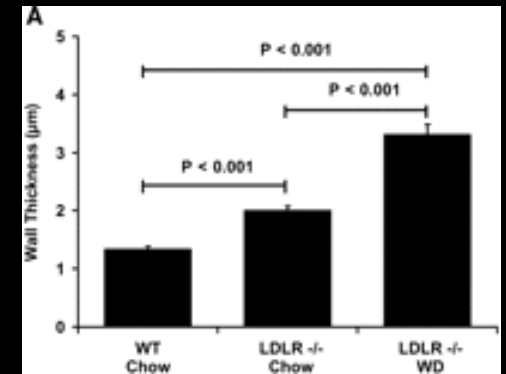
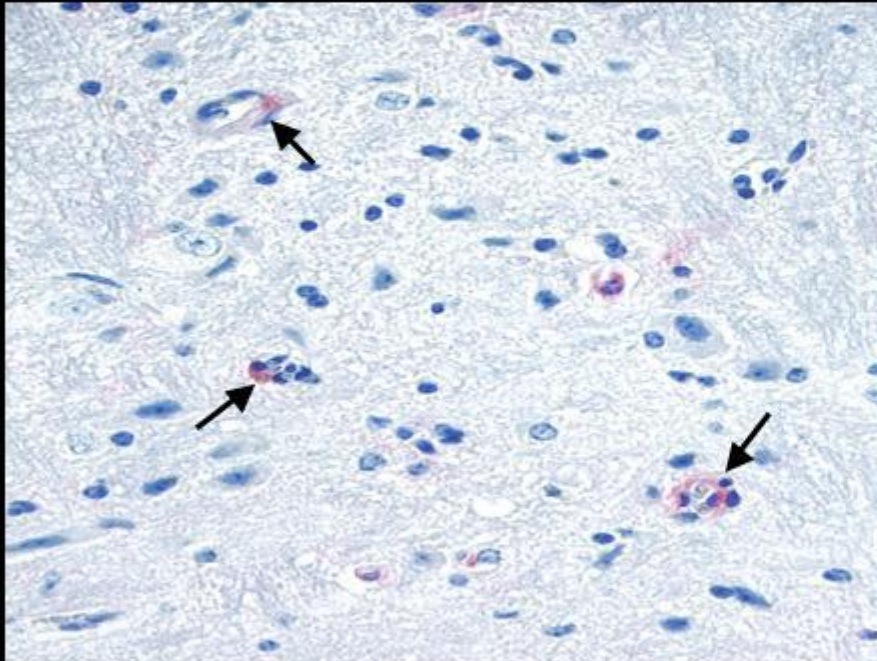


## F4/80 inflammatory marker

High fat high cholesterol diet (WD) in LDLR mouse,  
In the brain



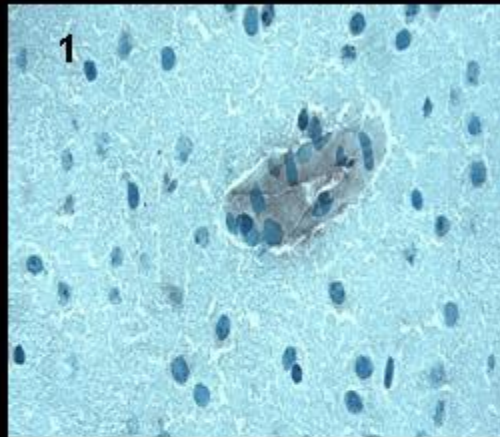
Thickened arteriol wall



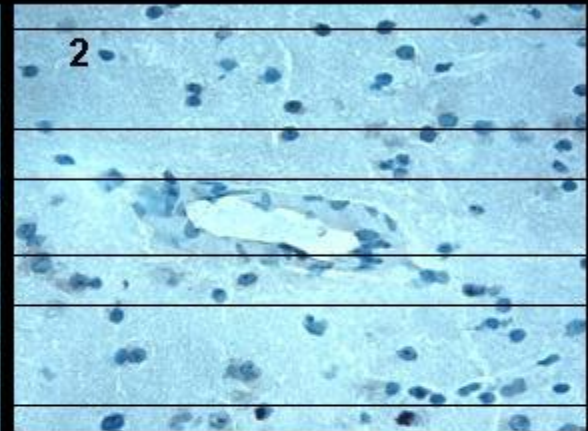
# inflammatory markers

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MIP-1 $\alpha$

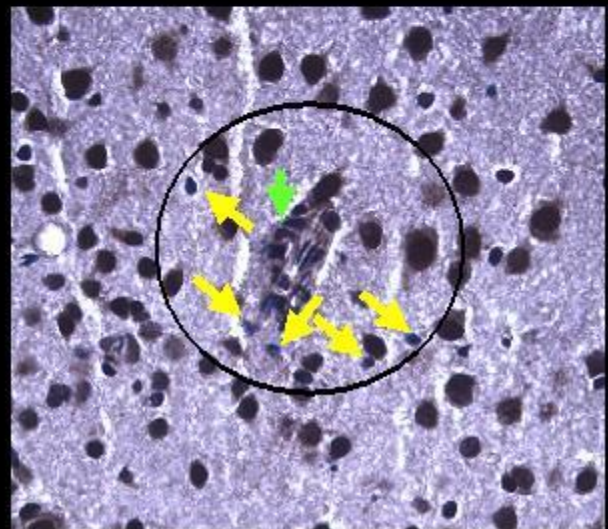


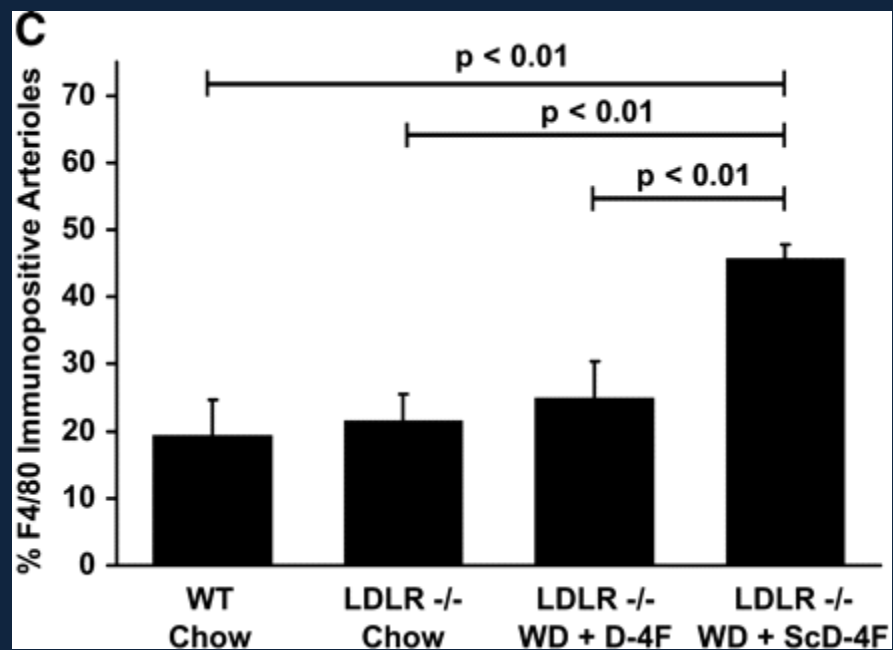
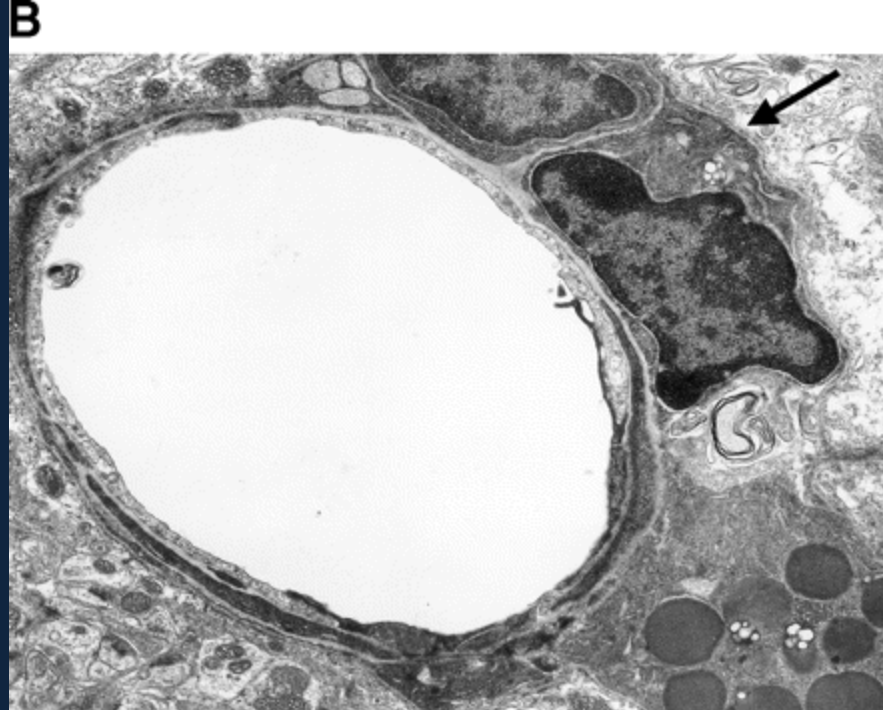
Scr 4F



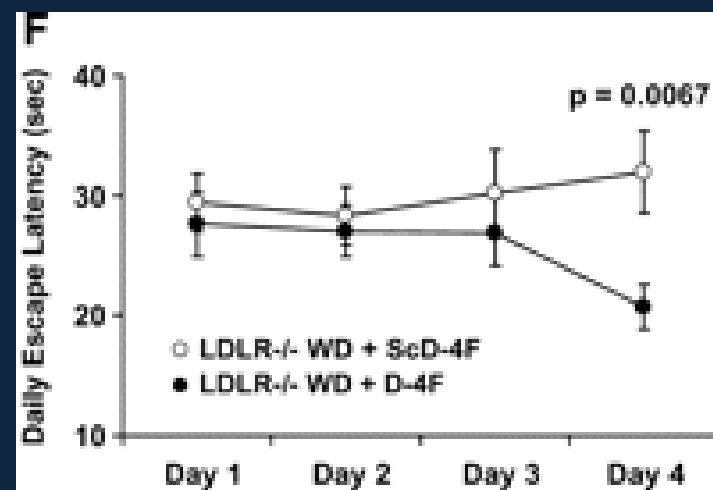
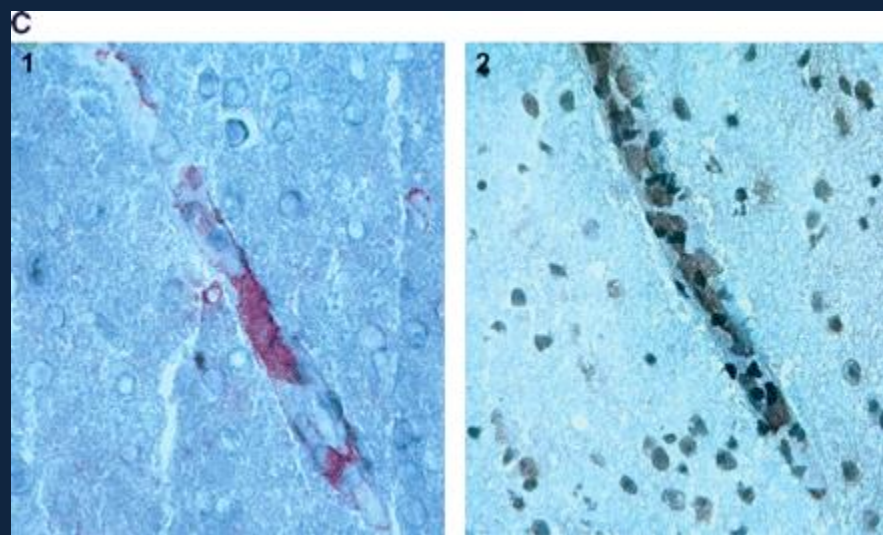
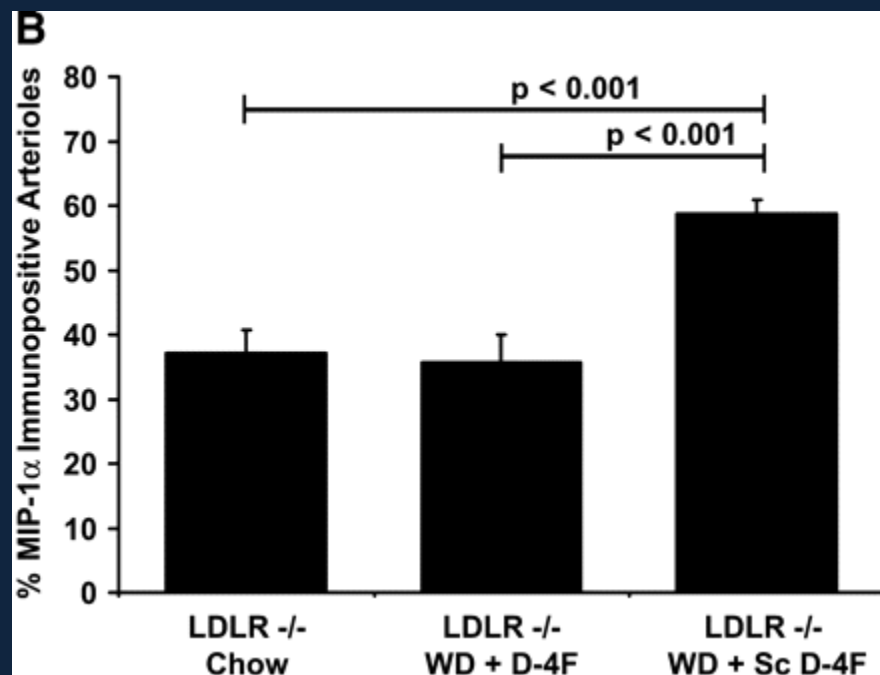
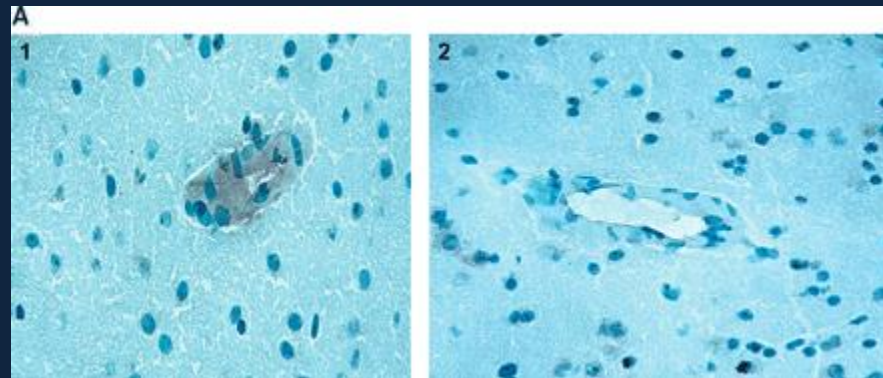
4F

MCP-1,  
inflamed  
brain cells





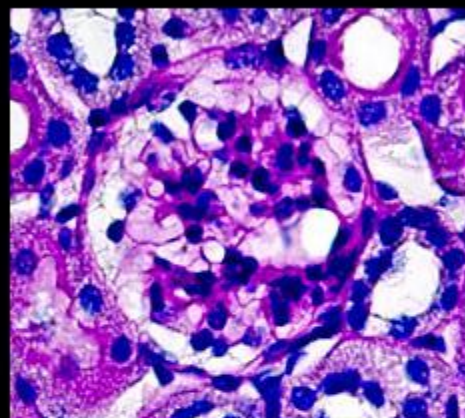




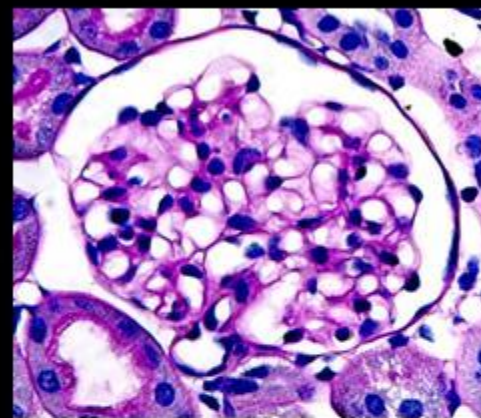
# Hyperlipidemia-induced Increase in Mesangium in the kidney was Reduced by Oral 4F

---

PAS Staining of Glomeruli

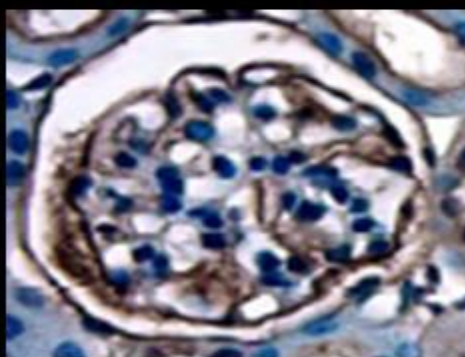


WD + Sc-4F

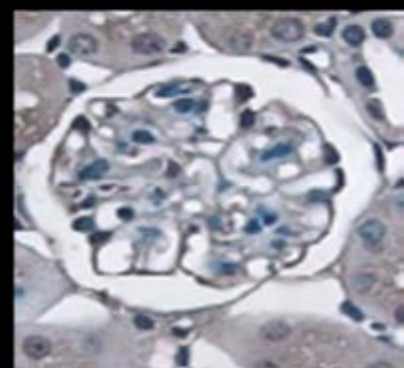


WD + 4F

MCP-1



WD + Sc4F



WD + 4F

# Collagen induced arthritis

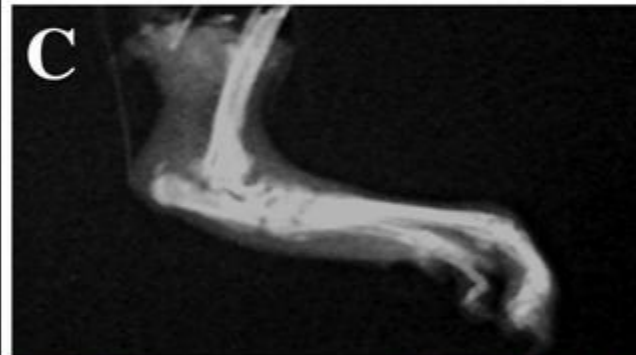
Vehicle

+peptide

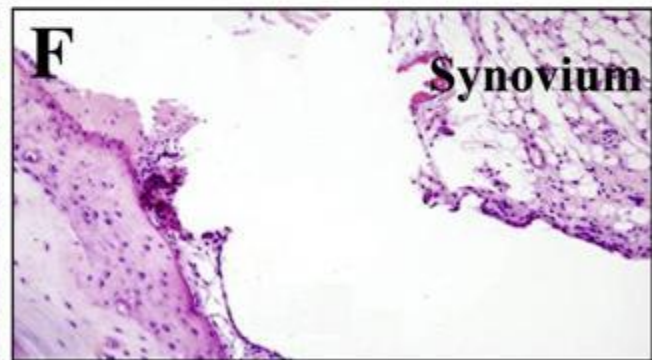
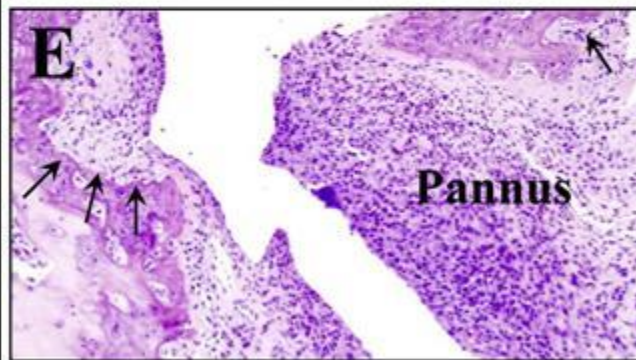
Clinical



Radiographic



Histologic



Christina Charles-Schoeman



Apolipoprotein A-I mimetic peptide 4F rescues pulmonary hypertension by inducing microRNA-193-3p.

Sharma S, Umar S, Potus F, Iorga A, Wong G, Meriwether D, Breuils-Bonnet S, Mai D, **Navab K**, **Ross D**, **Navab M**, Provencher S, Fogelman AM, Bonnet S, Reddy ST, Eghbali M.

Circulation. 2014 Aug 26;130(9):776-85. doi:

Apolipoprotein A-I (apoA-I) and apoA-I mimetic peptides inhibit tumor development in a mouse model of ovarian cancer.

**Su F**, Kozak KR, Imaizumi S, Gao F, Amneus MW, Grijalva V, Ng C, Wagner A, Hough G, Farias-Eisner G, Anantharamaiah GM, Van Lenten BJ, **Navab M**, Fogelman AM, Reddy ST, Farias-Eisner R.

Proc Natl Acad Sci U S A. 2010 Nov 16;107(46):19997-20002. doi:

# Phase 1



Dan Rader

20 Controls

50 patients with CAD

60 with CAD, on statins and other meds

# Safety, pharmacokinetics, and pharmacodynamics of oral apoA-I mimetic peptide D-4F in high-risk cardiovascular patients\*



LeAnne T. Bloedon<sup>\*</sup>, Richard Dunbar<sup>\*</sup>, Danielle Duffy<sup>\*</sup>,  
Paula Pinell-Salles<sup>\*</sup>, Robert Norris<sup>†</sup>, Bruce J. DeGroot<sup>§</sup>, Rajesh Mowva<sup>†</sup>,  
Mohamad Navab<sup>\*\*</sup>, Alan M. Fogelman<sup>\*\*</sup> and Daniel J. Rader<sup>1, \*</sup>

Need to go high dose oral, observe events.

Novartis: Too expensive..

## *ApoA-1 mimetic peptides.*

2F      Ac-D-W-L-K-A-F-Y-D-K-V-A-E-K-L-K-E-A-F-NH<sub>2</sub>

3F      Ac-D-W-L-K-A-F-Y-D-K-V-A-E-K-L-K-E-A-F-NH<sub>2</sub>

4F      Ac-D-W-F-K-A-F-Y-D-K-V-F-E-K-L-K-E-A-F-NH<sub>2</sub>

5F      Ac-D-W-F-K-A-F-Y-D-K-V-F-E-K-L-K-E-F-F-NH<sub>2</sub>

 6F      -D-W-L-K-A-F-Y-D-K-V-A-E-K-L-K-E-A-F

7F      Ac-D-W-L-K-A-F-Y-D-K-V-A-E-K-L-K-E-A-F-NH<sub>2</sub>

*Circulation 2003*

Intestine may be a major site of action for the apoA-I mimetic peptide 4F whether administered subcutaneously or orally.

**Navab M, Reddy ST, Anantharamaiah GM, Imaizumi S, Hough G, Hama S, Fogelman AM.**

J Lipid Res. 2011 Jun;52(6):1200-10. doi: 10.1194/jlr.M013144. Epub 2011 Mar

D-4F-mediated reduction in metabolites of arachidonic and linoleic acids in the small intestine is associated with decreased inflammation in low-density lipoprotein receptor-null mice.

**Navab M, Reddy ST, Anantharamaiah GM, Hough G, Buga GM, Danciger J, Fogelman AM.**

J Lipid Res. 2012 Mar;53(3):437-45. doi: 10.1194/jlr.M023523. Epub 2011 Dec

Transgenic 6F tomatoes act on the small intestine to prevent systemic inflammation and dyslipidemia caused by Western diet and intestinally derived lysophosphatidic acid.

**Navab M, Hough G, Buga GM, Su F, Wagner AC, Meriwether D, Chattopadhyay A, Gao F, Grijalva V, Danciger JS, Van Lenten BJ, Org E, Lusis AJ, Pan C, Anantharamaiah GM, Farias-Eisner R, Smyth SS, Reddy ST, Fogelman AM.**

J Lipid Res. 2013 Dec;54(12):3403-18. doi: 10.1194/jlr.M042051. Epub 2013 Oct

Source and role of intestinally derived lysophosphatidic acid in dyslipidemia and atherosclerosis.

**Navab M, Chattopadhyay A, Hough G, Meriwether D, Fogelman SI, Wagner AC, Grijalva V, Su F, Anantharamaiah GM, Hwang LH, Faull KF, Reddy ST, Fogelman AM.**

J Lipid Res. 2015 Apr;56(4):871-87. doi: 10.1194/jlr.M056614. Epub 2015 Feb 2.

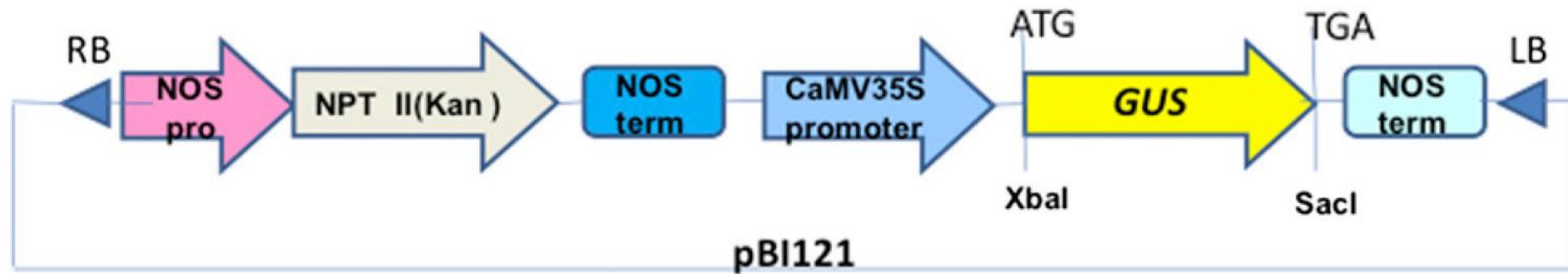


# Significance of the intestine

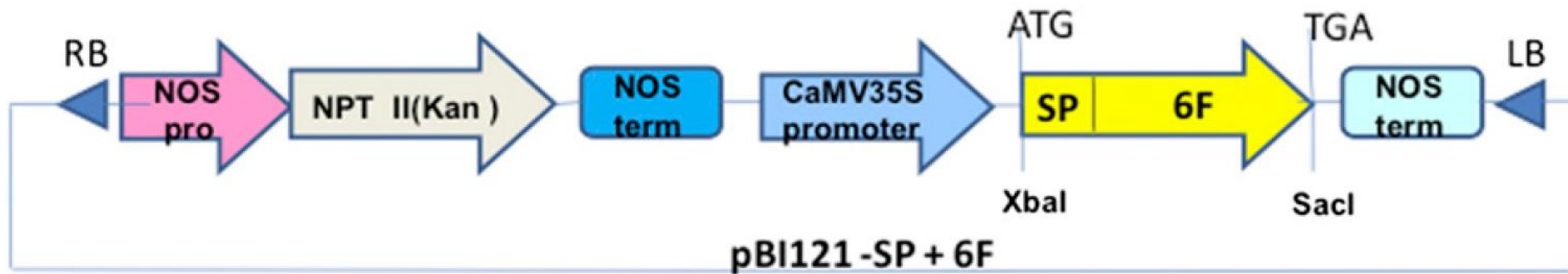
- Preparing and packaging vital nutrients
- Eliminating toxic waste
- TICE,
- Immune system site, leukocytes
- Microbiome

Chemical synthesis of  
the mimetic peptides is costly.

# Expressing the 6F peptide in edible plants



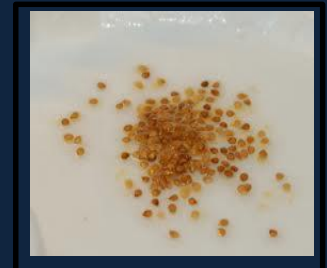
## Empty Vector (EV)



## Vector for Expressing 6F Peptide

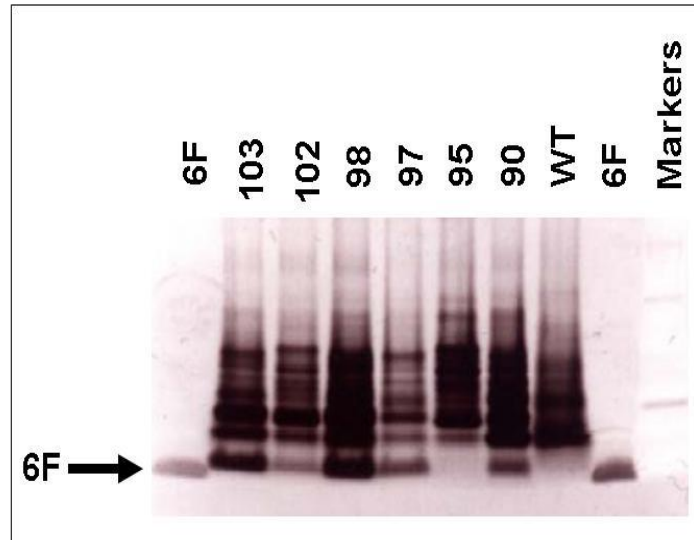
## Expressing 6E

- Plant cotyledons were used for transformation.
- Cotyledons were regenerated into plants in selection media with kanamycin
- Kanamycin resistant plants were tested by qPCR and protein gels for 6F
- Seeds were collected from positive lines and further germinated.  
Homozygous lines were established



07/02/2017

# Some (but not all) Plants Expressed the 6F Peptide

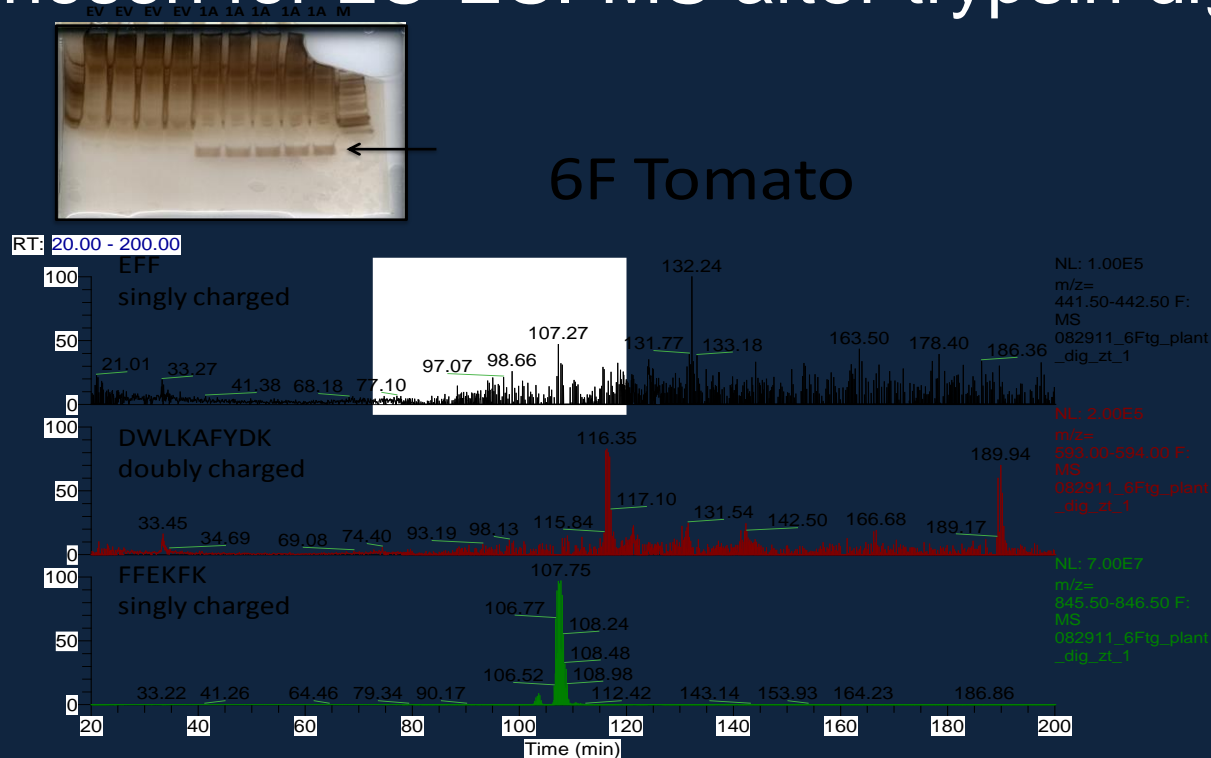


07/02/2017



# LC-ESI-MS Signature peaks of Authentic 6F

- Transgenic plants expressing 6F peptide were chosen for LC-ESI-MS after trypsin digestion



07/02/2017



**Freezedried fruits**



**Powdered Western diet**

**Freeze-dried fruit**

**Powdered Western diet**



LDL, Triglycerides,  
SAA, ox-lipids

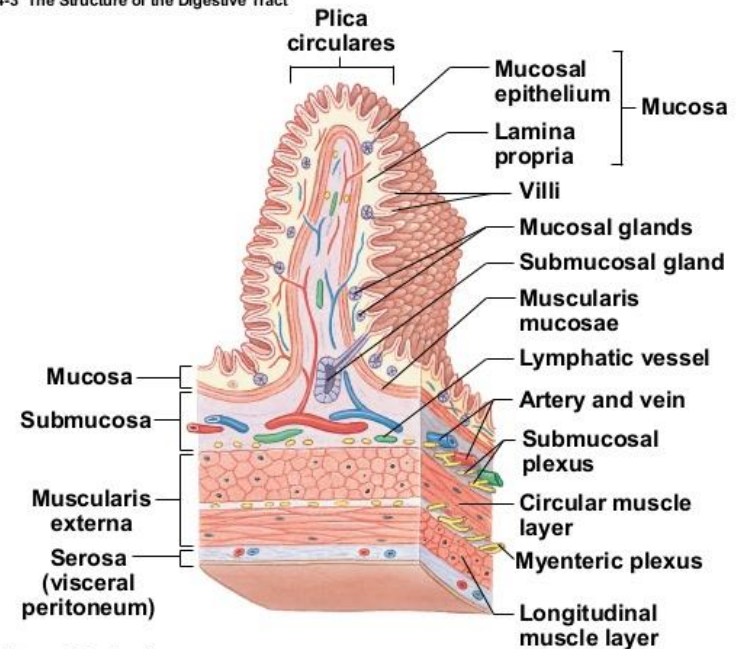


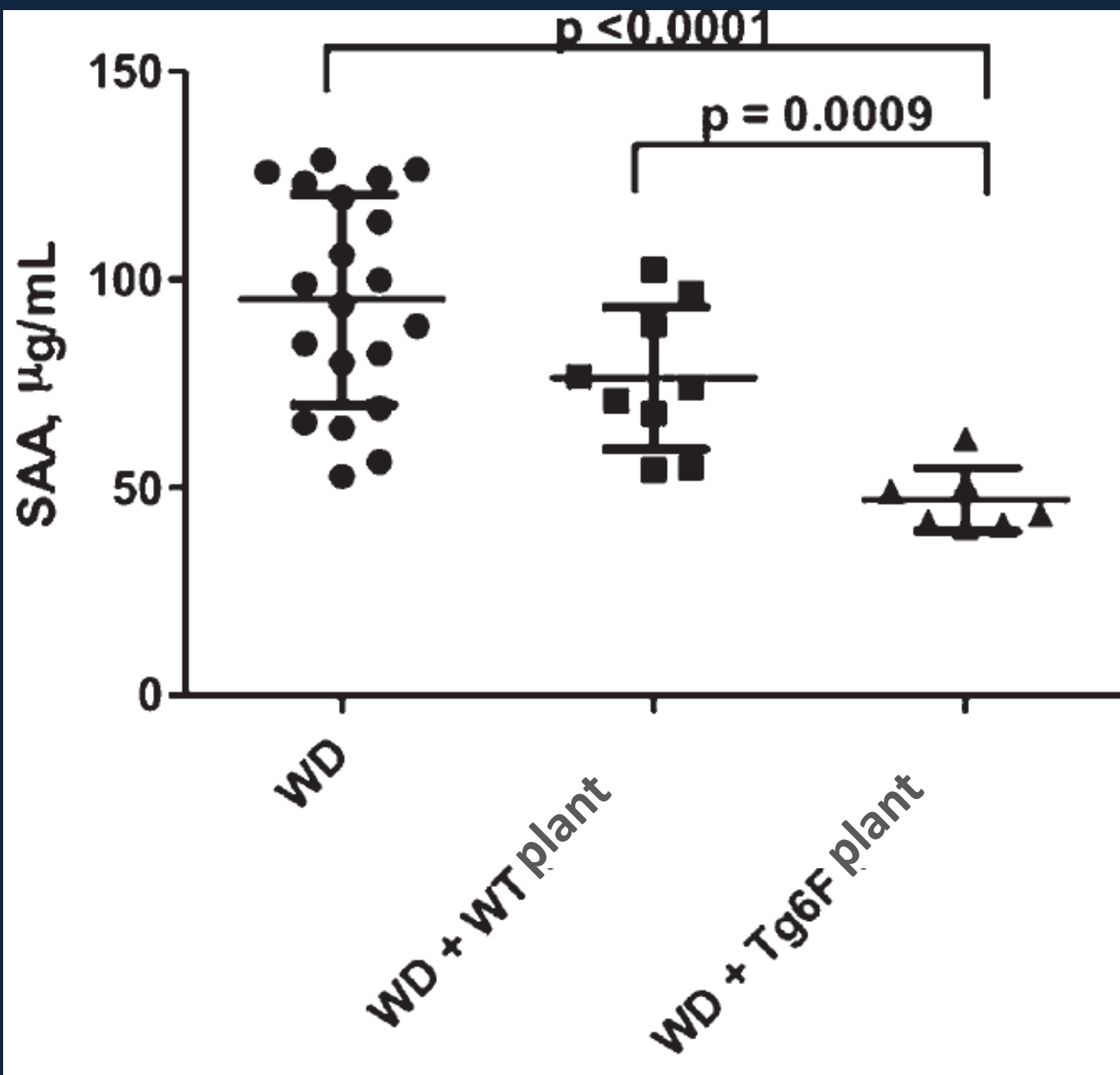
HDL, Paraoxonase



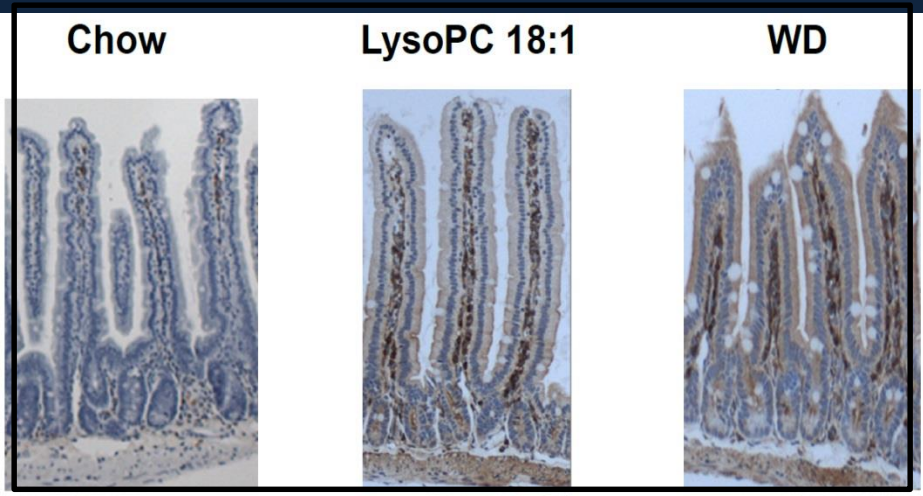
Macrophages, neutrophils,  
T-cells, in the aorta and in  
the small intestine

Figure 24-3 The Structure of the Digestive Tract

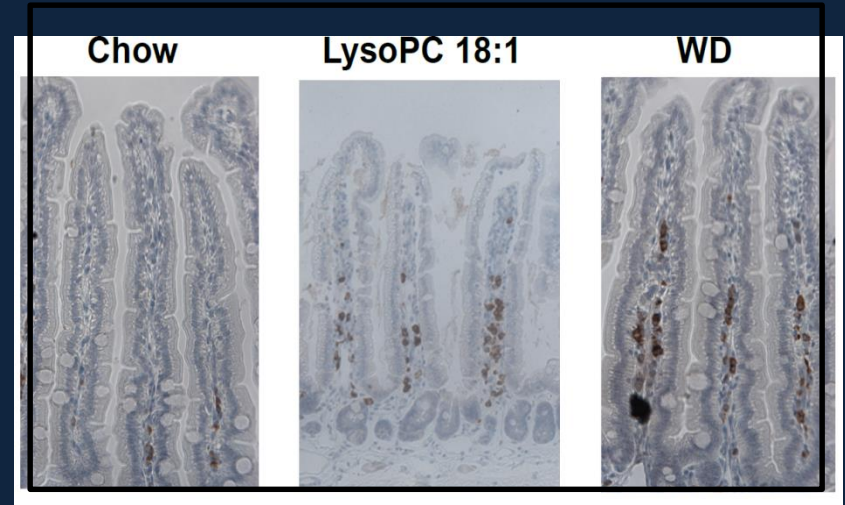




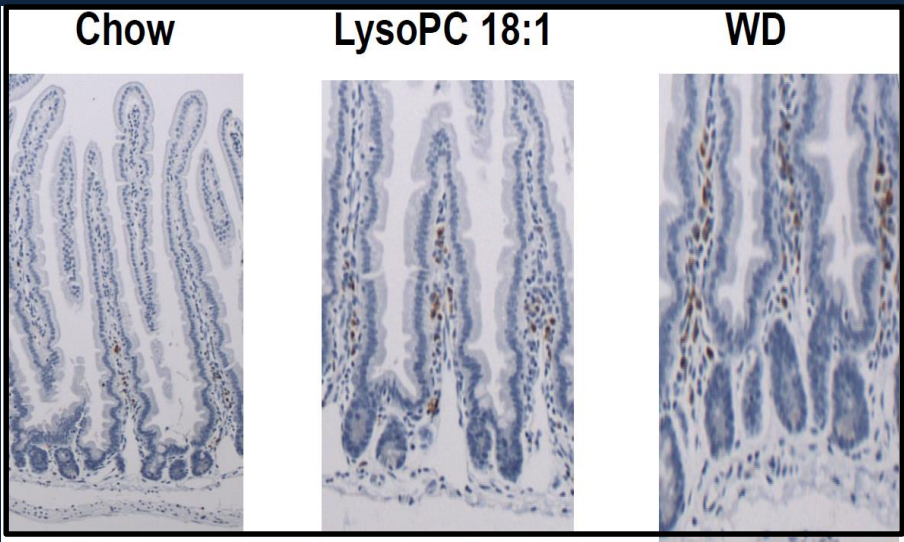
**F4/80**



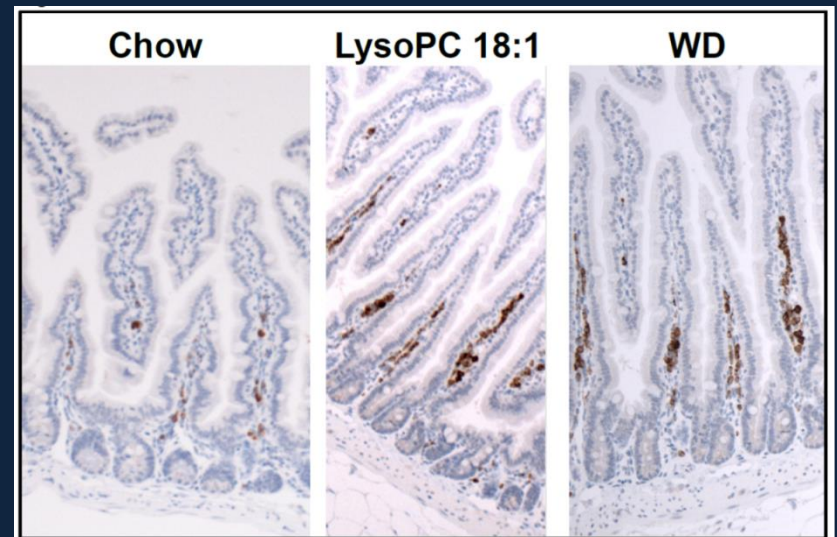
**Ly6G**



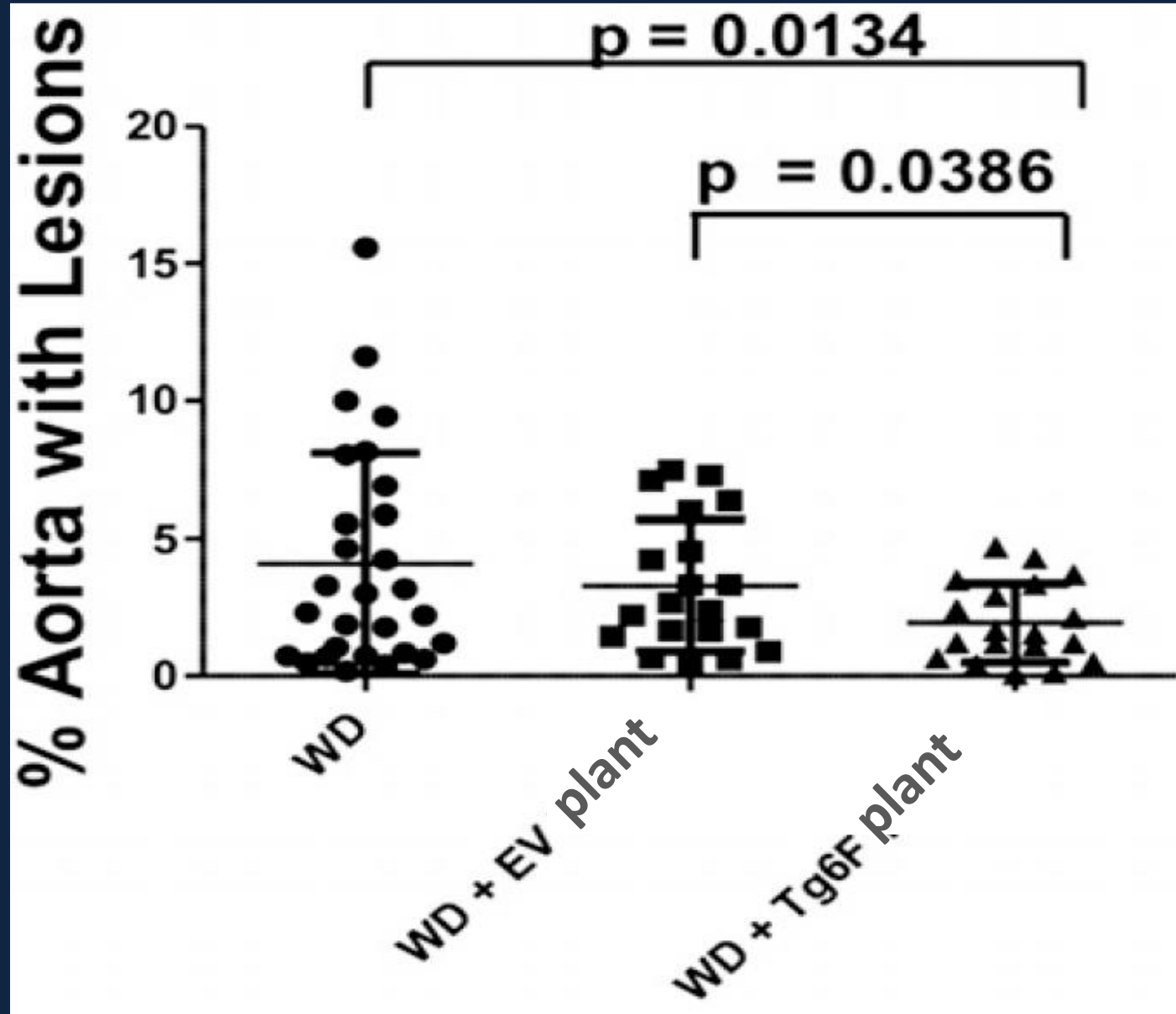
**CD103**, regul .T cell



**E06**









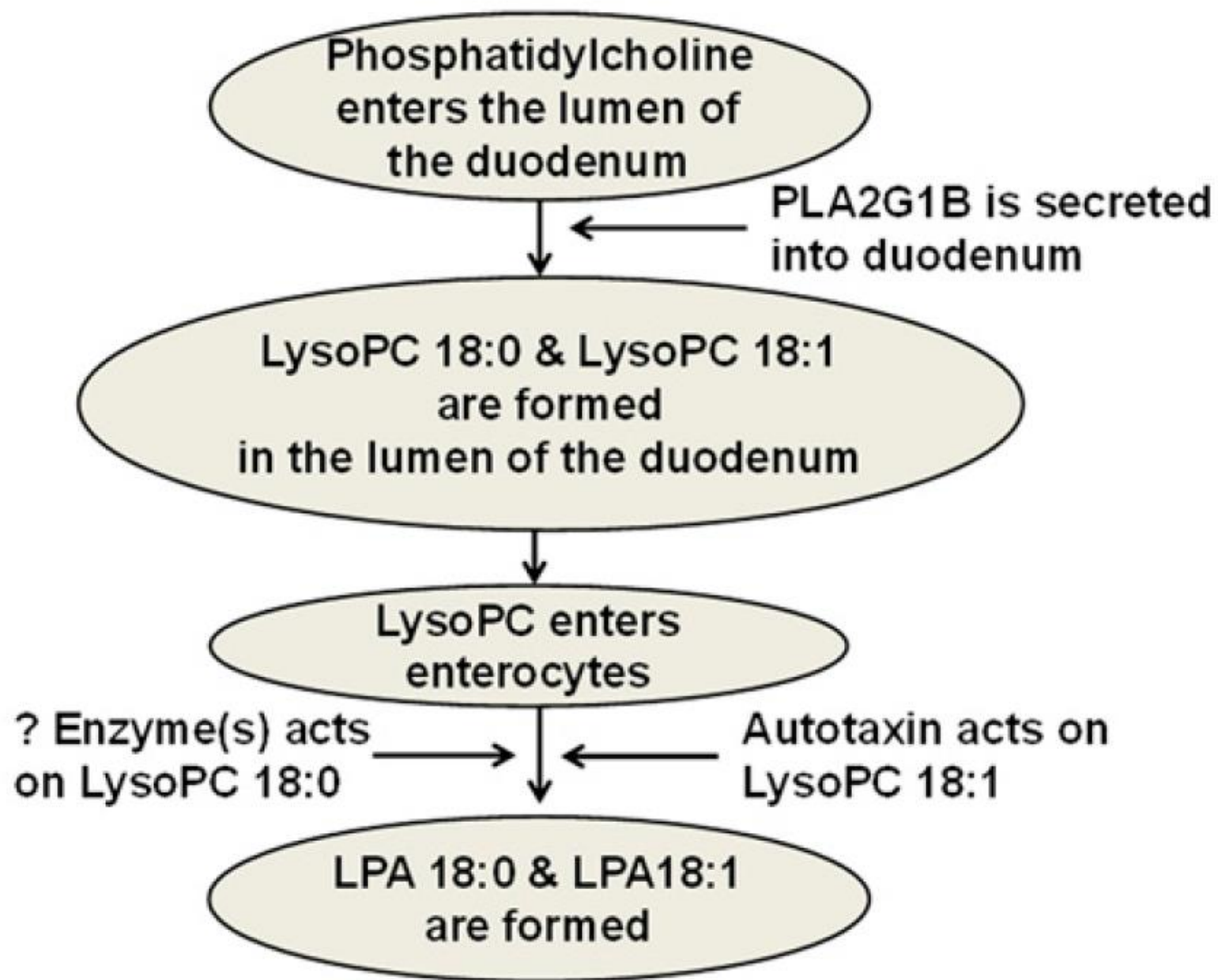
A High fat-high cholesterol diet changed many intestinal  
genes  
and  
the expressed HDL mimetic peptide reversed them.

TABLE 2. Genes downregulated by WD, prevented by adding Tg6F (but not EV)

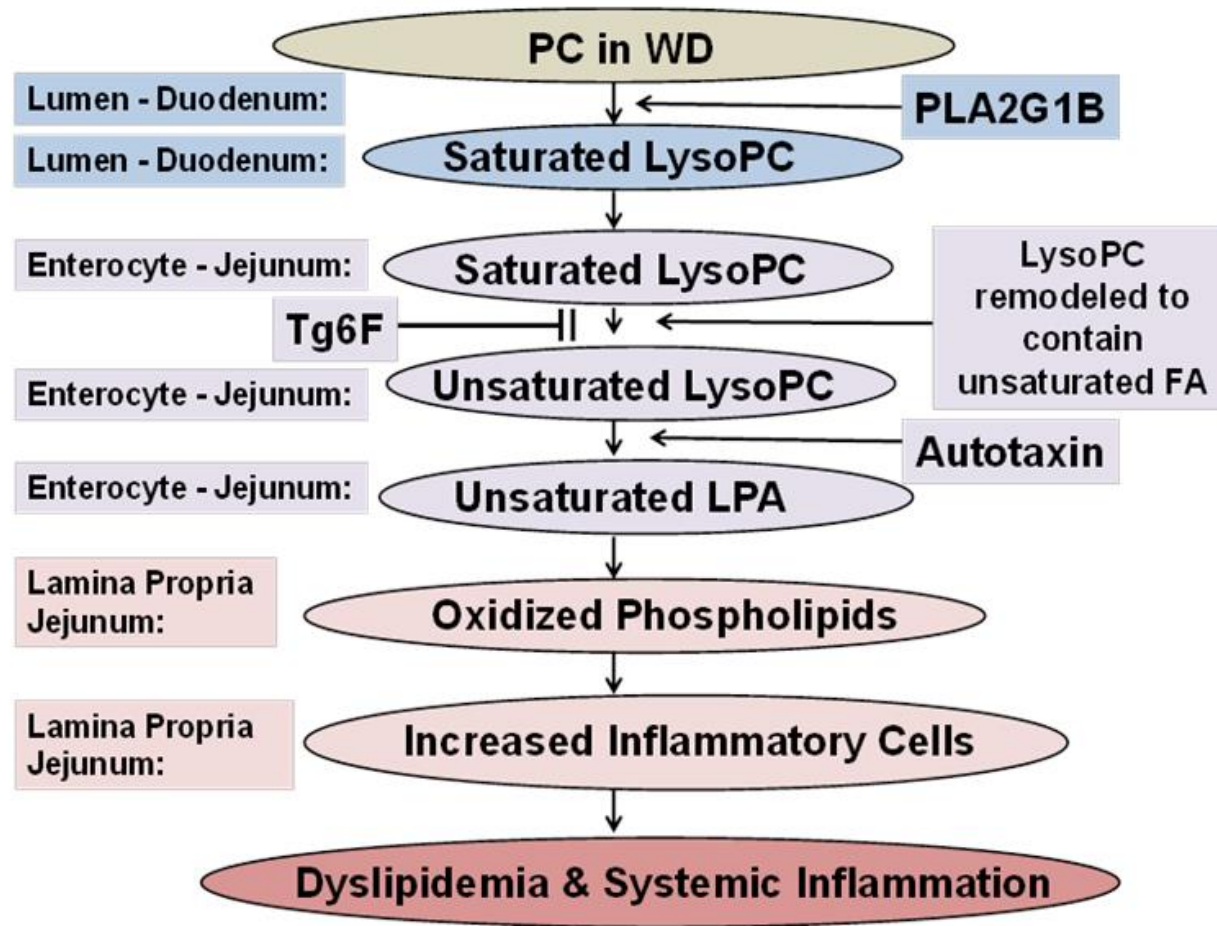
Gene Symbol	Fold Change	Gene Name
<i>Reg3g</i>	5.10	Regenerating islet-derived protein 3 $\gamma$ (Reg3 $\gamma$ )
<i>(Reg3<math>\beta</math>) or Pap</i>	2.52	Regenerating islet-derived 3 $\beta$
<i>AA467197</i>	2.16	Expressed sequence AA467197
<i>Plk6</i>	2.15	Protein tyrosine kinase 6
<i>Sprr2a</i>	1.80	Small proline-rich protein 2A; small proline-rich protein 2A3; predicted gene 6120
<i>Gadd45g</i>	1.80	Growth arrest and DNA-damage-inducible 45 $\gamma$ (Gadd45 $\gamma$ )
<i>Sqle</i>	1.73	Squalene epoxidase
<i>2010109I03Rik</i>	1.66	Riken cDNA 2010109I03 gene
<i>1700047I17Rik</i>	1.65	Riken cDNA 1700047I1 gene 2 and Riken cDNA 1700047I1 gene 1
<i>Ppp1r9a</i>	1.65	Protein phosphatase 1, regulatory (inhibitor) subunit 9A
<i>Ndor1</i>	1.65	NADPH-dependent diflavin oxidoreductase 1
<i>Klra7</i>	1.63	Killer cell lectin-like receptor, subfamily A, member 7
<i>Pof1b</i>	1.62	Premature ovarian failure 1B
<i>1810011O10Rik</i>	1.62	Riken cDNA 1810011O10 gene
<i>Pcsk9</i>	1.57	Proprotein convertase subtilisin/kexin type 9
<i>Cdc42ep3</i>	1.56	CDC42 effector protein (Rho GTP-ase binding) 3
<i>Tia1</i>	1.55	Cytotoxic granule-associated RNA binding protein 1
<i>Zfp692</i>	1.53	Zinc finger protein 692
<i>Hmgb2l1</i>	1.52	HMG box domain containing 4
<i>Ndfip2</i>	1.52	Nedd4 family interacting protein 2
<i>Ptma</i>	1.51	Similar to prothymosin $\alpha$ ; prothymosin $\alpha$
<i>Hmgcs1</i>	1.50	3-Hydroxy-3-methylglutaryl-CoA synthase 1
<i>Pls3</i>	1.49	Plastin 3 (T-isoform)
<i>E2f5</i>	1.45	E2f transcription factor 5
<i>2410019G02Rik</i>	1.42	Not annotated
<i>Myom1</i>	1.41	Myomesin 1
<i>2700055K07Rik, Tppp3</i>	1.41	Tubulin polymerization-promoting protein family member 3
<i>FAM125B, BC049806</i>	1.41	Family with sequence similarity 126, member B

TABLE 4. Genes upregulated by WD, prevented by Tg6F (but not EV) in the experiment described in Table 2

Gene Symbol	Fold Change	Gene Name
<i>Scd1</i>	6.31	Stearoyl-CoA desaturase 1
<i>Slc6a3</i>	5.89	Solute carrier family 6 (neurotransmitter transporter, dopamine), member 3
<i>Acot1</i>	4.95	Acyl-CoA thioesterase 1
<i>Srebf1</i>	3.52	Sterol regulatory element binding transcription factor 1
<i>Cyp4a10</i>	3.47	Cyp4a10, Cyp4a31, Cyp4a32, Gm10774, Gm13015, LOC100044218, POLR2L
<i>Acaa1b</i>	2.72	Acetyl-CoA acyltransferase 1B
<i>Pdk4</i>	2.65	Pyruvate dehydrogenase kinase, isoenzyme 4
<i>Retsat</i>	2.61	Retinol saturase (all trans retinol 13,14 reductase)
<i>Plscr4</i>	2.41	Phospholipid scramblase 4
<i>Pte2a</i> or <i>Acot3</i>	2.41	Acyl-CoA thioesterase 3
<i>Gdf9</i>	2.37	Growth differentiation factor 9
<i>Acadl</i>	2.36	Acyl-CoA dehydrogenase family
<i>Ltc4s</i>	2.24	Leukotriene C4 synthase
<i>Gm7049</i> , <i>LOC677317</i> , <i>ME1</i> , <i>Mod1</i>	2.04	Predicted gene 7049; similar to NADP-dependent malic enzyme (NADP-ME)
<i>Slc27a2</i>	1.97	Solute carrier family 27 (fatty acid transporter), member 2
<i>Unc93a</i>	1.94	Predicted gene 9992; predicted gene 8597; similar to unc-93 homolog A
<i>Mfsd2a</i>	1.91	Major facilitator superfamily domain containing 2
<i>Angptl4</i>	1.85	Angiopoietin-like protein 4
<i>GLTPD2</i> , <i>C730027E14Rik</i>	1.79	Glycolipid transfer protein domain containing 2
<i>Ahcy</i>	1.76	Similar to adenosylhomocysteinase (S-adenosyl-L-homocysteine hydrolase)
<i>Acaa2</i>	1.66	Acetyl-CoA acyltransferase 2 (mitochondrial 3-oxoacyl-CoA thiolase)
<i>Dhrs4</i>	1.65	Dehydrogenase/reductase (SDR family) member 4
<i>LOC192758</i>	1.65	Protein interacting with cyclin A1
<i>Por</i>	1.62	P450 (cytochrome) oxidoreductase
<i>HSD17B11</i>	1.62	Hydroxysteroid (17 $\beta$ ) dehydrogenase 11
<i>PLIN2</i> , <i>Adfp</i>	1.61	Adipose differentiation-related protein (ADFP)/adipophilin
<i>Cyp2d26</i>	1.60	Cytochrome P450, family 2, subfamily d, polypeptide 26
<i>Tgoln1</i>	1.57	Trans-Golgi network protein 2; trans-Golgi network protein 1
<i>Entpd5</i>	1.54	Ectonucleoside triphosphate diphosphohydrolase 5
<i>Mia2</i>	1.52	Melanoma inhibitory activity 2
<i>N4BP2L1</i> , <i>B230342M21Rik</i>	1.51	NEDD binding protein 2-like 1
<i>Ppp2r5c</i>	1.46	Protein phosphatase 2, regulatory subunit B (B56), $\gamma$ isoform
<i>Abcc2</i>	1.46	ATP-binding cassette, sub-family C (CFTR/MRP), member 2
<i>Rnf167</i>	1.44	Ring finger protein 167
<i>Slc35e3</i>	1.42	Solute carrier family 35, member E3; predicted gene 7341
<i>Pank3</i>	1.41	Pantothenate kinase



# Hypothesis for the proposed location and sequence of events leading to development of dyslipidemia and systemic inflammation







# The Importance of the **MICROBIOME** by the Numbers



**90%**

Up to 90% of all disease can be traced in some way back to the gut and health of the microbiome



**10–100 trillion**

Number of symbiotic microbial cells harbored by each person, primarily bacteria in the gut, that make up the human microbiota

**>10,000**

Number of different microbe species researchers have identified living in the human body



**100**

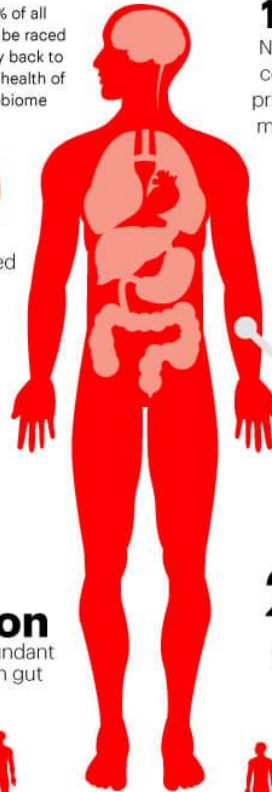
**100 to 1**

The genes in our microbiome outnumber the genes in our genome by about 100 to 1



**3.3 million**

Number of non-redundant genes in the human gut microbiome



**10X**

There are 10 times as many outside organisms as there are human cells in the human body



**22,000**

Approximate number of genes in the human gene catalog



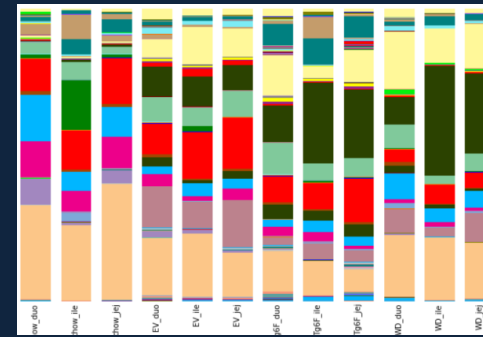
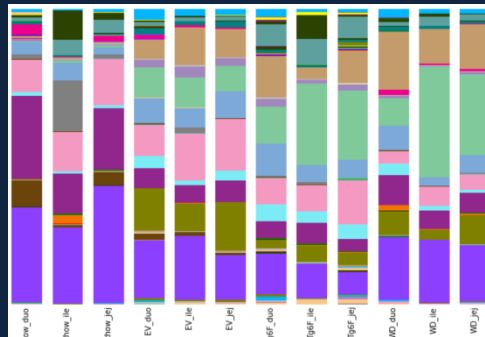
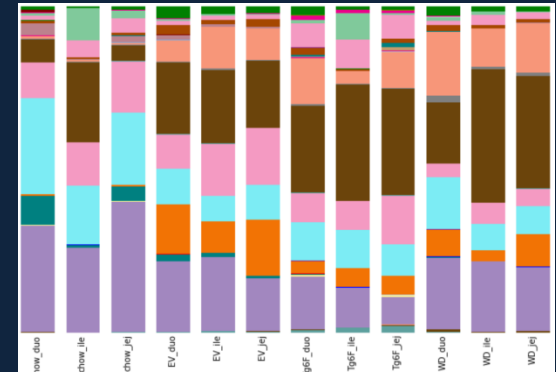
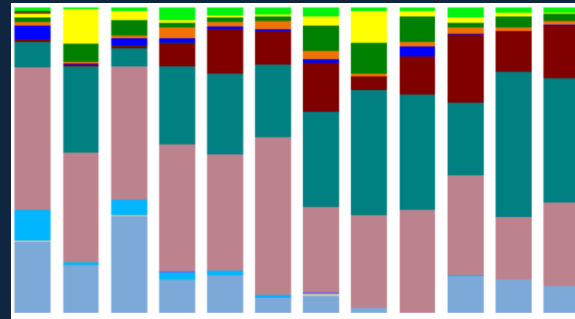
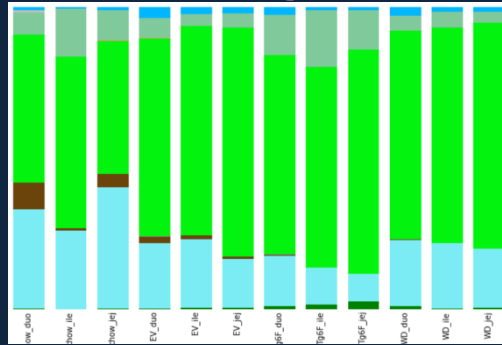
**99.9%**

Percentage individual humans are identical to one another in terms of host genome



**80%–90%**

Percentage individual humans are different from one another in terms of the microbiome



Abundance for many microbial genes  
was changed by  
Western diet.

Transgenic plant extract reversed it.

## Plans

- Following FDA approval
- 100 patients with ovarian cancer in 10 centers

10 trillion cells

21000 genes

100 thousand miRNA

100 trillion microbes

With 4 million genes



10 000 000 000 000 cells

10 000 000 000 000 molecules per cell

21 000 genes

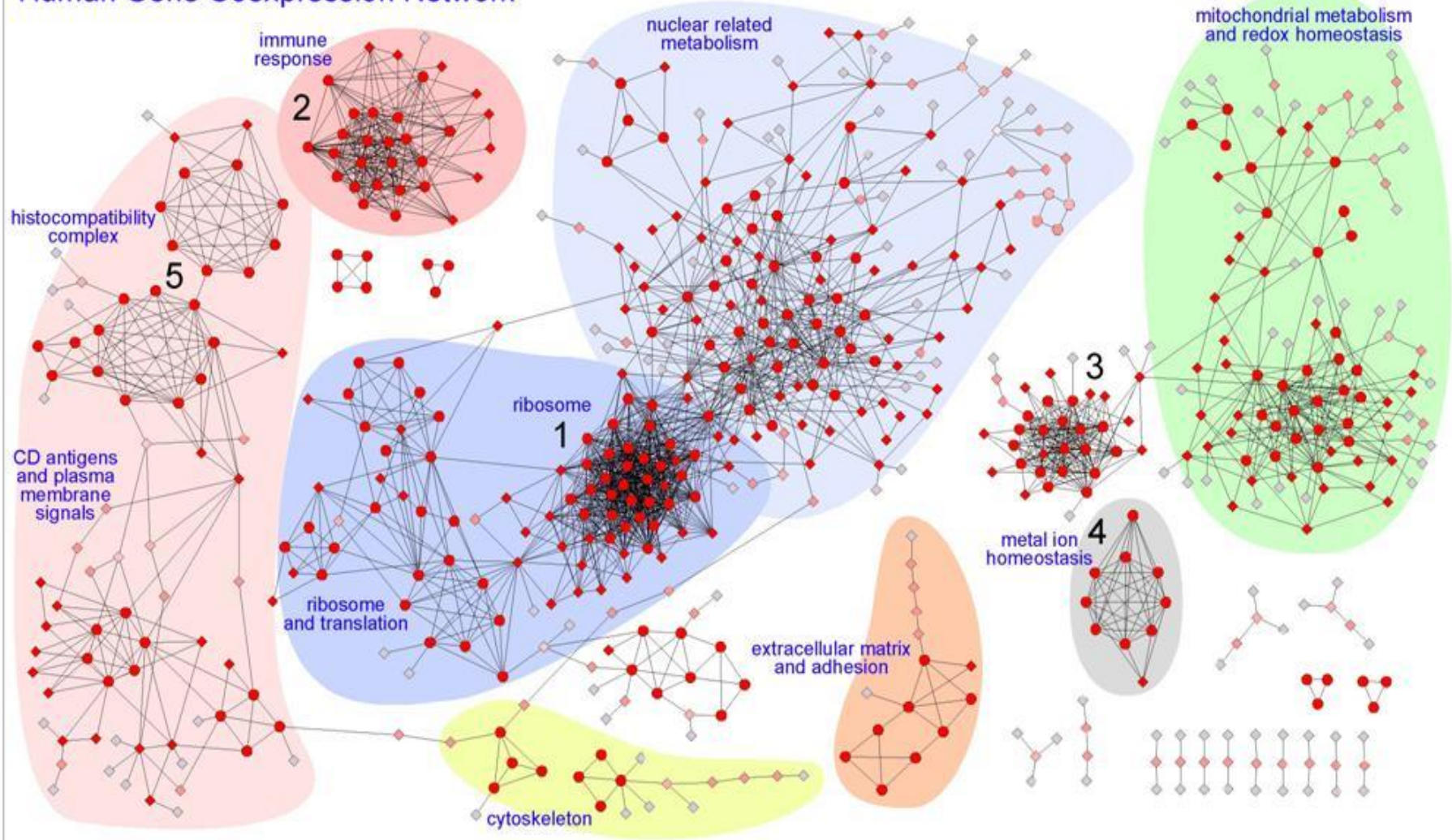
98 000 micro RNA

900 000 long non coding RNA

100 000 000 000 000 microbes

?

# Human Gene Coexpression Network



500 chemicals in our circulation

60% from us

30 % from other species

10 % from microbiome

Smart Life Style  
Proven Therapy

2000

**Meta  
bolomics**

1400  
Chemicals

**Proteomics**

3000 Enzymes

**Genomics**

25,000 Genes



2005

**Systems  
Biology**

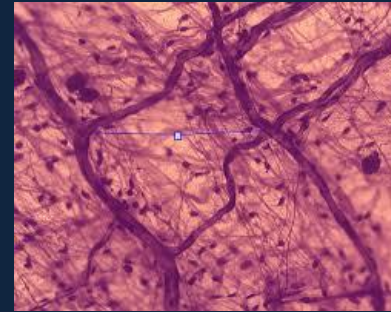
Heart, 100 000 times/day



200 gallons of blood



60 000 miles



2.5 million RBC per second





**Modern Medicine has**  
**doubled our life**  
**expectancy**  
**from 42 to 85 years.**

Thanks to our  
specialists:

Simple explanations

We Are Here to Enjoy.

*Moving is the best Medicine*





# We did a great job!







In fact,  
Our life should be like a salad bar



**TIME**  
**CHOLESTEROL**  
 And Now the Bad News...

After a decade of power, the Democrats brace for a liberation

WILLIAM SHUTZ/GETTY IMAGES



One study:

Our seniors

- Do not eat enough
- Not enough variety



Good sleep

Avoiding air pollution



# Stress management





# Stress management



Dr.  
Noushin  
Razani

# Mind

Mind:

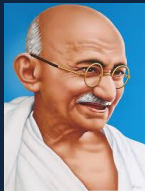
A process  
that regulates  
the flow of energy  
and information.

Although “The first thing is to discipline our mind...”



But remember..

it needs the patience of a man trying to empty the ocean with a cup..



My mind knows how to take me  
where I don't want to go

Go where your heart wants

But

Take your brain along.





# Anger, Fear, Depression



Fear



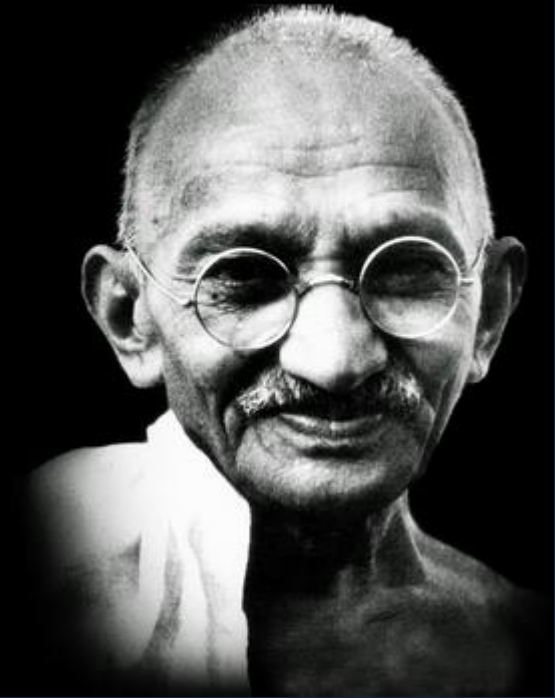
Anger



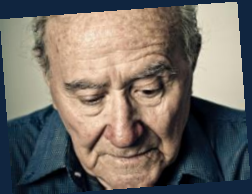
Depression

"THE ENEMY IS FEAR.  
WE THINK IT IS HATE;  
BUT, IT IS  
FEAR."

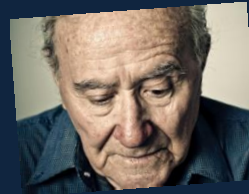
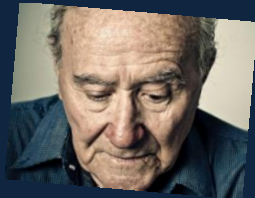
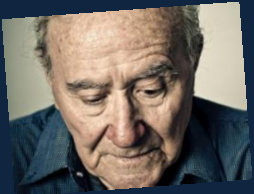
~GANDHI



Feel OK about how you feel.



# Feel OK about how you feel.

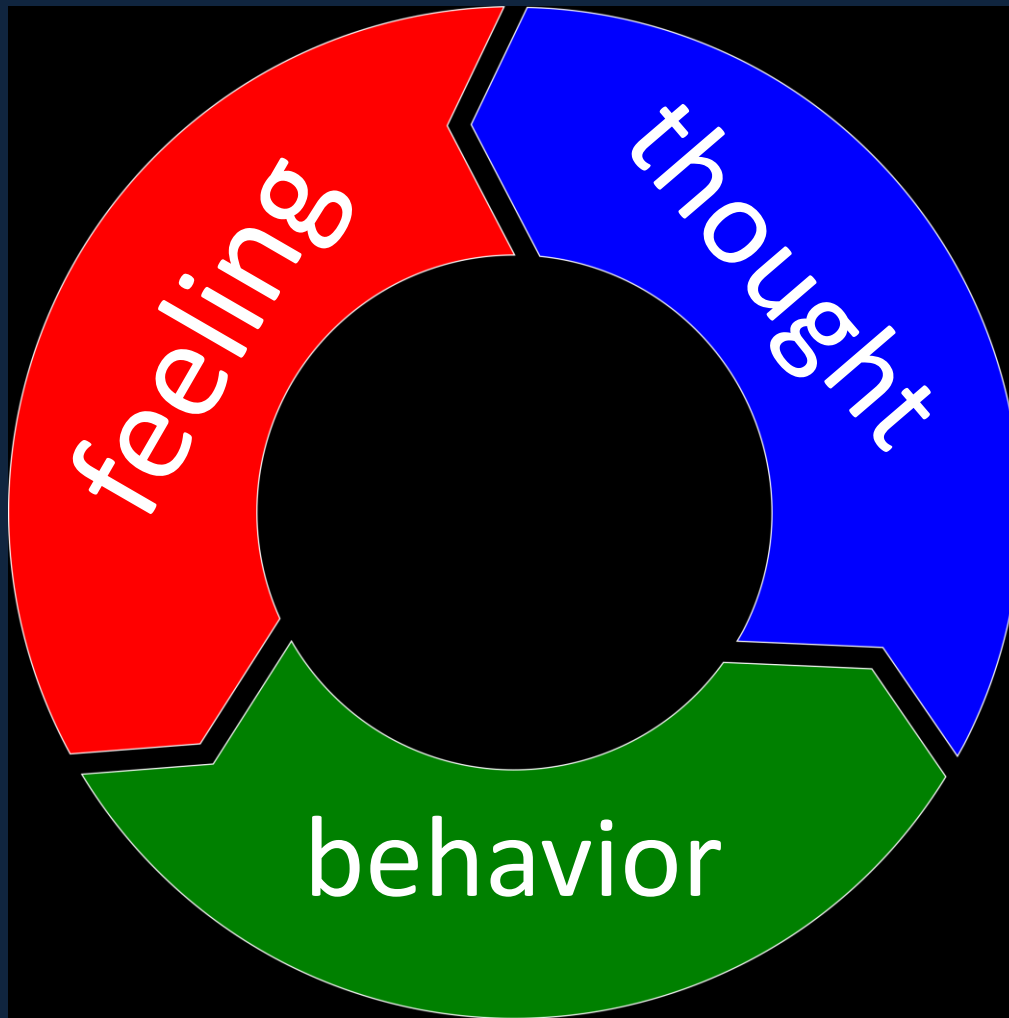




Leave your mind resting...

Just manage it

when wish to express a feeling



If a feeling keeps bothering us..

move to another one :)

# Vipassana



Esalen





**Love yourself,  
and the rest  
will follow.**

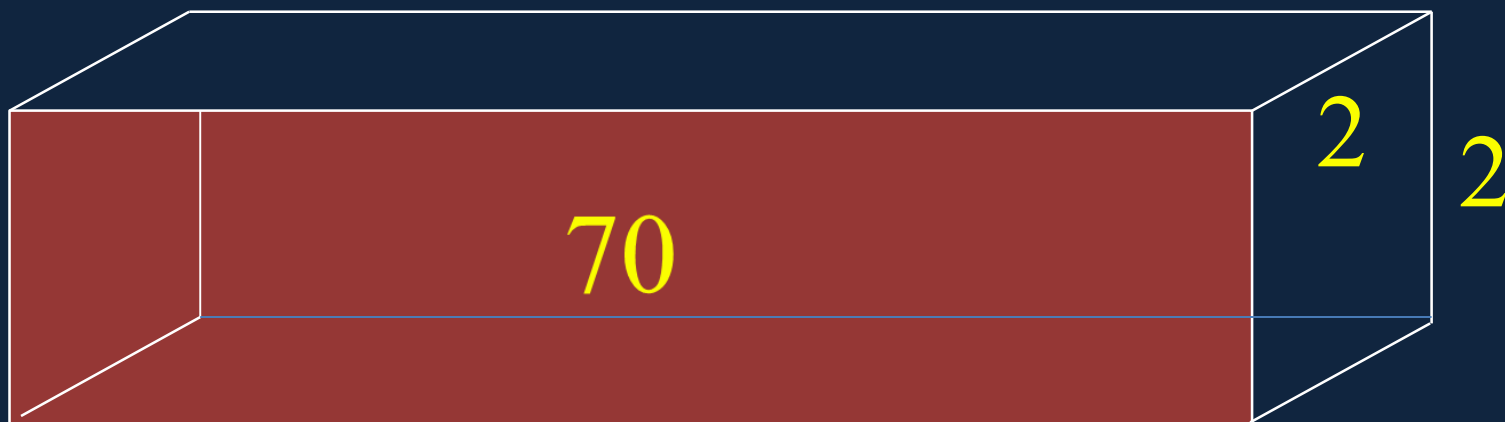
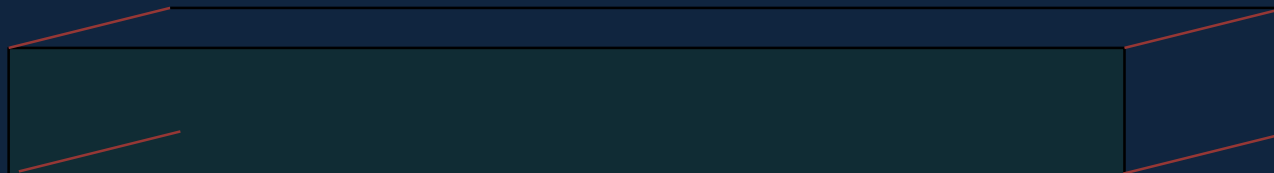




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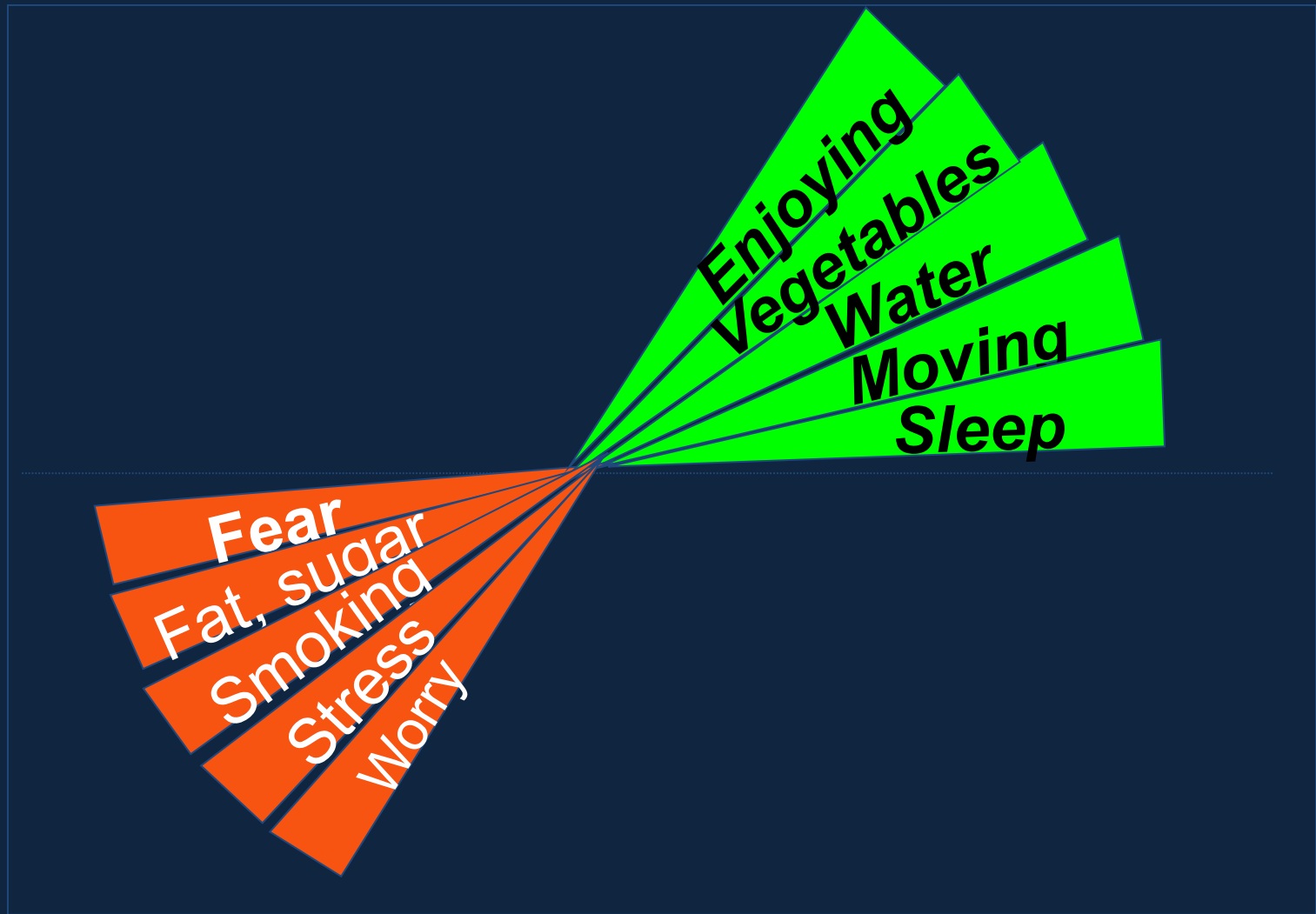
Life is not a line

طول عمر

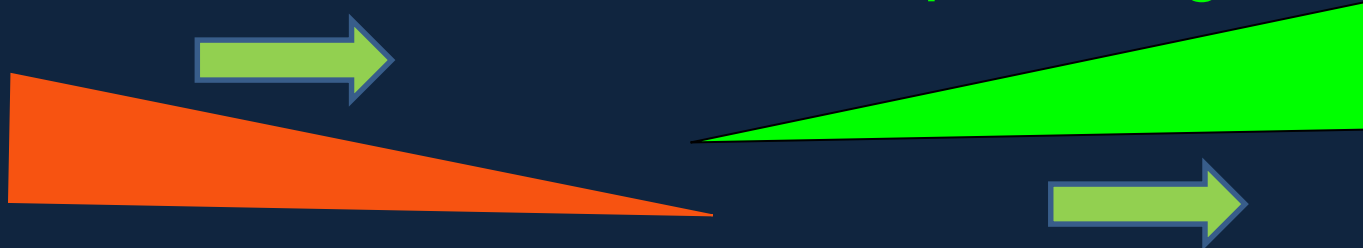


Health

Disease

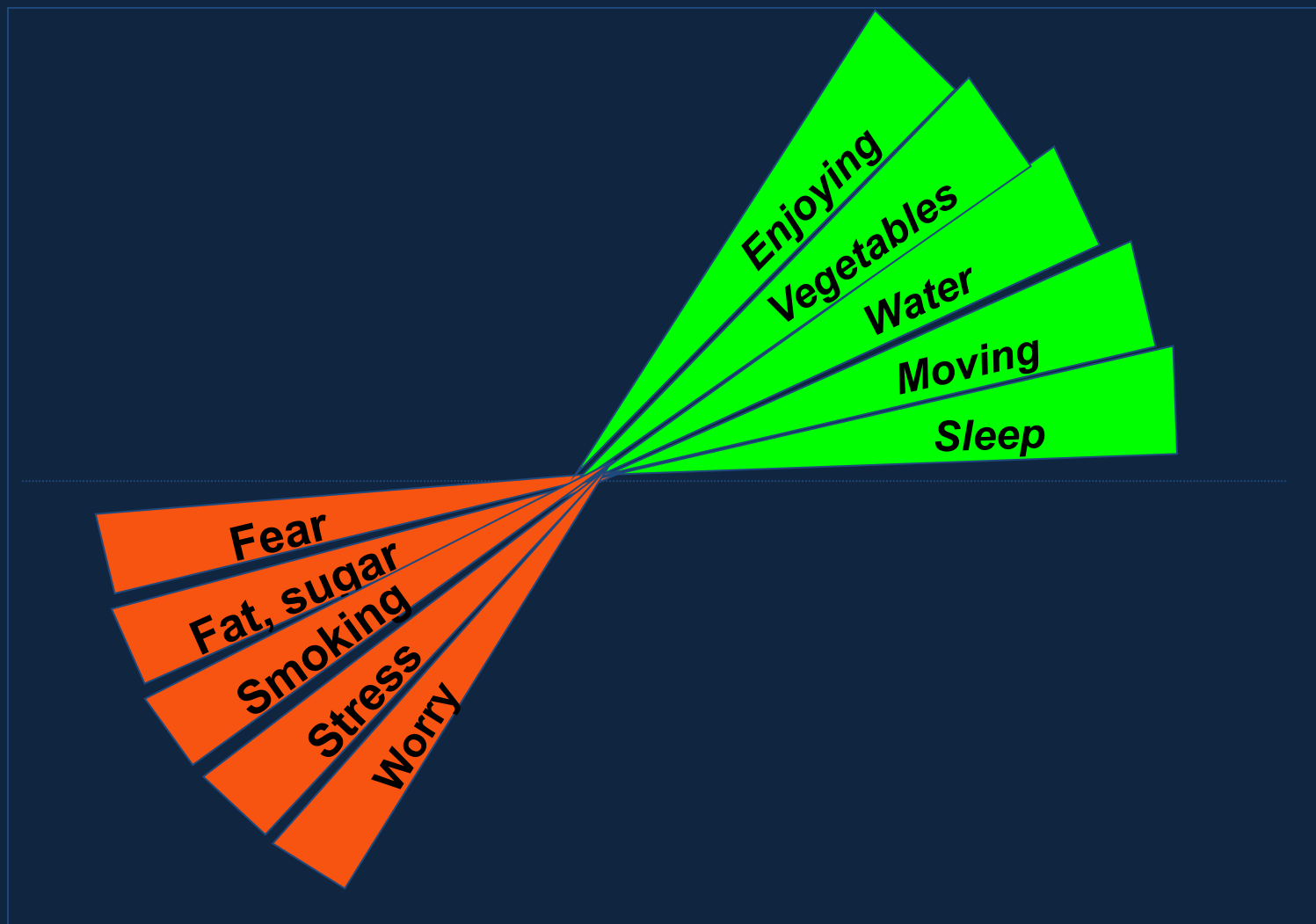


Decrease inflammation    Help our organism



Health

Disease



Adverse effects

Therapeutic effects



Thank you for your support  
and for your attention!