Fatty Acid and Triacylglycerol Biochemistry
- Omega-3 Fatty Acids -

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Lipids are biologic substances that are generally hydrophobic or amphipathic in nature and in many cases soluble in organic solvents.

Lipids are produced, transported and recognized by the concerted actions of numerous enzymes, binding proteins and receptors.

Lipids include: fatty acids, phospholipids, sterols, sphingolipids, terpenes and others:

- Fatty acids
- Glycerolipids
- Glycerophospholipids
- Sphingolipids
- Sterol lipids
- Prenol lipids
- Saccharolipids
- Polyketides

Phospholipids

- Contain one or more fatty acid molecule and one phosphoric acid radical and usually contain a nitrogenous base

Major types:
- **Lecithins**: phosphatidylcholine
- **Cephalins**: phosphatidylethanolamine
  - Some formed from inositol
- **Sphingomyelin**

- 90% are formed in the liver, but all cells can make them
- They are all lipid soluble and transported in lipoproteins and used throughout the body for structural purposes
- Phospholipids are donors of phosphate radicals which are needed for different chemical reactions in tissues
Lipid Classification

- Lipid Nomenclature
  - Stereospecific numbering (sn) method is used in describing glycerolipids and glycerophospholipids
  - The glycerol group is typically acylated or alkylated at the sn-1 or sn-2 position
  - Core names are used for sterols (cholestane, androstane and estrane)

Lipid Classification

- Fatty acids (acyl) group: repeating series of methylene groups that impart hydrophobic character
  - First subclass is the straight chain saturated group with a terminal carboxylic acid

- Glycerolipids are abundant as membrane constituents, metabolic fuels (acylglycerols) and signaling molecules

- Glycerophospholipids are ubiquitous and key components of the lipid bilayers of cells
  - Phospholipids may be divided by the nature of the polar head group at the sn-3 position of the glycerol backbone

- Sphingolipids are a complex family with a sphingoid base: ceramides, phosphosphingolipids & glycosphingolipids

Sterol Lipids are important membrane lipids

- Cholesterol and derivatives
  - Cholesteryl esters
  - Phyto, marine and fungal sterols
- Steroids ($C_{18}$, $C_{19}$, $C_{21}$)
- Secosteroids (Vitamin D$_2$ and D$_3$)
- Bile acids and derivatives
- Steroid conjugates
- Hopanoids

Lipid Classification

- Prenol lipids are synthesized from the five carbon precursors isopentyl diphosphate and dimethylallyl diphosphate from the mevalonic acid pathway.

- Saccharolipids (Glycolipids): Fatty acids are linked directly to a sugar backbone forming structures compatible with membrane bilayers. They exist as glycan or phosphorylated derivatives.

Fatty Acid Nomenclature

- Trivial and shorthand nomenclature have been in common usage.
- Gas liquid chromatography separates FA by chain length and saturation: nomenclature using this technology consists of two numbers separated by a colon.
  - The number before the colon gives the carbon number and the number after denotes the number of double bonds
  - Sometimes it is useful to number the double bonds from the methyl end: ie n-6
    - Older literature uses ω instead of n
  - Δ refers to a double bond: Δ-9 is a double bond at #9 position
  - The isomeric configuration around a double bond can be cis/trans or as it is now called Z/E
    - In the cis form the two hydrogen substituents are on the same side of the molecule and in trans form they are on opposite sides. Trans FA are rare.
  - Older systems numbered carbon atoms with Greek letters:
    - α refers to C2, β to C3 and ending with ω at the last atom, furthest from the carboxyl chain

Gurr MI et al. Lipid Biochemistry 5th Ed 2002 Blackwell Science Malden, MA
## Fatty Acid Nomenclature

### Commonly occurring acids

<table>
<thead>
<tr>
<th># Carbons</th>
<th>Systematic Name</th>
<th>Common Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>n-Ethanoic</td>
<td>Acetic</td>
</tr>
<tr>
<td>3</td>
<td>n-propanoic</td>
<td>Propionic</td>
</tr>
<tr>
<td>4</td>
<td>n-butanoic</td>
<td>Butyric</td>
</tr>
<tr>
<td>6</td>
<td>n-hexanoic</td>
<td>Caproic</td>
</tr>
<tr>
<td>10</td>
<td>n-decanoic</td>
<td>Capric</td>
</tr>
<tr>
<td>12</td>
<td>n-dodecanoic</td>
<td>Lauric</td>
</tr>
<tr>
<td>14</td>
<td>n-tetradecanoic</td>
<td>Myristic</td>
</tr>
<tr>
<td>16</td>
<td>n-hexadecanoic</td>
<td>Palmitic</td>
</tr>
</tbody>
</table>

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### Fatty Acid Nomenclature

**Commonly occurring acids**

<table>
<thead>
<tr>
<th># Carbons</th>
<th>Systematic Name</th>
<th>Common Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>n-octadecanoic</td>
<td>Stearic</td>
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<tr>
<td>20</td>
<td>n-eicosanoic</td>
<td>Arachidic</td>
</tr>
<tr>
<td>22</td>
<td>n-docosanoic</td>
<td>Behenic</td>
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<tr>
<td>24</td>
<td>n-tetracosanoic</td>
<td>Lignoceric</td>
</tr>
<tr>
<td>26</td>
<td>n-hexacosanoic</td>
<td>Cerotic</td>
</tr>
<tr>
<td>28</td>
<td>n-octacosanoic</td>
<td>Montanic</td>
</tr>
</tbody>
</table>

Gurr MI et al. Lipid Biochemistry 5th Ed 2002 Blackwell Science Malden, MA
Saturated Fatty Acids

- Major dietary determinant of LDL-C
  - For every 1% increase in calories from SF, serum LDL-C raises 2% or vice versa
- DELTA and beFIT studies have demonstrated benefit in improving LDL-C
- Reduced intakes show no compromised growth or development issues in children

NCEP ATP-III  Circulation 2002;25:3260
Unsaturated Fatty Acids

- **Monoenoic** (monounsaturated)
  - The more common have an even number of carbon atoms and a chain length of 16-22 carbons and a double bond with the cis configuration
  - Often the cis begins at the \( \Delta 9 \) position
  - The most common monoenoic acid is an 18 chain:
    - \( \text{cis-9-octadecenoic acid or Oleic Acid} \)

Gurr MI et al. Lipid Biochemistry 5th Ed 2002 Blackwell Science Malden, MA
Unsaturated Fatty Acids

- **Polyenoic** (polyunsaturated)
  - Unsaturated FA are very susceptible to oxidation; the more double bonds the more the susceptibility

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Unsaturated Fatty Acids

Commonly occurring acids

<table>
<thead>
<tr>
<th># Carbons</th>
<th>Systematic Name</th>
<th>Common Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>$\Delta-6,9$ octadecadienoic</td>
<td>Linoleic</td>
</tr>
<tr>
<td>18</td>
<td>$\Delta-6,9,12$ octadecatrienoic</td>
<td>$\gamma$-Linolenic</td>
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<tr>
<td>18</td>
<td>$\Delta-9,12,15$ octadecatrienoic</td>
<td>$\alpha$-Linolenic</td>
</tr>
<tr>
<td>20</td>
<td>$\Delta-5,8,11,14$ eicosatetraenoic</td>
<td>Arachidonic</td>
</tr>
<tr>
<td>20</td>
<td>$\Delta-5,8,11,14,17$ eicosapentaenoic</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>$\Delta-4,7,10,13,16,19$ docosahexaenic</td>
<td></td>
</tr>
</tbody>
</table>

Gurr MI et al. Lipid Biochemistry 5th Ed 2002 Blackwell Science Malden, MA
Synthesis of EPA & DHA

Neither linoleic or linolenic acid can be synthesized de novo in mammals.

Conversion of α-linolenic acid into its longer chain derivatives is not very efficient in adult humans especially males.
De Novo Fatty Acid Synthesis

Carbohydrate, protein carbon sources

Small precursor acetyl-CoA

Acetyl-CoA carboxylase
Fatty acid synthase

Long chain FA

Elongases
Desaturases

Unsaturated FA

Very long chain FA (>18C)

Modified FA

Other modifications

Gurr MI et al. Lipid Biochemistry 5th Ed 2002 Blackwell Science Malden, MA
Triglycerides are water-insoluble lipids consisting of three fatty acids linked to one glycerol molecule.

- They represent a concentrated source of metabolic energy contributing 9 kcal/gm.

TG are transported as core constituents of all lipoproteins, but the greatest concentration is in TG-rich chylomicrons and VLDL particles.

\[ \text{R} = \text{Fatty acid chain} \]

Substrates for Triacylglycerol Synthesis

Glucose

Glucose-6-P

Glc-6-Pase

PEPCK

PEP

Pyruvate kinase

Pyruvate

Acyl-CoA Synthetase

Acetyl-CoA

Fatty Acid Synthase

Malonyl-CoA

Acyl-CoA Carboxylase

Acetyl-CoA

Acyl-CoA

Citrate

ATP Citrate Lyase

Citrate

HMG-CoA Synthase

Ketone Bodies

Beta-oxidation

Mitochondria

CPT = Carnitine palmitoyl transferase

PEP = phosphoenolpyruvate

PEPCK = PEP carboxylase

Multiple steps

Plasma

Hepatocyte
Triacylglycerol (Triglyceride) Synthesis & DGAT Enzymes

Glycerol Phosphate Pathway

Glycerol-3-phosphate
FA CoA
Glycerol-3-phosphate
FA CoA
Lysophosphatidate
Phosphatidate
PPH-1
DGAT 1&2

Monoacylglycerol Pathway

Monoacylglycerol
MGAT
FA CoA
Monoacylglycerol
FA CoA
Diacylglycerol
DGAT 1&2

Triacylglycerol

GPAT = glycerophosphate acyltransferase
AGPAT = acylglycero-phosphate acyltransferase
PPH-1 = Phosphatidic acid phosphohydrolase-1
MGAT = AcylCoA:monoglycerol acyltransferase
DGAT Diacylglycerol acyltransferase

Regulation of Lipogenic & TG Genes

- Gene
- mRNA
- Precursor protein
- Nuclear form

SREBP-2

- Oxysterols
- Insulin
- LXR
- Fasting

SREBP-2 protein

- Sterol
- PUFA

Mature SREBP-2

Cholesterol Synthetic Genes

- SREBP-1c protein
- Glucose

Mature SREBP-1c

Fatty Acid and Glycerolipid Synthetic Genes

Coleman R & Douglass L. Prog Lip Res 2004 43;134-176
Nuclear Receptors (NRs) exist in inactive forms as multi-protein complexes.

Activation occurs when a ligand (fatty acid) binds to the NR and causes conformational changes
  • This alters the protein-protein interfaces of the molecule

Heterodimerization with the Retinoid X Receptor occurs further changing the conformation
At least 4 nuclear receptors (NRs) are affected by fatty acids and may regulate triglyceride metabolism.

- Liver X receptor (LXR)
- Hepatocyte Nuclear Factor-4-alpha (HNF-4-α)
- Farnesol X Receptor (FXR)
- Peroxisome Proliferator-Activated Receptors (PPARs)

These often heterodimerize with Retinoid X Receptors (RXR)
Peroxisome Proliferator-Activated Subfamily of Nuclear Receptors (PPARs)

- PPAR and LXR subfamilies account for 5 of the 48 nuclear receptors that have been identified in human and mouse genomes.

- They possess a conserved DNA binding and ligand binding domains.
  - The DNA binding domain has two zinc finger motifs that mediate sequence-specific recognition of hormone-response elements in distinct target genes.
  - The C-terminal ligand binding domain determines the specific binding properties of each receptor and mediates ligand-regulated interactions with effectors or repressors of transcription.

Li, AC, & Glass CH. J Lipid Res 2004;45:2161-2173
Transcriptional Activities of Peroxisome Proliferator-Activated and Liver X Receptors

PPARs and LXRs possess the conserved DNA binding domain and the C-terminal ligand binding domain characteristic of nuclear hormone receptors.

PPARs and LXRs bind to specific response elements in target genes as heterodimers with retinoid X receptors (RXRs) which are also members of the nuclear receptor superfamily.

Li, AC, & Glass CH. J Lipid Res 2004;45:2161-2173
## Liver X Receptors (LXRs)

### LXR alpha

<table>
<thead>
<tr>
<th>Tissue expression</th>
<th>Ligands</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver, macrophages</td>
<td>24(S),25 epoxycholesterol, 22(S)-hydroxycholesterol, 24(S)-hydroxycholesterol</td>
</tr>
</tbody>
</table>

### Biological Functions

- Cholesterol absorption (intestine), cholesterol excretion (liver), cholesterol efflux (peripheral cells), fatty acid biosynthesis (liver & peripheral cells)

### Disease Targets

- Atherosclerosis

---

Li, AC, & Glass CH. J Lipid Res 2004;45:2161-2173
Liver X Receptors (LXRs)

LXR beta

**Tissue expression**
Broadly expressed

**Biological Functions**
Cholesterol absorption (intestine), cholesterol excretion (liver), cholesterol efflux (peripheral cells), fatty acid biosynthesis (liver & peripheral cells)

**Ligands**
24(S),25 epoxycholesterol, 22(S)-hydroxycholesterol, 24(S)-hydroxycholesterol

**Disease Targets**
Atherosclerosis

Li, AC, & Glass CH. J Lipid Res 2004;45:2161-2173
LXR Controls SREBP-2 and SREBP-1c

Sterol Regulatory Element Binding Protein (SREBP)-2 regulates the genes involved with cholesterol synthesis while SREBP-1C stimulates the lipogenic enzyme genes.
Liver X Receptors

- LXR, which prevents excessive cellular cholesterol is activated by binding of ligands such as oxysterols.
- LXR activation prevents excessive cellular cholesterol by:
  - Enhancing the expression of genes which stimulate bile acid synthesis (7-alpha-hydroxylase CYP7A).
  - Activates ABCA1 to promote cholesterol efflux into HDL.
  - Activates ABCG5, G8 to increase cholesterol flux from hepatic cells into bile and from intestinal cells into the lumen: in effect the latter inhibits cholesterol absorption.
- The net effect is reduced cellular cholesterol.
**LXR and Bile Acid Formation**

- **Heterodimerization with Retinoid X Receptor**
- **Liver X Receptor Upregulation**
  - Increased oxysterols
  - Increased Free Cholesterol (FC)
  - Hepatocyte

**Catalyzes formation of bile acids**

- Mitochondria
  - 27 OH-Cholesterol
- Peroxisomes
  - C24 acids
  - Cholate, Chenodeoxycholate synthesis

**Oxysterol 7α hydroxylase production**
Hepatocyte, enterocytes, or any other cell with excess cholesterol

Discoidal or Nascent HDL

Liver X Receptor (LXR) & ApoA-I Lipidation

Phospholipids
Free Cholesterol (FC)

LXR binding to RAR

Heterodimerization with Retinoid X Receptor

Liver X Receptor Upregulation

Lipid–free apoA-I or prebeta 1 HDL

Pre-beta2 or Discoidal or Nascent HDL

The FC is esterified by the enzyme LCAT to cholesteryl ester (CE) creating larger alpha HDL particles

ATP Binding Cassette Transporter A1 (ABCA1)

Rye K-A & Barter PJ. ATVB 2003;24:1-8
LXRs Activate ABCG5, ABCG8

Increased hepatic cholesterol stores activates LXR expression, which in turn increases expression of hepatic and intestinal ABCG5/G8.
Hepatic Nuclear Factor - 4-Alpha

- *Hepatic Nuclear Factor - 4- alpha* (HNF-4-α) binds to long chain fatty acyl-CoA with high affinity.
- Binding of saturated FA stimulates whereas binding of polyunsaturated FA (PUFA) inhibits HNF-4-α.
- HNF-4-α affects genes encoding proteins involved in both fat and carbohydrate metabolism including:
  - apoC-III, apoA-I, apoA-IV on lipoproteins
  - L-pyruvate kinase in carbohydrate metabolism
  - CYP 7A in bile acid synthesis
- Fibrates bind HNF-4-α and inhibit its transcriptional activity.
Hepatic Nuclear Factor - 4 -Alpha

Long chain FA activation or PUFA inactivation of HNF-4-α

Potential Targets
- apoC-III, apoA-I, apoA-IV (LP)
- L-pyruvate kinase (carbs)
- CYP 7A hydroxylase (BA)

Protein synthesis

HNF-4-α

Hepatocyte

Endoplasmic reticulum
Farnesol X Receptor (FXR)

- **Farnesol X Receptors** are activated by bile acids and PUFA. They appear to protect cells from bile acid toxicity

- FXR controls bile acid synthesis by inhibiting expression of CYP 7A hydroxylase and other bile synthetic enzymes

- FXR controls expression of the bile acid export pump (BSEP) also termed ATP binding cassette transporter B11 (ABCB11)

- FXR expression has hypotriglyceridemic effects by:
  - Inducing PPAR-α expression
  - Modulating lipoprotein lipase
  - Inhibition of Sterol regulatory binding element protein-1C (SREB-1c) which is mediated through the short heterodimer protein (SHP) negative effect on LXR
FXR and Bile Acid Formation

Heterodimerization with Retinoid X Receptor

Catalyzes formation of bile acids

↑ Oxysterol 7α hydroxylase production

FXR

Farnesol X Receptor Upregulation

Mitocondria

27 OH-Cholesterol

Peroxisomes

C24 acids

Cholate, Chenodeoxycholate synthesis

Hepatocyte
Peroxisome Proliferator-Activated Receptors (PPARs)

- Peroxisome Proliferator-Activated Receptors (PPARS) exist as three subtypes (alpha, beta or delta and gamma). They vary in their expression and biological function:
  - PPAR-α regulates genes in hepatocytes and vascular cells involved with multiple aspects of lipoprotein metabolism, fatty acid catabolism and vascular inflammation
  - PPAR-γ regulates genes in muscles and adipocytes involved with glucose control and vascular inflammation
  - PPAR-Δ is widely expressed and its function is not thoroughly understood at present
Role of Peroxisome Proliferator-Activated Receptors α (PPARs)
The heterodimer binds to response elements in promoter region of target genes.

PPARα

Nuclear Activity

Retinoid X Receptor

PPARs and Retinoid X Receptor heterodimerize

Recruitment of transcriptional coactivators or repressors

Gene transcription
Peroxisome Proliferator-Activated Receptors α Agonism

Nuclear Activity

mRNA leaves the nucleus and enters the cytosol
Peroxisome Proliferator-Activated Subfamily of Nuclear Receptors (PPARs)

**PPAR alpha**

**Tissue expression**
Liver, Heart, Kidney, Adrenal

**Cell specific expression**
Endothelium, Macrophages, Smooth Muscle cells

**Biological Functions**
TG-rich lipoprotein synthesis and metabolism, β-oxidation of FA, anti-inflammation

**Ligands**
PUFAs, 8(S)-HETE

**Disease Targets**
Hypertriglyceridemia

**Drugs**
Fibrates

HETE = hydroxyeicosatetraenoic acid

Li, AC, & Glass CH. J Lipid Res 2004;45:2161-2173
Peroxisome Proliferator-Activated Subfamily of Nuclear Receptors (PPARs)

**PPAR gamma**

**Tissue expression**
- Adipose tissue, spleen, adrenal, colon

**Cell specific expression**
- Macrophages, T cells

**Biological Functions**
- Fat cell development,
- Glucose homeostasis,
- Anti-inflammation

**Ligands**
- PUFAs, 15d-PGJ2, 13-HETE, 9-HODE

**Disease Targets**
- Type 2 diabetes

**Drugs**
- TZDs

HETE = hydroxyeicosoateraenoic acid
15dPGJ2 = 15-deoxyΔ12,14-prostaglandin J2
HODE = hydroxyoctadecadienolic acid

Li, AC, & Glass CH. J Lipid Res 2004;45:2161-2173
Peroxisome Proliferator-Activated Subfamily of Nuclear Receptors (PPARs)

PPAR delta

- **Tissue expression**
  - Many tissues

- **Cell specific expression**
  - Many cell types

- **Biological Functions**
  - Endothelial biology,
  - Energy utilization,
  - Lipid metabolism

- **Ligands**
  - PUFAs

- **Disease Targets**
  - Metabolic syndrome ?

- **Drugs**
  - - -

Li, AC, & Glass CH. J Lipid Res 2004;45:2161-2173
Transcriptional Activities of Peroxisome Proliferator-Activated and Liver X Receptors

In the absence of ligands, PPAR/RXR and LXR/RXR heterodimers can bind to target genes and actively repress transcription through the recruitment of corepressor complexes that contain NCoR, SMRT and histone deacetylases (HDACs).

In the presence of ligands, PPAR/RXR and LXR/RXR heterodimers activate transcription through the recruitment of diverse coactivator complexes that include nucleosome remodeling activity, histone acetyltransferase and histone methyltransferase activities, and directly or indirectly recruit core transcriptional machinery to the promotor.

PPARs and LXR agonists can inhibit the activities of other signal-dependent transcription factors, such as nuclear factor κB and activator protein-1 (AP-1). This repression function contributes to their anti-inflammatory actions.

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Li, AC, & Glass CH. J Lipid Res 2004;45:2161-2173
N-3 FA Direct NEFA away from TG storage to oxidation

Fatty acid metabolism
- Transport
- Oxidation
- Fatty Acid Binding Protein
- Ketogenesis

Adapted from Pegorier JP et al. J Nutr 2004;134:2444S-9S
### N-3 Fatty Acids on Nuclear Receptors Involved with Lipogenesis

<table>
<thead>
<tr>
<th></th>
<th>Effects on Gene Regulation</th>
<th>Expected Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Triglycerides</td>
</tr>
<tr>
<td><strong>PPAR-alpha</strong></td>
<td>Increase</td>
<td>↓↓</td>
</tr>
<tr>
<td><strong>LXR</strong></td>
<td>Decrease</td>
<td>↓↓</td>
</tr>
<tr>
<td><strong>FXR</strong></td>
<td>Increase</td>
<td>↓↓</td>
</tr>
<tr>
<td><strong>HNF-4-alpha</strong></td>
<td>Decrease</td>
<td>↓↓</td>
</tr>
<tr>
<td><strong>Net Effects</strong></td>
<td></td>
<td>↓↓↓↓</td>
</tr>
</tbody>
</table>
Peroxidation products of n-3 fatty acids increase PERPP which decreases the secretion of larger VLDL and subsequently lowers levels of its catabolic products (small LDL)

This may explain how n-3 FA shift LDL size

Clinical trials reveal only a slight reduction in apoB

Adapted from Krauss RM. J Clin Invest 2004;113:1253-55
N-3 Fatty Acids and Chylomicrons

- n-3 FA decrease VLDL secretion, which presents less competition for chylomicron lipolysis.
- n-3 FA supplementation does decrease chylomicron particle size, thereby improving clearance.
- n-3 FA increase pre-heparin lipoprotein lipase activity in the fed state but had no effect on post-heparin lipase activity.
- These combined effects support the use of n-3 FA as a valuable clinical tool for the treatment of hypertriglyceridemia.

Omega-3-Ethyl Esters and Lipids

Patients with TG > 500 mg/dL

<table>
<thead>
<tr>
<th>Lipid</th>
<th>Placebo</th>
<th>Omega-3 AEE 4g/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>TG</td>
<td>-45%</td>
<td>0%</td>
</tr>
<tr>
<td>HDL-C</td>
<td>6.7%</td>
<td>9.1%</td>
</tr>
<tr>
<td>Non HDL-C</td>
<td>-3.6%</td>
<td>-13.8%</td>
</tr>
<tr>
<td>TC</td>
<td>-1.7%</td>
<td>-9.7%</td>
</tr>
<tr>
<td>VLDL-C</td>
<td>-0.9%</td>
<td>-42.0%</td>
</tr>
<tr>
<td>LDL-C</td>
<td>-4.8%</td>
<td>p&lt;0.0001</td>
</tr>
</tbody>
</table>

Baseline Lipids:
- TG: 816 mg/dL
- HDL-C: 22 mg/dL
- Non HDL-C: 2711 mg/dL
- TC: 296 mg/dL
- VLDL-C: 175 mg/dL
- LDL-C: 89 mg/dL

Patients with TG > 200-499 mg/dL

- TG: -24.3%
- HDL-C: 9.1%
- Non HDL-C: -1.5%
- TC: -1.2%
- VLDL-C: -0.7%
- LDL-C: -0.6%
- Apo B: 11.3%

- Placebo: 1.7%
- Omega-3 AEE 4g/day: 8.4%

Dara on file, Reliant Pharmaceuticals
The cotranslational binding of lipids to apoB in the ER by microsomal transfer protein is affected by the various fatty acids available for utilization. ERAD and PERPP enhances apoB proteolysis and inhibits secretion of apoB lipoproteins. Their inhibition would facilitate apoB particle secretion.

Saturated fatty acids protect smaller lipoproteins from PERPP leading to increased secretion of small VLDL and IDL.

Adapted from Krauss RM. J Clin Invest 2004;113:1253-55