3.2: Treatments

One approach to treating hyperlipidemia is to initially reduce dietary intake of fats and cholesterol and increase cardiac exercise. Although this is important, ~80% of cholesterol is synthesized by the liver and only ~20% is obtained from dietary sources. Therefore, altering diet and exercise may be insufficient and reduction of cholesterol may require pharmacological intervention. There are three main strategies to reducing blood lipid concentrations: inhibit lipid synthesis, inhibit lipid absorption/uptake, or accelerate lipid degradation/clearance. Each of the therapeutic approaches below fit into one of these three themes.

Inhibiting Lipid Synthesis: Statins

The **statins** are a class of cholesterol-reducing agents that are the most prescribed drugs, and therefore it is important to have a thorough understanding of their mechanism of action. The statins are designed to block cholesterol synthesis. Cholesterol synthesis occurs in the liver through the mevalonate pathway, which is ~25 step biochemical pathway that begins with acetyl-CoA. One of the key features of the pathway is the rate limiting step which is the reaction that converts HMG-CoA to mevalonate. This reaction is carried out by the enzyme **HMG-CoA reductase**. Therefore, if this enzyme is pharmaceutically intercepted, the mevalonate pathway and cholesterol synthesis can be effectively shut down.

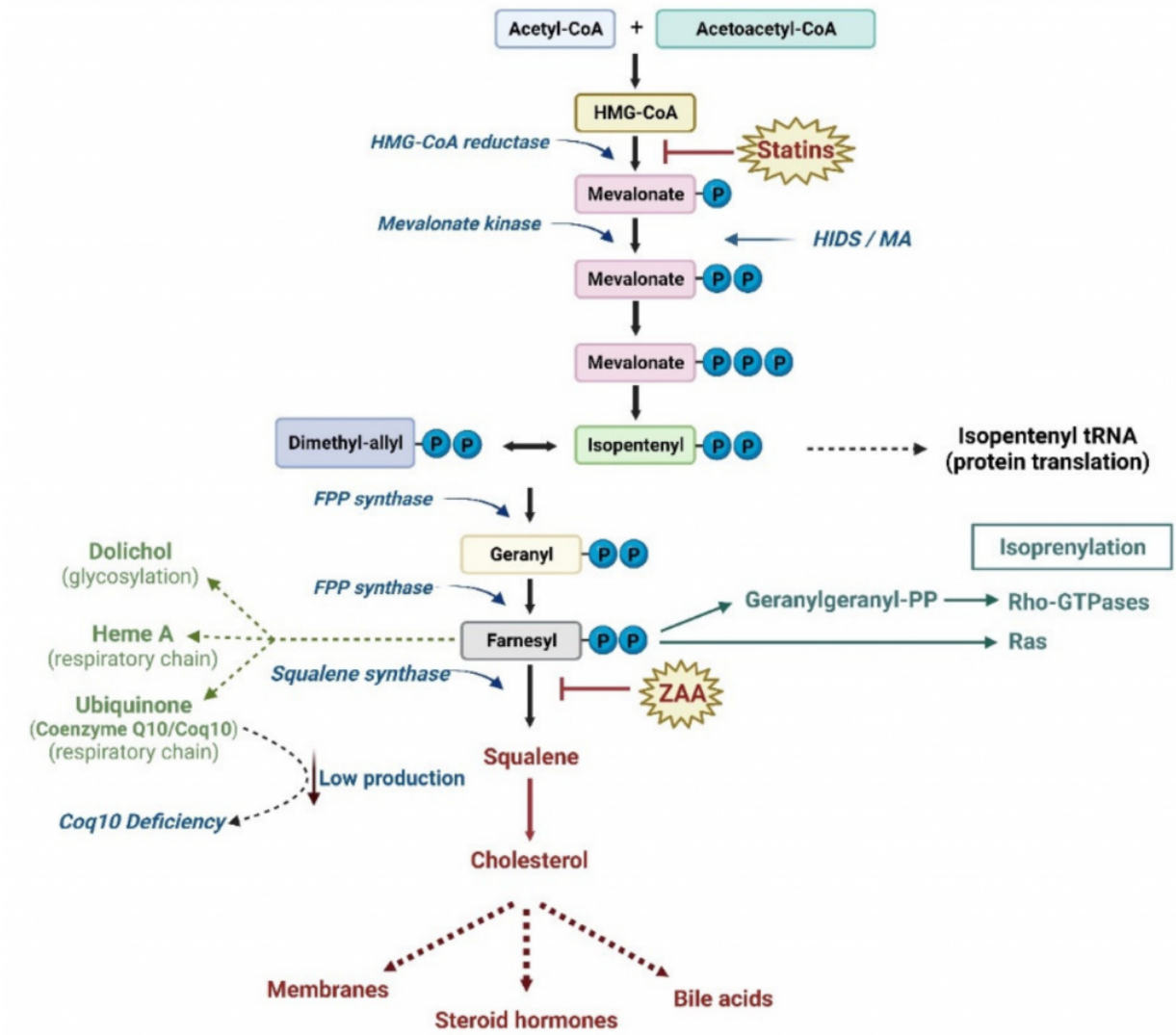

Figure 3.5 The mevalonate pathway leads to the synthesis of cholesterol among other biomolecules. Image Source: (Fig 1) by Simona Pisanti, Erika Rimondi, Elena Pozza, Elisabetta Melloni, Enrico Zauli, Maurizio Bifulco, Rosanna Martinelli and Annalisa Marcuzzi is used under a CC-BY 4.0 license.

HMG-CoA reductase catalyzes the reduction of HMG-CoA with 2 equivalents of NADPH to generate mevalonic acid. Initial approaches in identifying molecules that engage this enzyme involved large natural product screens in the 1970s. The first

molecule that was identified to inhibit the enzyme was compactin, produced by the fungi Penicillium. (Figure 3.6) Compactin has several important chemical features:

- Lactone ring: This ring functions as a pro-drug that opens up to form a carboxylate, whose anionic charge is necessary to engage a critical Lys735 of HMG-CoA Reductase. The hydrolyzed lactone mimics the 3,5-dihydroxylheptaonic acid of the natural enzyme substrate. Importantly, stereochemical configurations of the 3- and 5- position are important to engage with the enzyme.
- Didehydrodecalin ring: This hydrophobic ring engages with a pocket that forms upon the acid binding to the enzyme.

Compactin was ultimately not approved as a drug, due to safety concerns, but similar compounds were advanced, such as lovastatin and simvastatin. These drugs maintain the same lactone-spacer-didehydrodecalin chemotemplate. An interesting compound is pravastatin which does not contain the lactone, but closely resembles the 3*R*,5*R*-dihydroxyheptaonic acid moiety of the substrate, mevalonic acid. Note that all of these molecules have relatively short half-lives. Since cholesterol synthesis mainly occurs at night, it is recommended to take these medications in the evening so that they can be most effective in blocking cholesterol synthesis.

Although blocking HMG-CoA reductase inhibits cholesterol synthesis in the liver, the liver still requires cholesterol for proper functioning. The lower concentrations of cholesterol in the liver stimulate the uptake of cholesterol from LDL and VLDL in the blood. Therefore, extracting the LDL/VLDL from the blood will reduce the total cholesterol levels.

Second-generation statins retain some of the key structural properties that were identified above, including the dihydroxyhepatonic acid, which is critical for enzyme binding to Lys735, as well as the stereochemical configuration of the alcohol groups. However, the moiety that engages with the hydrophobic pocket was altered to contain heteroatoms, leading to atorvastatin (Lipitor) and rosuvastatin (Crestor). Both molecules contain *p*-fluorophenyl and isopropyl substituents which contribute to receptor affinity. The key distinguishing feature between these molecules is that atorvastatin contains an amide where as rosuvastatin contains a sulfonamide, which leads to differential properties. Atorvastatin is the most lipophilic statin and can cross through several cellular membranes including different muscles and tissues. Contrastingly, rosuvastatin is the most hydrophilic statin and the most potent. Both drugs have different CYP metabolic profiles, where atorvastatin is largely metabolized by CYP3A4 and rosuvastatin is metabolized by CYP2C9.

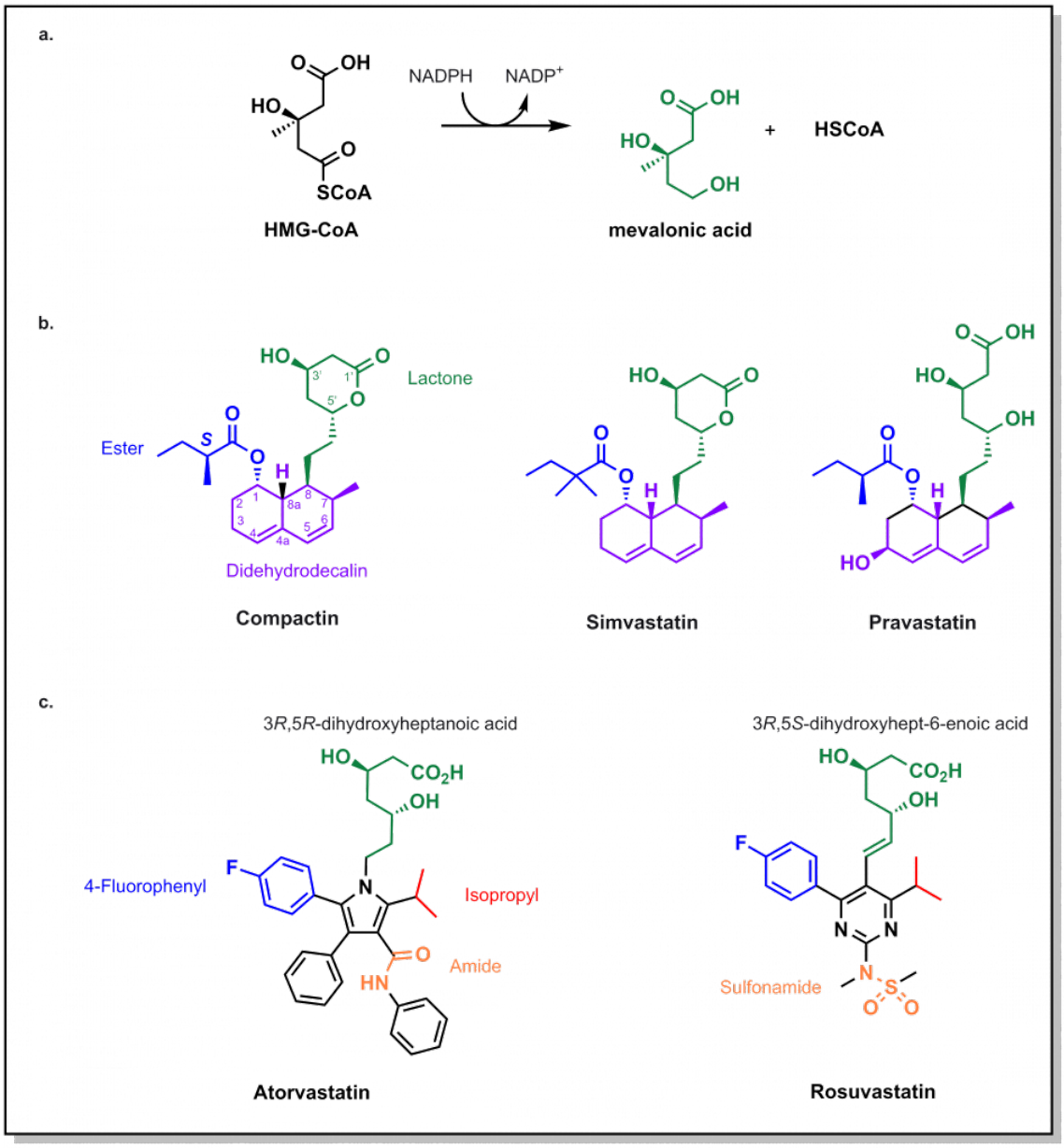

Figure 3.6 Inhibitors of HMG-CoA reductase (statins).

There is also controversy over the types of side effects observed with these statins, with the most common (1-25%) observed as muscle weakness and rhabdomyosis (where the muscle breaks down and releases substances in the blood which can lead to renal or cardiac damage). Although the mechanism is not fully understood, blocking HMG-CoA reductase and reducing mevalonic acid formation reduces the substrates for other biochemical pathways, such as synthesis of Coenzyme Q10 (which is a molecule that is important for muscles and energy usage, Figure 3.5). Although some patients can take supplements, the available data are inconclusive. Additionally, the more lipophilic statins can pass through the CNS which can lead to effects in the brain, including memory loss.

Inhibiting Lipid Synthesis: Niacin

Niacin (or vitamin B3) is a small molecule that has been used to block triglyceride synthesis from adipose tissue. (Fig 3.7) Although it has been in use in the clinics for >50 years, the mechanism of action is still not fully understood.

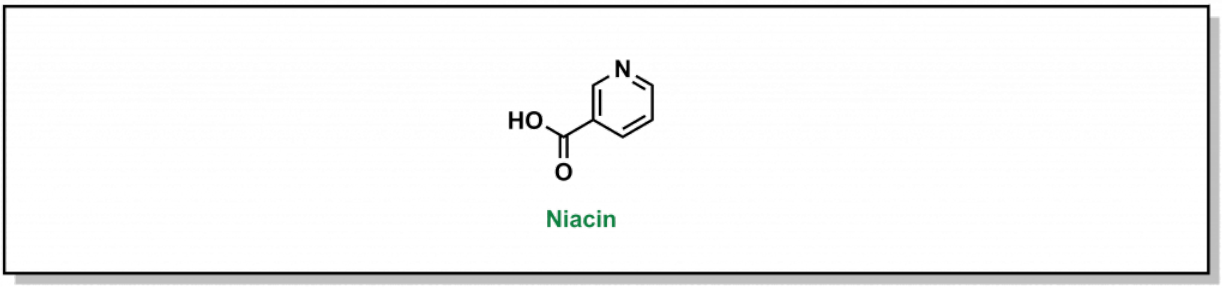

Figure 3.7 The structure of niacin.

Niacin binding occurs at GPR109A (a GPCR receptor) that ultimately inhibits adenyl cyclase activity (reducing the conversion of ATP to the secondary messenger cAMP). This blocks PKA activation, and subsequent Hormone Sensitive Lipase (HSL) activity. HSL is responsible for degrading triglycerides into free fatty acids that would be released into the blood stream. The reduced concentrations of free fatty acids in the blood, leads to lower VLDL formation and triglyceride synthesis in the liver. (Figure 3.8)

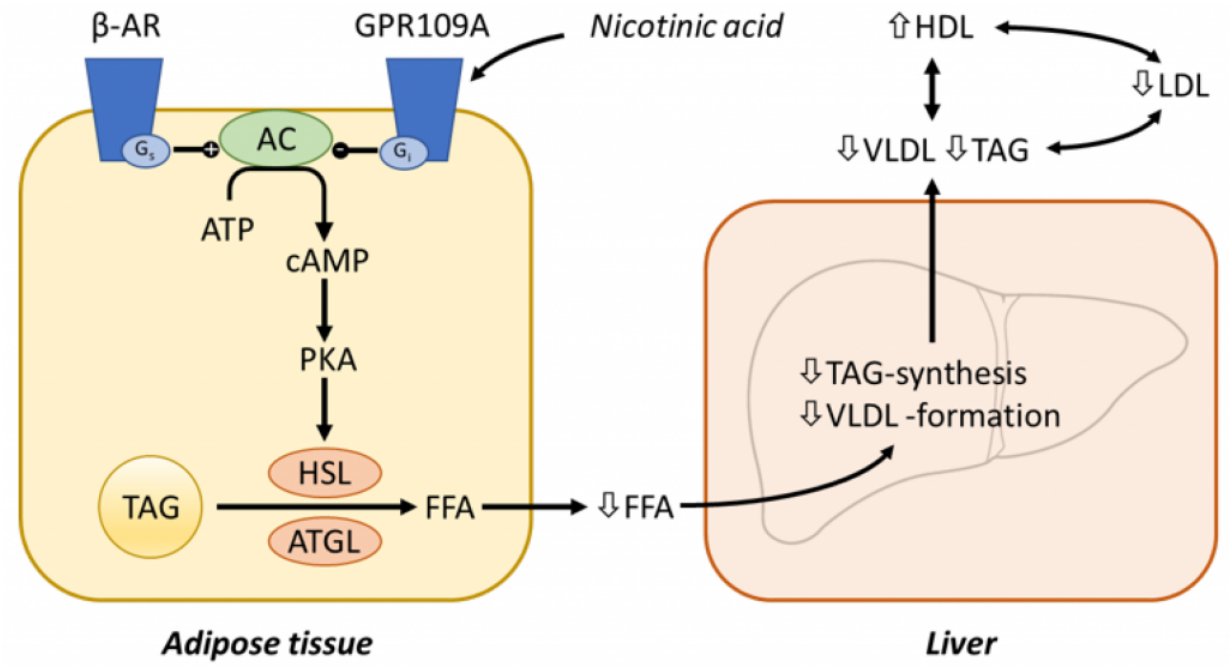

Figure 3.8 Biochemical inhibition of fatty acid synthesis by the action of niacin on GPR109A. Image Source: (Fig 12) by Marcel Hrubša, Tomáš Siatka, Iveta Nejmanová, Marie Vopršalová, Lenka Kujovská Krčmová, Kateřina Matoušová, Lenka Javorská, Kateřina Macáková, Laura Mercolini, Fernando Remião, Marek Máťuš, Přemysl Mladěnka has been modified (cropped) and is used under a CC-BY 4.0 license.

Inhibiting Lipid Uptake: Ezetimibe

Another mechanism for reducing cholesterol levels is to prospectively prevent cholesterol from being absorbed during food intake. Dietary cholesterol is absorbed in the small intestine via the action of a receptors called NPC1L1. (Figure 3.9) Cholesterol will bind these receptors, and the cholesterol-receptor complex will be internalized via the AP2-clathrin mediated processes.

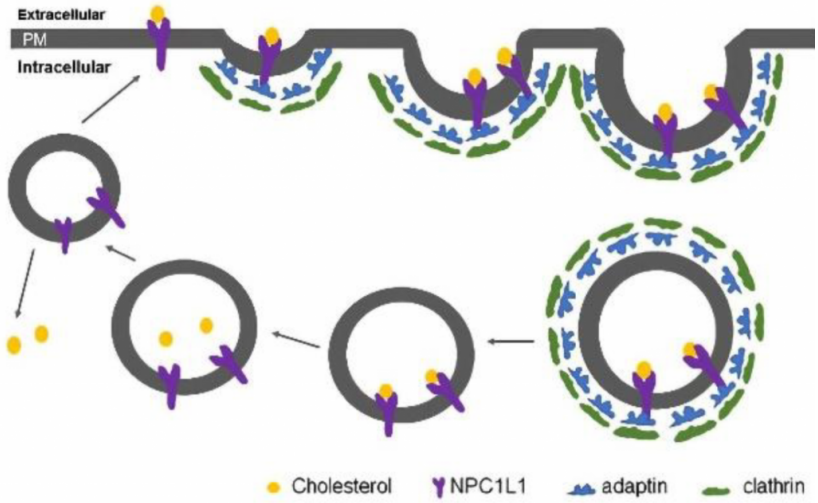

Figure 3.9 Clathrin mediated update of cholesterol. Image Source: (Fig 1) by Jun Zeng, Wenjing Liu, Bing Liang, Lingyu Shi, Shanbo Yang, Jingsen Meng, Jing Chang, Xiaokun Hu, Renshuai Zhang, and Dongming Xing has been modified (cropped) and is used under a CC-BY 4.0 license.

Ezetimibe is a drug that blocks the interaction between the NPC1L1 receptor and the clathrin molecules, which prevents the cell from absorbing cholesterol. The 1,4-diaryl-β-lactam structure is critical for activity. These drugs can be combined with statins to effectively reduce the amount of cholesterol that is absorbed as well as synthesized. (Figure 3.10)

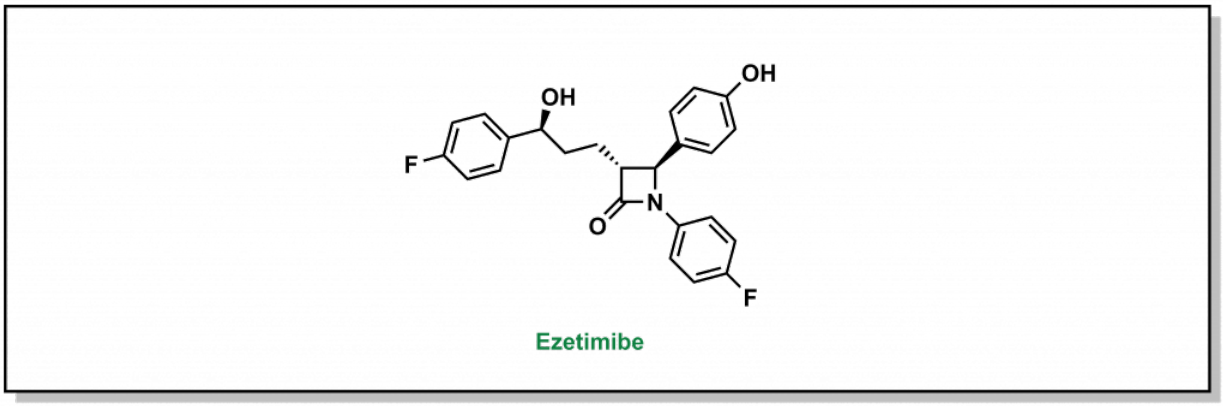

Figure 3.10 Structure of ezetimibe.

Accelerating Lipid Degradation/Clearance: Fibrates

Fibrates are a class of compounds that can reduce effects of hypertriglyceridemia. Fibrates activate **peroxisome proliferator-activated receptor alpha** (PPARα) which heterodimerizes with another protein called retinoid X receptor (RXR) and subsequently binds the PPARα response elements to regulate the expression of a cluster of genes involved in lipid metabolism. This increases HDL and reduces TG synthesis. (Figure 3.11)

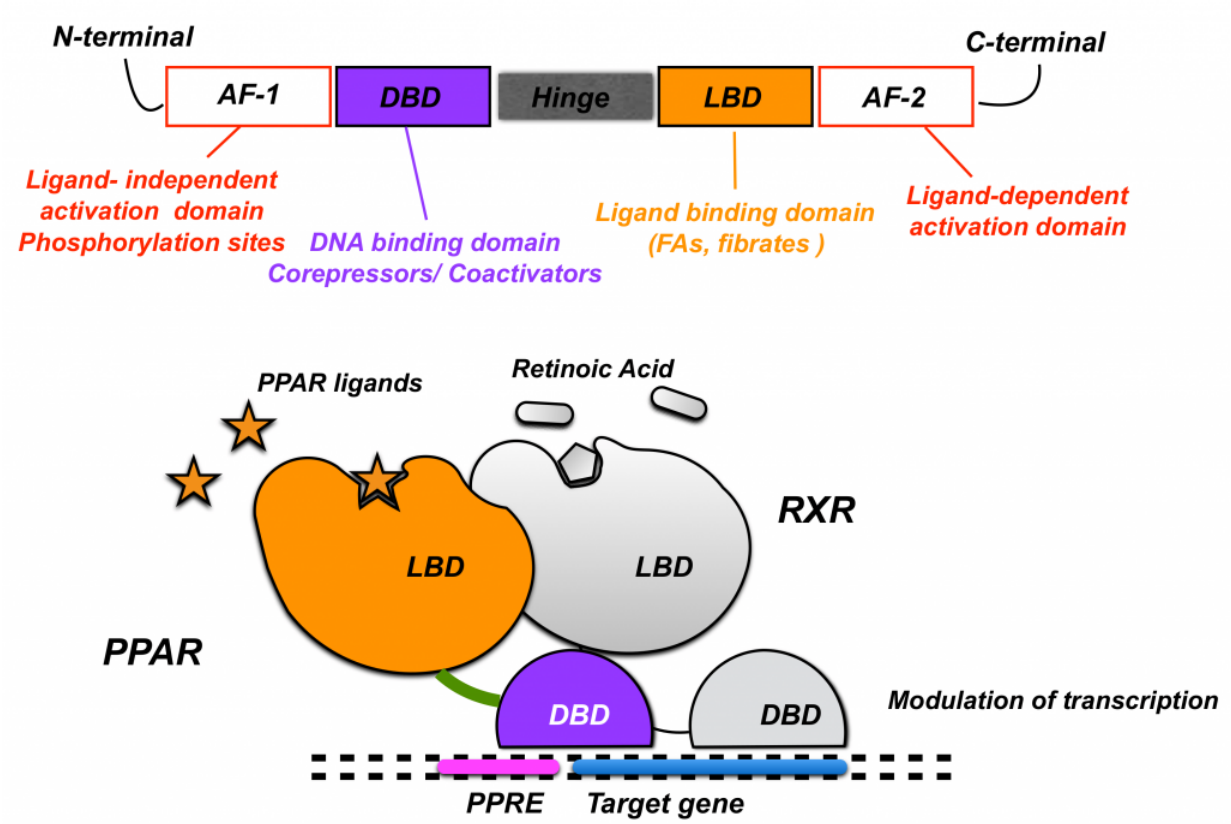

Figure 3.11 Mechanism of PPARα activation of genes involved in lipid metabolism. Image Source: (Fig 1) by Simona Scheggi, Graziano Pinna, Giulia Braccagni, Maria Graziella De Montis and Carla Gambarana is used under a CC-BY 4.0 license.

The main pharmacophore for fibrates binding and activating PPARα includes a phenoxyisbutyric acid, which forms an ionic-dipole interaction with a specific tyrosine residue (Tyr464) on PPARα. There are two main fibrates referred to as fenofibrate and gemfibrozil. (Figure 3.12)

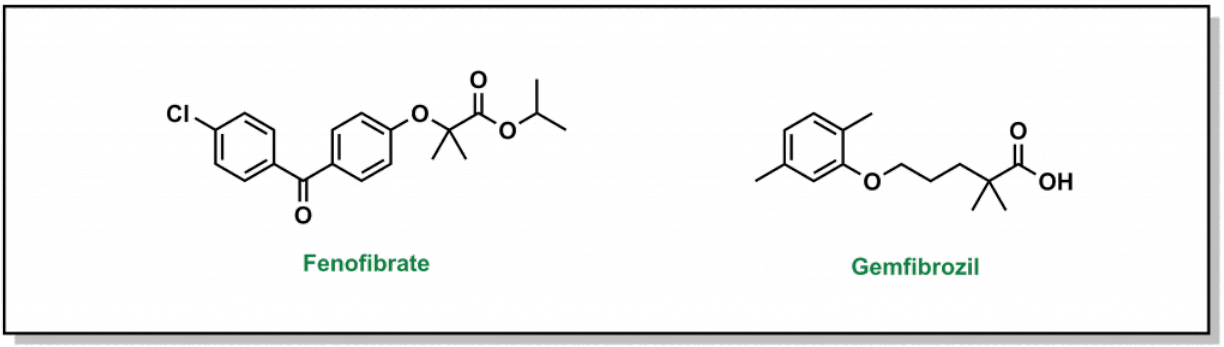

Figure 3.12 Structures of common fibrates.

Accelerating Lipid Degradation/Clearance: Bile Acid Sequestrants

As mentioned above, the hydrophobic nature of lipids can create challenges during digestion and absorption, considering the aqueous environment of the stomach and small intestine. Dietary lipids are digested with the help of bile (which is a complex fluid largely consisting of bile acids and cholesterol derivatives). Bile is produced by the liver and stored in the gall bladder. Following digestion, ~97% of the bile is re-absorbed in the ileum and stored in the gall bladder. However, the introduction of bile acid sequestrants will bind to the bile, which prevents it from being re-absorbed and causes it to be excreted. In response to this loss of bile, the liver synthesizes additional bile acids, which requires uptake of cholesterol and LDL from the blood, ultimately lowering the lipid concentration.

Bile acid sequestrants (**BAS**) are positively charged cations that will bind to negatively charged bile acids, and this interaction creates a complex that is incapable of being absorbed. BAS are normally powders that are taken orally. They are not absorbed by the small intestine, which limits any systemic adverse effects, but they can be challenging to consume and can cause different forms of GI distress.
