diseases.[30] As a result, a number of animal models have been designed to study the impact of potential therapeutic agents on their plasma concentration. New Zealand White rabbits, for example, can each serve as test animals for potential cholesterol-lowering agents, provided they are fed the appropriate diet. Hypercholesterolemia can be induced in these animals by maintaining them on an appropriate diet for 5–6 weeks (normal cholesterol levels of approximately 70 mg/dL are elevated to approximately 310 mg/dL). Once hypercholesterolemia is established, the animals can be treated with novel compounds designed to lower circulating cholesterol levels for an extended period of time (1–2 weeks). An analysis of blood samples to determine systemic concentration of the cholesterol and LDL during and at the end of the dosing period can be used to identify compounds that have a positive impact (e.g., lowering the cholesterol level closer to the normal levels). Statins such as Mevacor® (lovastatin, Figure 7.10(b)), inhibit HMGCoA reductase, the rate-limiting enzymes in the biosynthesis of cholesterol. They were identified using this type of animal model.[31]

Although the diet-induced model of hypercholesterolemia has been an effective tool in the development of cholesterol-lowering agents, it is not a perfect model. The ability to induce high levels of cholesterol and LDL does not necessarily lead to the formation of atherosclerosis in a manner similar to that observed in human. Atherosclerotic plaques in the rabbit model, for example, are significantly different from their human counterparts. The difference in plaque structure is not relevant in the identification of compounds capable of lowering cholesterol levels. It is, however, a limiting factor for the identification of compounds capable of altering the progression of atherosclerotic plaques. The rabbit model is not well suited to this task.

Fortunately, the apolipoprotein E-deficient (apoE$^{-/-}$) mouse model does not have this limitation. This transgenic animal has been genetically altered so that it does not express apolipoprotein E (Figure 7.11), which

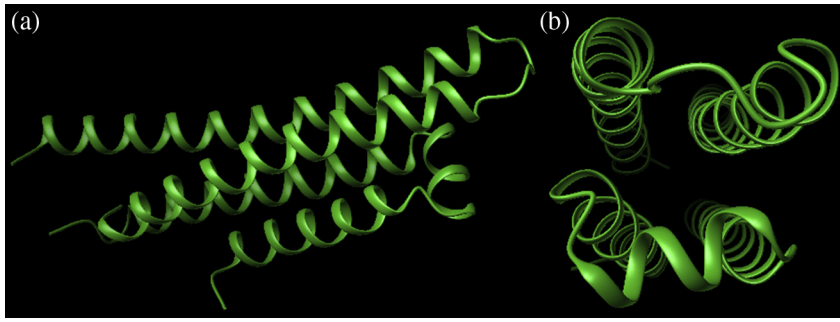

FIGURE 7.11 Structure of apolipoprotien E4 (a) viewed across the four α-helices and (b) viewed down the length of the four α-helices (RCSB 1b68).