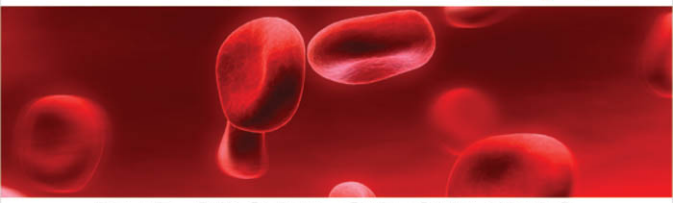
TRIUMPH OF THE HEART



THE STORY OF STATINS

Jie Jack Li

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The Story of Statins

Jie Jack Li

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To my former colleagues at Parke-Davis who contributed to the discovery and development of Lipitor

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FOREWORD

Jack Li has established himself over the past several years as a prolific writer on the history and science underlying the discovery of medicinal drugs. In this work he weaves a fascinating tale of two of the great victories in twentieth-century medicine—understanding the link between cholesterol and coronary artery disease and developing the statin family of medicines, which together greatly benefit humankind.

Central to this interesting and complex story are the important but little-known achievements of many individual scientists. As you read this book, you will be introduced to these major figures behind the dramatic advances in the prevention of atherosclerosis and cardiovascular diseases: Nikolai N. Anitschkov, Akira Endo, Konrad E. Bloch, Joseph L. Goldstein, Michael S. Brown, Alfred W. Alberts, Alvin K. Willard, Faizulla G. Kathawala, Bruce D. Roth, and Roger S. Newton. Because of their work, the lives of many millions of people are being significantly extended—they will enjoy extra years of health and productive life.

In this book Jack Li illuminates many critical aspects of the statin story beyond the science. For instance, he sharply depicts the challenge facing any company involved in the discovery of new medicines. He also raises some serious questions on the future of pharmaceutical discovery, which, as he points out, is quite uncertain at this moment. That future depends more critically than ever on faith, inventiveness, and perseverance in the discovery process and the willingness of the public and governments to share in the enterprise—to share the risks, costs, and uncertainty of a very unpredictable undertaking. The only certainties are that predictions are themselves risky and that more, not less, scientific and medical research is essential to modern societies.

E. J. Corey
Harvard University

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PREFACE

The story of statins is fascinating—not only because of its scientific and medical importance, but also because of the human aspects in the discovery and development of these drugs. Statins are used to treat patients with high cholesterol who are at risk for heart attack, stroke, or other coronary heart disease. Now millions of patients have benefited from statins in preventing coronary heart disease (25 million in 2005 in the United States alone). Statins, the new wonder drugs by all accounts, lower LDL cholesterol (low-density lipoprotein, the "bad" cholesterol) by inhibiting the action of a key enzyme in the liver involved in the biosynthesis of cholesterol. They are considered the gold standard therapy and are the most widely prescribed lipid-modifying drugs.

"Discoveries are made by men, not merely by minds, so that they are alive and charged with individuality."[1] In telling the story of Lipitor, Zocor, and other statins, I have tried to illustrate the human side of science as well as elements of luck, persistence, and insight that characterize major discoveries. Moreover, knowledge of the history of drug discovery is essential to an intellectual understanding of it. In preparing this book, I was torn between my scholarly and popularizing instincts. It is my sincere hope that I have achieved a certain balance of both. And I hope this book will find its way to the general public in addition to scientists in academia and the drug industry, health care professionals, and students in medicine.

I am indebted to Professor Akira Endo, the discoverer of the first statin, mevastatin, for providing his stories and photographs. I thank David Canter, Roger S. Newton, and Bruce D. Roth for taking the time to reminisce with me about the exciting days during the discovery and development of Lipitor. Nick Terrett and Ian Osterloh, the key players in the discovery and development of Viagra, graciously communicated with me about their experience.

I have incurred many debts of gratitude to my academic friends Professor E. J. Corey at Harvard University and Professor Phil S. Baran at Scripps Research Institute, who have offered much enthusiastic encouragement. Professor Baran and his students Jeremy Richter and Jonathan Lockner also kindly proofread the manuscript and provided many invaluable suggestions.

PROLOGUE

In the afternoon of that Friday, December 19, 2005, Judge Joseph J. Farnan, Jr., of the Federal District Court in Delaware handed down his judgment validating Pfizer's two patents on atorvastatin, the principal ingredient of the cholesterol-lowering drug Lipitor.[1] As a consequence, Pfizer was allowed to exclusively market in the United States the world's best-selling drug until June 2011, and it would now be illegal for the challenger, India's largest generic drug company, Ranbaxy Laboratories Ltd., to make a copycat version of Lipitor.

"Today marks a major victory for medical inventors and the patients who depend on them for important new therapies," Pfizer CEO Hank McKinnell commented.[2]

Although the New York Stock Exchange was closed when the court ruling was announced, the news sent the Pfizer common stocks soaring 11.3% to $25.14 during after-hours trading. The drug industry breathed a collective sigh of relief, knowing that innovation would be protected by U.S. patent law. The judgment also ignited a broad-based advance in other pharmaceutical industry stocks. Merck surged more than 7%, Bristol-Myers Squibb rose more than 3% at one point, and Schering-Plough climbed more than 5%.

How could the two patents for a single molecule, atorvastatin, be worth billions of dollars? To answer that question, we will need to take a look at another molecule, cholesterol, whose levels atorvastatin lowers in the human body.

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CHAPTER 1

Cholesterol

The story of statins starts with cholesterol because statins are a class of drugs that reduce low-density lipoprotein (LDL) cholesterol, the "bad" cholesterol. LDL cholesterol, in turn, is a major risk factor for coronary heart disease, the leading cause of death worldwide and projected to remain so through 2025. About 1.5 million Americans suffer heart attacks each year, and heart disease has emerged as the biggest cause of death in the United States, killing 911,000 people in 2003.

Before the 1940s, the average lifespan in America was 47 years, and heart disease did not contribute to mortality to a large extent because people often died of infections. Currently, an average American lives to celebrate her 77th birthday. As a consequence, heart-related disease has risen to be the number one killer. Coronary heart disease manifests in many forms: angina, arrhythmia, atrial fibrillation, congestive heart failure, hypertension, atherosclerosis, myocardial infarction (heart attack), and sudden cardiac death. Atherosclerosis, or blockage in arteries, results when a buildup of cholesterol, inflammatory cells, and fibrous tissue called plaques forms on an artery wall. If these plaques rupture, they can block blood flow to critical organs such as the heart or brain and can lead to heart attack or stroke.

Despite the many different forms of cardiovascular disease, the molecule cholesterol is a common denominator for most of them. Therefore, in order to understand coronary heart disease, we first need to take a look at the cholesterol molecule.

The Janus-Faced Molecule

According to Roman mythology, Janus is the guardian of portals and patron of beginnings and endings. Just like the two-faced Roman god, cholesterol is a double-edged sword for the human body. On the one hand, it is an essential building block for many crucial ingredients the body needs. On the other hand, it can be lethal when it forms plaques on the surface of the arteries and subsequently causes coronary heart disease.

Make no mistake, cholesterol is vital to our existence. It is most abundant in our brains—23% of total body cholesterol resides there, making up 1/10th of the solid substance of the brain. Red blood cell membranes are also rich in cholesterol, which helps stabilize the membranes and protect the cells. In addition, cholesterol is necessary for producing bile acids that help digest fats in our food. Moreover, it is the precursor molecule for the synthesis of sex hormones, including progesterone, testosterone, and estrogen. In fact, *all* steroids in the body are derived from cholesterol, which is converted into specific hormones by biochemical transformations catalyzed by enzymes. For instance, enzymes in testes convert cholesterol to testosterone, whereas enzymes in ovaries convert cholesterol to estrogen. Other enzymes in the body convert cholesterol to additional hormones, such as cortisol, a hormone secreted by the outer layer of the adrenal glands when we are under stress. Addison's disease is due to adrenal cortex deficiency and is characterized by the failure of the adrenal glands and the inability to produce cortisol.

It is apparent that cholesterol is an indispensable ingredient for life. But like everything else in life, too much of a good thing can be bad. By now, the experimental, genetic, and epidemiologic evidence all point to elevated cholesterol levels as a major risk factor for cardiovascular disease.

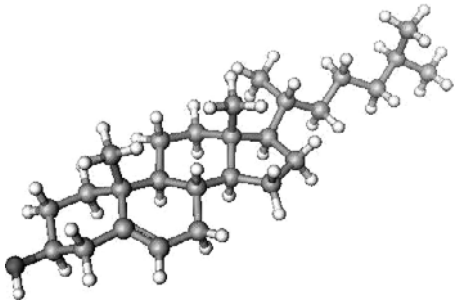

Figure 1.1 Molecular structure of cholesterol.

Cholesterol helps plaque build up, which constricts or blocks arteries and leads to angina, heart attack, and stroke.

Cholesterol in the human body comes from two sources. One is from intestinal absorption of dietary cholesterol. The other is generated inside the body, primarily in the liver, to meet the body's need if the diet is lacking sufficient quantities. The liver makes about 70% of the body's cholesterol—our bodies produce, on average, three or four times more cholesterol than we get from dietary sources.

Since it was first isolated from gallstones in 1784, cholesterol has fascinated researchers from many areas of science and medicine. Thirteen Nobel Prizes have been awarded to scientists who devoted major parts of their careers to cholesterol research.

Believe it or not, cholesterol comprises about three-quarters of a gallstone—the remainder is calcium salts. French physician-chemist François Poulletier was the first to obtain pure cholesterol from gallstones. At first, Poulletier erroneously identified cholesterol as a form of wax. Some 30 years later, French chemist Michel E. Chevreul shattered that notion by showing that cholesterol could not be saponified—wax is composed of esters and thus can be saponified. Chevreul named it cholesterine ("solid bile," from the Greek *chole* for bile and *stereos* for solid).

The exact empirical formula of cholesterol was accurately established in 1888 by Austrian botanist Friedrich Reinitzer,[1] who worked at the Imperial Institute for Plant Physiology at the German University in Prague. Interested in the biologic roles of cholesterol in plants, Reinitzer initially studied cholesterol isolated from the carrot root. However, its cholesterol content was so minute that Reinitzer resorted to purchasing cholesterol from a factory. After purifying the sample by treatment with alcoholic sodium hydroxide, Reinitzer treated cholesterol with bromine and obtained a compound that "precipitates out as *splendid crystals*."[1] Using a rudimentary but reliable method called elemental analysis involving combustion of the compound and then analysis of the carbon and hydrogen contents, he deduced the precise molecular formula. In his publication in the prestigious German chemistry journal *Monatshefte für Chemie* (*Chemical Monthly*) in 1888, Reinitzer was very confident: "The formula of cholesterol *must read* $C_{27}H_{46}O$."[2] Chevreul was still alive at the time of Reinitzer's publication and lived another year until he died at the age of 103.

The cholesterol molecule has four rings, which made its structural elucidation an extreme daunting challenge, occupying scientists for a good part