

## MEDICAL INNOVATION: STATINS (PHARMACEUTICAL: SMALL MOLECULE)

**Physicians: Akira Endo, biochemist who discovered the first statin, and Scott Grundy and David Bilheimer, lead investigators in clinical trials**

**Industry: Sankyo, Merck & Co., Inc**

### Situation

***A heart attack every 34 seconds***

Coronary artery disease -- the narrowing of blood vessels that supply the heart with oxygen -- affects 16.8 million Americans and stands as the leading cause of death in the United States. The American Heart Association (AHA) estimates that about every 34 seconds, an American will have a heart attack. In addition, the lifetime risk of having cardiovascular disease after age 40 is 2 in 3 men and more than 1 in 2 women.

One of the primary risk factors for coronary artery disease is high levels of LDL cholesterol, known as "bad" cholesterol because it can build up on the inside of arteries, causing them to become narrow from plaque. Until recently, people with high levels of LDL cholesterol had very few tools to lower this risk factor directly, and had to rely solely on radical diet modifications and other indirect means of combating this condition.

### Physician-Industry Collaboration

***Building on an earlier discovery***

In 1971, Akira Endo, a Japanese biochemist working for the drug company Sankyo, began the search for a cholesterol-lowering drug. Earlier research had already shown that the body manufactures cholesterol mostly in the liver, using a special enzyme. Endo and his team reasoned that certain microorganisms may produce inhibitors of this enzyme to defend themselves against other organisms. The first agent they identified was mevastatin, a molecule produced by the fungus *Penicillium citrinum*.

Mevastatin was never marketed, though, because of it was found to produce adverse effects such as tumors, muscle deterioration, and sometimes death in preclinical studies. However, Roy Vagelos, chief scientist and later CEO of Merck & Co., was very interested, and made several trips to Japan starting in 1975 to learn more about Endo's research and build on it. By 1978, Merck had isolated lovastatin from a fungus and began preliminary clinical studies of the drug, but had to discontinue the trials because of evidence that a closely related compound, compactin, caused certain cancers in preclinical studies. The lovastatin project appeared dead.

New data from separate trials revealed in early 1981 that lovastatin could raise liver LDL receptors in preclinical studies, and this led to a profound fall in LDL levels. In July 1982, several clinicians in the U.S. who followed this development, including Scott Grundy and David Bilheimer of the University of Texas, used lovastatin to treat patients with severe high cholesterol that was unresponsive to existing therapies.

The drug showed dramatic activity in lowering LDL cholesterol, with very few side effects. This led Merck to begin large scale clinical trials of lovastatin in patients at high risk and long-term

toxicity studies in dogs in 1984. The drug dramatically reduced cholesterol levels, was well tolerated, and no tumors were detected. In November 1986, Merck sent the New Drug Application (NDA) to the U.S. FDA and lovastatin received FDA approval to become the first commercial statin in September 1987.

## **Innovation Benefits**

### ***Extending the lives of millions each year***

In the quarter-century since they were developed, statins have quickly become the largest selling class of drugs currently taken by patients around the world. Today, an estimated 30 million people worldwide are taking statins, and the lives of millions of people have been extended through statin therapy. Over a dozen clinical trials involving 91,000 patients with atherosclerotic cardiovascular disease have documented a 30% reduction in heart attacks after treatment with statins.

Statin therapy is not just about living longer but about quality of life as well. Prior to the introduction of statins, the drugs available to lower blood cholesterol had many more side effects, and low-cholesterol diets prescribed by nutritionists were difficult to follow. Although clinical trials have shown that statins lower cholesterol most effectively when combined with dietary modification, a reduction of LDL cholesterol does not necessarily require abandoning moderate enjoyment of food.

## **Patient Benefits**

### ***No longer living in fear***

Though Sally R. exercised regularly and vigorously for years it became clear that exercise and diet were insufficient in controlling her high level of LDL cholesterol, which was over 300 at age 40. With a history of heart disease in her family, she was worried about rapid onset of coronary artery disease if she didn't do something fast.

Sally's family practitioner prescribed 20mg of Mevacor (lovastatin), and, after 3 months of use, her blood tests indicated a drop of more than 30% in her LDL. Combined with a healthy diet and exercise, Sally is no longer living in fear of a heart condition as she did before.

"I do yoga, cardio, strength and resistance training, and eat right because I owe it to my family to stay healthy," she said. "But my doctor said that wasn't enough. Now, with my cholesterol-lowering medication, I know I am doing everything I can and am looking forward to a long and heart-healthy life!"