The Road to Lipitor

- Background: Inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase) can lower serum cholesterol levels. This enzyme is early and rate-limiting in cholesterol biosynthesis.

\[ \text{HMG-CoA reductase} \]


The Road to Lipitor

- How do these inhibitors work? They bind to the enzyme as the "open acid" and function as transition state analogs.

\[
\begin{align*}
\text{R}''^\text{H} & \\
\text{CH}_3 & \text{COOH} \\
\text{H} & \text{H} \\
\text{H}_3\text{C} & \text{O} \\
\text{HO} & \text{H} \\
\text{H}_3\text{C} & \text{H} \\
\end{align*}
\]

\[
\begin{align*}
\text{H}_3\text{C} & \text{COOH} \\
\text{HO} & \text{O-H} \\
\text{H} & \text{SCoA} \\
\end{align*}
\]

\[
\text{K}_i \text{ for compactin is } 1.4 \times 10^{-9} \text{ M; mevacor } 6.4 \times 10^{-10} \text{ M} \\
7000-16,000 \text{ times higher affinity for the enzyme active site} \\
\text{than the natural substrate! (K}_m 1 \times 10^{-5} \text{ M)}
\]

- In 1981 Parke-Davis decided to make a synthetic HMG-CoA reductase inhibitor. In 1985 they prepared atorvastatin... looked about as good as mevacor...
The Road to Lipitor

• The Business of Atorvastatin/Lipitor...

1. Merck firmly established that statins could prevent 4 out of 9 second heart attacks in a huge Scandinavian study.

2. Merck had the large ($5 billion) cholesterol-lowering market in its pocket with Zocor and Mevacor.

3. Parke-Davis considered dumping the Atorvastatin project after successful, but unremarkable, early animal trials. In 1985/6 they could anticipate being the 4th or 5th drug to market. A LOSING proposition.

4. They pushed one more step to Phase I human trials and saw remarkable activity! Why? ortho and para hydroxylated metabolites are as active as parent... extends drug lifetime in the body.

5. Large clinical trials were not needed. Merck did 'em!

6. In a STUNNING move Atorvastatin/Lipitor was priced the same as Zocor. General wisdom would have said "you won't capture a large market share - so price it high!"
The Road to Lipitor

• The Business of Atorvastatin/Lipitor...

7. In 1997 Merck held 70% of market with Zocor and Mevacor.

8. Lipitor cut Merck's share to 40%. Lipitor holds 37% of market.

9. Lipitor Worldwide sales $1 billion. Expected to take 50% of market next year.

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Take home message:

"Success is fragile, because there is one thing certain in a business like ours, and that is that technology will be superseded"

- Joe Zammit-Lucia, Drug Company Consultant
PHARMACEUTICALS

BRISTOL-MYERS STUDY BACKFIRES

Firm loses out in comparison with Pfizer cholesterol drug

A new study of cholesterol-reducing drugs in the statin family holds good news for heart disease sufferers but bad news for the study's sponsor, Bristol-Myers Squibb.

The study is called Pravastatin or Atorvastatin Evaluation and Infection Therapy, or PROVE IT. Bristol-Myers launched it in 2002 in an effort to demonstrate that its Pravachol brand pravastatin works as well as Pfizer's Lipitor (atorvastatin calcium) at preventing major cardiovascular events.

The results, revealed last week at the American College of Cardiology meeting in New Orleans, were not what Bristol-Myers was expecting. The Harvard Medical School researchers who conducted the study found that patients taking Lipitor had a 16% lower risk of heart attacks or death than those taking Pravachol.

Lipitor is already the biggest selling statin— and the number one drug in the world—with 2003 sales of $9.2 billion. In contrast, Pravachol's sales were $2.8 billion last year and are in danger of slipping in the wake of the findings.

For heart patients, the study could herald a new era of aggressive statin-based therapy. According to Eric J. Topol, chairman of cardiovascular medicine at the Cleveland Clinic and author of an editorial in the New England Journal of Medicine edition in which the study appears, the conventional therapeutic approach has been to lower patients' low-density lipoprotein (LDL) cholesterol levels to less than 100 mg per deciliter of blood.

However, the high doses of Lipitor given in the PROVE IT study reduced LDL levels to well below that—62 mg on average. LDL levels among Pravachol recipients, on the other hand, averaged 95 mg.

Based on the improved mortality associated with the much lower cholesterol levels, Topol predicts that "there will soon be a sea change" in the prevention and management of cardiovascular disease.—MICHAEL MCDONALD

ORGANIZED LABOR

CHEMICAL UNIONS FORM ALLIANCE

Workers aim for joint action on a variety of workplace, political issues

Two of the largest U.S. chemical industry unions announced last week that they are exploring a merger and have meanwhile formed a "strategic alliance" to work closer together on organizing, bargaining, taking political action, and addressing health and safety issues.

The Paper, Allied-Industrial, Chemical & Energy Workers International Union (PACE) and the United Steelworkers of America (USWA) are industrial unions that have similar histories and many chemical and petroleum industry members, say union officials.

The alliance will formalize cooperative activities already under way, said USWA President Leo W. Gerard in a statement.

PACE has created strategic alliances with several companies, said PACE President Boyd Young in a statement, adding that it made sense to try the same thing with other unions.

Both unions hold members from many industrial sectors, and officials estimate overall U.S. and Canadian membership to be 275,000 for PACE and 600,000 for USWA. Officials estimate union membership in the chemical sector at 20,000-50,000 workers for each union.

Union officials predict that the chemical industry will see a difference through the alliance.

For instance, they say USWA intends to adopt PACE's rapid-response safety program, which investigates industrial accidents, and its medical screening programs. PACE plans to develop political action and education programs modeled after those of USWA.

The alliance will give the unions a real-world evaluation of what a merger would mean for the membership, say union officials.—JEFF JOHNSON
Statin Drugs In the Active Site of HMG-CoA Reductase

Istvan and Deisenhofer, Science 2001, 292, 1160