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By Learning From Failures, Lilly Keeps Drug Pipeline Full

Dr. Nyikiza Uses Math Skills To Save Cancer Treatment; A Surprisingly Simple Fix

Lessons of an Antelope Hunt

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INDIANAPOLIS -- Five years ago, **Eli Lilly** & Co. had high hopes for an experimental chemotherapy drug called Alimta. But after three patients taking Alimta died suddenly in 1999, Lilly halted trials of the drug. It looked like a fatal blow for Alimta -- despite strong evidence that it could reverse tumor growth.

Paolo Paoletti, the Lilly doctor running the trials, begged for two weeks to save the drug. He teamed up with a Rwandan mathematician, Clet Nyikiza, whom Lilly keeps on staff largely to study drug failures. Dr. Nyikiza had been fascinated by why complex processes fail ever since his grandfather taught him as a boy in East Africa the telltale signs of an unsuccessful antelope hunt. By analyzing blood samples and medical records, Messrs. Paoletti and Nyikiza identified a surprising problem with an unexpectedly simple solution.

Today, Alimta is an approved treatment for mesothelioma, a rare type of cancer caused by exposure to asbestos. It's under Food and Drug Administration consideration as a treatment for lung cancer, a much more common ailment.

SECOND CHANCES

See a chart detailing Lilly drugs that arose from earlier failures.

Alimta's resurrection helps illustrate why Lilly is coming out with a flood of new medicines even as many of its competitors struggle to replace blockbuster drugs coming off patent. Lilly has long had a culture that looks at failure as an inevitable part of discovery and encourages scientists to take risks. If a new drug doesn't work out for its intended use, Lilly scientists are taught to look for new uses for a drug. In the early 1990s, W. Leigh Thompson, Lilly's chief scientific officer, initiated "failure parties" to commemorate excellent scientific work, done efficiently, that nevertheless resulted in failure.

Other drug companies are also seeing the importance of tolerating -- and learning from -- failure, a valuable strategy since about 90% of experimental drugs in the industry fail. For example, **Pfizer** Inc. originally developed the blockbuster impotence drug Viagra to treat angina, or severe heart pain.

Lilly has taken this approach to unusual lengths. It assigns someone -- often a team of doctors and scientists -- to retrospectively analyze every compound that has failed at any point in human clinical trials. Blair Sheppard, a management professor at Duke University who's done consulting work for Lilly and other pharmaceutical companies, says that Lilly developed "a formalized and thoughtful process in which it reviewed failures more honestly, more deeply and started the process sooner than anyone else."


Paolo Paoletti

Many Lilly drugs have risen from failure. Evista, now a $1 billion-a-year drug for osteoporosis, was a failed contraceptive. Strattera, a hot-selling drug for attention deficit/hyperactivity disorder, bombed out as an antidepressant. A promising cardiovascular drug called a PPAR-alpha-agonist, which lowers fat levels in the blood, arose from a failed asthma project. The antidepressant Cymbalta, for which Wall Street has high hopes, failed in its original trials until a Lilly scientist upped the dosage.

In an industry where getting two new drugs approved by the FDA is considered a banner year, Lilly already has six approved so far in 2003 and 2004 combined and hopes to get another two approved by year-end. And it has another 11 promising drugs in the middle- to late-stage pipeline.

Still, Lilly's share price has been in the doldrums because of other factors. In August 2001, the company's patent exclusivity on the antidepressant Prozac expired and most of the $2.6 billion in revenue from the drug quickly evaporated. More recently, Lilly was hurt badly when the FDA blocked approval of some new drugs for more than a year because of quality and record-keeping problems at two Indianapolis Lilly plants. In addition, some of Lilly's drugs, including Evista, the osteoporosis medicine, have run into tougher-than-expected competition. Just last week, Smith Barney lowered its profit outlook for the drug maker.

Lilly sales rose to $12.58 billion in 2003 from $10 billion in 1999, including a 14% jump in 2003 from 2002. But earnings per share slipped some over the same period, to $2.37 a share in 2003 from $2.46 a share in 1999. Without one-time gains and charges, earnings per share rose to $2.58 in 2003 from $2.28 in 1999.

The pipeline of new drugs has helped keep Lilly's price-to-earnings ratio consistently at the high-end of the drug industry. Lilly traded yesterday in the New York Stock Exchange at $72.25 a share, down $1.15 for the day.

The story of Alimta's salvation begins in 1992 with an out-and-out failure: a new drug called lomotrexol that made patients ill in its trials. For the post-mortem analysis, Lilly tapped Dr. Nyikiza, the Rwandan mathematician, who specialized in the failure analysis of complex systems -- a branch of math called stochastic processes.


Clet Nyikiza

Dr. Nyikiza, who grew up on a peanut and banana farm, developed this interest on boyhood hunting trips in Rwanda and neighboring Tanzania. From his grandfather, he learned all about the myriad factors that lead to a successful hunt or a disastrous one. Among them were wind speed and direction, grass conditions and the presence of predators. "Don't hunt a lone antelope," his grandfather cautioned, because lone antelopes tend to attract lone lions.

Dr. Nyikiza ended up in a gifted program at a Rwandan high school run by Jesuit missionaries. After getting a bachelor's degree in statistics and applied economics in Rwanda, Dr. Nyikiza worked on a project funded by the U.S. Agency for International Development, doing population analysis for the government of Rwanda. Then the U.S. agency and the Rwandan government sent him to Indiana University where he got a doctorate in mathematics.

Before joining the drug industry, Dr. Nyikiza analyzed failures in everything from aircraft engines to truck transmissions. In a job for the Swiss National Science Foundation, he looked at what makes certain paper money prone to counterfeiting.

In 1990, a research executive from Syntex Corp., since acquired by Roche Holding AG, sat next to him on a flight from Zurich to Chicago and concluded Dr. Nyikiza's expertise would be useful in an industry where almost everything fails. He moved to Lilly from Syntex in 1993.

At the time, Lilly was trying to learn from the failure of lomotrexol. Like Alimta, lomotrexol had induced neutropenia, a white-blood-cell disease causing immune deficiency, severe diarrhea and sometimes death. Lilly asked Dr. Nyikiza to find out why the drug failed. He and three colleagues spent most of a year on the effort, analyzing blood samples and traveling to question world experts. They settled on 64 blood markers that might predict which patients would be afflicted by the devastating side effect. Finally, one called homocysteine emerged. Every patient sickened by lomotrexol had high levels of homocysteine, a common amino acid.

Homocysteine is produced when human cells lack the vitamin folic acid. The conclusion from Dr. Nyikiza's team -- that the patients who died had a deficiency in folic acid -- would become crucial during the crisis in the Alimta mesothelioma study.

Mesothelioma is a lethal cancer developing in the membranes surrounding the lungs of shipyard personnel, construction workers and others exposed to asbestos. In very early tests, Alimta shrank mesothelioma tumors in five of 12 patients -- a startling success. By 1999, Lilly undertook clinical studies in 90 people with mesothelioma, mostly in Europe.

Then suddenly, things went awry. That summer, the first death from neutropenia took place. Another occurred in the fall. Neutropenia is a white-blood cell deficiency that can lead to dangerous infections in which the bowel cells die. By November, a third death had occurred.

Dr. Paoletti decided Alimta just seemed too unpredictable. He halted the trial, notifying U.S. and European regulators and more than 200 clinical investigators. To Dr. Nyikiza, though, the symptoms seemed to resemble those of the lomotrexol patients seven years earlier. He persuaded Dr. Paoletti that they should, once again, seek out leading authorities on the class of drug, called antifolates, that includes lomotrexol and Alimta. Among other things, these drugs deprive cancer cells of folic acid needed to proliferate. Dr. Paoletti in turn went to Lilly senior executives, pleading for and winning two weeks in which Alimta might be saved. The Alimta team starting pulling all-nighters to meet the deadline, analyzing medical records and blood samples.

Once again, it emerged that patients with the most severe side effects were those with high homocysteine -- and low folic acid -- in their blood. The researchers decided on a disarmingly simple solution: Give all patients folic acid pills in addition to their dose of Alimta. "When I first heard about it, I thought it was crazy," says Bruce A. Chabner, clinical director of the Massachusetts General Hospital Cancer Center.

Lilly resumed the trial, with folic acid supplements. One concern was that the vitamin pills might cure toxicity, yet destroy the drug's effectiveness. As the trial resumed, so did the tension. A week passed, and no severe side effects arose. Two weeks turned into a month, then several months. The severe toxic side effect had almost disappeared.

Alimta's effectiveness hadn't been lessened at all. It lengthened by several months the average survival time of patients with mesothelioma compared with patients taking cisplatin, another type of chemotherapy used for this disease.

Mesothelioma is a fairly rare cancer, with about 15,000 new cases world-wide each year. Lilly has also been testing Alimta against nonsmall-cell lung cancer, the most common type of lung cancer, the No. 1 killer among cancers. Lilly has submitted data to the FDA, for possible further approval of Alimta, showing that Alimta lengthens survival as much as Taxotere, a standard chemotherapy treatment for nonsmall-cell lung cancer. But Lilly's research shows that Alimta has a significantly better toxicity profile -- no hair loss, and only 5% of patients had any neutropenia, compared with 40% of patients on Taxotere.

"Another company might have given up on Alimta," says Dr. Chabner.

Other promising new Lilly products have come out of earlier failures, including the one-time antidepressant that flopped. When some Harvard psychiatrists wanted to try another Lilly drug to treat attention deficit/hyperactivity disorder, a Lilly doctor named John Heiligenstein got them to try Strattera instead. Dr. Heiligenstein knew that Strattera worked on the chemical norepinephrine and that this brain chemical seemed to play a role in the condition. Strattera, competing with stimulants such as Ritalin and Adderall, has achieved sales of $511 million since its January 2003 launch.

Some cardiovascular drugs in Lilly's pipeline have their origins in a failed asthma drug program. Patrick I. Eacho, now Lilly's head of atherosclerosis drug discovery, was in the company toxicology department in 1983. He terminated the asthma project because the drug stimulated receptor cells in the liver and elsewhere, resulting in lowered fat levels in the blood; scientists didn't understand why this effect was occurring.

Dr. Eacho and colleagues suspected the lower fat levels could be a good thing. He grew intrigued and kept studying the phenomenon even though there was no evidence it would lead to a marketable drug. His research was paid for by a Lilly "blue-sky fund" that pays for projects that don't appear to make immediate commercial sense. Lilly scientists generally are encouraged to spend 10% to 20% of their time on such blue-sky projects. Dr. Eacho's research now has led in part to the PPAR-alpha drug that's in trials for vascular disease because of its fat-lowering tendencies. There are also seven other related drugs under study at Lilly for vascular disease and diabetes.

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Second Chances

Lilly drugs arising from earlier failures

Drug	Status	History
Strattera	Marketed for ADHD treatment	Failed in depression studies
Evista	Marketed for osteoporosis	Failed for birth control
Alimta	Marketed for mesothelioma	Trial had been stopped
Cymbalta	Reviewed by FDA for depression	Failed at lower dose
MEPM	In trials for cancer	Failed for psoriasis
Gemzar	Marketed for cancer	Failed as antiviral agent
PPAR-alpha agonist	In trials for cardiovascular disease	Failed asthma trial
Ghrelin blocker	In preclinical trials for obesity	Failed frailty study

Sources: Eli Lilly; WSJ research

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