Answers That Matter.

Eli Lilly and Company
Contact: Judy Kay Moore
Global Marketing
Communications
Phone 317 277 6265

Discovery, Reality and Hope: A Brief History of Alimta®

The average person's understanding of drug research and discovery is often limited to reading or hearing about news of a successful R&D outcome -- a new medication that treats a disease. Beyond the headlines, however, there often lies a deeper and equally compelling story about teams of scientists and clinicians working together toward a common goal – developing a breakthrough medicine where none has existed before or for which an existing medicine leaves much to be desired.

Drug discovery is a slow and laborious process, but it is often punctuated by key turning points; sometimes, it may be a moment of new understanding that leads researchers in a previously unexplored direction. And sometimes, scientists may arrive at a solution by pure serendipity. Whatever the route to discovery, the story of the journey can be as exciting – and as filled with human drama – as any "reality" show that has ever been developed for television.

The years of laboratory and clinical research that led to the introduction of Alimta® is a story of perseverance, joy, disappointment, anxiety, hope and, ultimately, significant accomplishment. It is also a lesson in cooperation between a world-renowned academic research institution and an innovative pharmaceutical company with the expertise, resources and vision to transform a promising molecule into the world's first treatment for malignant pleural mesothelioma, a devastating cancer of the lining of the lungs.

Where it Started

The development of the molecule that became Alimta was part of a larger collaboration that spanned many years and largely involved a team at Princeton University led by Edward C. Taylor, Ph.D, a distinguished professor and organic chemist (now retired), and a team of researchers and physicians at Eli Lilly and Company of Indianapolis, Ind.

Dr. Taylor's research focused on unlocking the therapeutic potential of inhibitors of folic acid. Many people associate folic acid with preventing birth defects of the brain and spinal cord, but this compound is also essential to building DNA and is thus required to sustain all forms of life. This latter understanding ushered in a new era in cancer research that began during the late 1940's. Experts theorized that drugs that interfere with folic acid might be able to inhibit the

spread of cancer by disrupting the ability of tumors to process folates (folic acid and its many forms or derivatives) and synthesize DNA, which is necessary for cell division and growth.

Indeed, the introduction of the anti-folate drug methotrexate led to remissions in childhood leukemia. Unfortunately, when methotrexate was given by itself, the drug was associated with serious side effects that could be life threatening. Dr. Taylor committed himself to finding compounds that would disrupt the processing of folic acid only in cancer cells, thereby leaving the healthy ones alone.

In 1985, after conducting chemical investigations on hundreds of compounds, Dr. Taylor and his team believed they had a promising candidate, a molecule called DDATHF. "At that point, it was clear we couldn't carry out much further work without collaboration," said Dr. Taylor. "As a synthetic organic chemist in academia, I'm neither trained nor equipped to investigate the biological properties and medical potential of the compounds we design and synthesize. I turned to Lilly for that," a company Taylor had consulted with for many years. As a result, a formal Lilly-Princeton collaborative research project emerged.

An Intriguing Molecule

The Lilly bench scientists-- led by Homer Pearce, Ph.D., Charles Barnett, Ph.D. (now retired), the late Gerry Grindey, Ph.D., and Joe Shih, Ph.D. – immediately went to work with their Princeton partners. "We wanted to explore the possibilities for drug discovery stemming from Professor Taylor's original discovery of DDATHF," said Dr. Pearce, then a chemistry group leader and now a Lilly research fellow. "At the time we didn't know how many drugs we would ultimately develop, but we believed there was a wealth of opportunity to pursue given the insight that we had with DDATHF."

By 1994, three potential drugs had emerged from the Lilly-Princeton partnership. One of these was a significant chemical departure from DDATHF that had also been conceived and synthesized at Princeton by Dr. Taylor. The Lilly scientists conducted intensive studies of the physical, chemical and pharmacological characteristics of this new substance, the results of which led to the initiation of patient-based trials. This compound would ultimately become Alimta.

"Alimta stood out because of a unique and unexpected set of biochemical properties," said Dr. Shih, now a Lilly research fellow. By closely examining the active metabolites (polyglutamates) of Alimta in isolated biochemical enzyme assays and cellular systems, Dr. Shih and his team found that Alimta could simultaneously target and block at least three key folate-requiring enzymes (thymidylate synthetase; dihydrofolate reductase; and glycinamide ribonucleotide formyltransferase) that cancer cells need for cell division and tumor growth. The Lilly-Princeton collaborators theorized that this multi-targeted action was the reason for Alimta's potentially promising anti-tumor activity.

A Setback and a Solution

One of the first clinical trials of Alimta involved evaluating this agent's safety and efficacy in combination with a commonly-used oncology drug known as cisplatin. Among the cancer patients enrolled in this trial were 11 with malignant pleural mesothelioma, a cancer often associ-

ated with exposure to asbestos. "About half of these patients responded to Alimta, and you can imagine how exciting that was considering that mesothelioma is such a lethal disease," said Paolo Paoletti, M.D., who was then in charge of Alimta's clinical development and is now Lilly's vice president of oncology clinical research.

Based on the encouraging preliminary findings, Lilly launched a large Phase III clinical trial, where the first major hurdle in the patient care setting emerged. Clinical investigators reported early on that a significant number of patients receiving Alimta were experiencing hematological and gastrointestinal side effects (including low white blood cell counts and diarrhea) that were very severe and potentially life-threatening. "It was a very intense time," said Dr. Paoletti, "because, by then, the drug's clinical benefits were abundantly clear. Alimta was too important a compound to give up on, and we became tireless in our efforts to find the cause and then the solution."

Among the experts involved in this complex problem solving was Clet Niyikiza, Ph.D., a statistician and mathematician from Lilly. Dr. Niyikiza scoured the existing clinical data for similarities and "behavior" patterns among anti-folates. After assembling numerous parameters with the help of experts from around the world (especially Hilary Calvert, M.D., of New Castle General Hospital in England, and Robert H. Allen, M.D., of the University of Colorado Health Sciences) and conducting what is known as a multivariate analysis, Dr. Niyikiza made a critical discovery: the patients experiencing the most severe side effects to Alimta were the same ones who had elevated levels of two blood substances: homocysteine and methylmalonic acid.

"That was very exciting because now, for the first time, we could identify beforehand those patients with the highest risk of a toxic response," said Dr. Niyikiza. More importantly, these patients could quickly and easily be treated because elevated levels of homocysteine and methylmalonic acid are markers for folic acid and/or vitamin B12 deficiency. With an insufficient amount of folic acid and B12 in the body, Alimta was having an effect on non-cancerous as well as cancerous cells. That in turn led to more toxic effects for the patient.

Everyone agreed that supplementing Alimta with folic acid and vitamin B12 made sense from a safety standpoint. But would supplementation affect Alimta's efficacy? Dr. Paoletti reasoned that if patents could not safely tolerate Alimta, then efficacy would not make much of a difference. And so, in consultation with independent experts, he mandated that the study protocol be amended to require that all patients receive supplements of folic acid and vitamin B12.

Results showed that supplementation ameliorated toxicity (i.e., CTC Grade 3/4 neutropenia decreased from 41.4% to 23.2%)[1] without reducing efficacy. "The simple decision and the risk taking of the low dietary dose folic acid and B12 supplementation from Lilly scientists was the key turning point for the development of Alimta," said Paul Bunn, M.D., a professor of medicine at the University of Colorado Health Sciences and former president of the American Society of Clinical Oncology.

[1] Vogelzang NJ, Rusthoven JJ, Symanowski J, et al: Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J Clin Oncol 21: 2636-2644, 2003.

Added Dr. Allen, whose expertise at the University of Colorado is in vitamin B12 and folate deficiencies: "This observation (of homocysteine and methylmalonic acid as markers for toxicity to Alimta) probably has applications for other anti-folates and other chemotherapeutic agents that have hematological and gastrointestinal toxicities."

Compassionate Use Program

The final results of the Phase III trial were presented in a plenary session at the 2002 annual meeting of the American Society of Clinical Oncology. The principal investigator of the Phase III study, Nicholas Vogelzang, M.D., professor of medicine at the University of Chicago Cancer Research Center, reported that "Alimta, in combination with cisplatin, for the first time demonstrates the prolongation of survival in patients with a very devastating and difficult to treat cancer."

A short time later, Lilly began the process of submitting a New Drug Application to the U.S. Food and Drug Administration (FDA) for the use of Alimta, with cisplatin, in the treatment of malignant pleural mesothelioma. Meanwhile, because no satisfactory treatment alternatives were available for patients with this inevitably fatal disease, Lilly, in cooperation with the FDA, provided Alimta free of charge to medically eligible patients. More than 1,000 patients in the U.S. were treated under this expanded access program; similar programs were set up outside of the U.S. as well.

Alimta Now and Beyond

Alimta was approved by the FDA on Feb. 5, 2004 for use with cisplatin in the treatment of malignant pleural mesothelioma. It is the first approved treatment for a disease that was once considered hopeless**.**

The story of Alimta does not end with mesothelioma. Ongoing clinical trials are suggesting that Alimta may have benefit in a wide range of tumors. Lilly is evaluating the drug's effectiveness in lung, pancreas, colon and breast cancers.

Alimta was literally decades in the making. It began with one man's inspiration and dedication, and then came fully to life through the efforts of a team comprising some of the world's finest researchers from academia and industry. The end result is a major advance in the treatment of cancer. "In drug development, many are called, but few are chosen," said Dr. Pearce of Lilly. "Every successful drug has to pass through a gauntlet of issues, and Alimta was certainly no exception. It's really a remarkable development."

Alimta® (pemetrexed), Lilly