Partnership Yields Revolutionary Cancer Drug

Eli Lilly and Co.

Princeton University

The brimstone butterfly adorns the business cards of Edward C. Taylor, Ph.D. A fitting homage to his life's work, the butterfly symbolizes Taylor's inspiration to develop the anticancer drug Alimta (pemetrexed).

Alimta is currently approved in the United States to treat recurrent, or second-line, non-small cell lung cancer, the most common form of lung cancer. It is also approved in combination with another drug called cisplatin for the treatment of malignant pleural mesothelioma, a cancer often associated with exposure to asbestos.

The development of Alimta dates back to 1946 when Taylor, now a retired distinguished professor and organic chemist at Princeton University in Princeton, N.J., entered graduate school and was looking for a thesis topic. He came across an article describing the discovery of a compound found in human liver that, bizarrely, possessed a structure of which a portion was identical to the structure of pigments in the wings of butterflies. Taylor's curiosity about this unexpected discovery eventually led him to make a major advancement in the fight against cancer.

The compound from the liver was later determined to be folic acid, a vitamin that plays an essential role in making cell division possible. "It was found that folic acid is essential for all forms of life," says Taylor.

It was then he saw the potential for an anticancer agent. Like all cells, tumor cells need folic acid, or folates, to divide and multiply, allowing the tumor to grow. “If you could inhibit it, you would have a good way of arresting the growth of tumors,” he says. “The challenge was to inhibit the growth of the tumor and not healthy human cells. People tried for years, but no one succeeded.”

Trust is Essential to Success

In the 1970s Taylor resumed work on an antifolic agent that might selectively target tumor cells. After years of work, he came up with a promising compound called Dideazatetrahydrolic acid (DDATHF). But he knew his work could only be carried so far at Princeton, and he needed help. “I needed facilities and expertise that Princeton didn’t have,” he says. “If I wanted this compound thoroughly looked at, who would do it?”

Taylor enlisted the help of Eli Lilly and Co. in Indianapolis. At the time, Taylor had already been consulting with Lilly for years, and had established close relationships with the company, so in the early 1980s he sent DDATHF to them.

> *The compound turned out to be one of the most effective antitumor agents that Eli Lilly had seen.*
>
> Edward C. Taylor

Knowing they might be on the brink of a major breakthrough, Taylor (through Princeton) and Lilly in the mid-1980s set up a collaborative effort to explore the potential of what appeared to be an extremely promising new area of cancer research. During the following four years, approximately 800 new drug candidates were synthesized and evaluated through this collaboration. DDATHF, the original lead, eventually failed clinically because of toxicity, but another compound finally emerged that proved to be the compound of choice for development, and that compound became the drug named Alimta®.

This was also a pioneering time for technology transfer at Princeton.

By this time, Princeton had a well organized technology transfer arm, but at the time of the project’s initiation, the partnership was forged out of mutual trust.

The Princeton-Lilly joint research project that culminated in the discovery of Alimta“was the first big collaboration that Princeton had undertaken, and it proved to be a major success because there was complete trust and integrity on both sides,” according to Taylor.

Partnership, Perseverance Overcome Obstacles

As a pharmaceutical company, Lilly focused on understanding how the compounds behaved in humans. “Our role was to conduct evaluations and animal studies to determine which compounds were candidates for clinical trial,” says Joe Shih, Ph.D., a distinguished research fellow at Lilly.

A key part of Lilly’s role was to understand the compounds’ toxicity in humans and how to mitigate it. That turned out to be a crucial element.

Early clinical trials with Alimta® were plagued by unpredictable toxicity issues. Although the majority of patients in the trials responded well, some experienced serious, life threatening side effects. While the drug’s clinical benefits were clear, these problems threatened to end the project. That’s when another member of Lilly’s team saved the project.

Clet Niyikiza, Ph.D., at the time a statistician and mathematician with Lilly, stepped forward to solve the problem. “He

said, 'Give me three weeks,'" recalls Taylor, "and he would solve the problem."

Scouring the clinical data to find the common thread among patients who experienced the side effects, Niyikiza, determined that the patients who experienced side effects had a pre-existing folic acid deficiency. Researchers had not anticipated this problem, since they were attempting to inhibit folic acid activity. But Niyikiza's work led to changing the protocol to co-administering folic acid and vitamin B-12 to patients, and this amended treatment saved the drug.

"It tipped the balance critically," says Taylor.

"Alimta is a single compound that targets the utilization of many folate based processes essential for the growth of tumor cells," Taylor explains. "Other cancer drugs usually can target only one specific biological process, making it attractive for patients to receive a 'cocktail' of several drugs. But this strategy also means that the patient is subject to the combined toxicities of each component of this cocktail.

"Since Alimta is a single drug that has multiple targets, it is harder for tumors to develop resistance to it," he continues. "That is part of the reason Alimta is one of the least toxic cancer drugs known."

Since its approval in the U.S., Alimta has gone on to be approved by regulatory authorities in more than 85 countries. Unlike most chemotherapy treatments for cancer, Alimta is easy to administer, requiring only a 10-minute infusion every three weeks.

Collaboration is the Cornerstone

Alimta's development is the result of decades of work and partnership between Taylor and the research team at Lilly, without which the drug would have never made it to initial trials.

"The attrition rate in drug development is enormous," says Taylor, citing that only one out of every 5,000 to 10,000 potential candidates ever becomes a drug. "It's a discouraging and extraordinarily expensive process."

He added that Lilly's agreement to collaborate with Princeton, and to help develop the drug, demonstrated Lilly's trust in Taylor and in the promise the early compounds held.

From Taylor's perspective, the partnership with Lilly and its evaluations of drug candidates, gave him, as well as his Lilly colleagues, the feedback needed to continue research in the direction that eventually led to the discovery of Alimta.

"In drug development, you have to evaluate constantly what you are making so you don't go in the wrong direction," he explains. "Such feedback is not available in an organic synthesis lab."

It was the willingness of Lilly to perform extensive biological testing that made Alimta possible.

Shih views the development of Alimta as a model of how a pharmaceutical company and a university can work together.

"The science is being conducted all over the world at top research institutions like Princeton," he says. "Big pharmaceutical companies don't have the resources to conduct research at that scale. These institutions help us to identify interesting discoveries that can lead to new drugs."

Lilly is working with many institutions worldwide in the research and development of drugs for oncology, diabetes and neuroscience.

Summing up the importance of partnerships between research institutions and the private sector, Shih comments, “Collaboration is a cornerstone of this process.”

Taylor says Lilly’s help was invaluable. “Without this kind of collaboration, Alimta would still be a curious compound sitting on a shelf in my lab.”

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