Drug's critical phase

Firm's cancer pill must show results next month in order to have a chance at being OKd for sale

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Lee Arnold has two grown sons and a 9-year-old daughter, but his fourth "child" is still just a toddler.

Arnold, a medicinal chemist with a focus in oncology, has worked with a molecule now known as Tarceva for more than a decade. He studied it in the lab, helped to secure its patent and worked tirelessly with it through its early stages.

Now he's the vice president of research for OSI Pharmaceuticals Inc., the biotechnology firm behind the drug, and is watching as Tarceva approaches a key phase in its development: the results of its late-stage clinical trials against lung cancer, which are due out next month.

If all goes as planned, Tarceva could be OSI's first blockbuster product, turning its losses into profits that could top a billion dollars and putting the still-small company on the pharmaceutical map.

It also might be a complete flop.

"It's such a roller-coaster ride," Arnold said of the path of a prospective new drug. "You don't want to get too high on the successes because then you have farther to fall. But you have your fingers crossed."

That's how it often goes in the drug industry. While the research may be carefully planned and methodically done, the process of actually bringing a drug to market is long and sometimes more random, with many unforeseen twists and turns.

In that respect, Tarceva, a homegrown drug from a tiny Long Island company, is typical. It offers a window into the complicated drug development business of finding potential cancer drugs, testing them, getting them approved, and finally offering them for sale.

Like so many others, Tarceva has taken a long road since the initial compound was first discovered in the 1990s by a relatively young company then known as Oncogene Sciences. It traded hands twice over the years, and has seen other drugs pass it by in the race toward the marketplace. And like many drugs, there's a great deal of money at stake - more than half a billion dollars invested so far on a treatment that, by one reckoning, could have sales of up to $700 million a year.

Some success seen

Will the bet pay off? It's too soon to say. But in the lab and in the clinic, Tarceva has seen some success, surprising scientists who never thought it would have the impact it did.

In the early 1990s, Oncogene, originally out of Cold Spring Harbor Laboratory, was primarily a screening company that studied various molecules and compounds with medical potential. It then passed them on to its partners - far larger drug companies with much greater research capabilities. Those drug giants often had libraries containing thousands of compounds, which they and their partners like Oncogene would screen.

Oncogene was looking for one that blocked certain targets in live cells that help cancer to grow and spread. One such target was the epidermal growth factor receptor, a protein found on the surface of some cells, and at particularly high levels in cancer cells. Out of literally hundreds of thousands of compounds that were tested, Tarceva, then a no-name molecule, hit its mark.

But that was as far as Oncogene could go, at that point. Oncogene passed the compound back to its partner, Pfizer Inc., where Arnold was a chemist in the early 1990s.

"If it wasn't for that, the whole program wouldn't have gotten off the ground," Arnold said.

Race against time

At the time, researchers from Pfizer, including Arnold, were racing against the clock and fellow drugmakers to get a patent for an anti-cancer product. The goal, of course, is to be first to market. To do so, Pfizer needed to secure a patent and stay ahead throughout the developmental process.

In the early stages of research around Tarceva and other molecules that inhibited cancer cell growth, Arnold and his team of researchers were "scooped" by two other companies working on very similar molecules, with very similar structures. Those two companies - AstraZeneca and Park Davis, a division of Warner Lambert - each secured patents before Pfizer. "I began to suspect someone was reading my garbage," Arnold recalled. "But it was a good sign that everyone converged on the same structures."

Early tests yield results

Eventually, Arnold and the other researchers came across a piece of the molecule that had not been patented - and jumped on it. This time, they were not beaten by the others.

"In this business, you need to be an eternal optimist," Arnold said of the long, grueling effort to find a successful drug. "I liken medicinal chemists to inflatable punching clowns. We keep getting knocked down, but we get back up smiling."

Early testing gave them reason to smile, as Tarceva, then known as OSI-774, blocked tumor function and growth in mice. By 1995, the drug was ready to go into more significant development stages. Even as the first patients began taking OSI-774 in Phase I trials, researchers knew they were on to something.

"I think I gave the first pill to the first patient," recalled Dr. Manuel Hidalgo, at Johns Hopkins Kimmel Cancer Center. "We all got very excited when the first responses were seen."

But those early trials quickly led Pfizer to put a yearlong halt to its development of Tarceva, after it first encountered one of the drug's major side effects: rash. The rash, an unknown side effect in an

unprecedented drug, made Pfizer executives and scientists nervous, Arnold recalled.

"This was their first oncology clinical drug and they were very nervous about any side effects," he noted. "They weren't used to dealing with these kinds of toxicities."

Falling behind

That put Tarceva behind in the race to usher targeted therapies through the clinical trial process, allowing AstraZeneca and its drug, Iressa, to catch up and pull ahead. It may also have helped assure Tarceva's ultimate success by putting it back in the hands of OSI.

By this time, Oncogene Sciences itself was floundering. It lacked the capital or new technology to gain ground, it was very dependent on partnerships, and even then, it wasn't benefiting much from any of its own discoveries.

"It was a company that was dead and didn't realize it," recalled Colin Goddard, who at the time was a fast-rising star at Oncogene. "We were the jack of all trades and master of basically none."

Goddard was an unlikely savior. He came from a working-class family outside of London, where his family lacked both a car and a television. While an undergraduate at York University in England, Goddard was a top soccer player, headed for a career in sports management.

By his own description, he was more of an athlete than a scientist, and more of a socialite than a student. "I was much more interested in sport than in my studies in college," he recalled.

Then, at age 22, Goddard lost his athletic director and good friend, Barry Blenkinsop, to brain cancer. Suddenly, the young athlete's priorities changed - and he began studying oncology, pursuing a doctorate in cancer pharmacology at the University of Aston in Birmingham.

Not what he seemed

Even then, the personable Goddard didn't strike many as someone who would eventually lead a publicly traded company toward its first major cancer drug breakthrough. "He wasn't driven in the same way he is now," said John Slack, who was then a researcher at Birmingham and Goddard's mentor, and now serves as OSI's vice president of development.

While still working in the labs and playing soccer on the side, Goddard found time to court Amanda Hansen, a medicinal chemist who came to England to study as part of a program with the National Cancer Institute. Right after he finished his degree, in the fall of 1985, they were married. Shortly thereafter, they headed to the United States to work at the National Cancer Institute in Maryland.

Three years later, a little company on Long Island called Oncogene Sciences caught his eye. "It was a small, fairly dynamic, young biotech company," Goddard said. But even with such a positive first impression, Goddard never planned to stay. "I'm a pretty eclectic personality. I could have never envisioned a career in one particular place."

Nonetheless, the young scientist quickly absorbed far more than his one corner of the company, understanding its limitations and quietly analyzing Oncogene's needs and what it could be. "It was apparent to me that I got it, and all the other people didn't," Goddard said.

He quickly rose through the ranks, taking on executive positions. Soon, he was being groomed for the

top slot, and in 1998, became chief executive.

At the time, the company was a $2 stock with no capital to speak of, Goddard said. "We were in a bigger hole than a lot of people realized."

So, Goddard set out to raise money and turn the company from one based on old technology to one based on new drugs.

Changing the company

He also set out to change the culture. He began turning the company on its head, hoping to transform OSI into an oncology franchise. "When I took over, people were expecting more of the same," Goddard said. "It was a bit of a shock."

Employees acknowledge that Goddard's energy and charisma were daunting and overwhelming to some, while reassuring and invigorating to others. "Sometimes, you need to tell him, 'You're going a little too fast. You need to slow down,'" said OSI vice president Pedro Santabarbara.

While most everyone attributes much of OSI's success to Goddard's perseverance, it might never have happened without Pfizer's decision to take over Warner Lambert in 1999. The merger had nothing to do with Oncogene, but the deal caught the eye of the Federal Trade Commission, which is charged with breaking up monopolies. It told Pfizer it would have to divest one of two cancer products - Tarceva or Warner Lambert's own very similar drug.

Pfizer didn't want to delay the deal, and getting rid of Tarceva was its easy way out. Goddard was interested and met with FTC representatives during the whole process to regain the rights to Tarceva. Pfizer officials weren't available to comment, but they were apparently so anxious to do the merger - that they gave it back to OSI in June 2000 without asking for dime in return. It was a savvy business deal, and one of Goddard's greatest moments, industry watchers said.

"It's more than plain luck, that's for sure," said biotech analyst David Bouchey, with C.E. Unterberg Tobin in Colorado. "He engineered it. He had to be very active with the regulatory agencies. ... It was Colin behind the scenes."

Missteps along the way

Whether luck or skill, it was a watershed event in the history of the small company. "It was an incredible windfall for OSI, which pretty much changed their fate," said scientist Arnold, who was by now watching from the sidelines, having left Pfizer in 1995.

A year later, OSI secured $430 million in financing, and Goddard began to redefine the company as one built around oncology, with Tarceva as its centerpiece. Since then, he made several acquisitions to give OSI added capabilities in research and development, regulatory affairs and sales.

To be sure, there have been missteps. There were layoffs and consolidations within the past three years. His drive is credited with building the company, but investors and analysts have faulted him for paying too much for certain pieces of his empire.

Goddard, now 44, concedes that "making a difference" is important to him - but he'll take the battle against cancer only so far. "I can't afford for it to be a crusade," he said. "I can't do my job if it is."

Meanwhile, Phase II trials on Tarceva began. There, the response was even more stunning than earlier studies had showed. At the conclusion of its Phase II non-small cell lung cancer trial in winter 2001, for instance, tumors shrank by more than 50 percent in 12.3 percent of the 57 patients tested.

"We were expecting the pill would slow growth, but not shrink the tumor," recalled Dr. Roman Perez-Soler, the chairman of the oncology department at Montefiore Medical Center, in the Bronx who now owns OSI stock. "But in the first response ... we saw rash, and we saw the tumors start shrinking. This is like the lottery!"

Deals completed

Perhaps even more significantly, OSI also inked deals with Genentech Inc. and Roche as its research and marketing partners on Tarceva's development. They have handled some of the drug's clinical trials and will have a significant part in its commercialization.

As with most drug-related partnerships, these have had their problems and there continues to be competitiveness between the firms.

"It's always difficult when you have strong, smart people to decide who's leading what," said Genentech vice president of hematology and oncology Gwen Fyfe. "We definitely have had growing pains."

Most recently, OSI and Genentech suffered a setback in summer 2003, when Tarceva failed to work in combination with chemotherapy. The results were not entirely a surprise, since the drug's main competitor, AstraZeneca's Iressa, had a similar response a year and a half ago.

The Iressa results led OSI to double the size of its other Phase III trial, which is studying the use of Tarceva alone in late-stage lung cancer patients.

"When AstraZeneca's data came in, I watched this company be very swift and very strategic," said Janna Christy-Bittel, OSI's clinical research director, who had to ramp up Tarceva's single- agent trial when Iressa's disappointing results came in. "We had to make the best of the situation."

Now, it's simply a waiting game: for trial results, for submission of an application to the Food and Drug Administration, for approval and for the first drug bottle on the shelves.

Ready to celebrate

Inside OSI, that makes for tense, yet exciting times. Executives in Melville joke about the champagne that's already on ice, while research scientists in Farmingdale, who are working on projects in far earlier stages, listen for every bit of news. But the anticipation may be highest in Boulder, Colo., where many employees are completely focused on Tarceva - from the current trial now being completed to the New Drug Application that's already being prepared.

Pedro Santabarbara, OSI's vice president of clinical research and oncology, has been through this before - yet he's still frantic. Formerly with Bristol Myers-Squibb, Santabarbara was involved in the development and approval of Taxotere, a widely used chemotherapy drug. Later, he also was involved in the approval of Campath, which treats chronic lymphocytic leukemia.

"The problem is these moments are preciously few," Santabarbara said. "But if you hit it, it's worth your career. I hit it twice. If we hit it with Tarceva, it's going to be even more of a thrill."

Back in Farmingdale, younger scientists are working on compounds far newer than Tarceva - and say they are not as directly impacted by the current spotlight on the drug.

"We feel a lot more removed from Tarceva," said senior associate scientist Kristen Mulvihill, a chemist. "Really, we have nothing to do with it. ... We're now trying to find the next best thing - the next Tarceva."

Looking for clues

To do that, chemists like Mulvihill sift through compound after compound, all of which are in a library of sorts. They "throw everything" at a target that might impact tumor growth. Then, they will take those compounds that have some effect and will try to modify them in the lab to make them even more potent and successful.

They're also combining many of the new compounds they study with Tarceva, hoping that a combination of more than one drug will have an even greater impact than just a single agent.

"It's like a three-legged stool," said Mulvihill. "If you take two of the legs out, it's going to fall over."

But it's an uphill process. Mulvihill and other Farmingdale scientists are quick to note that even their successful efforts could take many years to show results, while other testing might produce immediate failure. Both ends of the scale, said Mulvihill, come with their share of frustration.

"As a chemist, you never want to get too personally attached to a molecule," Arnold said. "Because there are a thousand that bite the dust."