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It's Alive! Meet One of Biotech's Zombies

Berkeley, Calif.

EVERY year, Dr. Patrick J. Scannon spends a month hacking through jungles and wading through the crocodile-filled swamps of Palau, a sprawling archipelago in the South Pacific. His hobby — his obsession, really — is to find the wrecks of American fighter planes shot down during World War II and the remains of the crews that once flew them.

"When you meet the families, who for the last 60 years haven't known what happened to their family members, and you see the closure that comes from that, it's a big deal," he said.

Dr. Scannon has brought the same determination to his day job — as founder and chief biotechnology officer at Xoma Ltd., one of the nation's oldest biotech companies. But discovering drugs has proved more difficult than uncovering plane wrecks, and in that endeavor Dr. Scannon has yet to achieve closure.

Xoma, which Dr. Scannon started in 1981, has never earned an operating profit or marketed a drug of its own. And in the quarter-century since its birth, Xoma has managed to burn through more than $700 million raised from investors and other pharmaceutical companies.

In most other industries, companies could not survive that long — and churn through piles of cash — without turning a profit. But Xoma, while perhaps an extreme case, illustrates a truism of the ever-promising biotechnology business: For every successful company like Amgen, there are many more that never make it or that take huge amounts of time and money before they do.

Other unprofitable companies, like ImmunoGen, Repligen, Immunomedics, Biopure and Cytogen, have been around roughly as

long as Xoma. OSI Pharmaceuticals, which expects to finally break into the black this year on sales of a cancer drug, has lost $1.3 billion since its inception in 1983.

“It’s sort of baffling in a way, an industry that stays afloat, sort of defying the laws of economic gravity,” said Gary P. Pisano, a Harvard Business School professor. “After 20 years or 15 years, you kind of would expect companies to be profitable or be gone. You just kind of wonder: Is this an efficient way for industry to operate?”

Mr. Pisano’s answer, put forth in a new book, “Science Business: The Promise, the Reality and the Future of Biotech,” is that the biotechnology industry is inefficient — or at least no more efficient at drug development than traditional big pharmaceutical companies. That conclusion runs contrary to popular belief that scrappy, driven biotechnology entrepreneurs can run rings around the bureaucratic drones of Big Pharma.

Biotechnology has been “one of the biggest money-losing industries in the history of mankind,” Arthur D. Levinson, chief executive of Genentech, told analysts in New York last year. He estimated that the biotech industry as a whole has lost nearly $100 billion since Genentech, the industry pioneer and one of its most successful companies, opened its doors in 1976. Only 54 of 342 publicly traded American biotech companies were profitable in 2006, according to Ernst & Young.

Most biotech enterprises face a host of daunting challenges. While they can work much more nimbly than their brethren in Big Pharma, they also lack some of the hard-won experience that large corporations bring to the drug pipeline. Moreover, biotech companies often aim at harder-to-conquer diseases and use more experimental technologies, further complicating their quests.

Part of the magic of American capitalism is, of course, that torrents of money are available to fund inspiring start-ups that may amount to nothing more than ill-conceived fliers. At the same time, torrents of good money also often chase torrents of bad money, regardless of the

flaws behind certain ideas or products. Nowhere, perhaps, do these two dynamics coexist as visibly and as starkly as they do in the biotech business.

Much of that is explained by the fact that investors are willing to keep underperforming biotech companies on life support because they are looking for the rare hit that will make them rich — or even a stock that can rise modestly. For every round of investors who get burned, there always seem to be others willing to buy in, usually at a far lower price, to fund the next project. The companies themselves can cut expenses to the bone to stay in operation, allowing them to plod on for years in a zombielike state.

“These biotechs never die,” said Samuel D. Isaly, managing partner of OrbiMed Advisors, an asset management company that invests heavily in the sector. “They just find someone else they can convince or someone else who likes Kool-Aid.”

XOMA, which went public 20 years ago, is a case study of unfulfilled promise in the biotech business. It may also be a story that ends happily, if very belatedly, with success. The company’s management and some investors, including OrbiMed, say they are convinced that what they describe as Xoma’s dogged determination is finally making headway, or at least that its stock has room to grow.

The company’s stock has nearly doubled over the last year, hitting a 52-week high on Friday of $3.30, before closing at $3.04. Still, that is well below the stock’s record high of $32 a share, reached in both 1987 and 1991.

Xoma has had one setback after another in drug development — on drugs for bacterial infections, acne and a complication of bone marrow transplants. In some cases, this was because the technology it chose, monoclonal antibodies, wasn’t quite ready for prime time. And some of the diseases it went after were hard to treat.

Some of this is endemic to the biotech sector. Profitability is elusive because it takes about seven or eight years, on average, to bring a drug to market, according to the Tufts Center for the Study of Drug Development. Moreover, only one of five drugs that are tested on humans get to market. Big drug companies can better handle these blows because they work on dozens of drugs at once and, though most fall by the wayside, a few will cross the finish line. Smaller companies like Xoma typically focus their limited resources on one or two drugs. If those fail, a whole new seven- or eight-year development cycle kicks in.

YET even Xoma's successes have been limned with problems. It did help develop Genentech's psoriasis drug, Raptiva, in exchange for a cut of any profits the product generated. But Raptiva, approved in 2003, has had disappointing sales, dashing the hopes of Xoma executives that the drug would help lead their company to profitability.

Such disappointments have been routinely blunted at Xoma by a revolving door of financial backers and emergency cost-saving measures that have given the company shots of adrenaline or helped keep it breathing: it brought in big drug companies as partners to shoulder some of its costs, it laid off employees to lower the rate at which it burned through cash, and it found investors willing to focus on the potential windfall offered by the next exciting drug.

"All along the way, we've had investors willing to believe in us," Dr. Scannon said in an interview in his office here. Soft-spoken, with a trim white beard, Dr. Scannon, 59, seems little like a jungle bushwhacker. He believes that potential investors "sense our dedication, and they also sense the scope of our capabilities."

New cadres of Xoma investors, however, have usually bought shares at lower prices than those paid by earlier investors, substantially diluting the ownership stakes of the previous shareholders. When it went public in 1986, Xoma sold its shares for $16 apiece. In 2005, it raised $60 million through a debt offering that allowed investors to convert their stakes to shares worth $1.87 each.

Xoma executives say that such patience and trust will start to pay off for its investors. At long last, they say, Xoma is poised to turn a profit in 2008. They say the company will pull off this feat without needing to have a single one of its drugs approved, because it sells access to technologies and excess manufacturing capacity it has developed over decades. The field of monoclonal antibodies — which are customized versions of the proteins the body uses to fight germs and are the company's specialty — is hot right now, and large companies like Schering-Plough and Takeda have brought Xoma aboard to help them develop such drugs.

The federal government has also enlisted Xoma in the biodefense effort, giving it two contracts worth a total of $31 million to help manufacture drugs to treat botulism. More than 45 companies, meanwhile, have licensed a Xoma technique for making proteins in bacteria. The first marketed drug made using that technology, Lucentis, Genentech's eye disease drug, was approved in June, and Xoma will be entitled to a royalty that analysts estimate at a little less than 1 percent on sales that could top $1 billion annually.

IN all, Xoma has signed deals in the last two years that could bring in $250 million over a number of years — if the drugs being developed succeed.

Rodman & Renshaw, a brokerage firm, began recommending Xoma's stock in January. "What's old is new again," the analyst Michael G. King Jr. wrote, adding, "After many fits and starts, we believe Xoma has rebuilt itself."

Many of Xoma's employees have joined the company in the last few years, and they say that there is a fresh spirit at the place. "Xoma to me is like a start-up with infrastructure," says Mary Haak-Frendscho, vice president for preclinical research, who has worked for the company for four years.

When Xoma actually was a start-up, back in 1981, it lacked the pedigree of many of the other early biotechnology companies like Genentech,

Amgen, Biogen and Chiron. Academic superstars started each of those companies. In contrast, Dr. Scannon had just finished his medical residency and, despite his doctorate in chemistry, he remained a neophyte when it came to business.

“I’d never talked to a venture capitalist,” he recalls. “I’d never talked to anyone.”

But he began pounding the pavement in 1980 in search of investors, starting with physicians he knew. At first, the going was tough, he said. But in October of that year, Genentech went public and its stock soared on its first day of trading, from $35 to as high as $86. After that, Dr. Scannon said, investors sought him out.

Early investors were intrigued by Xoma’s plans to develop monoclonal antibodies. The monoclonals were hailed at the time as potential “magic bullets,” able to home in on disease-causing molecules in the human body.

By the end of the 1980s, Xoma was in advanced testing of a drug to treat sepsis, a potentially fatal reaction by the body to bacterial infection. Pfizer had licensed the rights to market the drug. Xoma had a second drug, in a partnership with Johnson & Johnson, to treat a sometimes fatal complication of bone-marrow transplantation. In 1992, anticipating commercial success for its drugs, Xoma hired an experienced pharmaceutical executive, John L. Castello, as its chief executive.

But sepsis, a rapidly progressing disease, turned out to be a minefield, not only for Xoma but also for other companies that followed it. Within weeks of Mr. Castello’s arrival, the company learned that the Food and Drug Administration would not approve the sepsis medicine. Drugs from other companies also failed to win approval, and it became apparent that monoclonal antibodies’ day was yet to come.

Instead of a leading a commercial drug company, Mr. Castello found himself saddled with an enterprise in need of a turnaround. “When I got

here, I didn't expect to be sitting here 14 years later talking about getting profitable," says Mr. Castello, who is still at his post.

Rather than fold up shop, the company decided to keep fighting by moving on to the next project. This decision, Mr. Castello said, stemmed partly from a lesson he learned when he was a prize fighter in his youth: "It's very difficult to beat somebody if they will not stay down on the floor."

At the time, Xoma still had $80 million and a drug it had licensed from New York University that was not yet in clinical trials. So it cut its number of employees twice over the next couple of years, raised some extra money at low stock prices and concentrated on the new drug, called bactericidal/permeability-increasing protein, or BPI, a bacteria-fighting substance made by certain human white blood cells.

But in 2000, the F.D.A. told Xoma and its partner, Baxter, that the data were not good enough for approval to treat meningococcemia, a deadly bacterial infection that largely afflicts children and can kill them within hours. Many of the patients died before they even received the drug, so the trials Xoma conducted could not demonstrate that the drug, called Neuprex, increased patients' survival rates.

In 2004, a derivative of BPI failed in a midstage clinical trial as a treatment for acne. Xoma officials said they thought that the drug would have worked had it penetrated the acne lesions better. For some Xoma investors, that was the last straw; the company's stock sank, briefly falling below $1 in April 2005.

Xoma still had one hope. Genentech, which had too many drug prospects to handle on its own, had earlier asked Xoma to help develop a new psoriasis drug. Xoma was to pay 25 percent of the costs and share 25 percent of the profits associated with the drug, called Raptiva.

Regulators approved Raptiva in 2003, but by Genentech's standards, the drug has been a dud, partly because of competition and partly because of dermatologists' and insurers' reluctance to prescribe and pay for

newfangled, injected biotech drugs. Xoma, unable to shoulder its share of the marketing costs for Raptiva, renegotiated its partnership with Genentech. Now it gets a roughly 5 percent royalty on sales without having to contribute to marketing and developing costs. Sales in the first nine months of 2006 were a combined $115 million for Genentech and Serono, which sells the drug in Europe.

IT was during the dark days at Xoma that Dr. Scannon began his quest for plane wrecks in Palau, a string of more than 200 islands about 600 miles east of the Philippines that was the scene of the one of the deadlier, if lesser-known, battles toward the end of World War II.

In 1993, Dr. Scannon and his wife, Susan, a former scuba diving instructor, were invited by friends on a diving mission to find a Japanese trawler sunk during the war by former President George H.W. Bush when he was a Navy pilot. Enthused after finding it, the Scannons hired a guide to see what other wrecks they could uncover. He took them to the jungle where they found a 65-foot wing and a twisted propeller.

So began the BentProp Project, which Dr. Scannon says has found about 25 wrecks of American planes and about 12 sets of remains. Like developing a drug, searching for a lost plane can take years of methodical research and lead down numerous false paths. Dr. Scannon and a team of about a half-dozen volunteers scour military archives, prod long-dormant memories from hundreds of veterans and Palauan elders and canvass Palauan fishermen and hunters for tips. Each year's monthlong mission takes the other 11 months to plan, with Dr. Scannon working on it most nights and weekends.

While in Palau, Dr. Scannon stays in touch with Xoma by spending as much as two hours a day on e-mail. Those who have seen him in the jungle say they are impressed with his fastidiousness and knowledge.

"I learned more about my father in five minutes from Pat Scannon than I did in my whole life from the government," said Tommy Doyle, a high school football coach in Snyder, Tex., whose father, Jimmie, was lost

over Palau in 1944. In 2004, after several years of searching, Dr. Scannon and his team found the wreck of the B-24 in 70 feet of water.

Dr. Scannon says his trips to Palau do not detract from his stewardship of his company. He also says that he has not become discouraged by Xoma's setbacks and that he is not envious of more successful competitors. On the wall in his office are three paintings of space aliens and U.F.O.'s, a reminder, he said, to focus on the future and the discoveries yet to be made. Others at the company seem to be following suit. Instead of being embarrassed by its age, Xoma displayed placards from its ceilings last year celebrating its 25th year in business.

Dr. Scannon and Mr. Castello, the chief executive, do not appear to have been under much pressure from Xoma's board to improve the company's performance. Directors range in age from 59 to their late 80s, and many have been on the board for years. Dr. Scannon and W. Denman Van Ness, a venture capitalist who was an original backer of the company, have been on the board since its inception.

DR. ARTHUR KORNBERG, an emeritus professor at Stanford and board member since 1991, said he stuck with the company because he was impressed by Xoma's "capacity to do innovative and honest science." Dr. Kornberg, who won a Nobel Prize in Medicine in 1959, wrote off the lack of results, saying, "They've been unlucky in a way that their work has not resulted in a blockbuster drug, but that's a matter of chance."

It does not appear that the board has come under pressure from outside shareholders.

Dr. Greg Schmidt, a physician in Tulsa, Okla., has been an owner of Xoma stock since 1996, selling some of his stake when prices rose and buying back when prices dropped. As for management, he says, "I don't think there's any other management in the entire universe that could have kept that company alive."

Mr. Castello, who has been paid a base salary of $500,000 every year, is now 70. He seems intent on hanging on until Xoma achieves profitability and then retiring. “I have an interest in getting where we’re going and fading into the sunset,” he said.

With monoclonal antibodies now back in favor, there is some speculation that Xoma, which has a market capitalization of about only $308 million, could be acquired by a company wanting that technology. AstraZeneca and Merck have acquired other antibody companies in the last year.

Even with the prospect of profitability, the company is still in a relatively weak financial position. It probably could not afford to license a product from another company to bolster its pipeline.

It is also adding more debt to its balance sheet, having recently borrowed $35 million from Goldman Sachs. And while its new strategy of servicing other companies depends on those drugs becoming successful, companies like Allergan, Cubist and Onyx have dropped drugs they were working on with Xoma.

Moreover, mere profitability is not really the payoff that biotech companies aim for, and servicing other companies only allows Xoma to stay alive longer until it can develop its own drugs.

THE company hopes to win approval by 2009 for Neuprex as a treatment for meningococcemia in Europe under new rules granting easier approvals for certain drugs. It plans to restart trials this year on its acne drug using a new formulation that it believes is better able to penetrate acne lesions. It is in early clinical trials, in partnership with Novartis, on a cancer drug. And it hopes to begin human testing of an arthritis drug this year.

But a big hit is still likely to be several years away.

“We can’t see yet the thing that would give us the greater, the Xoma-writ-large story,” said David Webber, an analyst at First Albany who has

followed Xoma since the 1980s, and is one of just a handful of analysts who cover the stock. He rates it neutral.

Dr. Scannon himself acknowledges that he is still pursuing drugs, as he set out to do a quarter-century ago. “Our core strategy right now is financial sustainability, and we’re going to use every vehicle to achieve that,” he says. “But at heart you should understand that we have been and will remain a pharmaceutical development company.”

So Dr. Scannon still faces years of slashing through thickets — the scientific sort that Xoma confronts and the leafier, greener versions in the jungles of Palau. He departs for the South Pacific tomorrow.