Taxol's Next Stand

Jonathan Fahey Contributor

Cancer researchers are honing new chemotherapies to attack the toughest tumors—and, it is hoped, save a few lives.

Taxol is one of the most successful cancer drugs ever produced. Since 1992 it has added months to the lives of 800,000 patients with cancers of the breast, ovary or lung. It now turns in $1.5 billion a year in revenue for maker Bristol-Myers Squibb .

But Taxol, known chemically as paclitaxel, is no wonder drug. Part of a family known as taxanes, paclitaxel is blunt chemotherapy that kills healthy cells alongside tumorous ones It causes often debilitating side effects, such as nausea, low blood count and hair loss. It seems powerless against some cancers, including colon cancer. And when Taxol fails to kill off all cancerous cells, a tumor can grow back with resistant mutations, unimpeded on its morbid path.

Now, after years of fruitless efforts to deal with taxanes' shortcomings, Bristol-Myers and rival Aventis (which produces another taxane called docetaxal, under the name Taxotere) each have promising new variations. A parallel quest, pursued by Bristol-Myers and Novartis , has yielded a new class of drugs called epothilones—culled from bacteria found in dirt—that could prove to be far more effective against drug-resistant tumors.

In early clinical trials all of these new remedies have shrunk or destroyed tumors that otherwise resist taxanes. One Aventis entry could become the first chemotherapy effectiv against tumors that have traveled to the brain. If any of these compounds emerge as an effective drug—and all could falter later in larger human trials—it could let patients slow the progression of their disease for months and possibly years.

"If these drugs deliver what they promise, they are going to be big," says Renzo Cannetta Renzo Cannetta , Bristol's oncology trials chief. "We have a couple of molecules that in the clinic—not just in the lab, but in the clinic—seem to keep up with the prediction that they could be better than Taxol."

Bristol-Myers needs a big score. Taxol sales grew 40% a year since 1993, but they fell 14% in the first quarter. That's because rival Ivax introduced the first generic version last fall, after Bristol lost a bitter battle to keep it off the market. In April an appeals court rejected Bristol's claims that Ivax had infringed on its patents for a delivery system for the drug; the case is pending. (Aventis' Taxotere, with annual sales of $670 million, has patents lasting until 2011.)

Researchers at the National Cancer Institute first discovered paclitaxel's promise in 1963, but it never inspired much enthusiasm among drug companies because of a looming supply problem. Paclitaxel comes from the Pacific yew, a small, slow-growing fir found in small pockets in the Pacific Northwest. (Docetaxel comes from the European yew.) Devising a synthetic version is difficult because the chemical is exceedingly complex, marked by concentric rings of carbon, hydrogen, nitrogen and oxygen.

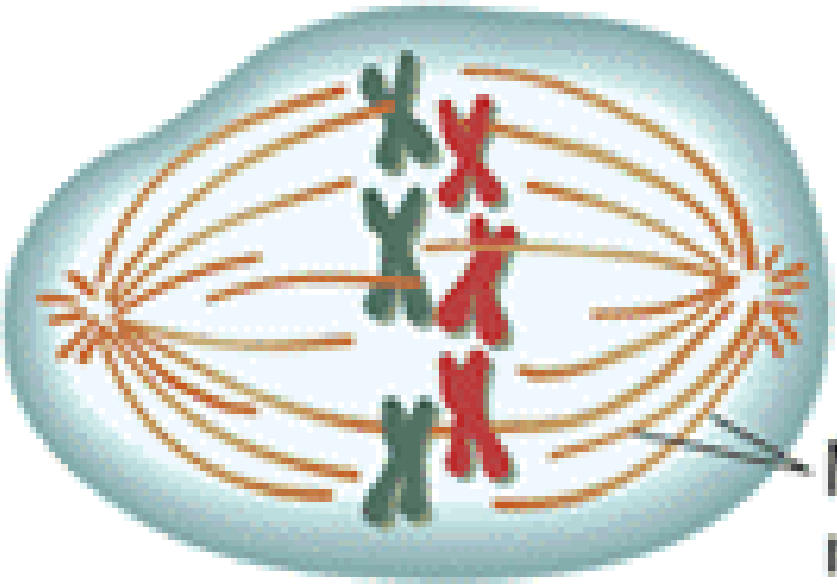
But in 1991 Bristol-Myers contracted with the National Cancer Institute to develop the drug anyway, in exchange for exclusive marketing rights that expired last year. They successfully designed a semisynthetic version by 1995, gleaning insights into the molecule that would be invaluable in building better ones later.

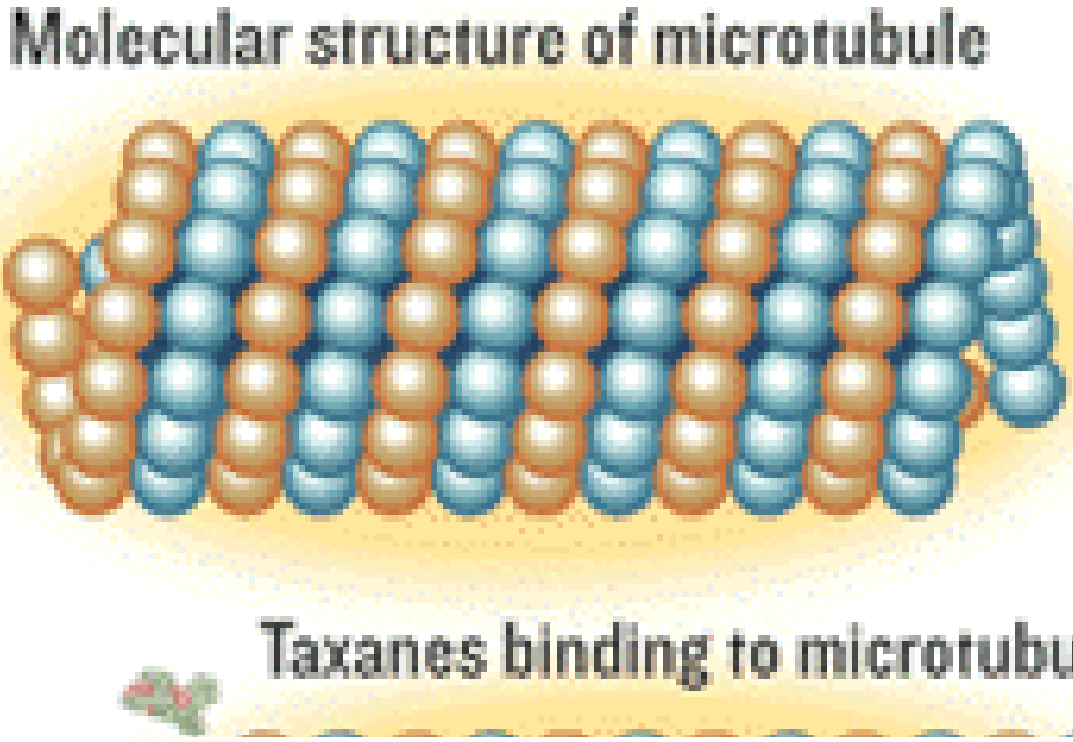
Taxanes and epothilones work by crippling cells' ability to divide. The drugs bind to rod-like structures inside the cell called microtubules that, like moving train tracks, help chromosomes arrange and split in two during cell division. Binding freezes the microtubules, halting division. The cell quickly dies. (Healthy dividing cells are killed along with tumors, leading to side effects. While most adult cells divide rarely, gastrointestinal, blood and hair-producing cells divide often. Bathed in taxanes, they die, causing nausea, low blood counts and hair loss.)

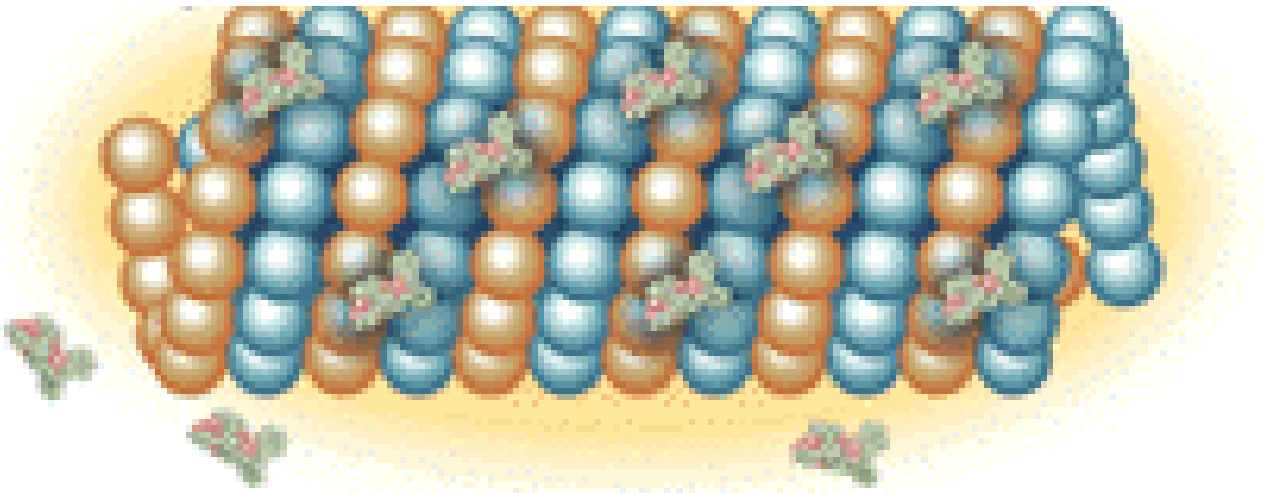
Some cancers, though, are armored against taxanes: Their cell membranes carry a multiple-drug-resistance pump that identifies taxanes as a threat and pumps them out

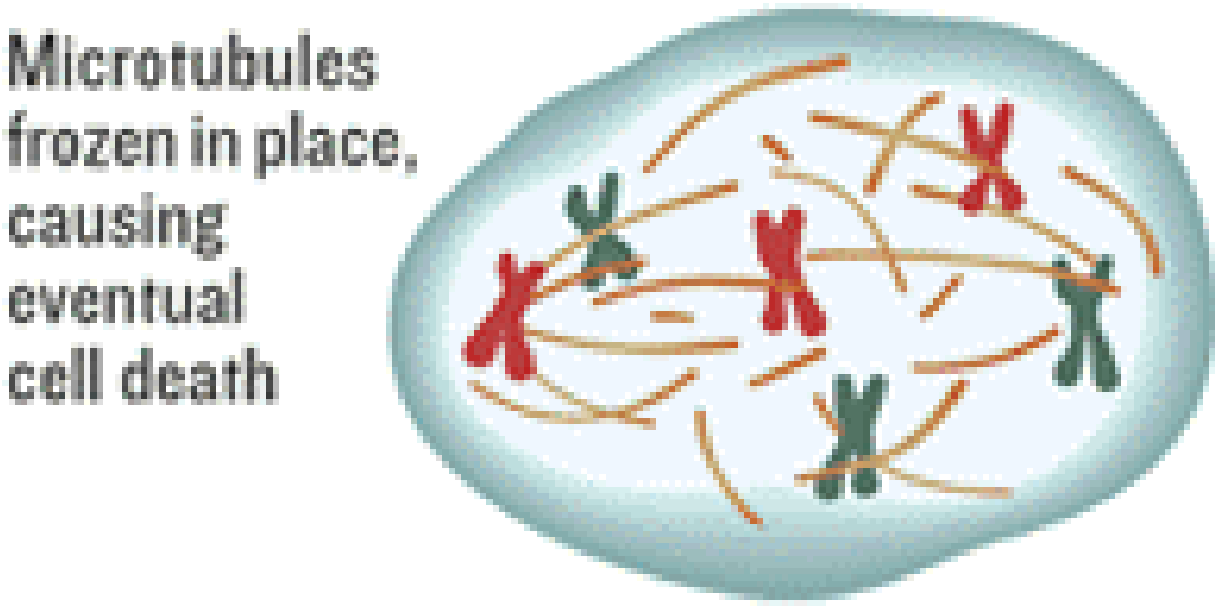
Down the Microtubes

Taxanes attack cancerous and healthy cells by crippling their ability to divide. These intricate molecules gum up the microtubules that assist in splitting chromosomes. Cells die soon after.









before they can infiltrate the cell. Even when a tumor is all but eliminated by Taxol, a few cells with mutated microtubules that are invulnerable to the drug can remain, growing into more deadly tumors.

In an attempt to elude the pesky pumps and overcome mutations, Bristol-Myers scientists engineered more than 1,200 taxane molecules. Using three-dimensional images of microtubules and taxanes, projected like a hologram into the middle of a conference room, researchers systematically manipulated the drug's chemical arms and legs to find a structure that might bind better to both normal and mutated microtubules. The more promising candidates were then cooked up and injected into a test tube holding a notoriously resistant form of ovarian cancer preserved from years ago. The surviving compounds were then tested against tumors in mice and dogs.

After six years Bristol-Myers has narrowed the hunt to two drugs, BMS184476 and BMS188797. In September 1999 Daniel Sullivan Daniel Sullivan , an oncologist at the Moffitt Cancer Center in Tampa, gave the latter chemical to a patient with kidney cancer. "Kidney cancer doesn't generally respond to much, but this patient was treated for nine months and continued to respond the entire time," he says. Tumors in her lungs shrank, large abdominal mass stopped growing and a year after ending therapy her cancer was still in remission.

Aventis' taxane, called 109881, is slightly different, with a knack for squeezing through what is known as the blood-brain barrier, a tight network of cells with drug-resistance pumps that line the capillaries in the brain. The brain is often cancer's safe haven, where tumors continue to flourish even after a blast of chemo has been injected elsewhere in the body.

Bristol-Myers and Aventis also are working separately on taxanes that can be administered orally, instead of in hour-long intravenous doses. Doctors hope small, regular oral doses can prevent the formation of capillaries that feed a tumor's growth. "We're trying to get to a point where people are dying with cancer, not of cancer," says Robert Kramer Robert Kramer , Bristol-Myers' head of oncology drug discovery.

Epothilone has the potential to be even more effective against taxane resistance because it has a different chemical structure that may let it bind better with microtubules.

Epothilone comes from a strain of myxobacteria found in dirt; researchers discovered it had a lethal ability to wipe out other microorganisms in its vicinity. In 1995, while looking for paclitaxel-like compounds, Merck was the first to show that epothilone binds to microtubules, but the company didn't pursue it.

David Spriggs David Spriggs , a clinical oncologist at Memorial Sloan-Kettering Cancer Center in New York, is testing Bristol-Myers' epothilone, called BMS247550. Spriggs gave the drug to a patient with advanced-stage abdominal cancer who wasn't responding to paclitaxel or other treatments. With epothilone, her cancer disappeared entirely after three months and remained in remission for another two months. "This is one of the more promising drugs to come along in some time,"Spriggs says. "We're going to be

testing it in melanoma, lung cancer, ovarian cancer, breast cancer. I think it's going to be better than Taxol."

Skeptics, however, question the benefit of tweaking Taxol to squeeze out more potency. Eric Rowinsky of San Antonio's Institute for Drug Development championed Taxol back in the late 1980s when many had given up on it. He is now testing one of Bristol-Myers' new taxanes, but he doubts the original can be improved upon.

"Everyone and their brother has looked at taxane analogs, and most have ended up on th shelf," he says. "I don't think that's where we should put our eggs in cancer chemotherapy. We should be looking at new targets." Rowinsky believes better results may come from developing drugs that would alter signals—often corrupted in cancerous cells—that tell cells to divide or trip their suicide mechanism. Another promising area is in learning to kill the capillaries that feed tumors.

But such major breakthroughs are years away, and patients need help today. That is why Robert Kramer, Bristol's oncology chief, focuses on the near term even though he wishes he could devote himself solely to chasing a cancer panacea. "You have patients showing up at doctors' offices every day with three to six months to live. What are you going to give them?" he says. The Taxol-tweaking and related agents "are the only ones showing some chance of increasing survival."

In cancer's grim world, where success is measured in terms of extra months spent with loved ones, chances this good are plenty to go on.

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I'm a reporter at the Associated Press in New York, where I cover energy. I left Forbes in September, 2010 after a great 10-year run. At Forbes, I covered energy, the au... **Read More**