

A Tale of Taxol

By Frank Stephenson

The tortured trail of the best-selling cancer drug in history began 40 years ago this summer. A thunder-clap of uncommon science and luck, it's a grand story still in the telling.

Arthur S. Barclay stood sweating, hands on hips, staring at his quarry—a stand of small, scraggly trees hugging the shade of their dignified cousins, tall Douglas firs reaching up into a tepid summer breeze.

It was Aug. 21, 1962. Barclay, a 32-year-old Harvard-trained botanist working for the U.S. Department of Agriculture, was winding up a four-month field mission, his first since returning to the states from a seed-gathering trip to South Africa. He'd been sent out West by his bosses in Maryland to collect samples of trees, shrubs, weeds, seeds—anything in the plant kingdom—for a government program aimed at finding natural chemicals that might be of some use as medicines. Barclay was one of only a handful of field agents doing the collecting—and the others were scattered from Canada to Capetown.

Barclay's quest on that August day 40 years ago this summer was a bag of samples pulled from a Pacific yew tree, a nondescript native of old-growth forests that despite stepped-up logging still clung to rugged parts of the Pacific Northwest. The twisted, 20-foot samples Barclay gazed at were growing on a hillside deep within the Gifford Pinchot National Forest, flanking the old lumber town of Packwood, Washington, near the foot of Mt. St. Helens.

With his companions—three botany grad students on a field trip—Barclay stripped off some leaves—needles, in this case—twigs and pieces of the tree's paper-like bark, cramming about 15 pounds of the stuff into a burlap bag, which he tossed among others already piled in his carry-all. The men soon wound their way seven miles back to camp.

Once there, Barclay and his helpers emptied their bags onto the floor of a nearby abandoned house—their impromptu staging area—labeled their collections for the day, and left them to dry. A few days later, the yew material—now less than a third of its green weight—was bundled up, labeled and finally shipped regular mail to Robert Perdue, Barclay's boss, at USDA headquarters in Maryland. Some weeks later, Perdue lined up all of Barclay's samples for routine pre-screening tests for biological activity.

Wall's Call

As Barclay dried his yew samples, a continent away in Durham, North Carolina, Monroe Wall busied himself in what passed for his organic chemistry lab. A medicinal chemist long in government service, Wall had come to North Carolina two years earlier from Philadelphia. He had worked there 20 years for the USDA's eastern regional office as part of the agency's plant screening program, eventually becoming its chief.

Wall's last nine years at USDA had been consumed by a hunt for certain types of plant steroids that could be used as starting materials for making cortisone, a government priority. One of the dozens of plants Wall's team screened was a large shade tree, *Camptotheca acuminata*, known as the "happy tree" in its native China. Wall soon became fascinated by the plant—in lab tests, its extracts showed an ability to kill cancer cells better than anything Wall had ever seen.

When it became clear that his agency wasn't interested in much beyond cortisone chemistry—and even that interest was waning—Wall took stock of things. Should he ride a moribund program to retirement or gamble on what these crazy people in North Carolina were telling him?

In July 1960, the 43-year-old Wall walked away from his senior government job and one of the best-equipped organic chemistry labs in the world to take a chance on something called the Research Triangle Park, a concept gamely struggling to take shape and rise above the rolling pinewoods connecting the university towns of Raleigh, Durham and Chapel Hill.

Temporarily (10 years, as it turned out) set up in Durham, Wall was given *carte blanche* to crank up a program in natural products chemistry from scratch. Heady stuff for a still-young chemist, even one with Wall's credentials—his reputation in natural products chemistry was already made, and his contacts in academic and government circles included some of the best minds and influential figures out there.

Not the least of these was Jonathan L. Hartwell, himself an organic chemist working for the National Cancer Institute in Bethesda, Maryland. Wall had become friends with Hartwell in the 1950s, regaling him with excited accounts of his favorite Chinese tree. By the time Wall unpacked in Durham, Hartwell was sitting as special assistant to the chief of the NCI's new Cancer Chemotherapy National Service Center, easily among the most colorful, if not successful, research programs ever spawned by the federal government.

The impetus behind the center was a theory—held by a sufficient number of bureaucrats and government scientists—that somewhere in the world—in a test tube, a beaker of crude oil, a lost ravine or even under a rock—unknown chemicals existed with wondrous powers to fight cancer. Initially, the program set out to screen primarily manmade chemicals, but in 1960 emphasis shifted to screening extracts drawn from both plants and animals, including insects.

To put a rope on the process, Hartwell sought out key phytochemists (scientists who specialize in plant chemistry) working in academe. That took some doing. At the time, few university chemists outside pharmacy schools cared much about working with natural products. Hartwell soon forged collaborations with only three campus-connected groups, at the universities of Arizona, Wisconsin (subsequently U. Virginia) and at Research Triangle with his good friend Monroe Wall. (Hartwell also sought out another friend, Werner Herz, of Florida State University. Herz had become a well-known phytochemist—at the time he may well have been the world's leading expert on the chemical nature of bitterweed—and Hartwell persuaded him to serve on the new center's site committee. Now retired from FSU's chemistry department, Herz recalls making numerous visits in the 1960s with Wall and Hartwell to check out promising research labs around the country.)

By 1960, the NCI had signed a formal agreement with the USDA aimed at making collections of plant specimens a lot easier. The ag agency had a huge network which could be tapped to supply beaucoup samples fresh from the field, and the order of the day was to mount as large a sweep of natural products as possible. Field agents generally followed the rule that if it grew, pick it.

The NCI's job would be to run the raw collections through batteries of bioassays to determine which, if any, showed an aptitude for killing cancer cells in rudimentary petri dish tests. Promising species would then be handed over to chemists like Wall, who specialized in squeezing out plants' active ingredients.

As Hartwell was about to dole out some samples to his new lab-coated partners, Wall let "Johnny"—as he called his NCI friend—know that he preferred to be sent only specimens that in preliminary lab screenings had proven to be highly toxic in a special kind of cancer-cell tissue culture known as "9KB." In his two years in North Carolina, Wall had learned from studying his "happy tree"—*Camptotheca*—that there was a high correlation between a compound's success against 9KB cultures and successful tests against leukemia in mice.

Hartwell obliged, and on Sept. 8, 1964, he copied Wall on a memo he sent to USDA botanist Robert Perdue directing him to ship Wall specimens of seven plants. As it turned out, all were collected from Western deserts and the northern Pacific coast.

Two weeks later, Wall took receipt of a crateful of desiccated plant parts. Among them was a package containing shriveled pieces of *Taxus brevifolia*, the lowly Pacific yew.

"Taxol"

In the arcane world of phytochemistry, Monroe Wall was known as a fractionator. The term comes from separating complex slurries of ground-up plant material into distinct "fractions" or isolated parts of a plant's often hideously complicated chemical composition. Even today, where machines take care of so much of the drudgery involved, such work demands extraordinary skill, intuition and patience. Not uncommonly, luck plays a critical role, too. In 1964, Wall was one of the best fractionators in the business. And he was feeling lucky.

Although there was no particular need to hurry, Wall was anxious to get the yew samples into his analysis pipeline. Thanks to his brand-new contract with the NCI, he was swamped with work. But by spring of 1965 he and his junior colleague, Mansukh Wani—an organic chemist whom Wall had hired in 1963—had begun their search for the cell-killing essence buried in the yew extracts. By December, they believed they'd found it.

Wall quickly sent a small vial of the concentrated, purified solution—which he dubbed "K172"—to a biological testing company. When he saw the results the following March, he wrote Hartwell that what he was seeing in "K172" was "the broadest spectrum of activity that we have ever noted in our samples and the first time we have observed activity in P-4 (a mouse leukemia)."

Wall was suddenly more eager than ever to get going on the crucial next step—finding out, in chemical terms, what exactly this "K172" was. But he was out of Pacific yew. He asked Hartwell to ship him 45 pounds of bark, twigs and needles as quickly as possible.

During the ensuing months, Wall would get his yew shipments, but rarely in the amounts he wanted. Hartwell was beginning to appreciate the problems with his yew connection. His friend in North Carolina was devouring the stuff—by Christmas of 1966 Wall was calling for 375 pounds of it. Hartwell soon realized that for every 30 pounds of dried bark he was shipping to Durham, Wall and Wani were producing barely half a gram of purified K172. Talk about a needle in a haystack, he mused.

Though the true identity of the compound they'd isolated was yet to show itself, by April 1967 Wall and Wani decided it was time to tell the world about what they'd found so far. At the 153rd meeting of the American Chemical Society, convened that year in Miami Beach, Wall issued a paper describing a yew tree extract that "exhibited an unusually broad spectrum of anti-tumor activity." He added a preliminary sketch of what he and Wani suspected to be the chemical structure of the new molecule, which he had now given a name.

Following a professional custom of naming newly purified compounds, Wall announced the isolation of "Taxol." He had deftly combined the yew's botanical family surname "*Taxus*" with "*ol*," a tag chemists use for compounds containing alcohol. Wall and his colleague Wani had learned that whatever this yew molecule was, it was most definitely "alcoholic," studded with the basic elements common to all alcohols.

To their surprise, it took the Durham chemists nearly three more years to finally figure out the true molecular skeleton of their yew compound. Awkward lab equipment (by today's standards) certainly

slowed the process, but a bigger problem was what Wall and Wani soon found themselves up against—a molecule the likes of which they never knew existed. They soon realized that Taxol was basically two molecules in one—a large, gangly molecule sporting a small "tail." It was a whimsical concoction only nature could come up with.

The May 1971 issue of *The Journal of the American Chemical Society* carried their findings, and chemists around the globe began to take note. One was a 27-year-old North Carolinian just starting post-doctoral training in California. When he saw Wall's article on Taxol, he adjusted his glasses.

"Wow," is all he said.

One Good-Looking Molecule

When Arthur Barclay was making his first foray into an Oregon national forest in the summer of '62, Robert Holton, a fresh graduate of Myers Park High School in Charlotte, N.C., was getting ready for college. He would wait until his junior year at UNC-Chapel Hill before finding some coursework that got his attention—organic chemistry. A high-school dream of becoming a doctor soon went "poof." The strange chemicals of life had grabbed Holton's attention, and he had set his hat to make his living mulling them over.

For a master's degree, Holton chose Florida State University. His career interests solidified, he advanced to the doctorate program as a student of Martin A. Schwartz, a synthetic organic chemist himself out of Stanford only three years earlier. Like his new FSU colleague Werner Herz, "Marty" was fascinated by the chemistry of plants—primarily the vast family of compounds known as *secondary metabolites*.

For decades, plant chemists had known about—and puzzled over—this curious class of chemicals found largely in the plant kingdom. Unlike most animals, plants habitually produce compounds that play only secondary roles, if that, in sustaining their lives. Plants spend a good deal of energy making these things, which typically are extremely complex molecules, specific to a particular plant—and not uncommonly, poisonous.

At FSU, Holton soon took a strong interest in Schwartz' research into flowering plants belonging to the large daffodil family. The pair were hot on the trail of some enormously complicated molecules—the kind only nature bothers to make—and it was fun. The object of the game was to isolate some beastly molecules and take a stab at making them artificially. Sort of cookbook chemistry, first in reverse, then forward.

"It took Bob a year to get settled in—he played his first year," Schwartz recalled recently, grinning. "But by his second year, he was a dynamo."

In his pupil, Schwartz saw a single-mindedness that struck him as remarkable. "The guy had an incredible drive, a focus, on the right object," Schwartz said. "I frequently didn't agree at all with his methods, but I always had to respect his objectives. He was always, push, push, push."

Holton's passion as a doctoral student didn't always work to his advantage. Showing up late one night to run a new batch of compounds through an NMR spectrometer, the best analytical tool around for telling chemists what they've really made, to his amazement Holton found the door to Werner Herz' lab—home to the only NMR machine on campus—locked, with not a soul in sight. Having no key—and no patience—Holton promptly pulled the pins from the door's hinges and dropped it to the hallway floor. Hours later, he ducked out for breakfast and a welcomed bed, leaving the door right where he left it.

When Herz showed up the next morning and surveyed the scene, he immediately called campus security and reported a break-in. By the time Holton casually strolled in around noon, hell was a-loose in the Herz lab. Holton quickly took the blame—to the great relief of his pal Lewis Metts, the only grad student of the day whose reputation for mischief may have exceeded that of his buddy Holton. Herz, convinced Metts was the culprit, was ready to have him arrested. Holton thought the whole incident was a hoot. In years to come, Metts would find it funny, too—and instructive.

Influenced by his major professor, Holton pursued post-doctoral training at Stanford. Now a bona fide synthetic organic chemist, Holton, like any prudent post-doc, kept his post post-doc future in mind at all times. What good-looking molecules were out there that could be prime candidates for a career in academic research?

When he first saw Monroe Wall's write-up on Taxol, Holton couldn't quite believe what he was seeing. Based on all he'd learned so far, he frankly didn't understand how a molecule so contorted—so *impossible*—could exist. But there it was.

Taxol was one hell of a good-looking molecule all right, but nothing a neophyte academic better try to make, if making tenure some day was part of the plan. Even the sharpest dude could spend a lifetime chasing down a monster like that—and still wind up holding the bag. Holton had to be realistic. He figured the best thing to do was to shelve thoughts of mucking around with the amazing find of Monroe Wall.

Forgetting it, though, was out of the question.

"Can You Help This Poor Girl?"

With the publication of Taxol's structure in 1971, Monroe Wall's work with the molecule was essentially done. Five years earlier, when he finally trapped the active ingredient in his "happy tree"—a compound he named *camptothecin* (camp-toe-THÉE-kin)—Wall had handed over all his paperwork to Hartwell. Now he would do the same with Taxol. It would be somebody else's job in the NCI to carry the Taxol ball from there.

Or not. In its first few years out of Wall's lab, not much happened with the molecule, despite the unusual pedigree it had earned in early lab tests. Taxol wound up on the shelf, along with Wall's camptothecin, while the NCI struggled with budget problems and the demands of keeping a handle on its plant-screening partnership with the USDA. In a dozen or so years, thousands of samples of plants, microbes, bugs and other critters had been snared by the program and the workload had become enormous.

Finally, in 1975 Taxol had a shot at being liberated from limbo. The molecule emerged from tests against two tumors—melanoma and a special form of lung cancer—with decidedly mixed, but interesting, results. Taxol was essentially impotent against the lung cancer cells, but its performance against B16, a melanoma tumor, vaulted it just over the bar—barely good enough to keep it alive as a candidate for further testing.

Meanwhile, Monroe Wall was fit to be tied. Not long after turning over Taxol to his friend Hartwell in '71, he began to chafe at the thought of the NCI just sitting on it. Wall had spent his entire career looking for a molecule that had even half a chance of becoming an important medicine. Despite his best hopes for his "happy tree" compound, he knew that Taxol was by far the most promising molecule the government's natural products dragnet had ever turned up. *Didn't the feds see that?*

Never shy about stating his case, Wall flew to NCI headquarters a dozen times in the early '70s, and always jawboned about Taxol. Last May, he talked to Research in Review about those visits.

"When I went to (see the NCI group) I incessantly talked about Taxol—probably *ad nauseum*," he recalled. "Problem was, I was a chemist—not an M.D.—and that's who they listened to. But finally, it broke through."

Even though his old friend Hartwell had retired in 1975, Wall's constant entreaties finally landed on the right ears. A new NCI hire, Matthew Suffness, a pharmaceutical chemist, was put in charge of the NCI's Plant and Animal Products Section, under the natural products program, in October 1976. At Wall's urging, Suffness—persuaded by the compound's marginal success in the B16 melanoma test—got NCI's internal screening committee to take another look. In April 1977, the committee narrowly approved Taxol for formulation studies—tests to see how it could be turned into a palatable drug. It was the first step to serious testing in animals, a pivotal moment for Wall's prize.

Meanwhile, Suffness picked up on the most urgent matter at hand—finding more yew material. More testing meant more demand for the stuff, and Suffness soon found himself immersed in the arcana of collecting yew bark (by this point, Suffness had rightly concluded, as Wall had earlier, that the tree's bark was the primary source of Taxol). In July 1977, Suffness called Perdue of the USDA and placed an order for 7,000 pounds of bark.

This request—the largest yet—represented the killing of up to 1,500 Pacific yew trees, which had to be felled and stripped quickly before their hides got too tough to peel off. Rumors already were coursing through circles of western environmentalists about the government's sudden interest in the heretofore unsung Pacific yew. Though disdained by loggers who regarded it as a "trash tree," the yew nonetheless held a niche in the virginal, old-growth complexes of forests throughout the Pacific Northwest. Scattered in often hidden patches among the millions of forested acres across the region, a full-scale assault on the yew could spell ecological disaster—not just for the yew but for whatever stood in its way. Perdue's new orders soon got the gossip pot boiling over.

Three thousand miles removed from the brewing controversy, Taxol continued wending its way slowly through the NCI machinery. But reports of the strange molecule's appetite for some nasty cancer cells were beginning to pique the interest of academic researchers. Among the more ardent was an associate professor within the Albert Einstein College of Medicine at Yeshiva University in New York.

Susan B. Horwitz, a molecular pharmacologist, had been after the NCI for months to get her hands on more Taxol. In preliminary tests with the few drops she'd manage to squeeze from government labs so far, she had become fascinated by how quickly and elegantly the stuff killed cells growing in culture. She and her lab partners were sure they had never seen anything quite like it, and they were determined to find out how the molecule worked. But they desperately needed more Taxol.

In August 1978, Monroe Wall opened a letter from John Douros—Hartwell's replacement and Suffness' boss—that read: "Dear Monroe: Can you help this poor girl?" Attached was a copy of Horwitz's letter asking for some specially prepared Taxol necessary to pursue her work.

Twenty-four years later, Wall could smile about the letter. " 'Poor girl,' indeed," he said, chuckling. "Without her, I'm not sure we'd be talking today."

Breakthrough

At the dawn of the 1980s, a genuine thrill-ride for Taxol boosters lay in store.

News from Susan Horwitz's lab made the pages of *Nature* in early 1979 and touched off a flurry of excitement among cell biologists the world over. Her team had found the secret of Taxol's lethal talents in cell-culture tests. It turned out to be a mechanism completely new to science.

Horwitz was accustomed to seeing compounds kill cancer cells by interrupting their abilities to divide. The substances typically did this by wrecking the proteins needed to make ultra-fine filaments called microtubules. To be able to divide, a cell needs to make millions of these tiny structures to use as scaffolding for building the foundation of a new cell. Once the new cell gets fleshed out, so to speak, the microtubules automatically disassemble into fragments of tubulin, the structures' original protein building blocks.

Horwitz had discovered that Taxol didn't work that way at all. Instead of preventing microtubules from forming, Taxol served as a powerful stimulant for their growth. In the presence of Taxol, cells go into overdrive churning the things out, eventually clogging up a cell's innards. What's more, the process was found to be irreversible—Taxol locked the thickets of microtubules into place and blocked their abilities to disassemble. Choking on their own growths and with no way to divide, the cancer cells soon collapsed and died.

Horwitz's finding suddenly put Taxol on the top shelf of targets sought by cell biologists near and far. At the NCI, Suffness saw the scientific hoopla as a welcomed selling point for pushing the Taxol project forward. He was well on his way to becoming the bureaucracy's chief champion for what some already were calling a "miracle drug-in-the-making." And now he had academics everywhere hollering for the stuff.

The scene grew even brighter. Later that same year, Taxol would prove its mettle once again in the laboratory. This time it was a showdown against a human breast cancer tumor implanted in a new breed of lab mice. Called "nude" mice because they lacked the gene for growing hair, the animals had no immune systems, either. Human tissue could be grafted onto the animals with no fear of rejection—a great leap in the search for effective drugs. Against the mammary tumor, Taxol not only stopped it from growing, but shriveled it. It marked the second time that the chemical had shown an ability to arrest a truly tough customer in the cancer line.

But on the heels of the good news came a crushing discovery by the NCI drug formulation team. Taxol was found to be virtually insoluble in water. For that matter, the compound wouldn't dissolve very much in any solution researchers tried. ("It had the solubility of a brick," one scientist observed.) No matter how good the stuff was, without a way of getting it into a patient, what was the point of continuing expensive anti-tumor testing? Taxol's future, so bright of late, suddenly lost much of its luster.

In truth, the problem nearly derailed the Taxol project right there. A dozen or more compounds were in the pipeline that showed results as good as—if not better in some cases—than Taxol. Nowhere was the solubility issue as big a challenge as it appeared to be in Taxol. And time was slipping by.

A year later, with hope all but gone, perseverance delivered. The NCI team found something that Taxol would dissolve in that might work as a reasonably safe, intravenous solution in humans. The answer was a special elixir made of castor oil and marketed as **Cremophor EL**. Few considered the solution to be the perfect answer, but for the sake of keeping the Taxol project alive, it was the only answer. The breakthrough triggered a green light, and Taxol moved into "stage 2B" of toxicological studies. A happy Suffness made another call to the USDA to order more bark.

This time he needed 10 tons.

The NCI Bails

The calendar read April 6, 1984. A chemical called Taxol stood cleared by the U.S. Food and Drug Administration for take-off into Phase I clinical trials in humans. From this point forward, the odds of it becoming a drug stood at one in 10,000.

But the molecule had already whipped odds far worse. When the NCI-USDA screening program finally was shut down in 1981, Taxol was about all the government had to show for more than 20 arduous years of sifting through natural products. From 1960 to 1981, the program had screened 114,045 plant extracts and more than 16,000 extracts from animals. Yet of all these exquisite molecules made by nature, in the rarefied air of advanced testing, Taxol stood alone. In its wake were emetine, maytansine, thali carpine, bruceantin and dozens of other early hopefuls—each compound having consumed countless man-hours and research dollars largely in futility.

Now, Taxol was on the brink of its first test on sick people. The trip had taken 22 years.

But the improbable journey was about to lead straight into a firestorm of controversy that would eat up the energies of federal and state officials, civic and community leaders, environmental groups, drug manufacturers, private business owners and even desperate, individual cancer victims for a solid decade.

Well before FDA gave Taxol its stamp of approval for human trials in 1984, the difficulty involved in finding, collecting and processing bark from the Pacific yew were well known to the NCI. But these problems paled when, in March 1988, the FDA released the final results of Taxol's Phase II trials against the most virulent forms of ovarian cancer. The report revealed a response rate that averaged 30 percent—at least three of every 10 victims of the disease were seeing their tumors shrink. In some tests the response rate hit 60 percent. These were unheard of odds in ovarian chemotherapy, and it took little time for the word to spread.

Suddenly, people everywhere were begging for Taxol. NCI officials did the math, and calculated that if Taxol was made available to all ovarian cancer victims in the U.S. that year, the NCI would have to come up with roughly 240 pounds of the drug. This would require the death of 360,000 trees.

To anyone paying attention, it was clear where this equation was headed. Because of the yew's status of being worthless as timber, no one really had much more than an educated guess about how many of the trees were left in the forests. The overriding fact that was known: Unlike cancer, the Pacific yew was finite. Though some denied it, cultivating the tree was not a rational option—botanists knew that it grew on a glacial scale, on average only eight inches a year. And the pitiful amount of Taxol the trees produced approached the impossible—technicians did well to coax a half a gram of Taxol from the bark of a 40-foot specimen, a tree that easily could be 200 years old.

What also was clear by 1988 was that environmentalists out in Oregon and Washington were gearing up for a fight. A Save the Yew Foundation, sprung up in the '70s, had succeeded in making the yew issue a political one that dovetailed nicely with the white-hot controversy over logging's impact on the endangered spotted owl.

From almost Day One, Suffness had seen the writing on the wall. Now sitting as chief of the NCI's natural products branch, he predicted that if the government killed yew trees at the rates projected, bark supplies from the national forests would dry up "within the next two to three years." He was convinced that if Taxol had any hope at all of someday becoming a drug, that hope lay entirely in finding a way to get it from somewhere other than the woods out west.

But Suffness' concerns hardly ended at some lumberyard loading dock on the other side of the continent. A glance at his bottom line told him that Taxol was bleeding his budget dry. Thirty-ton shipments of bark were starting to become common, and a load like that might work up to 100 grams of purified Taxol at a cost of a cool \$1.5 million. Monroe Wall's old number K172 was costing the NCI more than \$250,000 a pound!

By the spring of 1988, Suffness had reached three conclusions about Taxol's future: The compound was inexorably headed for the market and a supply train wreck at the same time; the government couldn't afford to stay in the Taxol business very much longer; and some smart people out there had to find a way to make the stuff on the cheap and in a test tube.

He then reached for his list of scientists working with NCI grant money and who had ever done anything on Taxol, and picked up the phone.

Short-Cutting Nature

In the aftermath of Susan Horwitz's discovery about Taxol's unique way of killing cells, academic interest in the molecule skyrocketed. It wasn't long before university researchers also learned about Taxol's tenuous hold on the universe of available natural products.

In 1980, a group of French scientists led by Pierre Potier and Andrew Greene became the first to take a serious look at what could be done about making Taxol artificially, possibly using big pieces of the molecule that could be found abundantly in other yew species. The thinking was that such a semisynthesis process, if practical, could solve Taxol's supply problem forever.

From the needles of the ubiquitous English yew (*Taxus baccata*)—a shrub that grew in profusion just outside his lab window—Potier extracted a compound that seemed to fit the bill. The substance was 10-deacetylbaccatin (dee-ah-SEE-tull-bah-COT-ten) III, commonly heard more simply as 10-DAB. Other scientists had already found the compound in a *Taxus* species growing in the Himalayas, but in small amounts. By comparison, *Taxus baccata* was loaded with the stuff, and it was a cinch to isolate. What's more, English yew needles could be harvested by the ton with no negative environmental consequences.

Chemically, 10-DAB is a unique framework of bonded carbon rings (dubbed "taxane rings" for their discovery in *Taxus* species) adorned with bits of alcohol; metaphorically, it's the mother of Taxol. But the French scientists learned that only with the greatest of effort could the mother be persuaded to give birth in captivity.

After six years of trying, Potier and Greene finally got 10-DAB to marry up with Taxol's lesser half—a cluster of 34 atoms strung together like a snowflake. This was Taxol's "tail" that had fascinated Wall and Wani 15 years earlier. Semisynthetic Taxol was suddenly a reality.

But as a practical route to solving the Taxol supply problem, the French process was hopeless. At best, the process delivered a 52 percent yield, and often much less than that. Typically, about half of the starting material-10-DAB-was wasted. Back in the states, Suffness was not impressed.

But the development was hardly a total failure. The French scientists had revealed a lot about the chemistry of Taxol's "mother molecule," and what's more, had pinpointed an unlimited supply of it. The news got the attention of top-notch synthesis labs around the world, and soon the NCI was handing out Taxol research money hand over fist. Finding a practical way to turn 10-DAB into Taxol had now become the number-one priority in the hyper-competitive world of synthetic organic chemistry.

A Call South

Down in Tallahassee, Florida, Robert Holton had been following events with increasing interest. He was returned to his alma mater, a tenured professor in the chemistry department and now a colleague of his former boss and long-time friend Marty Schwartz.

Holton's career had taken him from his Stanford post-doctoral work to teaching and research first at Purdue, and from there to Virginia Tech. His life had taken a totally unexpected turn in 1985, when he followed Marie Krafft, his wife and rising star in synthetic organic chemistry, to FSU to assume her first full-time teaching post.

Holton felt like he had come home. He was walking the halls of where he got his first real taste of chasing outrageous molecules into the dead of night. He felt invigorated.

The hoopla over Taxol had caught up to him at Virginia Tech and at the best possible time. Tenure meant he could finally take his Taxol dreams out of the drawer, and in 1982 he produced his first Taxol paper. Another, two years later, put him on the road to becoming a respected player in the now wildly competitive game of Taxol chemistry. To be sure, he was coming back to Tallahassee more than mildly infected with Taxol fever.

But in Holton's eye, the real prize in Taxol chemistry didn't lie in coming up with a way to ease the supply woes that were starting to choke the life out of the compound's chances as a cancer drug. Truth was, he couldn't bring himself to believe that Taxol would ever live to see a single day as a commercial product.

Holton's experience—and that of so many of his fellow synthetic chemists—was that this sort of thing happened only in a few starry-eyed people's dreams. So what if Taxol had wowed some biologists up in Bethesda? Big deal. Over the years, a gazillion natural products had done the same thing—kicked butt in lab tests only to wind up on the molecular scrap heap. Holton knew that the NCI would be lucky if even one in a hundred thousand of its nature-made concoctions ever came close to a drugstore.

To Holton, Taxol's supply dilemma was an abstraction, a sideshow to the main event. What fired his imagination was the molecule itself, the fact that it even existed. Still every bit there was the awe he had felt 17 years earlier when he first saw its twisted skeleton in print. It was the "wow" molecule of all "wow" molecules. He wanted to make the damn thing!

The way he saw it, the fact that his favorite molecule was wearing the cachet of a hot anti-cancer prospect merely sweetened his grant proposals to the NCI. By his second year back at FSU, his lab was riding on more than \$1 million in NCI funding, and for a workaholic organic chemist with a bit in his teeth, Holton was in hog heaven.

In September 1988, Holton's team made news with the announcement that it had succeeded in synthesizing *taxusin*, a naturally occurring compound and a cousin to Taxol. The achievement was a milestone in Taxol chemistry, because the taxusin molecule contains the core atomic structure—the familiar taxane ring system—of the 10-DAB heart of Taxol itself. Holton's feat was seen as the first step toward making Taxol in the lab from scratch.

While coming down the home stretch on taxusin, Holton read about the French scientists' breakthrough in semisynthesizing Taxol. He noted their low yield, and immediately put the French process in the "didn't work" category. Nice enough try, though, he thought—for somebody not interested in climbing the *real* organic Everest. That was building the molecule piece-by-piece from the ground up, a nifty bit

of wizardry Holton fully intended to pull off in time. In his view, this was the only serious challenge in the entire Taxol world.

Then his phone rang. The caller was the guy who—purely by coincidence—had toiled at the same lab bench during his own post-doc years at Stanford just before Holton's arrival there years before.

Matt Suffness was on the line.

"This One's Gonna Be a Drug"

A full-blown crisis was looming for the Taxol project. Demand for Taxol from academic researchers and clinicians—not to mention desperate cancer victims—was ratcheting up daily, and the NCI was kicked into high gear trying to keep a lid on things.

By late 1988, the agency had worked out deals with U.S. Forestry Service officials and private loggers to step up the pace of bark collection; had signed a contract with the forest products giant Weyerhaeuser to start a yew seedling project, had spread the chemically tedious job of separating Taxol from the tree to more private partners—and had tried to put as good a face as possible on the festering environmental sore that characterized the government's yew harvest.

Suffness didn't mince words with his FSU Taxol scientist.

"He basically told me it was time I got off my butt and did something, that this was going to be big stuff," Holton recalled in a talk with *Research in Review* last spring. "He was telling me to invent a damn semisynthesis."

Suffness swept away Holton's skepticism about Taxol's chances of ever hitting the market.

"Matt knew what the story was better than anybody. He said 'Bob, this one's gonna be a drug, and somebody's gotta figure out how to make it.' After that call, I realized I needed to change my way of thinking."

As his taxusin project was winding down, Holton down-shifted and headed in another direction. Eighteen months later, Holton had out-raced a field of chemists in the United States, Europe and Asia feverishly running for the same brass ring. By late 1989, word had spread that Holton had found a semisynthetic pathway to Taxol that delivered a yield twice that of the French process. On the strength of his discovery, Holton began firing out letters to some major drug companies, hoping to find one interested in putting his process into commercial development.

An alarm soon sounded at the headquarters of the largest maker of cancer drugs in the world.

Bristol in the Breech

Holton remembers Suffness telling him that the NCI was getting out of the Taxol business. It had become the tail wagging the dog—there simply was no way the government could justify the enormous costs of keeping Taxol in the pipeline. By 1988, developing Taxol had cost the NCI over \$25 million. Other promising compounds were getting squeezed out of the competition because of this single, impossible-to-get molecule. It was time for the NCI to bail on Taxol.

In other words, the government was eager to find a deep-pocket pharmaceutical company willing to take a chance on turning Taxol into a marketable drug. Thanks to a novel tool Congress had just created

via the Federal Technology Transfer Act of 1986, Suffness & Co. could legally hand over the commercial rights to Taxol—a substance found and then preened all the way to the market's front door by taxpayer dollars—to any private company the NCI chose.

In August 1989, the agency advertised that it had a Cooperative Research and Development Agreement (CRADA) to grant the company submitting the best proposal. Four companies rose to the bait, including Rhone-Poulenc which held the French Taxol patents, and the New Jersey-based pharmaceutical giant, Bristol-Myers, soon destined to merge with Squibb, another huge pharma. To no one's real surprise, in December, the CRADA went to Bristol.

The decision would be second-guessed for a few years to come—in fact becoming the focus of a Congressional hearing in 1991—but the fact was that Bristol-Myers had done its homework. It helped that the company had built a good track record in working with the feds on a previous drug, DDI, an early treatment for AIDS. But the company's proposal to the NCI chieftains showed that it had thoroughly investigated Taxol's number-one problem—the supply dilemma—and had worked out detailed plans for dealing with it. One of the rounds in Bristol's chamber was what it had learned from talking to the folks down in Tallahassee.

Handed the keys to Taxol, Bristol took off. The company consolidated control over the entire bark collection and compound extraction apparatus out west, picking up the NCI's contract with the Boulder, Colorado-based Hauser Chemical Research Corporation. Then, on April Fool's Day, 1990, the company signed a contract that changed forever not only the future of Taxol, but of Florida State University and one of the most fortunate faculty members ever to set foot on a college campus.

Although FSU officials couldn't know it at the time, they had just brokered the deal of a research university's lifetime. Bristol-Myers Squibb was handed an exclusive licensing agreement to use Bob Holton's spanking new semisynthesis patent plus any related patents that his research might cook up over the next five years. In exchange, FSU was entitled to royalties on any money Bristol made using any of its Taxol patents, and Holton got a five-year research collaboration deal with Bristol chemists worth \$1.7 million.

FSU also got Bristol to agree to cover all costs associated with patenting anything Holton's lab came up with, including Taxol derivatives. At the time the agreement was signed there were no such animals. But Holton knew they were right around the corner. His relentless pursuit of total synthesis, now stoked with new money, would most likely generate a bunch of them, and soon. Who knew? Some of these derivatives, or analogs, might even prove to be better cancer-killers than the mother molecule itself.

Wouldn't *that* be cool, he wondered.

Yew-Turn

For the variegated worlds tied to Taxol, the first half of the 1990s was a blur of politics, science and technology set on a canvas of anxiety, wildly oscillating hope and, so some have charged, old-fashioned greed.

First off, Bristol got a big, unexpected bonus early in its new partnership with Bob Holton's chem lab. In 1992, shortly after Taxol won FDA approval for use against ovarian cancer, FSU patented a vastly improved version of his original semisynthesis. Known as the metal alkoxide process, the method produced an overall yield of better than 80 percent in only four steps.

Here was the recipe for Taxol that Bristol had been looking for all along. Suddenly the door was open to an easier, more cost-efficient way to scale up the drug's synthesis using as a starting material 10-DAB extracted in bulk from the needles of the English yew. Bristol was excited. The company whisked the process into the hands of its scientists working at the company's start-up manufacturing plant in Swords, Ireland, and ordered an all-out effort to bring it on line as soon as possible.

Without undue fanfare, in January 1993, Taxol—now officially trademarked as a Bristol product—made its debut in cancer pharmacology. Trumpeted as the most important cancer—fighting drug to come along in two decades, Taxol finally stood—a fully fledged cancer drug—before the world's marketplace.

From bark to business, the molecule's development had taken 31 years, had cost the government roughly \$32 million, and had already hit up its foster parents, Bristol-Myers Squibb, for 10 times that in ramp-up costs. Before 1993 ended, a single gram of the new drug was selling for \$5,846. Taxol was hobnobbing with the priciest potions ever made.

Out west, Taxol's emergence as a commercial product proved to be both a blessing and a curse. In August, Bristol announced that it would not renew its contract with Hauser, predicting that within two years their new semisynthesis process would make bark collection unnecessary. For hundreds of Hauser employees, it was the end of the line—the Bristol contract represented better than 90 percent of the company's revenues.

But the news sparked nationwide jubilation among environmentalists and among government and civic leaders who had grown tired of coping with the issue. Finally, the boil over the destruction of the Pacific yew had been lanced. On a meteoric ride, a little known tree that had gone from trash—in the minds of many—to treasure was now on the road back to obscurity. But to ecologists, the entire episode would long be remembered as a prime object lesson in the intrinsic wisdom of protecting wild resources regardless of their obvious benefits to anyone.

Big Drug, Big Bucks

Meanwhile, at Bristol things were hopping. By June 1994, Taxol was trademarked in more than 50 countries around the world—Sweden had been the first to sign up the year before. Hope in the form of an IV solution began to spread first to thousands of victims of ovarian cancer, and following the FDA's approval of Taxol's use as a treatment for breast cancer in later that year, thousands more. By 1995, untold numbers of gravely ill women were seeing their lives given back to them thanks to a precious fluid found in a plant.

The picture, though, wasn't all rosy. As a cancer-fighter, Taxol had muscle, to be sure, but the drug had some serious drawbacks. For hundreds of cancer patients, the drug simply bounced off their tumors, doing little if any good. Side-effects were a real headache, too. Taxol's castor-oil carrier was suspected as the culprit behind much of the misery, which included nausea, vomiting, joint pain, appetite loss, brittle hair and tingling sensations in hands and feet. People soon began to realize that the much ballyhooed drug was no panacea, but also that it was still the best thing out there.

And the numbers soon showed it. Sales of Taxol began to grow exponentially, and by 1995 the drug was the hottest selling cancer medicine on the planet, passing half a billion dollars in revenues that year. Bristol-Myers Squibb would see an average of 38 percent annual growth in sales of its blockbuster drug for the next seven years, until sales peaked in 2000 at nearly \$1.6 billion.

From the get-go, however, the company's incredibly good fortune did not escape the attention of critics of the pharmaceutical industry, which included members of Congress. In Taxol's debut year, 1993,

Bristol officials were obliged to sit before yet another Congressional panel, this time to trot out their reasons for the drug's high price. Sen. Ron Wyden (D-OR) was alarmed that the company was charging 20 times what it was paying for raw product. Bristol argued that its investment in the drug—which the company claimed approached \$1 billion—justified Taxol's lofty pricetag. The matter was dropped, but foreshadowed major legal and PR battles to come.

In Tallahassee, Taxol's rocketing sales sent shockwaves through a research administration that scarcely could believe what was happening. Robert M. Johnson, vice president for research at FSU during Taxol's ascent, was in charge of dealing with "a good problem," as he put it to *Research in Review* last spring, as best he could.

"We all knew that Taxol had great potential in the market," he said. "But not in our wildest dreams did we ever think it would do what it did."

Johnson found himself obliged to beef up his operations to deal not only with Bristol royalty checks, which by the beginning of 1994 were starting to show up in seven figures, but also with the fine print of the agreement, over which Bob Holton was growing increasingly frustrated. Creation of a research foundation in September 1993 helped to put a box around the administrative side of things, and Johnson's associate vice president at the time, Michael Devine, emerged as the university's go-to guy for dealing directly with a restless Holton.

Devine, a professor of industrial engineering from the University of Oklahoma, had become a self-taught student of what was known as technology transfer. In the 1980s, Congress had passed a spate of bills aimed at making it easier for university inventions to get commercialized. "Tech transfer" had become academia's hottest buzz phrase. Soon after coming to FSU in 1987, Devine had made it a personal crusade to drum up interest in tech transfer on a campus that had little experience in the field. Devine soon found in Holton a source of energy he could not have imagined.

"He struck me right off the bat as being incredibly driven," Devine recalls. "I didn't know chemistry, but I did know that here was a guy who meant business."

Bristol Bows Out

On Dec. 9, 1993, Bob Holton and his 13-member lab team were jubilantly celebrating an early Christmas present—and not because Taxol had done so remarkably well its first year in the marketplace.

Holton announced that his team had become the first to reach a total synthesis of Taxol, a feat that a decade earlier some had written off as impossible. Florida State scientists had hit the tape first—by a nose—in a race to finish a tantalizing puzzle that had taunted more than 100 academic groups the world over. For science, the discovery was hailed in *The New York Times* and professional journals as among the most extraordinary achievements in the annals of synthetic organic chemistry.

But for the business of making and selling Taxol, Holton's accomplishment was viewed as meaning very little. The process required no less than 40 steps, and the yield was abysmal—only two percent. These were numbers anathema to any corporate P&L statement. Still, Holton had scaled the mountaintop of Taxol chemistry, and the trip up had taught him volumes about the molecule's inner secrets.

Along the road to total synthesis, Holton's research had spun off a variety of Taxol derivatives, just as he had predicted it would four years earlier. In fact, the ink was hardly dry on FSU's contract with Bristol before Holton's lab was cranking out Taxol analogs like crazy. Every one of them was patentable. FSU found itself in need of a specialist in patenting law, and soon found one in the St. Louis law firm of

Senniger, Powers, Leavitt & Roedel. Ed Hejlek (HAY-leck), a 35-year-old attorney who had done some earlier patenting work for Marty Schwartz, got a call. The young attorney and Holton immediately hit it off, and suddenly Hejlek was in the Taxol analog patenting business big time.

"Ed's attitude was, if it moved, patent it," Holton said. "His strategy turned out to be brilliant."

Holton and Devine were taking no chances with FSU's Taxol goldmine—the plan was to cover all bases and put pressure on Bristol to hold up its end of the deal, which went well beyond just paying for Hejlek's patent applications. The company also had agreed to run every analog through biological screening, find out which ones showed promise for further research and then load them into their drug development pipeline.

As the end of Holton's five-year contract with Bristol neared in 1995, it was clear to all parties that a serious clash of personalities and professionalism was at hand. The company had shown little progress in developing any of the analogs, and Holton was accusing the company of sitting on them. Bristol replied that what it was sitting on wasn't worth pursuing—Holton's analogs were testing too toxic in mice, the company claimed. Hogwash, said Holton. From where he stood, Bristol was dragging its feet, content to milk its cash cow Taxol rather than fiddle with anything that might turn out to be a competitor to its blockbuster drug.

Charge and counter-charge led to Bristol's decision by the end of 1994 to give up its stake in Holton's Taxol analog factory. The company signaled FSU as much by letting Hejlek's relentless patenting bills go unpaid. By early 1995, Bristol let FSU know it was prepared to hand over all its rights to develop and market Holton's analogs—with one exception. Bristol claimed that a technicality in its agreement with FSU brought Holton's metal-alkoxide technique under its own exclusive patent umbrella and flatly refused to allow the university to use it.

"They were saying we could have our analogs back, but we couldn't have the only way out there to develop them," said Devine. "What good was that to us?"

Devine and Holton knew that the key to unlocking the potential of Taxol chemistry lay in having unrestricted use of the metal-alkoxide process. "Bristol knew that if it could block the use of this technique, they could block all their competition. To us, it was that simple," Devine said.

Johnson, meanwhile, had grown tired of giving money to lawyers—over the years, the Taxol trail had fattened the wallets of more than a few. But in this case he had no choice—too much was on the line not to mount a full court press. Bristol felt the same way. In one saber-rattling meeting on campus with Bristol in 1995, Johnson counted a total of 18 hired guns on both sides.

In January 1996, a compromise defused what was shaping up to be an ugly legal battle. FSU got the rights to use the metal-alkoxide process to develop its own analogs when it agreed to split 50/50 with Bristol any royalties the university derived from licensing the process. Except for the exchange of royalties, the FSU-Bristol partnership was history.

Recalling those testy years, Bristol senior executive Dianne DeFuria, gave her perspective to *Research in Review*. Now retired, DeFuria spent 30 years at Bristol, mostly as a negotiator for marketing deals with outside entities. She suggested that in hindsight, the agreement Bristol signed with FSU in 1990 was weighted in favor of the university's interests, a situation which she said may have been unavoidable under the circumstances.

"The agreement was hammered out even before we had the CRADA in place, when we knew what we were going to be required to do for Taxol's development," DeFuria said. "In the end, so much was required in a very short timeframe, and the resources to evaluate all those analogs and the wisdom to do that was lacking. It wouldn't have served anybody to divert (resources) from the Taxol effort (to pursue) these little known, little characterized compounds."

Then there was the "overall gestalt," in DeFuria's words, of the agreement's progress. "I think the relationship between Bristol and FSU and some individuals involved was kind of patchy," she said. "Some of us got along well, others didn't. So continuing the intimate relationship was thought not to be the better way for parties to go."

Despite their differences, DeFuria described Holton as "passionate" and "clearly committed to good chemistry and to cancer drug development." She said that at no time did she or anyone at Bristol question Holton's motives for pushing Bristol so hard on the analogs. "Bob wasn't in it for the money, I do believe that. He really had a sincere desire to get Taxol and other drugs (made) more widely available."

Holton, Inc.

In 1996, Florida State University was the envy of the tech-transfer world of U.S. research institutions. That year alone, the university's research foundation received more than \$28 million in Taxol royalties. By decade's end, the university's Taxol revenue would top \$200 million, among the largest patenting pay-offs for a single university in history.

A handsome incentive the university had created for its research faculty in the early 1980s—entitling inventors to 40 percent of any royalties forthcoming from their patents—had made Bob Holton a wealthy man.

On a professional level, it hardly mattered. To no one's great surprise, Holton's intensity remained unfazed by his sudden fame and fortune. His new intimacy with old Monroe Wall's molecule had worked in him a resolve to see what lay hidden in the chemistry of the world's best cancer drug.

His university now had a free hand to explore the more than 35 patents on Taxol analogs passed over by Bristol-Myers, and Holton had a surprise in store. He had found out what he had suspected all along—that Bristol's conclusions about his analogs were dead wrong. He'd hired his own biologist to run toxicity tests in mice on every single one of them, "price be damned," in his words. To his delight, Holton had learned that the batch of chemicals were, on the whole, far less toxic than Taxol itself. It was time to get moving.

Once again, Holton's timing was good. In November 1996, a Berkeley-trained biochemist from Canada came to FSU as the university's first certified expert in technology transfer. John A. Fraser essentially picked up reins originally pulled together by Mike Devine, who left FSU in 1995 for a vice chancellorship in research at the University of Tennessee-Knoxville. Steeped in both the corporate and university worlds of licensing, patenting and marketing technologies for two decades, Fraser spoke a language Holton was all-ears to hear.

In their first meeting—in a cafeteria on campus—Fraser learned that Holton wanted to start his own company to pursue the development of his growing portfolio of Taxol derivatives. His experience with Bristol had soured his taste for dealing with another big pharma. He was creating his own nonprofit foundation, which he named Molecular Design, Synthesis and Research, that he planned to set up as the parent for a spin-off for-profit company.

Fraser recalled the gist of that first encounter with the good professor Holton: "Here's a man, personally wealthy, who believed in something so much that he was willing to put his own money behind it. You can't ask for much more than that.

"He didn't know how to structure such a company, but that's what I was there for."

A year later, Taxolog, Inc. was up, if not running. Holton's MDS Research Foundation still faced a long gauntlet of sign-offs with the FSU Research Foundation to secure rights to use the analogs returned by Bristol. Holton revealed himself to be a "ferocious negotiator," in the words of a top FSU administrator. The FSU chemistry professor was learning some corporate-type things from the newly installed head of his new company, a colorful figure from his doctoral days at FSU.

Lew Metts, son of a Mississippi Baptist preacher and Holton's irreverent comrade-in-arms 27 years earlier, was back. Metts, now a senior executive in the pharmaceutical industry, had let his old college pal talk him into doing something he'd first dismissed as nuts—start up a drug-development company from scratch (see page 25).

With Fraser at the fore, it took a year and a half to bang out a highly complicated deal with the FSU Research Foundation. Basically, the foundation's board members knew they were rolling the dice. They weighed their only options—shop around for another drug-maker willing to gamble big bucks on Holton's grab-bag of taxanes, go with an eager start-up company with a zero track record—or do nothing.

"I told the research foundation board that the basic issue was whether or not we put our trust in Bob Holton," Fraser said. "Let the man do what he wanted to do with his own money, was the argument I made. The university wouldn't have a dime in the deal. It was Holton's money to lose."

In April 1998 Holton's MDS Research Foundation was licensed by FSU to develop and commercialize its analogs exclusively through Taxolog, Inc. The company also got a restricted license to use the metal-alkoxide technique. In exchange, FSU would get not only a share of any royalties on the sale of any Taxolog product, but also a matching grant program from MDS that would funnel money directly into projects aimed at beefing up FSU's strengths in graduate training and research.

Making the deal exceedingly more palatable to the FSU Research Foundation was a proviso—originated by Holton himself—that neither he nor any member of his family would ever hold any stock in Taxolog nor profit directly from its business. For his job as chief scientist at Taxolog, Holton agreed to a salary of a dollar a year.

Civilizing Bob

"It's been interesting. But the ballgame's not over."

Such was Holton's cursory assessment last spring of his previous 13 years. He touched on the human side of his experience—the manic pace of work, where his students and post-docs kept the lab fires burning 'round the clock months on end; the hundreds of calls he took from cancer victims and their loved ones after word broke of his success in making Taxol; of the distraught football coach from Iowa who broke into his lab late one night desperate to find some Taxol for his dying mother; of his plunge into the corporate world and his distaste of what he saw there; of the envy—if not enmity—that commonly comes with uncommon success.

"I had no earthly idea back then what I was getting into," he said. "Matt Suffness rings me up one day and says somebody better do something about this thing. Enter Ed, enter Mike, enter Bristol. I kinda got caught up in it."

These days, Holton finds himself caught in a web of work that would tax the nerves and stamina of any Fortune 500 CEO (whether under indictment or no). With his ties to business, family, research and teaching (he's still at the helm of one grad course a year), spare moments are hard to come by.

Typically, his days begin at 4 a.m. with a half-hour ride to campus. Barring speeding tickets, he's in his office by 4:30 and on the phone to "Uncle Lew," as he calls his friend and partner Metts. At 6:30 he's back home, helping his 6-year-old son get ready for school, and picking up Marie, his wife and colleague. By 9:15 he's back on campus.

Days are often end-on-end telephone conference calls with Taxol scientists in New Jersey, corporate types of various stripes, and Ed Hejlek and his merry band of patenting attorneys, still going strong after more than 13 years of chasing the Taxol rainbow. He somehow sandwiches it all between conferences with his post-docs and grad students working in his lab next door. By 5:30, the second time that day he's headed home, staying true to a personal rule never to take work home (or use cell phones—he doesn't own one.) He makes a point of getting to bed early so he can start over well before sunrise. It's a routine he's used to, and it's the life he loves.

His insane work habits today are the same as they were in 1970, says Marty Schwartz. "He was a workaholic then, too, and every bit as single-minded and serious as he is now," he said. "That's not always been a good thing, but that's Bob Holton."

Schwartz knows his former student much better than most. He knows that Holton's success has not come without a price—his stubborn, damn-the-torpedoes approach toward his work has cost him some collegial respect over the years, and sank his first marriage as well. He also knows that what drives Holton isn't money, as anyone might guess.

"He's never been motivated by money, I guarantee you that much," Schwartz said.

If anything, Holton has used his newfound wealth largely as a means of building a better place for research and education at his university—something he's deadly serious about—and for "a whole new series of ways to pursue this craziness more efficiently," Schwartz said. (So far, Holton's main concession to the substantial spike in his financial status is a Lear jet, which gets him to and from frequent out-of-town meetings in a quarter of the time he once spent flying commercially.)

Construction of a \$46 million chemistry research building, to be called the Center for Molecular Recognition, is set to begin next year on central campus. An \$11 million gift from Holton's MDS Foundation, combined with other Taxol-related revenues will pay for most of it.

Over the years, Holton's largess to FSU and the Tallahassee community has been felt in other ways as well. In 1997, Fraser persuaded the FSU Research Foundation to use Taxol revenues to create the Cornerstone Research Program, a competitive grant program annually offered FSU faculty. The university also has used Taxol monies to strengthen academic departments across campus through an endowed professorship program, named in honor of Francis Eppes, a force in the earliest history of FSU's institutional foundation in Tallahassee. Since it began in 1998, the program has installed nearly a dozen distinguished scholars and researchers as Eppes Professors around campus.

Schwartz said the only things that he sees different in Holton these days are his attitude and his focus. He said Holton has "gotten more civilized, more patient," a change that is starting to pay him dividends in professional circles. "Bob's much more respected now. People listen to him."

But it's Holton's new direction in research that is most striking, Schwartz said.

"For years and years, it was strictly 'let's climb the next (molecular) mountain—find a way to make this horribly complex molecule.' Now, it's not that at all.

"Now, he really believes he's on a track to cure cancer."

Beyond Taxol

Holton is on the horn with Uncle Lew, and it's a sane hour—one-thirty in the afternoon. He wants an update on how things stand with Taxol's leading compound—an analog tagged "TL-139." It is May 2002, and the molecule is working its way through the first phase of clinical trials at Johns Hopkins and one other research center. Holton hangs on Uncle Lew's every word.

TL-139 has been a constant source of excitement from the first day it was tested in mice. After studying the charts, one veteran cancer researcher went on record saying that the compound was the most powerful anti-tumor agent he'd ever seen.

For Holton, this is now the prize. All his energies, skill, intuition, thoughts—luck—are coalesced these days into a concerted effort to push his family of patented analogs further down the road to their destinations. TL-139 is the lead horse, and so far, the fans are still on their feet.

Curing cancer? With a magic bullet? Surely the stuff of science fiction—cancer kills 1,500 Americans a day, and seems to find insidious new ways to do its murderous work all the time. Since the ancient Egyptians 5,000 years ago, the role of drugs in cancer treatment has been to contain the disease and give victims a way to cope with it. Contain and cope—not cure. Despite profound, hope-inspiring advances such as Taxol, not much has changed on that score.

Holton is keenly aware of that. And he stubbornly refuses to believe that's the way cancer chemotherapy will always be—just fuzzy hope in a bottle. His crusade these days is to try to separate the possible from the impossible, the probable from the improbable—to synthesize cancer's first genuine wonder—drug. If there's a right road to this peculiar Holy Grail, Holton firmly believes he's on it, and for all the right reasons—he's sitting at the head table of the most powerful family of cancer-killing compounds ever developed, and he doesn't give a damn about dollar signs.

Money can't buy what he has now, he said. He confesses that his love of chemistry is as strong as ever, but his zeal of late is less abstract, more defined in human terms. Amazingly, he confesses that he's never lost a close friend or loved one to cancer, although the ironic death of Matt Suffness—the man he credits with saving Taxol's life in its crib—is never far from his mind. In June 1995, Suffness lost a fight against leukemia, with his stalwart friend Monroe Wall at his bedside.

"When I started down this path, I really didn't think much about (the human cost of cancer), but I do now. Just the other day, a person came up to me and said that Taxol had kept his father alive for an extra three years, and he wanted to thank me. That's pretty powerful stuff.

"So, there are things I feel obligated to do. If you have the opportunity to do something that could save someone's life, you just have to do it.

"And as I said, the ballgame's not over."

Editor's Note: Since 1993, Bristol-Myers Squibb has introduced only one cancer drug to the pharmaceutical market—Taxol. As of August 2002, Taxol is still the only taxane product in its line of oncology drugs. When the company's exclusive, five-year right to market Taxol under the CRADA expired in 1997, technically opening the door to generic brands of the drug, the company successfully fought off the introduction of generics until December 2001, a move that added more than \$4 billion to lifetime Taxol sales that by last August approached \$11 billion. Last June, attorneys general in 29 states—including Florida—filed a lawsuit against Bristol charging that the company committed fraud in filing patents to keep lower-priced generics off the market

If you have the opportunity to do something that could save someone's life, you have to do it." - Bob Holton

Tomorrow's Blockbuster? Now in human trials is this derivative, or analog, of Taxol that has shown unequaled success against various cancers in lab animals. The compound, which bears the lab designation "TL-139," is being developed by Wyeth Pharmaceuticals under a licensing agreement with Taxolog, Inc., the private company spun off by Holton's research at FSU.

"It's 1000 times better than Taxol was at this same stage of development." *Lew Metts, Taxolog, Inc.*