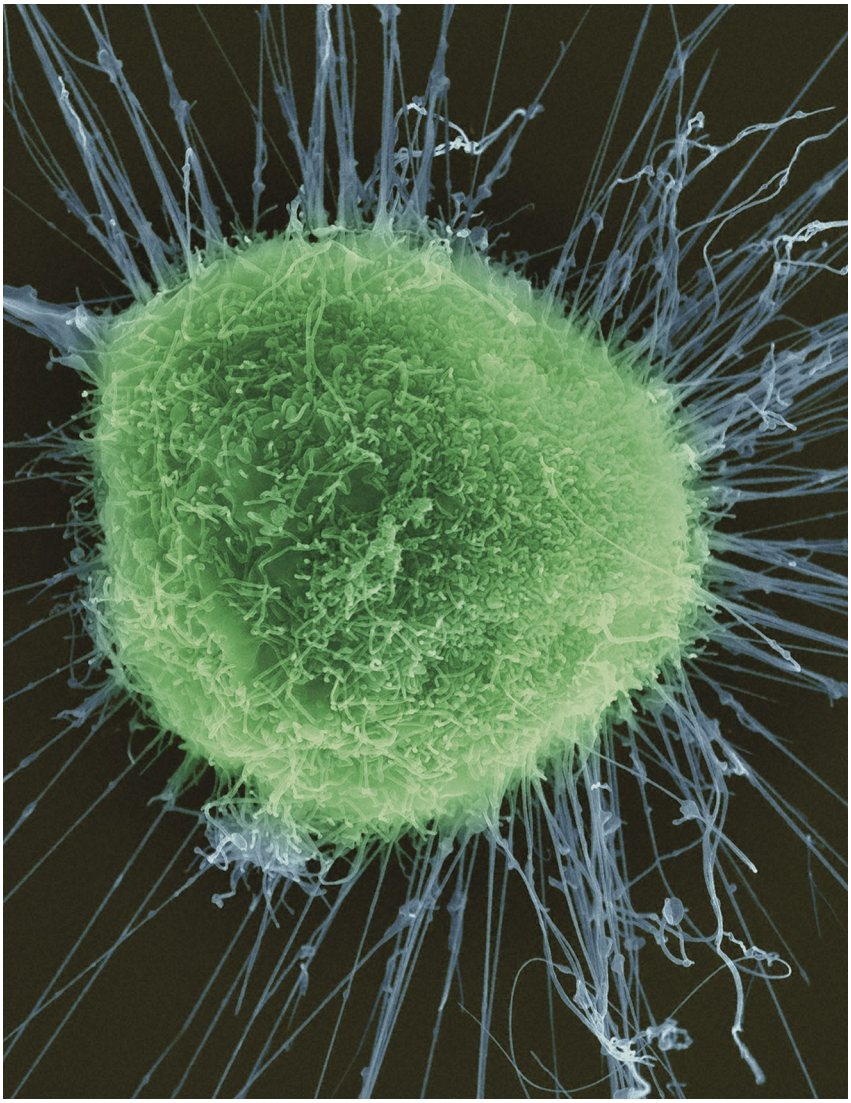
Sweet Revenge

By Douglas L. Smith



A scanning electron microscope photograph of a breast cancer cell, magnified 4,600 times.

Mary Davis was diagnosed with breast cancer at age 36 in April 1995. Her husband, Mark Davis, the Schlinger Professor of Chemical Engineering, began keeping a diary that recorded the nausea, weakness, and hair loss that attended the chemotherapy that followed. In January 1996, the dosage was ramped up. "By Valentine's Day, Mary had lost all her hair for the second time," Davis would write later. "She was unable to eat, was constantly vomiting or felt nauseous, and was given nutrition by IV. She had completely lost her immune system and was in isolation for three weeks. I recall bringing chocolates for all the nurses that day before going in and spending the day in isolation with Mary." Shortly thereafter, she said, "There's got to be a better way—I was feeling fine before the diagnosis, and the treatments are making me sick. Treatments should make you feel better." When Davis replied, "Mary, it's not my field; what could I possibly do?" she fired back, "You people at Caltech are smart, go work on it."

Heavy-duty chemotherapy works by interfering with cell division, which has run amok in cancer cells. But the drugs aren't at all selective, so they also affect cells that are supposed to be dividing rapidly, like those that line your stomach (hence the nausea), and the follicles from which hair grows. Fingernails and toenails can fall out as well, if the cuticle cells succumb. These drugs are given intravenously, and thus permeate your body as they circulate in the blood. At least the few molecules you retain do—most of each and every dose goes straight to urine. Says Davis, "Your kidney is a big filter that removes anything smaller than 10 nanometers in diameter. And most drugs are a nanometer or less."

What we call cancer actually comprises more than 100 different diseases, each with its own characteristics, including survival rates and treatment protocols. But all result from unchecked cell division. Not that cell division is a bad thing: some 50 to 70 billion cells—the equivalent of your

Site	All stages	Local	Regional	Distant
Breast (female)	86.6	97.0	78.7	23.3
Colon and rectum	62.3	90.1	65.5	9.2
Liver	6.9	16.3	6.0	1.9
Lung and bronchus	14.9	48.7	16.0	2.1
Melanoma	89.6	96.7	60.1	13.8
Ovary	53.0	94.7	72.0	30.7
Pancreas	4.4	16.6	6.8	1.6
Prostate	97.5	100.0	--	34.0
Testis	95.5	99.1	95.0	73.1

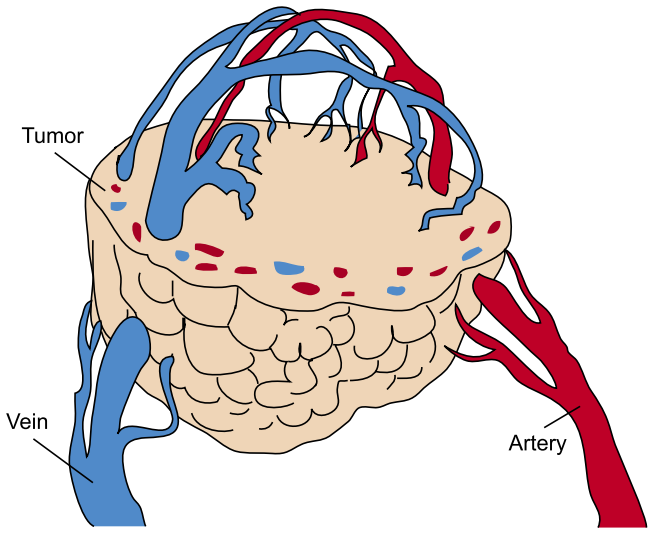
Cancer is really many different diseases, some more lethal than others. This 2004 data from the American Cancer Society shows the five-year survival percentages for various cancers listed against the degree to which they had spread through the body by the time they were discovered.

own body weight—are born within you every year. We'd all look like Eddie Murphy in a fat suit, were it not for the fact that an equal number of cells die at the same time. Some, like skin cells, slough off. Others get tagged for termination for various reasons, usually because they're defective or infected. And some self-destruct when an alarm clock in their DNA goes off. It takes a number of accumulated mutations—some to which we're genetically predisposed, some triggered by environmental factors, and some for no apparent reason—to disable these self-protective systems, and when something is that broken it becomes very hard to fix.

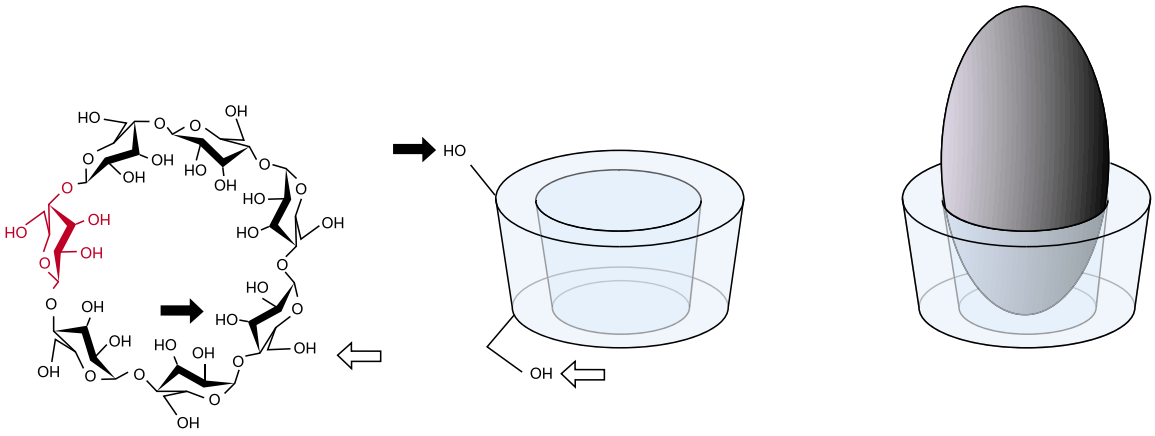
You'd think cancer cells would be easy to find and kill, because they should stand out from the crowd. Alas, they don't. Your cells have molecular tags on their surfaces that prove they are legal residents, and cancer cells, having sprung from your own tissues, still carry a valid ID. Cancer can be invisible to the immune system, unlike foreign cells such as bacteria, or virally infected cells of your own that have begun sprouting foreign markers. A cancer cell's chief difference is its behavior, which is why chemotherapy uses the cell's profligate breeding habits to attack it.

If each cancer confined itself to a single tumor, surgery might suffice. But things go downhill fast when a process called metastasis kicks in. Fast-growing cancer cells tend to be sloppy proofreaders of their own genetic instructions, so mutations continue to accumulate. Eventually some cells acquire the ability to leave the tumor via the blood vessels. Once on the road, every cancer type has its own itinerary: melanomas (skin cancers) move into the lungs, colon cancers head for the liver, and prostate cancer goes straight to the bones. But the new tumors still behave like their original cell types, and need to be treated as such. This can complicate matters immensely, says Davis. "Say you have a bad cough, and you get a chest X-ray, and the doctor sees a shadow in your lung. He might think that it was lung cancer until the biopsy comes back and shows it's a melanoma. And, unfortunately, many different cancers like to go to the lungs—melanoma, pancreatic, breast. . . ."

But wait—there's still more bad news. One of the body's defenses against poisons is a set of molecules called p-glycoproteins that, when summoned into action, sprout on the cell surface and act like little vacuum cleaners, sucking up oily molecules and shooting them back out into the intercellular medium, away from the cell. The newer, more potent anticancer drugs are very oily indeed, and glycoproteins aren't choosy once they get turned on. Says Davis, "These proteins will not only spit out the drug you're using, they'll spit out other drugs you try after that." Multidrug resistance and metastasis frequently go hand in hand, and these cancers are the most deadly.



A fast-growing tumor needs more nutrients and oxygen than the normal cells around it. It commands the circulatory system to grow more blood vessels, stat, and the result is a slapdash network of corkscrewy, leaky plumbing.



Adapted from Davis and Brewster, *Nature Reviews Drug Discovery*, vol. 3, pp 1023–1035, December 2004

A cyclodextrin molecule is a ring made up of six to eight simple sugar molecules, one of which is shown in red. (Davis uses seven-sugar cyclodextrins.) In the top view of the molecule (right), the parts sticking out of the plane of the page are drawn with heavy lines. By convention, carbon atoms are implied at every vertex where two or three line segments meet. The molecule behaves like a hollow, truncated cone, as shown in the even more simplified side view (middle), and other molecules can fit inside it (far right).

Size Matters

When a tumor grows to about a millimeter or so in diameter, it begins to outstrip its food supply. "So," says Davis, "it sends out chemical signals to your blood vessels that say, 'grow some new ones fast, and bring me more blood!'" The vessels oblige, but like many rush jobs, the workmanship is sloppy. "The blood vessels in a tumor are immature. They're weird, they're chaotic, they even form loops. They're also very leaky. They'll let particles as big as 400 to 700 nanometers [billionths of a meter] out into the tumor." What leaks there stays there—like a basement with bad pipes and no sump pump, the tumor lacks proper drainage by the lymphatic system.

It's easy to make drug-laden particles small enough to enter the tumor but too big to be flushed away. But you can't just make them, say, 500 nanometers across, because they will not move throughout the tumor. In the tradeoff between payload and penetration, the trick is to carry as much stuff as you can sneak in—not unlike smuggling watches past Customs. "We think that the 'sweet spot' is about 50 nanometers," says Davis. Particles this size can circulate in the blood for days and days, giving them all ample time to find the tumor, leak out of the new blood vessels, penetrate the entire mass, and enter the cancer cells.

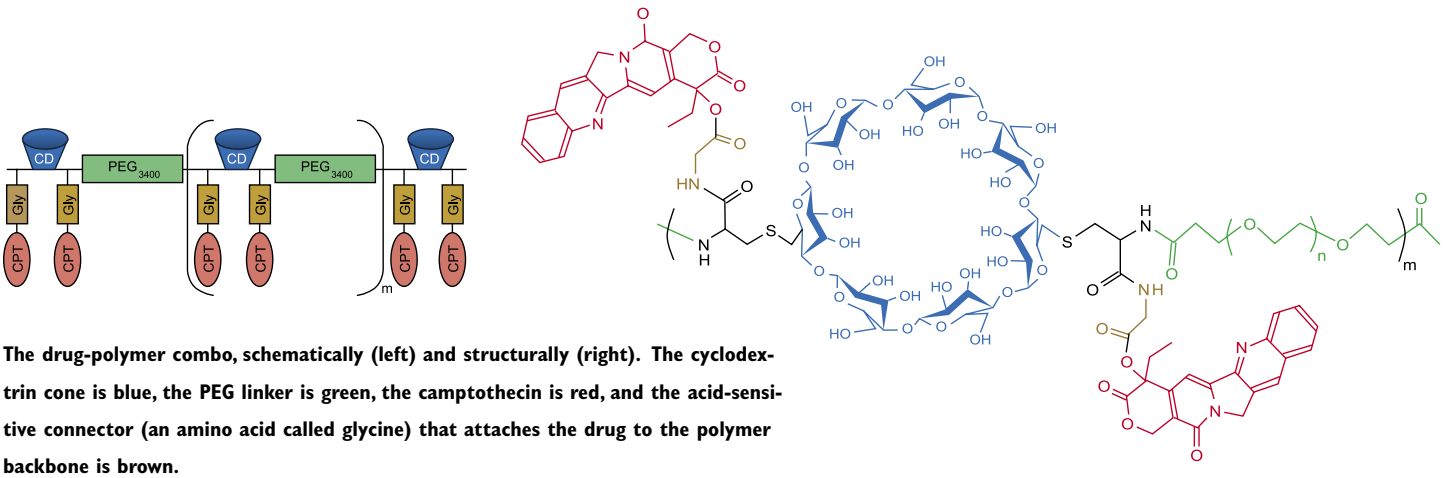
Building a Better Molecule

Davis, the chemical engineer, rose to the occasion. Nanoparticles, which range from 1 to 100 nanometers in diameter, are all the rage in the high-tech community. But they're also a mainstay of the brick-and-mortar economy—when they're suspended in liquid, they're called colloids. Paint is a colloid, as is milk. A particularly handy colloid can be assembled from cyclodextrin, which is a molecule composed of six to eight simple sugars arranged in a truncated, hollow cone—a sugar cone, if you will, with the tip bitten off. Cyclodextrin is made chiefly from cornstarch, and it's nontoxic, water-soluble, and doesn't set off the immune system—after all, it's just sugar. Its cone is a splendid place to stash molecules that are not water-soluble—which, alas, describes those oily anticancer drugs; oil and water don't mix. The first patent on using cyclodextrins to make drugs more soluble was issued in Germany in 1953, and they're still used for that purpose today. But once injected into the body, cyclodextrin molecules quickly release the drug, so Davis needed to find a way to keep the ice cream frozen in the cone, as it were, long enough to enter the tumor cells. And, ideally, once in the cell the ice cream should slowly melt, rather than the entire scoop falling out at once.

Both of these things happened when the cyclodextrin molecules were assembled into chains, using a molecule called polyethylene glycol—PEG to its friends—as a linker. (PEG is used in products from soft drinks to skin creams; on occasion, it's even added to ice cream as a thickening agent.) The resulting polymer looks like a long string of pearls, with round cyclodextrins alternating with linear PEGs.

A drug called camptothecin was chosen to be the payload. Despite its effectiveness against cancer in mice, camptothecin never made it commercially. Besides the usual complaints of being hard to dissolve and highly toxic, it flip-flops between an active and an inactive form. At the blood's slightly alkaline pH, the inactive form predominates. But by reacting the drug and the polymer together, the Davis lab created a chemical bond between the polymer's backbone and the drug, which stabilized it in its active form. The resulting molecule is about 10 percent camptothecin by weight.

This whopping construct still isn't big enough to be refused by the kidneys, so here's the really



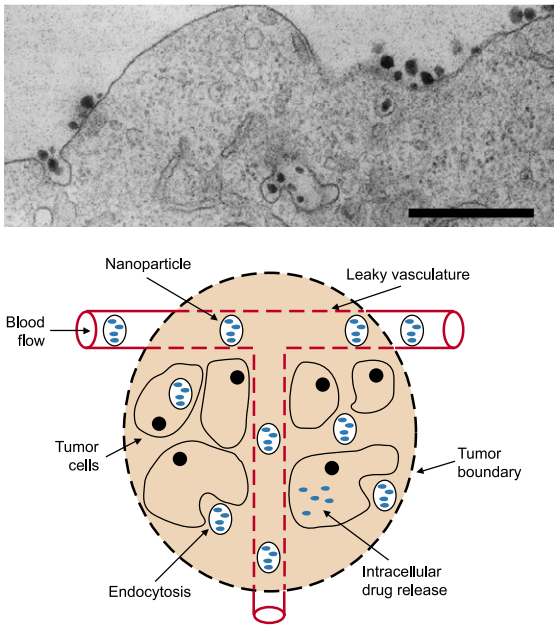
The drug-polymer combo, schematically (left) and structurally (right). The cyclodextrin cone is blue, the PEG linker is green, the camptothecin is red, and the acid-sensitive connector (an amino acid called glycine) that attaches the drug to the polymer backbone is brown.

clever part. The combo is packaged as a dry powder. The powder dissolves in water in a couple of shakes, and the camptothecins dangling from the polymer backbone promptly stuff themselves into the sugar cones. Enough of these cones are on other polymer molecules that the whole wad knits itself together into nanoparticles about 40 nanometers across. Says Davis, "We designed this so that it could be kept in any old office, and any nurse can administer it. You don't have to be at a research hospital. You don't need to store it in liquid nitrogen. It just sits on the shelf in a little vial, and you add water to it and stick it in an IV bag."

These nanoparticles elude the oil-repelling glycoprotein pumps because the cancer cell thinks they're food. It engulfs them into little sacs called vesicles that also contain enzymes to digest proteins. These enzymes only work at low pH, so as the vesicle moves into the cell, it slowly fills with acid to activate them. This influx of acid breaks the chemical bond between the polymer backbone and the drug. The camptothecin then works its way free of the sugar cones in dribs and drabs—an automatic time-release mechanism—escapes through the vesicle wall, and sets to work. The empty polymer molecules eventually exit the cell and wind up in the urine.

The nanoparticle was tested on seven varieties of human cancer induced in mice—colorectal (two kinds), pancreatic, breast, non-small-cell lung cancer, small-cell lung cancer, and Ewing's sarcoma. After one dose a week for three weeks, all the non-small-cell lung cancers and most of the Ewing's sarcomas were completely gone, and all the other cancers showed significant reductions. Since one of the forms of colorectal cancer is known to resist irinotecan—an anticancer drug that grosses a billion dollars in sales a year—by activating the glycoproteins, it was clear that the drug-polymer combo was eluding their vigilant vacuuming. By contrast, giving irinotecan to other mice with non-small-cell lung cancer worked for a while and then pooped out. Says Davis, "The tumors came back, and the animals died."

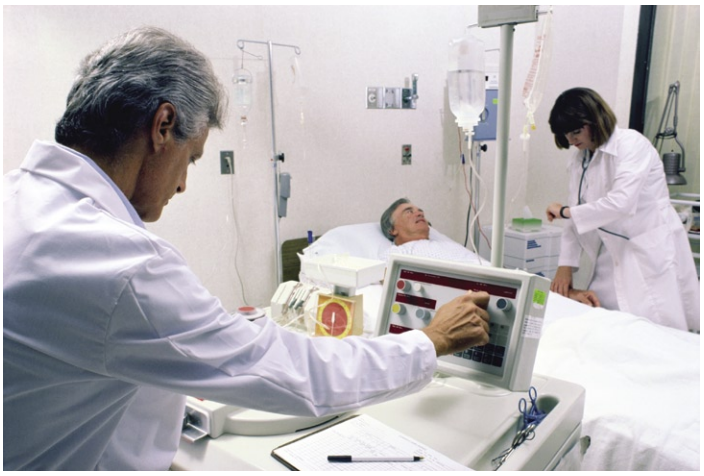
"In all of the animal models that we've done, we've never had one fail yet," says Davis. "No matter what tumor type we use, we've had good results."



Courtesy of Insert Therapeutics.

Top: In this scanning electron micrograph of a cell, the nanoparticles show up as black blobs. At the left of the picture, a vesicle is beginning to engulf some of them—a process called phagocytosis. Another vesicle that has already swallowed several of them can be seen in the middle of the picture. The scale bar is 500 nanometers.

Bottom: A schematic of the whole drug-delivery process.



Besides offering state-of-the-art treatment, at any given time the staff at City of Hope is conducting more than 300 clinical trials, exploring ways to fight cancer, diabetes, HIV/AIDS, and other killers.

The very first vial of the cancer-fighting nanoparticle ever administered to a human subject.

Enter the FDA

There's a long, long road between Caltech and the clinic, and trying to get a drug to market single-handedly is a task well beyond even a Caltech professor's capabilities. So in 2000, after three years of lab work, Davis formed a company called Insert Therapeutics to shepherd things along. Before a drug can be sold in this country, the Food and Drug Administration requires three sets of clinical trials. Phase I is strictly about safety—is the cure worse than the disease? To find out, some 20 to 80 people are treated and then tracked for a year or so to look for aftereffects. Phase II tests efficacy—does it actually work? This involves a few hundred patients in order to gather enough statistics, and at best takes a couple more years unless the results are really spectacular. Phase III compares the new treatment to existing ones, involves thousands of patients, and can drag on for a decade.

The volume of paperwork is absolutely stupefying, and the staggering sums of cash required to see the process through are much easier to get from venture capitalists than university donors. Says Davis wryly, "There are lots of methods in lots of labs and lots of animal studies, but the translation from that into humans is huge, as far as effort and expense. The classic line is, if you could make any money curing mice, we'd all be millionaires by now. And it's true. There are significant differences between mice and humans, and as soon as you get into human studies, you see differences that tell us a lot, from a scientific and mechanistic point of view, about what's going on. But Insert Therapeutics, spearheaded by Thomas Schluep as chief scientific officer, is successfully translating laboratory materials to the clinic."

The nanoparticle, now christened IT-101 (for Insert Therapeutics 101), is midway through Phase I trials under the aegis of Dr. Yun Yen, director of the department of clinical and molecular pharmacology at City of Hope, a research hospital just a few exits east of Caltech on the 210 freeway. Since Phase I trials are the first foray into the human body, they're a treatment of last resort—the participants have already failed other approaches and have nothing left to lose. There are currently numerous patients participating, with a whole spectrum of cancers—lung, pancreatic, kidney, ovarian, and breast. The early results were so encouraging that one patient broke the wall of confidentiality and gave an interview to the *Pasadena Star-News* in September 2006.

This gentleman was diagnosed with pancreatic cancer in 2002, and two-thirds of his pancreas was removed. Two months of chemotherapy followed, but a little more than a year later the cancer returned, spreading into his lungs. "I did another three or four months of chemo, but it didn't work. The cancer began progressing faster, and I quickly reached Stage IV [the last of cancer's four stages]." The chemo "was very tough. I had to lie in bed for four or five days afterward to recover. Just no energy. And I had hardly any white cells left, so I had to avoid people. I couldn't even go to the supermarket. I used to dread every week I had to go in for it." He joined the IT-101 trial in July 2006, and the difference has been like night and day. "I don't notice it much. It doesn't break the immune system, so I don't have to take any supplements for my blood. And the next day I can move around, go shopping. I'm feeling much better, gained some weight." The only side effect he noticed, and he calls it "very tolerable," is that some foods taste a little funny.

Four-Part Harmony

Meanwhile, Davis continues to explore even newer approaches. One particularly promising one uses the cell's own machinery to, in effect, throttle back a runaway gene. RNA is the messenger

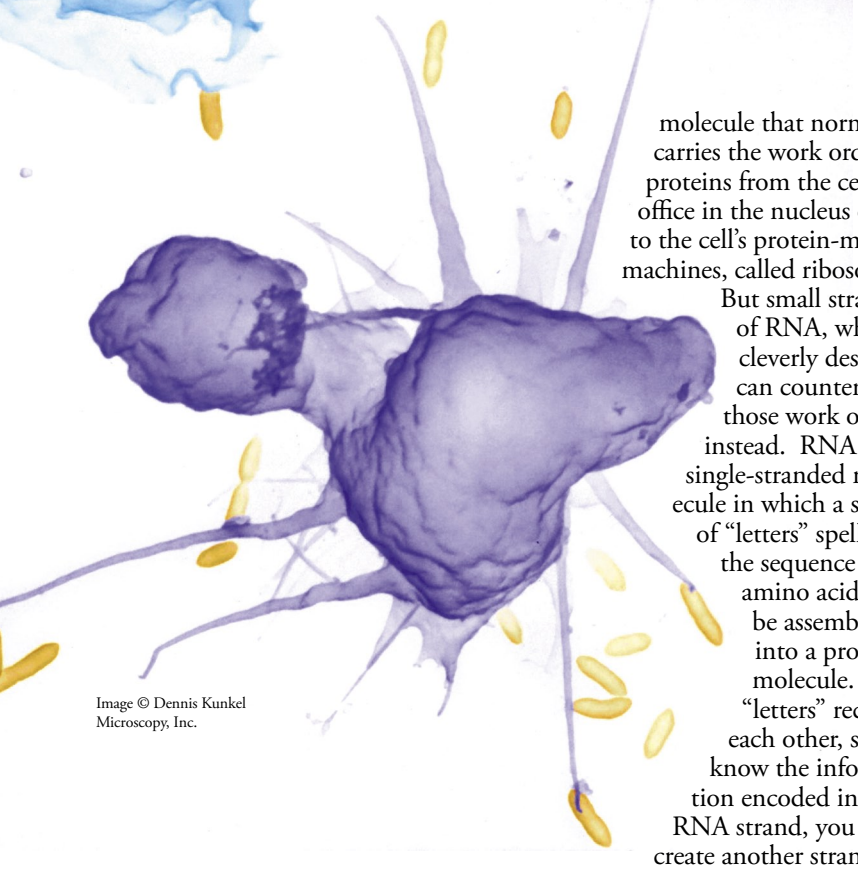


Image © Dennis Kunkel Microscopy, Inc.

A macrophage (blue, and shown 3,900 times its actual size) chows down on some *E. coli* bacteria (yellow) that had managed to sneak into the pleural cavity between the membranes surrounding the lungs.

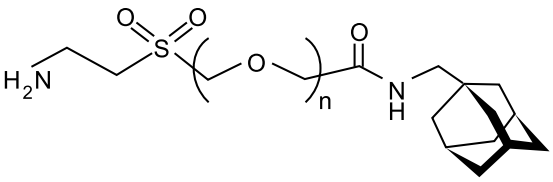
molecule that normally carries the work orders for proteins from the central office in the nucleus out to the cell's protein-making machines, called ribosomes. But small strands of RNA, when cleverly designed, can countermand those work orders instead. RNA is a single-stranded molecule in which a series of "letters" spells out the sequence of amino acids to be assembled into a protein molecule. These "letters" recognize each other, so if you know the information encoded in an RNA strand, you can create another strand that uses the cell's machinery to bring those two RNA strands together and destroy the messenger RNA strand. This phenomenon, called RNA interference, won the 2006 Nobel Prize in Physiology or Medicine for the folks who figured out its workings. If you could get the appropriate siRNA (for small interfering RNA) into a cell, you could essentially turn off a gene that is making it cancerous—just what the doctor ordered. Better still, siRNAs are short molecules that can be made synthetically in bulk.

"We had started trying to use nanoparticles to deliver genes into the nucleus, which is a very hard problem," Davis recalls. "And then you have to control their activity, which is even harder. But when the RNA-interference concept came out in the late '90s, we immediately recognized that this was a much better way to go." But those groundbreaking studies involved injecting a high-pressure, high-volume solution of the siRNA molecules into a mouse's tail vein. Scaled up to human size, the dose would be equivalent to getting shot up with some seven liters of water in the space of a couple of seconds. Malpractice suits would undoubtedly result.

As luck would have it, siRNA molecules have negative charges scattered all along their lengths, and the cyclodextrin polymers can be made with positive ones. Mix the two together, and static cling takes over. The siRNA is woven throughout the nanoparticle, and some of the resulting nearly neutral nanoparticles are safe from the warrior cells called macrophages that roam the body. All cells—your own as well as bacteria, fungi, and viruses—are negatively charged, and macrophages engulf negatively charged entities that don't have proper ID.

In this design, the sugar cones sit empty, so the Davis lab promptly stuffed them with other things. Colloidal particles can agglutinate into glop balls, a process that chemical engineers fight by enshrouding each particle in a "brush layer." The brush's protruding bristles repel other particles, and PEG makes a dandy bristle. So PEG chains were anchored to the nanoparticles by attaching them to molecules of adamantane, which fit neatly into the vacant sugar cones on the nanoparticles' surfaces.

It almost didn't work. "The adamantanes just kept popping in and out, even as the RNA began to bind," says Davis. "But once we got to PEG of a certain size, the brush layer actually imparted an energy of stabilization as it formed, and that keeps the system assembled. It took us forever to figure out what was happening. It's really amazing—without that extra energy, the whole system would just fall apart."



The brush's PEG bristles are attached to molecules of adamantane, whose four fused six-membered carbon rings look like the blades of an eggbeater.

A smattering of the PEG chains end with a molecule of transferrin, an iron-carrying protein that is ingested by rapidly growing cells. Iron atoms are crucial to many enzymes, and cancer cells are gluttons for the metal, so they sprout lots of transferrin receptors on their surfaces. This helps the nanoparticles home in on them. Normal cells have only a handful of transferrin receptors, and the nanoparticles do not compete for these receptors as well as single transferrin molecules do. But a nanoparticle sporting an Afro beaded with a controlled number of transferrins can out-compete the individual molecules for the cancer cell's receptors because its high density of transferrins allows it to bind several receptors at once. "A nanoparticle is the only kind of drug-delivery system with enough surface area to allow you to do this," says Davis. "Multivalency is used by biology everywhere, but trying to do it correctly on a particle is state of the art."

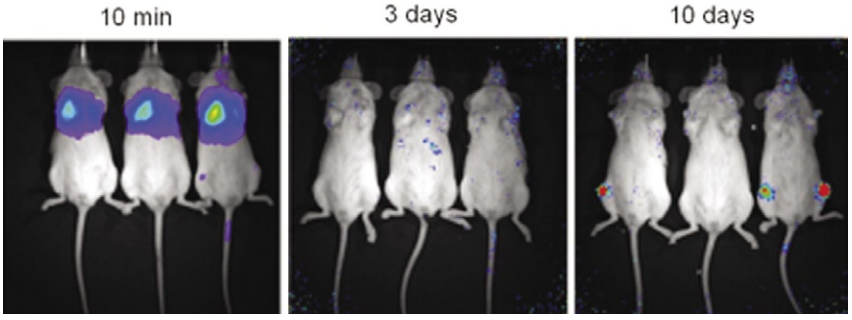
If these nanoparticles lingered in the cell's vesicles, the siRNA would be digested like any other nutrient. So the Davis lab wired in a self-destruct switch. When dunked in acid, an amine group on each end of every polymer molecule picks up a proton, giving the nanoparticle a substantial positive charge that literally blows it apart.

Water simultaneously floods in as osmosis acts to dilute the charge, and the vesicle explodes like an overinflated balloon. The siRNA then gets picked up by molecules that initiate the RNA interference mechanism.

The approach has now been tested in mice with collaborators from Children's Hospital Los Angeles. Cancer cells in 85 percent of patients with Ewing's sarcoma have a genetic rearrangement in which a piece of DNA that normally lives on chromosome 11 somehow winds up on chromosome 22. This "fusion gene," called *EWS-FLI1*, is thought to activate other genes that help the cancer grow, and shutting it down has been shown to retard tumor growth and proliferation. Many cancers, including pancreatic, liver, and numerous intestinal cancers have similar fusion genes. Ewing's sarcoma hides in the bones, and by the time most patients are diagnosed they already have micrometastases—teeny, tiny tumors too small to see and well-nigh impossible to get rid of, even with whole-body chemotherapy. Ewing's is also a nasty bit of business because it frequently develops multidrug resistance.

Ewing's sarcoma hides in the bones, and by the time most patients are diagnosed they already have micrometastases—teeny, tiny tumors too small to see and well-nigh impossible to get rid of.

To mimic these micrometastases and track their spread, mice were injected with Ewing's sarcoma cells that had been modified to include the gene for luciferase—the protein that puts the fire in fireflies. The cells circulated freely through the blood, lodging in all sorts of places, and wherever they wound up, they lit up. Then, for the next five to eight weeks, their travels were followed with an ultrasensitive CCD camera system adapted from astronomical designs by Xenogen, a biological imaging company. Essentially, you strap a tiny gas mask on the mouse, give it anesthesia, lay it on a tray in a dark cabinet, and look for the faintest of glows. Sarcomas turned up in the mice's femurs, lungs, and brains, among other places.



Ten minutes after injection into the tail vein, most of the luciferase-containing sarcoma cells can be found in the capillaries of the lungs. As the cells disperse, the signal scatters and fades until substantial tumors develop.

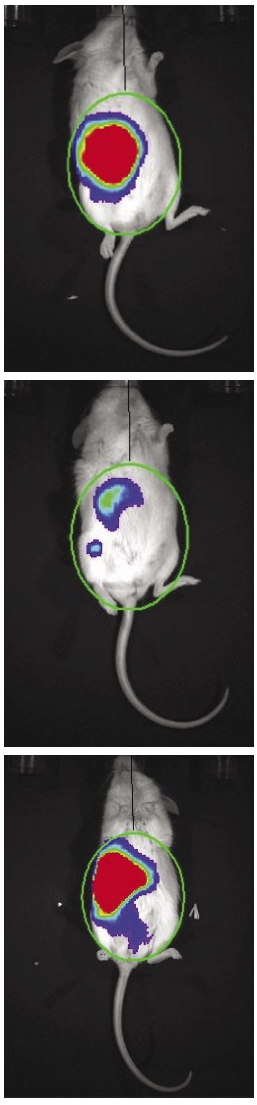
From Siwen Hu-Lieskvan, et al., *Cancer Research*, vol. 65, no. 19, October 1, 2005, pp. 8984–8992.

At about the five-week mark, some of the mice were given a shot—0.2 milliliters of solution, or four drops, a much more manageable dose—of a nanoparticle containing an siRNA against *EWS-FLI1*, that fusion gene mentioned earlier. The intensity of the light they emitted dropped by more than 60 percent for two or three days, then rebounded to pretreatment levels as the cells resumed their unbridled division. "It's a dilution effect," Davis explains. "Each time the cell divides, half of the siRNA goes to each new cell. And these cells divide really fast—much faster than they do in people. So we might only have to dose a patient every few days, or possibly every week. If the cell wasn't dividing at all, the effect would last for a month or so."

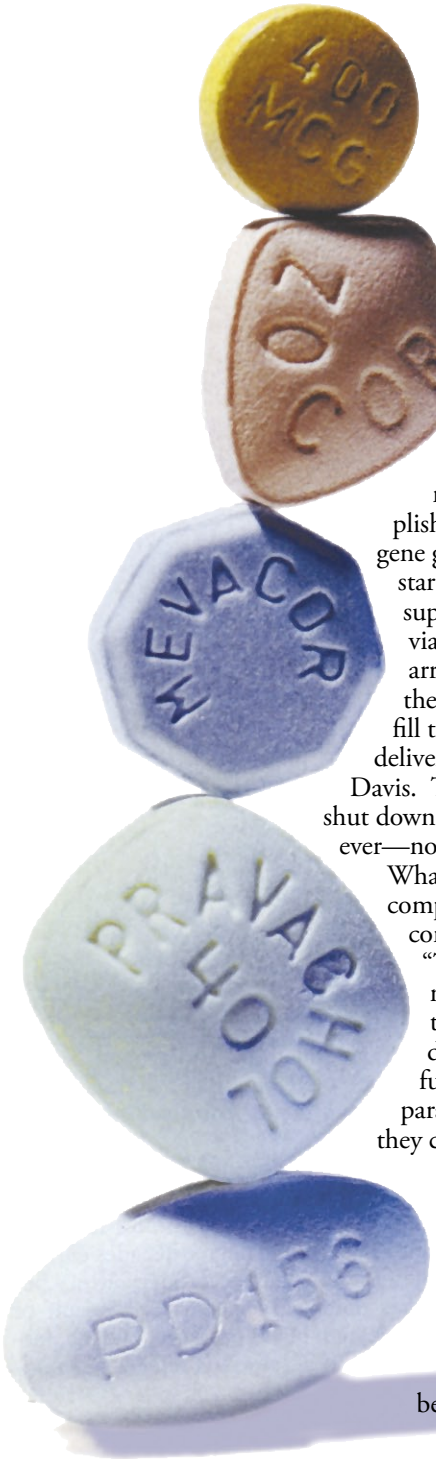
Other mice were given a nanoparticle containing an siRNA against luciferase itself. Two days later, the light from the tumors had dropped to less than 10 percent of its original intensity. "And that's the key result," says Davis. "It shows that the nanoparticles are getting to essentially all the cancer cells within the tumor mass." This glow, too, returned to full strength in another three days; the mice, meanwhile, showed no ill effects from either procedure.

And in a long-term study in which mice were given the anti-fusion-gene nanoparticles twice weekly beginning on the day they were also given the Ewing's sarcoma cells, only 20 percent of the mice developed tumors at all.

In 2005, Davis and others started a new company called



Above: These pictures of a mouse with a luciferase-containing tumor were taken, from top, 40, 43, and 46 days after being injected with Ewing's sarcoma cells. On days 40 and 41, the mouse got an injection of the anti-luciferase nanoparticle.



Courtesy of Taka Kawachi.

Calando Pharmaceuticals to bring the siRNA project to the clinic under the scientific leadership of Jeremy Heidel (MS '01, PhD '05). *Calando* is an obscure piece of musical notation that instructs a performer to fade to silence, so Davis chose the name in a nod to Mary, an accomplished flutist—the technology makes a gene go silent. Calando officials plan to start Phase I trials this fall. Calando will supply the polymer and both PEGs in a vial of dry powder, and the siRNA will arrive in a second vial. Once again, all the clinician has to do is add water and fill the IV bag. "It will be the first targeted delivery of siRNA in a human being," says Davis. The hope is that if the right gene is shut down, there will be no side effects whatsoever—not even funky food tastes.

What with its four different molecular components, it will also be one of the most complicated systems the FDA has seen. "They're Porsches, compared to earlier nanoparticles," says Davis—finely tuned machines with a lot of subtle design features. "That's what's really fun about it. There are many, many parameters that had to be understood so they could be engineered to work together."

Davis is keeping his fingers crossed that the trials will go smoothly. "The FDA has been helpful with the Insert trial. But the Calando one is going to be more complicated from a technological and regulatory perspective, due to its four components. Initial interactions with the FDA have been proceeding well."

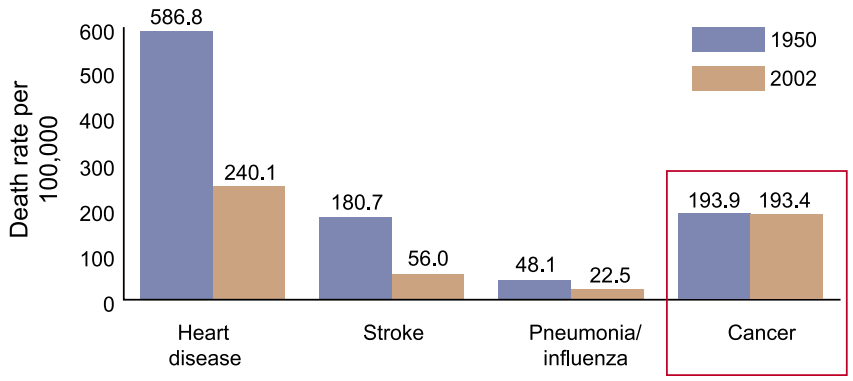
"We Started from Zero"

Before Mary's illness, Davis had spent his career improving the workings of zeolites, a class of minerals used as industrial-scale catalysts. While most of his research group continued to mine that vein, he struck out into virgin territory, heading into the mountains that separate chemical engineering from molecular biology. "Basically, we started from zero. We didn't know anything. Hector Gonzalez, an organic-chemist postdoc, started on the synthesis, and Suzie Jean Hwang [MS '98, PhD '01 (now Suzie Hwang Pun)], a grad student in Chem. E., started on the biology. We didn't even know how to culture cells. Suzie learned how to do it, and we just kind of pushed our way through and started building the facilities we needed."

The whole exercise has been a good argument for the tenure system. "It's like everything else—the first couple of years you just can't get anything right, and it was very frustrating," Davis laughs. "The one thing I think that really helped me was that I did it later in my career, so I could actually spend several years without results."

"I have to give credit to Caltech, too. It's very easy to go and talk with people here, and everybody was very helpful getting us started with cells, getting us started with mice. Just mastering the language was difficult—I'd go to medical meetings, sit in the back of the room, and try to battle through the jargon. And the other good thing was I could call up someone and say, 'I'm a professor at Caltech,' and I'd get in to see people that might have been really hard to talk to, otherwise."

Getting the chemical synthesis right in quantities sufficient for use in animals and ultimately in humans was not easy. Their cyclodextrin molecules had 21 chemically equivalent places where the polymerization reaction could occur, and each molecule had to behave like a railroad car, with one coupler on each end. Early efforts yielded cars with one, three, or even more couplers, and the



While death rates from heart disease, stroke, and pneumonia/flu have plummeted in the last 50 years, cancer death rates have remained steady. Data from the American Cancer Society.

polymerization process became a complete train wreck. "When we first started working on this, I was talking with Bob Grubbs [the Atkins Professor of Chemistry and a Nobel laureate], and Bob said, 'Do you really want to start working on sugar chemistry?'" laughs Davis. "I wasn't sure what he meant by that, but after a couple of years, I understood."

They eventually figured out a way to attach two iodine atoms on opposite sides of the cyclodextrin molecule, and built a linker outfitted with a sulfur atom on one end and an amine on the other. The sulfur-iodine reaction was very efficient and very selective, churning out identical cyclodextrin-containing units, called monomers, with exactly two couplers each. "The high-purity, large-scale cyclodextrin monomer synthesis was the killer," says Davis. "Once we had that, everything else was downhill."

Prevention Is the Dream

"I would never have done this without having seen what Mary went through," says Davis. "I was reading cancer-therapy papers from the City of Hope's library while I was sitting in the isolation room with her, wearing a surgical mask so she wouldn't get some bug from me. We were in the middle of a nightmarish situation, but she survived all of it and is fine today. It's been a rough ten years, but when we treated the first patient last summer, that to me was the ultimate. He consented to let me watch the first infusion—the first time IT-101 went into a human being. You just hold your breath, because for the first ten minutes or so you don't know whether there's going to be an allergic reaction or something. Everybody's just standing there, waiting."

Davis is not allowed to communicate with any of the patients, and Dr. Yen can't go into specifics, but he does say that things are good—"the patients' platelet levels and white blood cell counts did go down somewhat, but most of them rebounded on their own. Pharmacology confirms that the drug is staying in the serum, and nobody has suffered nausea, vomiting, or hair loss." By the time the trial ends, he expects to have looked at 20 to 30 patients. Planning for Phase II trials is already under way.

In the meantime, the process has gone from making little bits of powder at Caltech to multi-kilogram lots at Insert and Calando. Even so, production costs have stayed acceptable, Davis says, because the starting materials are so cheap. "Relative to other therapeutics, this is going to be very reasonable."

"If we—and others—can create safe, effective therapies with minimal side effects, we're going to change the way in which cancer is treated. It's going to open the door to prophylaxis," Davis says. Doctors routinely prescribe statins—a class of drugs including Zocor and Lipitor—to prevent heart disease by lowering cholesterol. That's likely a part of the reason why deaths from heart disease and stroke have plummeted in the last couple of decades. "Could we do something like this with cancer? Right now, no way. But if you had a set of diagnostic signatures that told you, 'I suspect that there might be something there, but it's so low that I can't yet see it with an imaging agent,' and had a nontoxic treatment without those horrible side effects, why would you not go prophylactic, just to be on the safe side? That's my dream." □

PICTURE CREDITS: 22, 24, 28—Doug Cummings; 27—Mark Davis, City of Hope