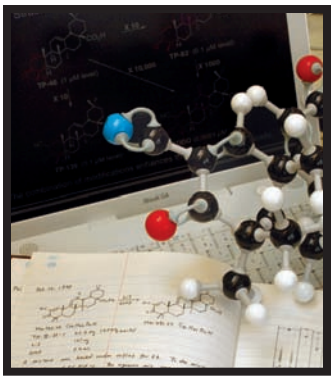


Compound interest

By Jennifer Durgin

What if the way to win the war on cancer is not to cure tumors but to keep them from forming in the first place? Dartmouth's Michael Sporn, known as "the father of chemoprevention," has devoted his career to that question. Now he and his collaborators have two compounds in clinical trials—compounds that may stop tumors before they start.

"What is a healthy mouse?" It's a simple question that Dr. Michael Sporn poses to the hundreds of scientists gathered in the huge conference hall. He answers it by flashing a photo of healthy-looking mice on the giant screens beside the stage. Even if one injected the animals with a potent carcinogen, Sporn continues, for weeks afterward anyone would say the mice still looked healthy. He puts up another photograph of perky mice to prove the point.

"But," he goes on, "could these mice get life insurance . . . because all their lungs look like this nine months later?" The giant screens now display four mouse lungs covered with white tumors. The mice may have looked fine for weeks after the injections, Sporn points out, but "some very nasty things" were happening inside their bodies.

Now he drives his metaphor home, asking, "What is a healthy person?" Is someone who shows no outward signs of disease necessarily healthy? "No," argues Sporn, who is the Oscar M. Cohn '34 Professor of Pharmacology and of Medicine at Dartmouth Medical School.

Like an avalanche, a cancer may seem like a single event set in motion by a single trigger. But both cancers and avalanches are the result of a whole progression of unstable conditions. Long before a tumor forms, it begins as a group of abnormal cells caught in the wrong place at the wrong time. A whole network of cell-to-cell and tissue-to-tissue communications must go awry—resulting in cell differentiation, proliferation, and motility taking place with few, if any, checks and balances. So even though a person shows no signs of cancer, palpable or microscopic, the regulatory networks that protect that individual's cells may be ailing. And when those networks become diseased, the door for cancer is opened. It may take years for a tumor to actually develop and metastasize, but once it does, the avalanche has begun.

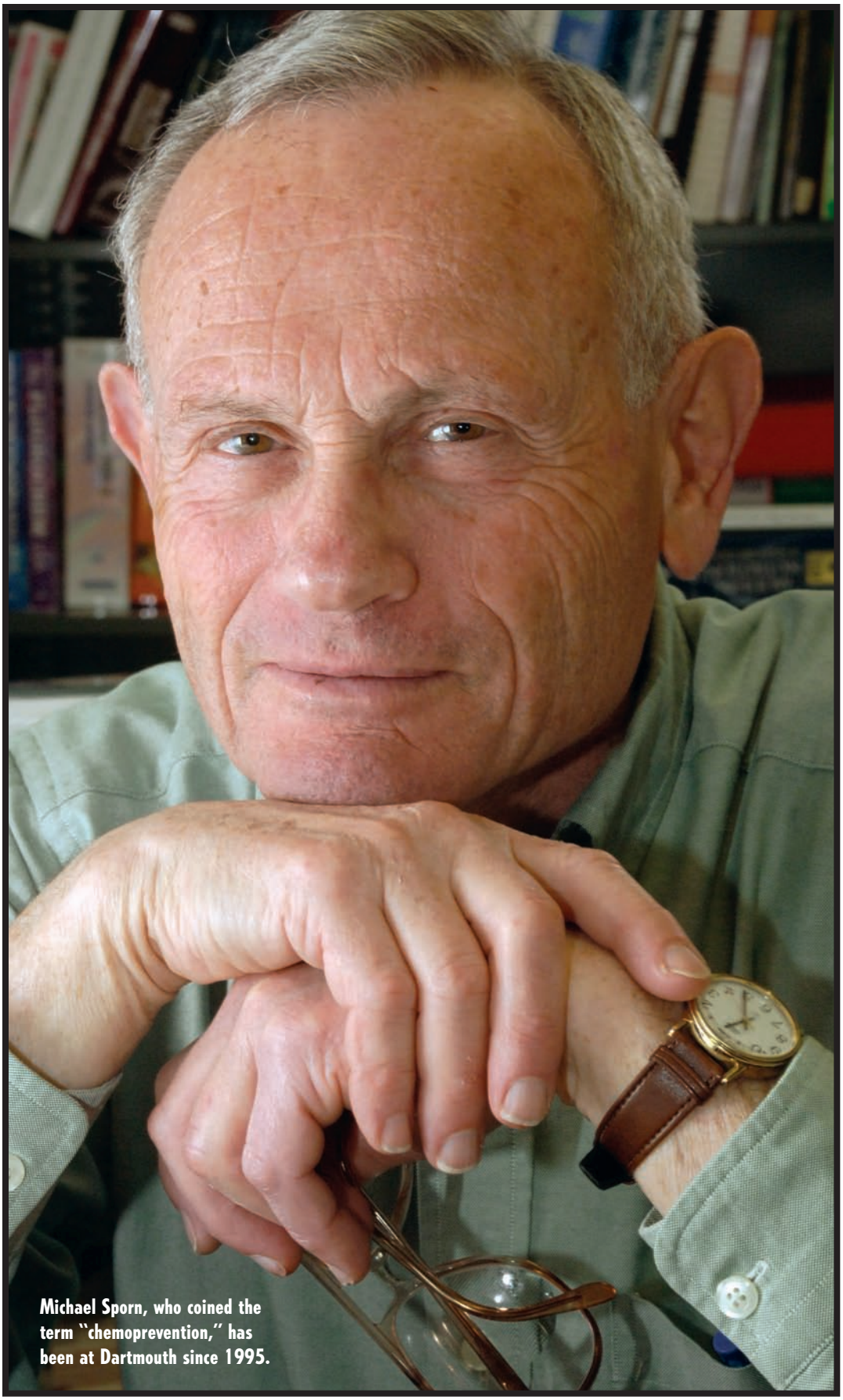
Sure, some skiers survive avalanches, just as some patients survive invasive cancers. But, argues Sporn, doesn't it make more sense not to allow the triggering conditions to form in the first place? For more than 30 years, he has been making the case that prevention and preemption offer the only real hope for winning the war on cancer—a war that he and others say we are losing.

In this conference hall, Sporn is preaching to the already converted. His talk is one of dozens at the annual cancer prevention research conference of the American Association for Cancer Research (AACR). It's a relatively small AACR conference, with about 900 attendees. (The organization's annual meeting, for example, draws about 17,000 people.) Sporn is a heroic figure to many of the attendees. "An inspiration," "a genius," "a prophet" is how they refer to him during other presentations and in one-on-one conversations.

But his lecture is more than motivational; it contains arguably the most exciting data presented at the four-day conference. Sporn and his collaborators—Dartmouth organic chemists Gordon Gribble and Tadashi Honda—have synthesized several compounds that not only

Jennifer Durgin is Dartmouth Medicine*'s senior writer.*

ALL: JON GILBERT FOX



Michael Sporn, who coined the term "chemoprevention," has been at Dartmouth since 1995.

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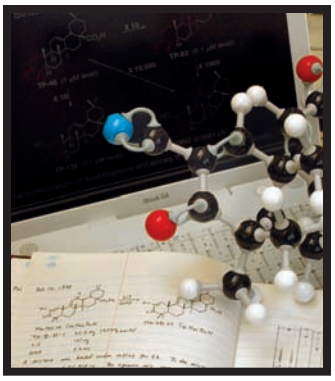


Sporn, Gribble, and Honda first began synthesizing the compounds, called triterpenoids, in 1995. Sporn had just left the National Institutes of Health, after 35 years there, to start a chemoprevention research laboratory at Dartmouth.

shrink existing tumors but also prevent them—with few, if any, apparent negative side effects. Although the drugs have been tested primarily in animals, they are now in clinical trials for the treatment of metastatic, late-stage, solid tumors. So far, the drugs seem to be performing well in humans, too. Sporn hopes that one day the compounds will be used to prevent cancer, not just treat it.

Sporn, Gribble, and Honda first began synthesizing the compounds, called triterpenoids, in 1995. Sporn had just left the National Institutes of Health (NIH), after 35 years there, to start a chemoprevention research laboratory at Dartmouth. That summer, he went looking for an organic chemist to partner with. He found Gribble, who had been on the Dartmouth faculty since 1968, and Honda, an expert in drug synthesis who had just arrived at Dartmouth from Japan.

"Mike had the idea [that] because trees can live a very long time—sequoia trees, for example, in California can live [thousands of years]—and because triterpenoids are ubiquitous in the plant kingdom, there might be a relationship between the presence of triterpenoids and the longevity of trees and plants," Gribble explains. "It's kind of a simple idea," he admits, "but that's what got us started."

Over the next three years, Honda synthesized numerous variations of naturally occurring triterpenoids, starting with commercial extracts from China. The goal was to magnify the mild anti-inflammatory and anticancer properties of the natural products. At first Honda changed the compounds' chemical structures randomly, sending each new derivative to the Sporn lab for bioactivity testing. "Tadashi would make something in his lab and two days later we'd tell him whether it was interesting or whether it was a dud," recalls Sporn. Getting such rapid feedback was unique, he explains. "If you go through conventional testing, this sort of stuff could take months and months and months."

"Our relationship is similar to a pair of wheels on a bicycle," Honda adds. "Good collaboration between biologists and chemists is definitely necessary for the discovery of drugs."

Honda's 46th compound was the first to show promise, but it was still not strong enough to develop into a drug. He continued to modify its chemical structure, hoping to develop a compound potent enough to begin testing it in animal models and eventually in humans.

While Honda was hunting for compounds, Sporn was hunting for funds to keep the project running. In addition to the staff of his own lab, Sporn supported Honda, too. It was "difficult to get funding just based on the chemistry," Gribble explains, because the chemistry behind the synthetic triterpenoids "is fairly simple." It was the compounds' medical potential that was exciting. But even in the cancer-research realm, funds to develop new chemoprevention drugs can be difficult to come by.

The federal funding agencies, like the National Cancer Institute, "talk a good game about [chemoprevention], but that's not where the money goes," says Clifton Leaf, a senior editor at *Fortune* magazine. "As a financial journalist, I look at where the money trail is." And it's clear, he says, from the number of grants, scientific papers, and conferences devoted to chemoprevention, that prevention "is not where the money is going."

Leaf—himself a survivor of Hodgkin's disease—began covering cancer and cancer research in 2004 with an award-winning article titled "Why We're Losing the War on Cancer and How to Win It." He went on to author several more cancer-related articles for *Fortune* and is currently writing a book about the "culture of cancer research, about how we got to where we are with the war on cancer," as he puts it. He estimates that he's interviewed more than 1,500 scientists, pharmaceutical executives, physicians, and regulators for his book, to be published by Knopf in late 2007.

Leaf's reporting has even earned him a place at the table in the discussion over the future of cancer research. In the past few years, he's presented testimony to the President's Cancer Panel, served as a panelist at a Capitol Hill forum on chemoprevention and early detection, and delivered keynote lectures at meetings of the National Cancer Institute, the AACR, and several other major medical and scientific groups. He was also recently elected to the board of directors of the Susan G. Komen Breast Cancer Foundation.

When Leaf started researching the 2004 *Fortune* article, he "thought that we were doing really, really well in cancer," he says. But then he looked at cancer deaths and changed his mind.

Although the death rates for many common cancers have edged downward since 1971—the year the National Cancer Act was passed—the numbers of deaths have increased. For example, in 1971 about 32 women out of every 100,000 died of breast cancer versus 25 out of every 100,000 in 2003—the latest year for which data is available. Given the increase in the U.S. population, that translates into about 33,000 women in 1971 and 40,000 women in 2003. The fact that people are still dying of cancer in such massive numbers is what troubles Sporn and Leaf.

"You can't talk your way around" the death figures, says Sporn. "There are so many dead bodies in the cancer pot."

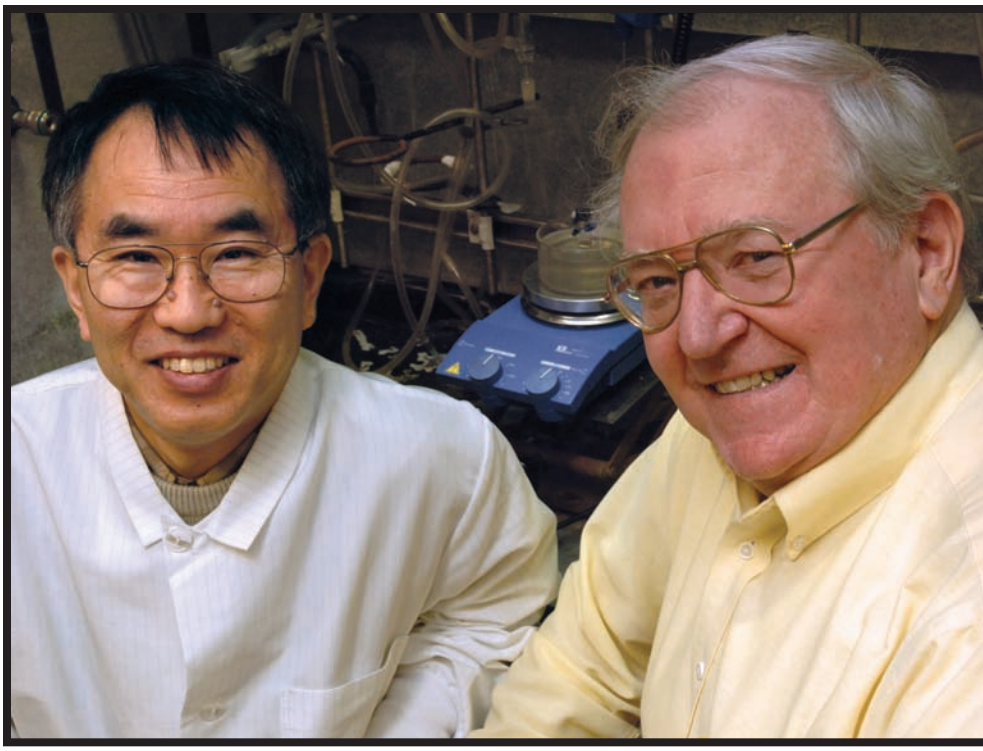
Sporn and Leaf have also come to similar conclusions about why the nation has made so little progress on reducing the total number of cancer deaths. A primary reason, they say, is the lack of money available for researchers who want to look at the cancer problem globally and from a chemopreventive point of view. Leaf explained the situation in his 2004 article:

"When you add it all up, Americans have spent, through taxes, donations, and private R&D, close to $200 billion, in inflation-adjusted dollars, since 1971. What has that national investment netted so far? . . . In short, scientists now know (or think they know) nearly all the biochemical steps that a healthy cell uses to multiply, to shut down its growth, and to sense internal damage and die at the right time—as well as many of the genes that encode for these processes. . . .

"Yet somehow, along the way, something important has gotten lost. The search for knowledge has become an end unto itself rather than the means to an end. And the research has become increasingly narrow, so much so that physician-scientists who want to think systemically about cancer or the organism as a whole—or who might have completely new approaches—often can't get funding. . . . The money goes almost entirely to researchers who focus on very specific genetic or molecular mechanisms within the cancer cell or other tissue. The narrower the research niche, it sometimes seems, the greater the rewards the researcher is likely to attain."

Sporn is even harsher in his criticism of research funding decisions. "The NIH study sections look askance at people who want to look at problems in any global way," he says. "They force everybody to fragment their ideas to the point that the data become trivial." He's especially frustrated with what he sees as an overwhelming emphasis on oncogenomics—the study of genes involved in cancer.

He explained his thinking on this point in an article published in the July 2006 issue of *Nature Clinical Practice Oncology*. "Cancer is genetic," Sporn wrote, but "everything in biology is genetic! If cancer is merely a genetic disease, why is it that there are so many more heavy smokers, most of whom incur DNA damage, than there are cases of lung cancer? . . . [Cancer] is a transactional disease. Cancer does not arise because something is wrong with one specific molecule; the problem is that the functional relationships between a set of critical molecules have been disrupted."



Organic chemists Tadashi Honda, left, and Gordon Gribble have worked closely with Sporn for over a decade on chemopreventive compounds. A molecular model of one of their compounds is depicted on the facing page (as well as on the cover of this issue), with Honda's lab notebook open to the day in 1998 when they identified CDDO; their first breakthrough compound, it is nearly half a million times more active than the natural triterpenoid that it's derived from.

Another problem Sporn sees with focusing too much on genetics is that tumors are genetically unstable. "As carcinomas progress, they become increasingly heterogenous," he wrote in *Lancet* in 1996. "The cells in advanced metastatic carcinomas may have numerous genetic abnormalities, and these abnormalities may vary from one cell to the next within the carcinoma. . . . Thoughts of gene therapy directed at single oncogenes or tumour suppressor genes in such a context seem hopelessly naïve."

Sporn emphasized this point in his recent AACR talk. "We're spending immense amounts of money to detect genetic abnormalities that might predispose [people] to carcinogenesis," he told fellow scientists, "but we're spending peanuts on what to do after we have obtained such data. Something's wrong here. There has to be some better balance."

Major drug companies aren't keen on investing in chemoprevention either. One might assume that a chemopreventive drug would have commercial appeal because it could be marketed to a broad population and would need to be taken for many years. But any drug has side effects, and the risk that apparently healthy people

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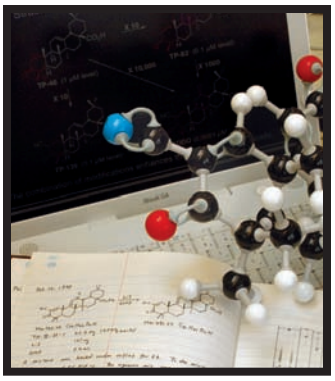


As hard a time as Sporn has had finding funding, he says it's even harder for young researchers interested in chemoprevention. "I'm able to stay afloat," he says, largely because of his long career and high profile in the field.

are willing to accept "is very, very, very low," explains Leaf. "You have to be . . . 'safer than thou' with a chemopreventive agent, and that's phenomenally expensive" for a pharmaceutical company to test and develop. The cost of running large, lengthy clinical trials—not to mention the risk of litigation if a subsequent problem turns up—scare most drug companies away from developing chemopreventive agents.

Early on in the triterpenoid project, Sporn says he contacted every major pharmaceutical company in the U.S. and Europe to ask for support, but none of them were interested.

Despite the financial challenges, Sporn has kept the triterpenoid project going with several NIH grants, funds from private foundations, and gifts from the Dartmouth College Class of '34. He has also maintained a small and highly efficient lab staff. While many top cancer researchers, at Dartmouth and elsewhere, have multiple postdoctoral fellows and a stable of graduate and undergraduate students, Sporn has one postdoc, one doctoral student, and three technicians. And as hard a time as Sporn has had finding funding, he says it's even harder for young researchers interested in chemoprevention. "I'm able to stay afloat," he says, largely because of his long career and high profile in the field.

On February 16, 1998, the triterpenoid project hit a breakthrough. Honda created the most exciting compound the team had seen to date—triterpenoid 151, later named CDDO (for 2-cyano-3, 12-dioxooleana-1, 9-dien-28-oic acid). It was 10,000 times more potent than the 46th compound and close to a half-million times more potent than the original, natural triterpenoids.

When Sporn and his postdoctoral fellow at the time, Dr. Nanjoo Suh, tested CDDO in various cell lines and rodent models, they discovered it had an amazing combination of properties. CDDO inhibited the proliferation of many tumor cells, suppressed inflammation (which is linked to cancer and many other diseases), and, at the same time, protected healthy, noncancerous cells. And it did all this at extremely low concentrations—about a billionth of a gram—in cell cultures. Best of all, CDDO exhibited no negative side effects.

Over the next several years, Sporn's lab published dozens of papers in high-profile journals, such as *Cancer Research*, documenting CDDO's and its derivatives' anticancer, anti-inflammatory, and cyto-protective properties in numerous animal models. The compounds wowed Sporn and his collaborators at Dartmouth, Johns Hopkins, Rutgers, and elsewhere, yet he still couldn't garner support from any major drug companies. But the work did attract the attention of a small and unusual company in Texas.

"We were immediately interested in the project," says Warren Huff, founding CEO and president of Reata Pharmaceuticals, which has licensed CDDO and derivatives CDDO-Me and CDDO-Im for development in clinical trials. Reata, formed in 2002 as a spin-off from the University of Texas system, specializes in moving promising drugs developed in academia into the marketplace. It focuses on the aspects of drug development that are difficult for academic institutions to handle, Huff explains, such as actually making the drugs, managing the clinical studies necessary to look for side effects and to gain FDA approval, and handling all of the regulatory issues. "We don't try to replicate [what the academic institutions] do best," adds Huff, such as figuring out how the drug works in the body. If the results of the early human trials with CDDO-Me are any indication, Reata's investment in the triterpenoids is going to pay off.

CDDO-Me, the farthest along in the clinical testing pipeline, is in late Phase I trials at M.D. Anderson Cancer Center and Dana-Farber Cancer Institute; it's being used in patients with metastatic, late-stage solid tumors. (Phase I trials are small, include about 20-30 patients, and are designed to look at safety.) The results thus far have been "as good as it gets," says Huff. At very low doses, CDDO-Me seems to dramatically reduce a whole panel of immunoregulatory proteins that are markers for a poor prognosis—meaning the drug may help patients live longer. CDDO-Me, which is taken orally, also hasn't shown any negative side effects, according to Huff. Reata plans to begin Phase II trials by mid-2007. (Phase II trials look at a drug's efficacy, in addition to its safety.)

If CDDO-Me shows a benefit in Phase II, "it would definitely be eligible for an accelerated approval," says Huff. The best-case scenario is that the drug could be approved and available by 2009.

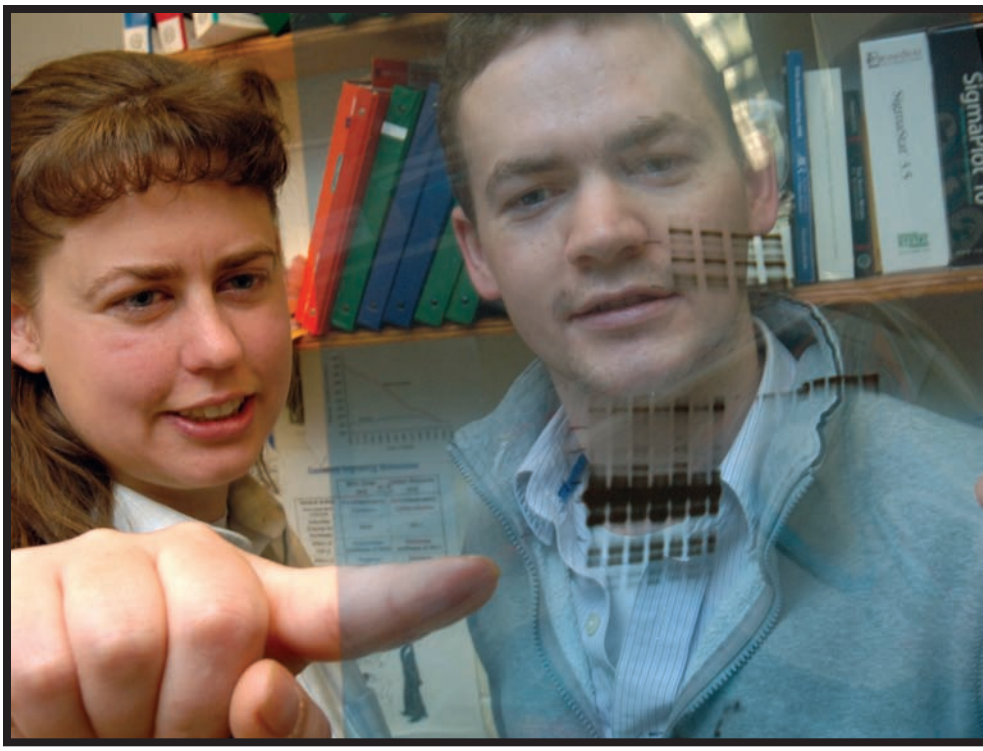
If CDDO-Me is approved for treatment of patients with metastatic, late-stage solid tumors, Reata would then begin trying the drug in patients with earlier stages of cancer, in the hope of eventually conducting prevention trials. The company has already begun working with Sporn's lab on lung cancer and breast cancer prevention studies using CDDO-Me in animal models. Dr. Karen Liby, Sporn's current postdoctoral fellow, led three of these studies and presented the results in a press conference at the AACR chemoprevention meeting.

In the first study, Liby (pronounced "LIE-bee")

tested whether CDDO-Me alone, as well as in combination with a drug called a rexinoid, prevents estrogen-receptor-negative (ER–) breast cancer—an especially difficult form of breast cancer to treat. She fed mice that had been engineered to develop ER– breast tumors either a control diet or one of three modified diets—containing CDDO-Me, the rexinoid, or both. By 40 weeks of age, 100% of the control mice had developed breast cancer. In contrast, Liby found tumors in only 12% of the mice fed CDDO-Me, 29% of the mice fed the rexinoid, and none in the mice fed the combo diet.

After an additional three months on the diets, 50% of the mice fed CDDO-Me and 43% of the mice fed the rexinoid had developed tumors. But still hardly any tumors were found in the mice fed both drugs.

Liby followed a similar protocol in two other studies, looking at the prevention of lung tumors; both of them used CDDO-Me, other CDDO derivatives, and the same rexinoid. All of the compounds dramatically reduced the number and size of lung tumors, too. Liby and Sporn hope to publish the results of all three trials soon.



Karen Liby, left, Sporn's current postdoctoral fellow, goes over some experimental results with Mark Yore, a Ph.D. student in pharmacology. Liby oversaw several of the early animal-model studies testing the effectiveness of CDDO-Me, one of the compounds that is now in human clinical trials; Yore also contributes to the chemoprevention research. Sporn's laboratory is small and efficient—he has just one postdoc, one doctoral student, and three technicians.

Given the lack of apparent side effects and the spectacular efficacy that the rexinoid demonstrated in Liby's studies, one might expect the maker of that drug to be very interested in collaborating with Sporn's lab and Reata. But it's not, according to Sporn. Ligand Pharmaceuticals had been developing the rexinoid, officially named LG100268, for a purpose other than cancer treatment and prevention. However, Ligand seems now to have abandoned the development of LG100268. It's not listed in the "product pipeline" on the Ligand website, and a company spokesperson declined to comment on it further.

Sporn first published data on LG100268 in the October 2002 issue of *Clinical Cancer Research*. He and his postdoc at the time, Nanjoo Suh, demonstrated that when used in combination with a drug called Arzoxifene, which was being developed by Eli Lilly, it was extremely effective at reducing the size and number of estrogen-receptor-positive (ER+) breast tumors. Four years later, in the October 2006 issue of the same journal, Sporn and Liby demonstrated that Arzoxifene and LG100268, when used in combination, completely suppressed the formation of ER– tumors in mice. All of the mice fed the control diet developed tumors, while none of the mice fed the combo diet did.

This should have been big news because, as Liby and her coauthors noted, no drugs exist to prevent ER– breast cancer in women. (In contrast, tamoxifen and raloxifene are effective for ER+ breast cancer.) Yet the findings were met with silence. "We're rather depressed that nothing has happened with this in the real world," Sporn told the scientists who attended his AACR talk.

"I've agitated with Eli Lilly," Sporn says. "I've agitated with Ligand." He's also tried to get the National Cancer Institute and breast cancer advocacy groups to promote the development of Arzoxifene and LG100268, he says. But a collaboration between two companies "involves getting their lawyers together to share intellectual property," he notes, "which they do not want to do."

Dr. Powel Brown, a professor at Baylor College of Medicine and another of the presenters at the AACR conference, has also found LG100268 to be highly effective at preventing ER– breast cancer in mice. "It's extremely frustrating to have an agent that is so active and so nontoxic, at least in mice, and to not be able to develop it."

For now, the best hope for new chemoprevention agents seems to lie with triterpenoids. Huff acknowledges the tremendous financial and litigation risks that pharmaceutical companies face when investing in cancer prevention drugs. But for Reata, the hurdles with triterpenoids

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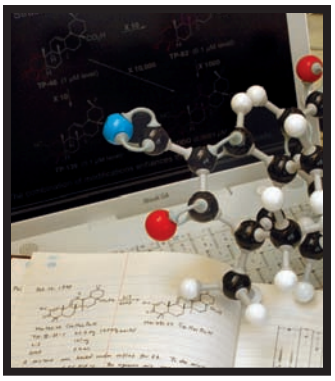

Sporn is hopeful, too, but also admits to profound frustration. Now 73, he's been preaching the gospel of chemoprevention and receiving praise for his ideas for more than 30 years. In fact, he's even been called the "father of chemoprevention."

Synthetic Triterpenoids: The Path from Creation to Clinical Trials

Design and synthesis of new compounds

Screening of compounds for good biological properties

↓

Identification of a lead compound

↓

Further modifications of the compound to improve its bioactive properties

Screening of new compounds in cell cultures and animal models

↓

Identification of a drug candidate

↓

Evaluation of its pharmacology and toxicology in animal models

Collaboration with other biological laboratories

Exploration of the potential for efficient, large-scale synthesis of the compound

↓

Collaborative preclinical animal studies

↓

Phase I-III clinical trials

↓

Approval by the FDA?

LEGEND

Steps overseen by the organic chemists

Steps overseen by the pharmacologists

Steps overseen by the drug company

are a little lower, he thinks. If a drug can be used only for prevention, then it's very difficult for a company to justify investing in it, he says. But because the triterpenoids are so potent and have such a broad range of activity, they can be used for much more than just prevention.

"This isn't a question of whether the drugs should be tried for prevention or not," Huff says. "They should be tried for prevention," as well as for several other inflammatory-related diseases. But first Reata will get the drugs approved for treatment of late-stage cancer—a less risky prospect—and then work toward prevention trials.

Huff is optimistic, as are Liby, Gribble, and Honda. All of them have high hopes for the triterpenoids that are now in clinical trials, as well as for the new ones that Honda continues to develop. (See **http://dartmed.dartmouth.edu/winter06/html/compound_interest_we.php** for several multimedia WEB EXTRAS with additional details about this long-time collaboration.)

Sporn is hopeful, too, but also admits to profound frustration. Now 73, he's been preaching the gospel of chemoprevention and receiving praise for his ideas for more than 30 years. In fact, he's even been called the "father of chemoprevention" for having coined the term "chemoprevention" in the 1970s. Yet neither medicine nor society in general has fully embraced chemoprevention.

"In recent years," says Leaf, "particularly in the last year, [Sporn] has gotten more and more frustrated with what he sees as the continuing growth of the problem, the cost of [cancer] drugs for treatment, and the lack of investment in the only model that can work. And by the way, this is a model that has worked in cardiovascular disease."

Since 1996, when Sporn wrote an article about the war on cancer for *Lancet*, he has been calling for the oncology community to follow the lead of the cardiovascular community. Cardiovascular deaths have plummeted over the past 30 years, largely because of an emphasis on prevention, Sporn argues. High blood pressure and high cholesterol are now universally accepted as precursors to cardiovascular disease and thus as warranting treatment with powerful and potentially dangerous drugs, such as statins. Even some of the most commonly used medications can have serious side effects. Aspirin, for example, can cause bleeding in the stomach and brain, kidney failure, and some kinds of strokes, according to the Food and Drug Administration. But people take it because its beneficial effects outweigh the small risk of those side effects.

"We should ask why the oncology community and the public at large have been so resistant to" taking a chemopreventive approach with cancer, Sporn wrote. Why not develop drugs to treat the molecular and cellular changes that occur in tissues before a tumor develops?

"We're so obsessed," says Leaf, "with the sins of commission—of giving someone a drug and having one in a thousand, or one in 10,000, have a reaction that's terrible—that it blinds us, or prevents us from acting in the only way that we can, which is to try to prevent cancer development in large numbers of people."

Earlier this year, Leaf was chatting with Sporn about this very problem. "Everybody talks about risk-benefit," Sporn remembers Leaf telling him, but "that's posing the question the wrong way. It's not a risk versus benefit situation; it's a risk versus risk situation."

Sporn liked that idea so much that he used it in his AACR talk. "The real risk for the prospective cancer patient may be to do nothing," Sporn told the audience. If you have a strong family history of breast or colon cancer, for example, your risk may be exceptionally high. "So you must measure the risks of using chemoprevention," said Sporn, against "the risk of doing nothing." ■

Sporn is pictured here with Charlotte Williams, a lab technician who has worked with him since 1995, when he arrived at Dartmouth after a 35-year career at the National Institutes of Health. He has been making the case for chemoprevention for nearly that long—arguing that intervening once a tumor is evident is too late. But he has become frustrated by the fact that chemopreventive approaches are not a high priority among the funders of cancer research.

Since 1996, Sporn has been calling for the oncology community to follow the lead of the cardiovascular community. Cardiovascular deaths have plummeted over the past 30 years, largely because of an emphasis on prevention, Sporn argues.