How Michael Milken helped transform the research and funding of prostate cancer by applying the lessons of Wall Street to the support of science

From Junk Bond King To Cancer Crusader

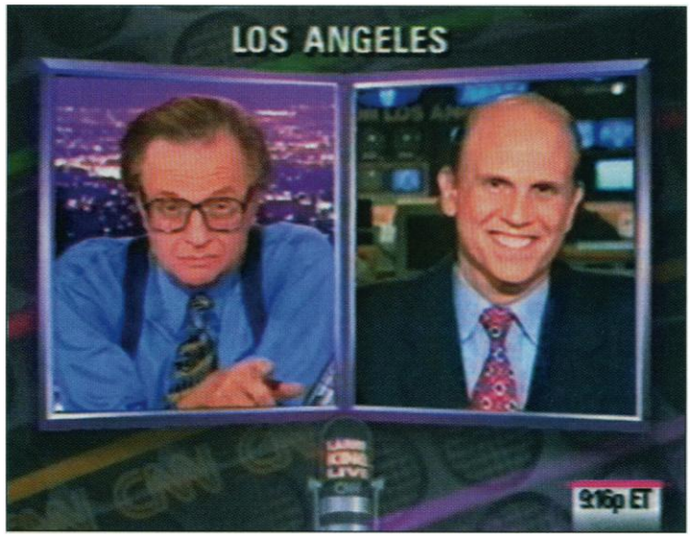
Paul Lange and Leroy Hood ran up against a familiar problem in 1995, when they were trying to identify genetic changes that occur in cancerous prostate cells: They desperately needed to locate and study families with several living prostate cancer victims—a tall order, since this cancer is typically diagnosed late in life. Frustrated by the glacially slow process of tracking down families through men who came in for treatment, the University of Washington, Seattle, scientists turned to an unusual ally: financial wizard and prostate cancer survivor Michael Milken.

Milken—a crusader for prostate cancer research since he was diagnosed in 1993 with an advanced case of the disease—came up with what Hood thought was "a hare-brained idea." Lange recalls that Milken said, "No problem, we'll just go on *Larry King Live*" to ask for volunteers. When King's producers at CNN were leery of such a depressing subject, Milken says he phoned some high-level contacts at the network. "I've known Larry for a long time and have been involved in the financing of CNN," he explains. And so, on 13 November 1995, King interviewed Milken, Hood, and prostate cancer survivor General Norman Schwarzkopf. More than 3000 people called in. In just 3 weeks, Hood and Lange signed up nearly 300 families—as many as most institutions typically enroll in several years.

Once called the most powerful man in American finance, before he was jailed for securities-law violations in 1991, Milken is a man with a mission. He has put the energy, contacts, and ambition that once earned him billions on Wall Street into finding a cure for prostate cancer, the second leading cancer killer among U.S. men. When he's not pulling strings to get the message out (see sidebar), his foundation has been bankrolling research, cajoling companies, and trying to break down barriers between institutions. Milken has brought to the field a survivor's sense of urgency, vast amounts of cash, and a knack for remaking organizations. And in the process, he is shaking up the culture of the prostate cancer research community.

Within 1 month of his diagnosis at age 46—when he was given less than 18 months to live—Milken set up a foundation formally called the Association for the Cure of Cancer of the Prostate, but widely known as CaP CURE. Observers say it has raised both the public and scientific profile of prostate cancer research. Indeed, Milken has achieved for prostate cancer what a well-organized coalition of breast cancer survivors has done for that disease: "CaP CURE has put prostate cancer on the map," says cell biologist Joy Ware of the Medical College of Virginia Campus of the Virginia Commonwealth University, in Richmond.

In a sense, the foundation, which to date has given $65 million to prostate cancer research, is Milken's own grand experiment: an effort to bring a business approach to the task of curing prostate cancer. "Everything I learned in business, in financing companies, I've tried to bring to bear here," he says.



Talking it up. On *Larry King Live*, Milken recruited hundreds of families stricken with prostate cancer from among millions of viewers.

CREDIT: CNN

Quick decisions and a sharp focus on a cure are hallmarks of that approach. Last month, for example, dozens of prostate cancer researchers cashed CaP CURE checks for a total of $7.5 million in grants they had applied for only a few months previously. Half of these grants relate directly to treatments for advanced prostate cancer. The foundation is sponsoring more than 80 clinical trials, and next month top clinicians will gather in New York City to hash out new clinical trial protocols at a CaP CURE meeting.

Has it worked? Certainly there's more research; the number of papers on the topic has risen by more than 150% over the last decade (see graph, p. 1101). It's not all Milken, of course: Since 1993, annual spending by the National Cancer Institute (NCI) on prostate research has risen substantially, to nearly $90 million. But observers say Milken gets credit for enticing fresh talent to the field and promoting other funding. And some of the tactics Milken and other innovative funders adopted early on—such as funding proposals rapidly and betting on unproven, "venture research"—are now spreading to other research foundations. "CaP CURE is breaking new ground on how the private sector handles research on a major medical problem," says Donald Coffey, a longtime prostate cancer researcher at Johns Hopkins University and a past president of the American Association for Cancer Research.

But despite all the activity, there are still no new treatments for patients with advanced prostate cancer—CaP CURE's original goal—much less a cure. And scientists say that the business analogy can be pushed only so far because in research, sometimes the best route to a goal is indirect. "Focusing so much on metastatic disease has been a weakness," says prostate cancer researcher Otis Brawley, a medical oncologist who directs NCI's Office of Special Populations.

Milken, whose own cancer is in remission, acknowledges that prostate cancer re-

Michael Milken's World

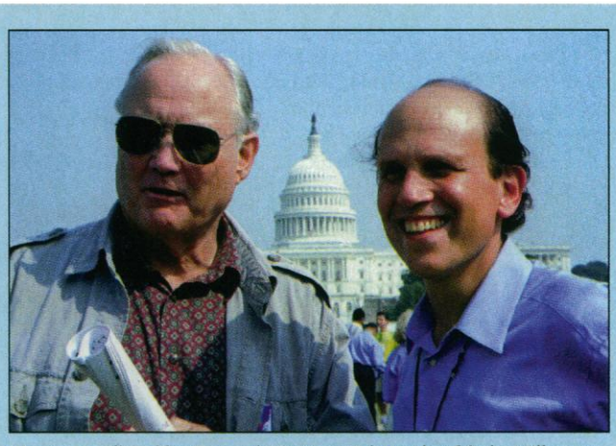
WASHINGTON, D.C.—One thing you quickly notice about Michael Milken is how easily he works large sums of money into the conversation. Take the following scenario: Sitting at a dinner table with several reporters at a posh hotel here, on the eve of a major cancer rally, he's holding forth on cancer research: "For just $20 billion, the government could test every known chemical compound against every known cancer cell line in 2 years," he argues. Tanned and healthy-looking at 52, prostate cancer survivor Milken talks nonstop about big ideas, ranging from his prostate cancer foundation CaP CURE (see main text), to how Congress could conquer all cancer, to his plan for drastically altering the American diet.

Thinking big is a Milken trademark. He rose to fame—and infamy—in the 1980s by pioneering the use of junk bonds (high-risk and potentially high-yield bonds) for corporate takeovers. This kind of paper money financed huge expansions at companies such as CNN and MCI, and it catapulted Milken into powerful circles, reaping him enormous riches—$550 million in 1 year alone. But in 1989, Milken pled guilty to six counts of securities-law violations, was fined $1.1 billion, and was sentenced to 10 years in a low-security federal prison in California. After serving only 2 years, Milken was released early. The next day, he was diagnosed with advanced prostate cancer.

Since that day, Milken has capitalized on his contacts in business and the entertainment industry to bring attention and funds to prostate cancer. Celebrities such as Bill Cosby, a member of CaP CURE's honorary board of directors, liven up foundation events. Arnold Palmer and other major sports figures help out with charity golf tournaments and baseball games. Last year, singer Rod Stewart had dinner guests dancing onstage at New York City's Waldorf Astoria Hotel, raising $3.5 million for CaP CURE. Throwing good parties is Milken's "personality, his history," says prostate cancer researcher Don Coffey of Johns Hopkins University, who advised Milken during the setup of his prostate cancer foundation but has no direct involvement in it. "I'm sure he was involved in financing everyone [at the Waldorf bash]," he says, "and he's called in all his chips."

Though Milken's foundation focuses mostly on medical research aimed at finding a cure, he's also concerned with prevention. His latest crusade is diet: He thinks low-fat, high-soy meals could slash cancer rates, and he's promoting his self-published cookbook with everyone from Martha Stewart to Barbara Walters. At the elegant but low-fat Washington dinner, for example, he points out that the mushroom soup, prepared by his personal chef in the hotel's kitchen, was creamed with barley. As always, Milken eventually brings the argument back to dollars, noting that America spends $100 billion on cancer treatment each year. Anything that prevents that expenditure, of course, only makes sense.

–E.S.



Big guns. Allies like General Norman Schwarzkopf help Milken put prostate cancer in the public eye.

mains a formidable foe. "Until it's no longer a problem, I'm not pleased."

Stirring up a backwater

Milken was diagnosed 6 years ago, just after he was released from prison, and at the time—as now—the only recognized treatment for advanced prostate cancer was a decades-old therapy: blocking testosterone and other androgens that prostate cells need to live. This works at first, but eventually prostate cancer cells can somehow become independent of androgens. Milken's remission was achieved this way—although he also consulted pop guru Deepak Chopra and radically altered his diet.

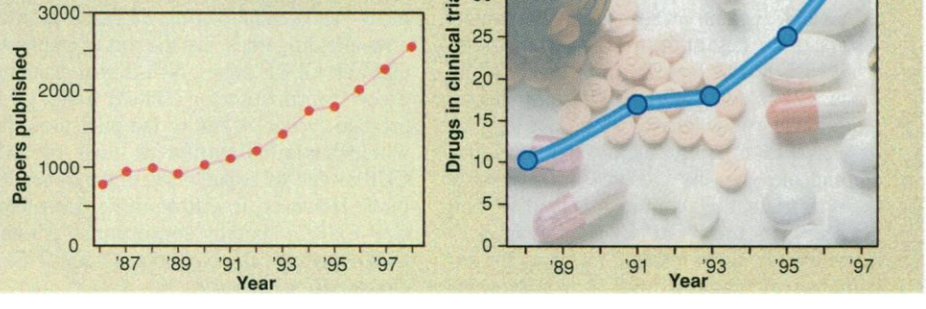
Meanwhile, the energetic parolee took a whirlwind tour of major cancer centers to learn why findings from prostate research were so meager. In his view, the first problem was the time-consuming burden of writing grants. "Scientists were used to a world where you spent a year, a year and a half, writing grants," says Milken, a period that to him as a patient seemed hopelessly long. "I had to find a way to drastically accelerate the science."

There were scientific obstacles, too. For starters, few prostate tissues were available for study; researchers had only three lines of prostate cancer cells and few animal models. "This was one of the real bottlenecks," says William Catalona, a urologist at Washington University School of Medicine in St. Louis who has been assembling a prostate tissue bank since 1989.

Milken's first step was to create CaP CURE, appointing his personal physician, Stuart Holden of Santa Monica, California, as its medical director. The two drafted a five-page application form for 1-year grants and pledged to write checks just 3 months after proposals were turned in. They opted for annual grants on the grounds that if businesses could work on a yearly schedule, scientists could too. In return, the foundation would fund risky projects: "We told people to submit novel ideas, the ones they dream about at night, rather than what they think will get approved," says Holden.

In the first year, perhaps 60 of the 86

Pumping the pipeline. With more researchers in the field, the number of papers on prostate cancer has swelled—and more drugs are being tested against the disease.



CREDITS (CLOCKWISE FROM TOP): CAP CURE; PHARMACEUTICAL MANUFACTURERS ASSOCIATION; MEDLINE

applications were basically identical, recalls Holden. "Everybody wanted to do gene therapy, because that's what was in favor at the NCI in 1993." But over time, more diverse ideas began to flow in, including the development and use of cancer vaccines and antibody therapies, which were being tested against other cancers but hadn't yet been tried on prostate tumors.

Milken and Holden also say that CaP CURE funding has encouraged researchers in other fields to apply their skills to prostate cancer. For example, cell biologist Michael Weber at the University of Virginia wondered if his work on signaling in fibroblast cells might relate to the androgen independence seen in late-stage prostate cancer cells. NIH had turned down a grant application from Weber in 1996 for lack of preliminary data, but he got $100,000 from Milken's foundation and went on to implicate a well-known signaling cascade in androgen independence. Last year he won a 5-year, $850,000 NIH grant to pursue his studies further. "CaP CURE money has allowed me to get started in a new area," he says, "even though I didn't have direct credentials in prostate cancer."

Despite the influx of proposals, Milken hasn't been content to sit back and wait for good ideas to come into CaP CURE's offices. Instead, he aggressively recruits people and institutions to work on the disease. Among them is Harvard's Judah Folkman, whom he funds to explore the feasibility of anti-angiogenesis therapy—a way of blocking the growth of blood vessels that tumors need to live—in prostate cancer. And researchers give Milken high marks for listening, too. When several scientists told him that their number-one lab problem was lack of tissue samples, he funded tissue banks at three top universities—the University of Washington, Johns Hopkins, and Washington University at St. Louis. CaP CURE now annually puts about $800,000 into the collections, which contain 11 cell lines and thousands of specimens.

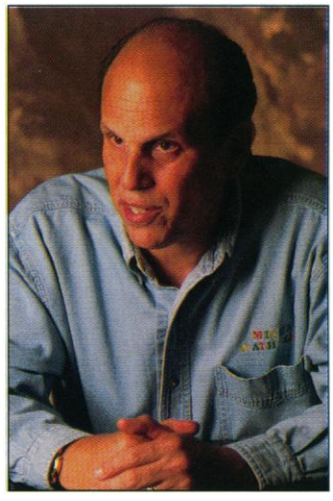
The bottom line

Perhaps because of Milken's frustration with his own limited treatment options, CaP CURE zeroes in on cures rather than basic research. The idea is both to create new treatments and speed them to patients, hastening the pace of clinical trials, says Howard Soule, the foundation's scientific director and acting executive director.

"I had to find a way to drastically accelerate the science."

—Michael Milken

As a first step in this acceleration, Milken wanted to overcome a lack of coordination—even competition—between cancer centers, which often left researchers working only with colleagues in their own institution. So in 1996, he offered leading medical centers $300,000 each in annual funding—but only if they all participated in planning and conducting joint trials. Most foundation-sponsored trials take place within this consortium, which now has 10 centers* that receive a total of $2.5 million from CaP CURE each year. The hospitals' computer systems are linked, thanks to a donation Milken secured from software giant Oracle (he had helped CEO Larry Ellison finance the company), so researchers can check on patient accrual and protocols at any center. In a typical month, several phase II trials are being jointly run by two or three centers, says Soule.



Although big pharmaceutical companies tend to arrange trials themselves, executives of smaller biotech companies say they are eager to work with the group. "It would be like doing a trial with the who's who of prostate cancer in the United States," says immunologist Frank Valone of Dendreon Corporation in Seattle. Dozens of companies have been and are collaborating with consortium members to test potential therapies, many of which come out of industry labs. The foundation doesn't fund companies directly, but hooks them up with academics who have CaP CURE grants and can therefore shoulder some of the cost of the trial, indirectly lowering costs for the biotech firms, explains Valone. "We're doing one [trial] this year that we otherwise wouldn't have," he says.

And even though major pharmaceutical companies are less involved in the consortium's trials, collaborations extend to their researchers too. "CaP CURE has made it possible for us to interact, to set up the exchange of reagents, and they serve as a matchmaker for potential relationships," says Blake Neubauer, an endocrine pharmacologist at Eli Lilly in Indianapolis.

To provide a venue for fostering more informal connections among academics and companies, Milken again harked back to his business glory days. He was famous for hosting an annual junk bond seminar known as the Predator's Ball, where corporate raiders, companies, and investors were entertained by the likes of singer-actress Diana Ross. Now, he sponsors an annual scientific retreat, where researchers from biotech and academia attend sessions that can last 12 hours.

The networking continues at a reception at Milken's Lake Tahoe mansion with such entertainers as singer-songwriter Paul Anka. Many researchers describe this invitation-only, all-expense-paid meeting as simply the best in prostate cancer—or any field. "It's like a Gordon Conference, only more intense," says Coffey.

Observers say all this activity has indeed helped speed potential therapies for prostate cancer. According to an industry survey of pharmaceutical companies (see graph, p. 1101), since 1993, the number of drugs in development has more than doubled, to 36. "CaP CURE has had a major role" in this proliferation, says Coffey. "They've funded almost every one of those developments." And compared to the early 1990s, when most new drugs were versions of anti-androgens, today's candidates are much more sophisticated and diverse, he adds. "From gene therapy to monoclonal antibodies, there is really interesting stuff coming," Coffey notes. "And there's more on the way."

No more business as usual

As activity in prostate cancer swells, other funders are picking up on some of Milken's business approaches. The Juvenile Diabetes Foundation, for example, will begin handing out next month the first of its new, 2-year, $100,000 "rapid response grants," reviewed in just 3 months. And this year, NCI will offer $10 million through a program called Rapid Access to Intervention and Development—an attempt to speed academic discoveries into drug trials, just the sort of emphasis that CaP CURE prizes. NCI is also planning a new consortium for clinical trials, with prostate cancer as one of the pilot projects, which has aims similar to those of CaP CURE's and will share many of the same features. However, it will be more open than CaP CURE's therapy consortium. "It's national; anyone can come into it," says NCI's director, Rick Klausner.

CREDIT: SAM KITTNER

* Columbia University, New York City; Dana-Farber Cancer Institute–Partners Care, Boston; Johns Hopkins Oncology Center–Brady Urological Institute, Baltimore; Memorial Sloan-Kettering Cancer Center, New York City; University of California, Los Angeles, School of Medicine; University of California, San Francisco–Mount Zion Cancer Center; University of Michigan Cancer Center, Ann Arbor; University of Texas–M. D. Anderson Cancer Center, Houston; University of Virginia Cancer Center, Charlottesville; University of Wisconsin Cancer Center, Madison.

Indeed, some researchers are bothered by the exclusivity of CaP CURE's meetings and consortia. For example, its prostate tissue banks at the moment are open only to the four universities inside the foundation's Genes and Family Studies Consortium, which Hood runs. CaP CURE also relies on a hand-picked coterie of specialists as grant reviewers—and much of the money is awarded to their home institutions. "Some people have said that it's an old-boy network, and to some extent they're right," admits Holden, who nevertheless says that the institutions involved with CaP CURE are "topnotch" by any measure.

And although everyone is happy to receive a check 3 months after submitting a grant, some researchers grumble about the limited 1-year duration of the awards. "A year makes people a lot more nervous," says Coffey, and makes it difficult to hire staff.

Meanwhile, although biotech executives praise Milken's promotional and fundraising skills, some are leery of getting too close to him. "Mike Milken, being the head of CaP CURE—and a convicted felon for stock fraud and manipulation—is not someone you can entertain as a supporter of a small start-up company," says virologist Daniel Henderson, CEO of Calydon in Sunnyvale, California. "You can't get quality investors to invest alongside him. So you have to stay away."

Most substantively, some researchers fault the foundation's focus on late-stage disease. Neither the NCI nor the American Cancer Society (ACS) takes that approach. "We like basic research, because time has shown that's where everything has come from," says Dawn Willis, ACS's director of research promotion and communication.

Holden and Milken are the first to admit that their efforts haven't paid off yet for patients in the most dire straits. "You can't say that a patient diagnosed with advanced prostate cancer in 1999 is going to live longer than he would have in 1993," says Holden. Still, many researchers say that CaP CURE has hiked the chances that new therapies will emerge sooner rather than later. "They've seeded the area," says Neubauer. "I think there are some signs that it's starting to bear fruit."

Hood and Lange would agree. After analyzing DNA from families recruited through *Larry King Live*, they have identified a gene that seems to predispose 15% of those men to prostate cancer. They've also uncovered more than 200 molecules that are overexpressed in cancerous prostate cells, and they're talking to pharmaceutical companies about trying to use these to diagnose and even treat the disease. If they and others succeed, Milken's entrance into cancer research may turn out to have been his most important business venture. **–ERIK STOKSTAD**

SPACE SCIENCE

To Mars, En Masse

A fusillade of probes heading to Mars in the next decade marks a new era in space exploration

PARIS—William Boynton labored for 8 years on the gamma ray spectrometer for Mars Observer, the first instrument he had ever built for space. Then disaster struck: the ill-fated spacecraft was declared missing, presumed dead, as it neared its target in August 1993, taking with it not just Boynton's instrument but a host of others. The $845 million mission had been the first attempt that U.S. scientists had made for Mars in almost 2 decades. When it vanished, the blow was crushing. "It was almost like a death in the family," recalls Boynton. "People in the building were uncomfortable. They didn't know what to say to us."

When Boynton first heard that copies of the Observer instruments were going to be sent back to Mars on a series of missions-on-the-cheap—with his slated to be on the last, due for launch in 2001—he thought it was a crazy idea. But a vibrant new Mars program has made Boynton, and many of his colleagues, converts. At a conference* here earlier this month hosted by the French space agency CNES, scientists described one new Mars mission after another, some major campaigns—the cluster of missions intended to bring samples of the planet back to Earth in the middle of the next decade—and others tiny. Current plans foresee 20 spacecraft making the voyage before 2010, of which five are en route, and a series of "micromissions," which could add many more (see table). The probes will scrutinize everything from subsurface ice to the edge of the atmosphere. No single setback can stymie all the new missions; there are more eggs in more baskets than ever before.

This is not just a matter of more Mars missions; it's a different approach to exploration. The missions are small, the risks are high, and the pace of innovation is quick. For example, the plans for carrying out the sample-return missions, of which the first is just 4 years away, have been completely rewritten in the past 6 months. To some, this continuous evolution is thrilling and satisfying: "It makes the whole program a hell of a lot more robust," says Cornell University's Steven Squyres, principal investigator on the 2003 Surveyor rover mission. Others are unsettled by the ever-evolving effort's breadth. "With the whole variety of different things which are being put forward on the smorgasbord table right now, I don't think things have been sufficiently focused to identify the highest priority goals," says Gerald Wasserburg, a geochemist at the California Institute of Technology in Pasadena.

Adding to the ferment is the increasingly international nature of the effort. While the lion's share belongs to the United States—Russia's program is so diminished that no Russians even made it to Paris—there are Japanese and European missions, and, above all, a critical role for France. CNES is now an integral part of NASA's efforts. Negotiated over the past year, the CNES–NASA deal is a huge boost for both sides: French science minister Claude Allègre satisfies his desire to steer his country's program from manned to unmanned spaceflight, while the United States gets someone else to pick up some of the tab for the sample-return program. "They bring a very high level of commitment and a great deal of technical capability," says NASA's Carl Pilcher. "From a program with very narrow reserves they've allowed us to convert to something much more robust."

According to the latest sample-return plan, the United States will gather the samples and the French will bring them back. The idea is that NASA rovers launched with companion landers every 2 years or so will pack about 40 samples of rock and soil into 15-centimeter-wide canisters mounted on simple three-stage solid-rocket boosters just big enough to put such a canister into a stable orbit round Mars. (The booster was originally designed for the U.S. Navy 40 years ago as a minimal response to Sputnik: Brian Wilcox, the son of that project's manager, happens to work at NASA's Jet Propulsion Laboratory and realized that it would do the sample-return trick quite nicely.)

The French will bring the samples back to Earth, with an orbiter and four "net-landers" to be launched in 2005, on an Ariane 5, which will also carry the second NASA rover. (The Ariane 5, which is considerably bigger than the U.S. launchers that NASA could afford within its Mars exploration budget, is a crucial part of France's contribution.) With the help of ra-

* International Symposium on the Mars Exploration Program and Sample-Return Missions, 1 to 5 February, the Veme.