hey’re elusive and ephemeral: chemical states that exist for just one billionth of a millionth of a second. But these whispers of molecules may hold the key to treating a wide variety of cancers.

“Transition states” form in every chemical change and whenever an enzyme does its job of converting one chemical (the substrate) into another (the product). The fleeting transition-state molecule is neither substrate nor product, but something in between—a ghostly intermediate to which the enzyme clings for that vanishingly brief time.

While it doesn’t last long, the transition state of a chemical reaction can be a powerful ally in the fight against cancer. The reason: Many types of cancer are caused by overactive enzymes. If a drug could knock the offending enzyme out of circulation, you’d have a powerful treatment—perhaps even a cancer cure.

In 1994, Einstein researchers started designing molecules, known as transition-state analogs, that do just that. Vern Schramm, Ph.D., professor and Ruth Merns Chair in Biochemistry at Einstein, leads this effort. The first cancer target was the enzyme purine nucleoside phosphorylase, or PNP.

In 1975, scientists had identified an infant born with a genetically deficient version of PNP. By age two, this infant lacking a functional PNP enzyme could no longer make T cells, which are vital for a healthy immune system. Scientists
MESSAGE FROM THE DIRECTOR

I. DAVID GOLDMAN, M.D.
Director, Albert Einstein Cancer Center
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Probing the Transition State (continued from page 1)

realized there was one situation in which a lack of PNP—and therefore no more T cells being formed—would be a good thing: in treating T cell cancers, conditions in which T cells multiply uncontrollably. Yet inhibiting PNP would not be easy.

“Seven companies had tried to make drugs against PNP, and all seven gave up,” says Dr. Schramm. “They never found a compound that was good enough.” Focusing on PNP’s transition state might do the trick. But how do you study something that appears and vanishes in almost the same instant?

“There’s no way to actually observe a transition-state structure—not by nuclear magnetic resonance, crystallography or any other technique we have,” says Dr. Schramm. So the research team deployed a series of indirect strategies that combined computer modeling and a novel use of isotopes called kinetic isotope effects to gain insight into PNP’s transition state.

After figuring out that state, the Schramm lab designed its analog—a molecule closely resembling it but with one big difference: the transition-state analog would powerfully inhibit PNP by binding to it and not letting go.

It took three years of difficult chemistry, including essential input from Peter Tyler, Ph.D., and Richard Furneaux, Ph.D., Dr. Schramm’s chemistry collaborators from Industrial Research Ltd., in New Zealand. “This type of molecule had never been synthesized before,” Dr. Schramm recalls. “But we constructed a drug that bound to PNP more than 700,000 times more tightly than the normal substrate did. It was a real eureka moment.”

That inhibitor, Immucillin-H, was licensed to BioCryst Pharmaceuticals and is now in a pivotal phase 2B clinical trial for treating T cell cancers.

“The preliminary results look very promising,” says Dr. Schramm. In less than a year, he predicts, Immucillin-H will be submitted to the FDA for approval.

Dr. Schramm and his chemistry team recently designed a transition-state analog against another enzyme very different from PNP. This enzyme, MTAP, helps synthesize polyamines, chemicals needed by rapidly dividing cells such as cancer cells.

Sure enough, this analog effectively inhibits MTAP. In animal tests, the MTAP inhibitor has shown promise against prostate cancer, lung cancer and cancers of the head and neck. It has been licensed to Pico Pharmaceuticals; Dr. Schramm anticipates that clinical trials could begin within the next year or two.

“Evidence so far suggests that this drug may be especially useful for preventing cancer from spreading, or metastasizing,” says Chandan Guha, M.B.B.S., Ph.D., professor and vice chair of radiation oncology, who collaborates with Dr. Schramm in testing the MTAP inhibitor in cancer cells in culture and in mice. “As a result, the progression of the cancer would be retarded, and patients would be able to live longer with their cancers.”

Cancer Q&A

Q: Are we winning the war on cancer?
A: Yes, but gradually. The cancer death rate has declined slightly (by about 5 percent) over the last 5 decades—from 193.9 per 100,000 in 1950 to 183.8 per 100,000 in 2005. There are three reasons:

More screening. Tests such as mammography and colonoscopy are picking up cancers at an earlier, more treatable stage.

Less smoking. Millions of people have gotten the message about the dangers of tobacco smoke.

Better therapies. Surgery, radiation and chemotherapy are now more effective than ever.

On the negative side, more Americans are becoming overweight or obese, which increases their risk of developing several types of cancer, including breast, colorectal, prostate and pancreatic cancer.
Interrupting the Colon Cancer Conversation

How does colon cancer begin? “Cross-talk” between colon cells and immune-system cells called macrophages don’t work so well in older people, because they’ve lost responsive immune cells known as naive T cells. Dr. Klampfer is trying to circumvent this problem in developing a vaccine to treat metastatic breast cancer. She and her colleagues have enlisted the help of a bacterium, *Listeria monocytogenes*. They are using the versatile microbe to combat breast cancer in three ways: arouse other immune cells called memory T cells (well preserved in older people) to attack cancer cells; trigger so-called innate immune responses (also well preserved in older people); and kill tumor cells directly by eliciting a sharp rise in levels of toxic by-products within the tumor cells.

Is Insulin a Carcinogen?

Breast cancer is much more common in postmenopausal women who are obese than in those of normal weight—a major concern in light of the U.S. obesity epidemic. But what are the molecular pathways through which obesity increases the risk of breast cancer?

Einstein researchers Howard Strickler, M.D., Marc Gunter, Ph.D., Thomas Rohan, M.D., Ph.D., and Geoffrey Kabat, Ph.D., recently completed studies of two large groups of women. They reported that while estrogen levels are increased in obese women, the elevated levels of another hormone—insulin—explained the obesity/breast cancer link. Their findings were published recently in the *Journal of the National Cancer Institute*.

In addition to its well-known role in sugar metabolism, insulin is a growth factor that can induce cells to multiply. Insulin’s growth-factor activity probably explains how this hormone promotes postmenopausal breast cancer, the Einstein scientists concluded.

“Research must focus on ways to reduce insulin’s effects on cell replication, while preserving its effects on sugar metabolism, and to determine insulin’s role in other obesity-related cancers,” says Dr. Strickler, professor of epidemiology & population health, who along with Dr. Rohan developed the studies. “By understanding insulin’s role,” he adds, “we may have an opportunity to prevent breast cancer in obese and high-risk women and reduce its recurrence in women being treated for the disease.”
Einstein’s National Women’s Division has launched a $3 million fundraising initiative in support of research in women’s health and cancers. It will benefit basic and translational research studies at the Einstein Cancer Center aimed at developing new prevention strategies and innovative treatments for breast, ovarian, uterine and cervical cancers.

The Breast Cancer Research Foundation has made a commitment of $600,000 to support research studies by Rachel Hazan, Ph.D.; Susan Band Horwitz, Ph.D., the Rose C. Falkenstein Chair in Cancer Research, and Haley McDaid, Ph.D.; and Thomas Rohan, M.D., Ph.D.

Jane and Myles P. Dempsey have made a $500,000 gift to fund innovative pilot projects as well as specialized technical facilities in support of the Breast Cancer Working Group, led by Joseph A. Sparano, M.D., at the Einstein Cancer Center. Dr. Sparano is professor in the departments of medicine (oncology) and of obstetrics & gynecology and women’s health. This research focuses on developing new approaches to diagnosing and treating breast cancer. Mr. Dempsey is founder and chairman of Tech Air, a leading provider of industrial, medical, and specialty gases.

Stand Up to Cancer and the American Association for Cancer Research have awarded a grant of $712,866 to Matthew Levy, Ph.D., assistant professor of biochemistry, for developing novel molecules that deliver anticancer drugs directly to their cancer-cell targets. Dr. Levy is one of 13 young scientists nationwide whose research is supported by a Stand Up to Cancer–American Association for Cancer Research Innovative Research Grant.

NOTABLE GIFTS AND GRANTS

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EVENTS

Einstein’s Cancer Research Advisory Board hosts events during the year that bring together people interested in supporting the work of the Albert Einstein Cancer Center with distinguished Einstein faculty members who share the latest developments in cancer research.

Allen M. Spiegel, M.D., the Marilyn and Stanley M. Katz Dean, and I. David Goldman, M.D., director of the Albert Einstein Cancer Center and the Susan Resnick Fisher Professor, were the featured speakers at two Einstein Lunch & Learn seminars in Palm Beach, FL. They spoke about new developments in cancer research and treatment at Einstein. Lively question-and-answer sessions followed. We are grateful to Roni and Stuart Doppelt and David J. Klein, who hosted the luncheon on March 8 at High Ridge Country Club, and to Einstein Overseers Marilyn and Stanley M. Katz, who hosted the luncheon on March 9 at Palm Beach Country Club.

Terri and Michael Goldberg hosted a cocktail reception on behalf of the Cancer Research Advisory Board at their home in New Jersey in October 2009. Dr. I. David Goldman described current studies at the Cancer Center, and Joseph A. Sparano, M.D., discussed the current status of breast cancer treatment and research. Thanks to the Goldbergs and to all the Einstein friends and supporters who attended.

To learn more about supporting the work of the Cancer Center, please contact:

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ALBERT EINSTEIN CANCER CENTER

Our mission: to promote and carry out research that will yield insights into the origins of cancer and lead to effective new approaches for preventing, diagnosing and treating malignant diseases

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Terri Goldberg, left, and Michael Goldberg with Einstein Overseer Betty Feinberg