The power to...
Exploit cancer’s vulnerabilities

By tackling cancer from many angles and with input from many disciplines, Salk’s scientists are finding universal ways to put a stop to the elements that allow tumors to thrive—no matter the cancer type.

The challenge
Cancers are notoriously difficult to treat, let alone cure. In many ways, physicians and patients play a chess game against the disease. Patients receive a new therapy; tumors counter with new ways to resist it.

Traditional cancer therapies, such as chemotherapy and radiation, work by blasting many cells and hoping cancer cells are affected more than healthy cells. The problem with this approach is twofold: the side effects can be devastating, and cancer cells are incentivized to adapt and resist the treatment. It’s a one-size-fits-all approach that doesn’t typically take into account the patient’s own unique genetic, cellular and environmental factors. All too often, the cancer wins.

Cancer is a maddeningly complex disease that must be attacked from many angles to contain and ultimately cure it. At the Salk Institute, we recognize the challenge, and though we are sometimes humbled by it, we will not be deterred. The Salk Institute was founded to take on the most difficult biological problems. As we like to say, this is where cures begin.

The Salk approach
Salk scientists look at cancer holistically—focusing not only on the tumor cells themselves but also on their surrounding tissues, the immune system, the microbes that live within us, and how each individual’s environment and habits influence their risk and therapeutic responses. These are the elements that, together, allow tumors to form, grow, spread and resist standard therapies.

By uncovering new information about how these elements influence all types of tumors, we are revealing new universal vulnerabilities—in cancer’s armor—for which we can customize new therapeutic weapons that may apply to many cancers, including pancreatic, brain, lung and breast.

Exploit vulnerability 1: genetics. If you squeeze an inflated balloon, no matter how hard you try to contain it, parts will poke through your fingers. Cancer also foils containment, developing genetic mutations that help it survive, grow and escape the immune system and many treatments.

However, this genomic flexibility can also make tumors less resilient. Every time a cancer cell mutates away from its normal cousins, it adopts a less efficient, and often irreversible, mechanism to gain a temporary survival advantage. As tumors go to plans B, C and D, these adjustments inform Salk’s overall strategy: We are finding multiple ways to pop those balloons. And a deep knowledge of the fundamentals of cell biology and genomics, coupled with computational expertise, is how we do it.

Already, Salk scientists have identified several genomic weak spots that make cancer cells easier to kill. We also recently used a computational approach to discover that a current cancer therapy, which works by targeting specific molecules encoded by cancer genes, may work for thousands more patients than originally thought.

Exploit vulnerability 2: cancer cell metabolism. Tumors grow fast and eat like a pack of wolves, constantly scouring their environments for new food sources. They often rewire their metabolism, such as switching their fuel source from glucose to the amino acid glutamine. This remodeling is an irreversible necessity for cancer cell survival, making metabolism a potentially powerful target for stopping cancer. What’s more, tumors with different genetic mutations rewire their metabolism in unique ways, providing another opportunity to target different subsets of cancer.

Salk scientists have been exploring this metabolic connection for more than a decade, providing critical insights. We are learning to hit cancers through their food supplies. These metabolic strategies could have a profound impact on tumors: depriving them of nutrients, altering their protective microenvironments and potentially empowering the body’s immune system to destroy them.

Exploit vulnerability 3: immune response. Immunotherapy—boosting a patient’s own immune system, allowing it to better detect and destroy cancer cells—has emerged as a powerful alternative (or addition) to chemotherapy. For some, these treatments are very nearly cures. But many patients receive no benefit from immunotherapy, a gap that must be filled.

Salk scientists are investigating how the immune system responds (or fails to respond) to cancer. They want to understand why T cells infiltrate some tumors and not others; whether macrophages and other immune components can be optimized to attack tumors; and how nutrient-starved tumor
microenvironments affect glucose-hungry T cells. Here, we circle back to metabolism, and this is no coincidence. Many cancer-related mechanisms interact with each other, making collaborative, interdisciplinary research essential.

**Exploit vulnerability 4: microbes.** Our microbiomes—the unique communities of microbes that live in and on our bodies—constantly interact with healthy and cancerous cells. These millions of bacteria, viruses and other microorganisms may influence how our immune systems react and how tumors survive. Scientists are discovering that the makeup of a person’s microbiome, the specific species of microbes and their relative quantities, may in part determine cancer risk and response to therapy.

**Exploit vulnerability 5: personal habits and environment.** Diet, exercise and body mass adjustments can put tumors at a disadvantage. However, there may be another even more profound weapon against cancer—sleep. It’s long been known that people who work the night shift are at greater risk of developing cancer. Salk research indicates that this night work may interfere with their circadian rhythms—our bodies’ 24-hour clock. By detaching their bodies from the normal day-night cycle, shift workers may be experiencing an overall decline in cellular health, increasing the risk that tumors can grow and thrive.

The research team realized this lack of circadian regulation in cancer cells might actually be a vulnerability. What happens if we re impose day-night discipline? When the researchers chemically re imposed circadian discipline on cancer cells, the cells simply couldn’t survive under the increased regulation. This was true in several types of cancer cells. By contrast, normal cells thrived.

**See the Salk approach at work: Pancreatic cancer**

Tumor microenvironments—the community of cells within and around a tumor—provide nutrition, thwart the immune system, block treatments and give cancers a safe ecosystem in which to grow. Together, the social network within pancreatic cancer’s microenvironment limits the efficacy of treatment and obscures the tumor from early detection. As a result, the five-year survival rate is only slightly above 10 percent. Nearly 50,000 Americans will die from pancreatic cancer this year. Salk’s strategy against pancreatic tumors is a microcosm of how we are approaching all tumors: unite the best minds from complementary disciplines to make revolutionary advances.

One example is the team that includes Professors Reuben Shaw, Ronald Evans and Tony Hunter and Assistant Professor Dannielle Engle. Shaw brings his cancer metabolism knowledge and experience. Evans is investigating how the microenvironment and other factors change how genes operate. Hunter focuses on kinases, enzymes that often drive tumor growth. Engle is creating 3D human tumor organoids (patient “avatars”) that will provide better, more realistic models to identify new targetable vulnerabilities in pancreatic cancer. Through such multipronged approaches, the group seeks to understand the signals that protect pancreatic tumors from therapies and the immune system and to develop innovative ways to overcome them.

This is a team of all-stars, something common at Salk. Past research by Evans and Hunter has led to pancreatic drugs in clinical trials. Evans’ lab modified vitamin D, transforming it into a molecule that can alter the microenvironment and perhaps soften pancreatic cancer’s protective shell. He and collaborators also recently found that a ketogenic and low-carbohydrate Atkins diet helps kill pancreatic cancer cells when combined with a triple-drug therapy, likely because the diet helps the immune system control tumors. Hunter has studied the crosstalk between cancer cells and the surrounding tissue. Normal cells present in the tumor microenvironment send signals that stimulate cancer cells (and vice versa). And Hunter’s work helped create an anti-cancer antibody drug that blocks these tissue-to-tumor signals.

**Why Salk**

For more than 60 years, the Salk Institute has pursued Jonas Salk’s vision of fearless, interdisciplinary science tackling some of the biggest challenges facing humankind.

The Institute is uniquely qualified to cut cancer’s roots. We have been a National Cancer Institute-designated Cancer Center since 1973, one of only 71 in the nation and one of only seven such centers focused entirely on basic research. More than 30 Salk labs are officially part of the center, and scientists throughout the campus collaborate to understand and eradicate cancer.

**Some of our past cancer breakthroughs include the following:**

1968 – Renato Dulbecco published his discovery that viruses can cause cancer by inserting genes into the chromosomes of infected cells. He was awarded the Nobel Prize for the discovery in 1975.

1979 – Tony Hunter and Bart Sefton discovered tyrosine phosphorylation, which led to the creation of a class of cancer drugs known as tyrosine kinase inhibitors, which includes Gleevec, Iressa and Tarceva.

1985 – Ronald Evans discovered a large family of molecules, called nuclear hormone receptors, that respond to various steroid and thyroid hormones as well as vitamins, revealing what are now primary targets in the treatment of many cancers.

**Why now**

In 2019 the Salk Institute launched the Campaign for Discovery—a seven-year, $750 million effort to accelerate Salk’s critical research.

The Campaign is focused on driving discoveries in six Centers of Excellence: Cancer Center, Center for Healthy Aging, Center for Plant Biology, Center for Neuroscience, NOMIS Center for Immunobiology and Microbial Pathogenesis, and Crick-Jacobs Center for Theoretical and Computational Biology.

To continue to lead the field in these areas, Salk is recruiting new faculty and other experts, investing in new technologies, and creating new collaborative spaces, including construction of the Joan and Irwin Jacobs Science and Technology Center.

As it has always been at Salk, there will be no barriers between disciplines. New ideas from multiple areas can mix and flourish, generating the most innovative, multipronged approaches to cancer.

**Join us**

Science is a collaborative pursuit, and we invite you to join us in accelerating life-changing discoveries: [www.salk.edu/campaign](http://www.salk.edu/campaign).