STORIES OF DISCOVERY

CANCER RESEARCH
at The Salk Institute
Cancer is not a single disease – it is many diseases. Yet, all cancer cells share one characteristic: Like weeds in a garden, they reproduce rampantly, crowding out the healthy cells that contribute to the functioning of our organs – our lungs, our livers, our brains.

People unfamiliar with science’s day-to-day workings will sometimes wonder why scientists do not simply go into a laboratory and emerge a couple of months later with a cure for cancer. While clinical research aims directly at finding and testing new treatments to weed out cancerous cells, basic research – such as the studies conducted at the Salk Institute – strives to understand the genetic and molecular mechanisms at the heart of this process, the genes and proteins that regulate normal cell growth but become corrupted in cancer cells.

For the last 40 years, Salk scientists have been asking very basic questions whose answers changed the course of cancer research forever. Time and again, the practical applications of understanding the fundamentals of how our cells work have led to major advances in diagnosing and treating many different types of cancer.

Here are some of their stories.

INTRODUCTION

Best known of Dr. Renato Dulbecco’s discoveries is that tumor viruses cause cancer by inserting their own genes into the chromosomes of infected cells. This first clue to the genetic nature of cancer revolutionized how scientists think about this devastating disease and led to Dr. Dulbecco being awarded the Nobel prize in 1975.

Twenty years ago, he was the first to boldly suggest that scientists from around the world come together in a huge collaborative effort to decipher the human genome. He was convinced that identifying all the genes within our genomes would greatly enhance our ability to understand how cells work, and would, for the first time, allow scientists to peer at cancer’s genetic make-up. In 2003, this monumental and historic achievement was completed.

And just as he predicted, our knowledge of the human genome has transformed cancer research. Building upon Dr. Dulbecco’s earlier work, scientists at Salk and around the world are trawling the human genome for the genetic abnormalities that drive cancer. They have now identified numerous genes that play an important role in the development and progression of cancer, and are exploiting this information to create new strategies for its treatment and cure.
By the time 16-year-old Tania was diagnosed with acute promyelocytic leukemia, immature, functionless blood cells had overwhelmed her young body. Her immune system didn't work properly, her skin bruised easily, and she just felt utterly exhausted. Just two months later, a brand new type of drug had forced her immature blood cells to grow up and do their job. The drug was a form of vitamin A.

Only a few years earlier, Dr. Ronald Evans had discovered how steroid hormones like vitamin A and cortisone accomplish their mission. Like messengers carrying an urgent message, steroid hormones sweep into a cell’s nucleus from far-flung senders. Meeting them inside the nucleus for the last leg of their journey are molecules called nuclear receptors. They grab steroid hormones that drift into a cell and together they clamp down in specific places on the chromosome where they tweak the activity of genes.

Dr. Evans has turned up nearly 50 different nuclear receptors, two of which – the receptor for vitamin A and its side-kick, the so called retinoid X receptor – are defective in certain cancers. Today, the resulting leukemia, Karposi sarcoma and a rare type of lymphoma are routinely treated with vitamin A derivatives, sold as Pancretin, Tretinoid, and Targretin. Dr. Evans' technology has been used to discover more than a half-dozen drugs for cancer, diabetes, and heart disease with many more on the way.

Tyrosine Kinases: the discovery that laid the groundwork for Gleevec™

While studying a cancer-causing virus, Drs. Tony Hunter and Bartholomew Sefton discovered a new group of enzymes called tyrosine kinases that are involved in the regulation of various vital aspects of cellular function such as cell growth and development. Today, 90 human tyrosine kinases are known, and about half of them have been implicated in cancer.

In one experiment, an overused lab solution serendipitously separated what turned out to be two forms of the amino acid tyrosine. One was the well-known form of the molecule, and the other was a form that was modified by the addition of a phosphate group. Rather than dismiss this result, Dr. Hunter got to the bottom of it and discovered that phosphorylating tyrosine, which is done by kinase enzymes, was a key event in the normal and abnormal growth of cells. More than two decades later, Dr. Hunter's original discovery has led to the development of a new generation of cancer drugs that specifically block the action of wayward tyrosine kinases, including Gleevec™, used for the treatment of leukemia, as well as Iressa™ and Tarceva™, used for the treatment of lung cancer.

Dr. Tony Hunter and Ms. Betty Sisk

How many of us think about, let alone get a chance to meet the basic researchers who toiled for years in the lab trying to understand how the human body functions at the levels of cells, proteins, and genes?

Ms. Betty Sisk got that opportunity when she met Dr. Tony Hunter at a Salk gala event. Almost three decades earlier, Dr. Hunter had set up the pivotal experiment that would prove crucial to the development of Gleevec™, a drug that gave Ms. Sisk a new lease on life when she was diagnosed with chronic myeloid leukemia (CML).

"It's amazing and unbelievable that, due to Dr. Hunter's discovery, I take four pills a day, and they are saving my life. I am so grateful," said Ms. Sisk. "It is very gratifying to know that this discovery has led to a successful drug for a devastating human disease. Nobody could have predicted it back then," said Dr. Hunter.

A “superfamily” that revolutionized the treatment of leukemia

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LIFESAVING FAILURE

An unsuccessful experiment led to an inexpensive and widely used leukemia drug

Imagine you discover a potentially important cancer drug. Thousands of lives could be saved if only producing it wouldn’t be so difficult and prohibitively expensive that only few – if any patients – will ever benefit. That’s cytosine arabinoside and the year is 1970. But that’s also when Drs. Leslie Orgel and Bob Sanchez pondered the origins of life.

Scientists have come a long way in understanding how a random collection of molecules could have slowly, over billions of years, combined into the complex living systems that we know today. But the chemical reactions that might have created the very first molecules on primitive Earth four billion years ago, particularly those that led to the origins of life, are largely left to speculation.

When trying to re-create the earliest ingredients of life in a test-tube, Drs. Orgel and Sanchez found something else instead – a molecule that in no time would turn from troublemaker into lifesaver. Unwittingly, the chemists had hit upon a simple and economical way to make cytosine arabinoside, a compound that is one of today’s most commonly used anti-cancer agents for the treatment of leukemia in adults and has literally saved thousands of lives.
Like a central command center, a brain area known as the hypothalamus regulates basic bodily functions: growth, thirst, hunger, temperature, day-night rhythms, reproduction, and stress. It sends out “master” brain hormones that stimulate the release of other hormones. (Hence the name “releasing factors.”)

Dr. Jean Rivier and his team of chemists, in collaboration with biologists Drs. Wylie Vale and Catherine Rivier, were the first to design molecules that nullify the action of these master hormones. Canceling out one of them, gonadotropin-releasing factor, effectively shuts down the production of estrogen and testosterone and is successfully used to treat prostate and breast cancer, as well as endometriosis.

The P53 protein stands guard over a cell’s genetic blueprint

A cell has to accumulate at least half a dozen genetic changes before it turns cancerous. Fortunately, normal cells have strict controls that prevent such changes. Only when a cell loses control and stumbles into the dangerous arena of genetic instability can enough changes accumulate to cause cancer. Dr. Geoffrey Wahl and his team identified the central player that stands guard over the stability of the genome and, not surprisingly, is mutated in more than half of all cancers, regardless of their origin. The protein, called P53, allows a cell to recognize DNA damage and forces the cell to commit suicide if the damage is beyond fixing. But mutations are not the only way to disarm P53. Proteins that interact with P53 can do the same, thereby explaining the high proportion of cancers with seemingly intact P53. Currently, the Wahl lab is determining how P53 is regulated in normal and cancer cells to reveal novel routes for the development of new anti-cancer therapies.
Chickens have played a central role in cancer research. The first virus known to cause cancer was discovered in chickens, and subsequently cancer-inducing viruses were found in other animal species. These so-called oncogenic retroviruses carry an additional, non-essential gene that leads to untrammeled cell growth. Dr. Inder Verma and his team identified and characterized several such viral tumor-causing genes and made a surprising observation: For each one of them, a normal counterpart existed in cells that had not been infected by an oncogenic retrovirus. These genes, he found, were directly involved in normal cell activities such as cell growth, differentiation, and development. But when out of control, the cell’s own genes have the ability to cause cancer, revealing that each cell carries the “enemy within.”

What if you could watch a breast tumor develop in its earliest stages to understand which controls fail in a tightly knit network of checkpoints? Dr. Walter Eckhart and his team are doing just that. They suspended human cells isolated from breast tissue in a three-dimensional matrix that mimics their natural surroundings. The cells spontaneously develop into hollow structures resembling tiny milk ducts, the most common site where invasive breast cancer arises. Turning on the signaling pathway for type 1 insulin-like growth factor changed the clearly-defined hollow tube into a misshapen blob of cells, reminiscent of an early tumor stage. Results from this study should help scientists to better understand the role that growth factors and hormones play in the initiation of breast cancer and may yield clues to the development of more effective therapies.
Each time a cell divides its telomeres, the protective “caps” at the end of all 46 human chromosomes, erode a little bit further. Some have likened this progressive shortening to a genetic biological clock that winds down over time leading to a gradual decline in our mental and physical prowess. Dr. Jan Karlseder recently discovered that a single missing telomere triggers the accelerated aging process in people with Werner’s syndrome, a rare genetic disorder that causes people to begin aging rapidly at around age 15 – usually leading to cancer and death by 40. Understanding how cells keep tabs on their biological age and detect catastrophic telomere meltdowns may lead to new approaches for therapies against cancer and even aging.

By and large, polyoma virus infections are harmless. Most of the time, polyoma viruses infect a host cell, multiply, and leave with a bang, causing only mild symptoms or no symptoms at all. But once in a while, a virus, unable to multiply, hangs around and wreaks havoc on cellular growth controls, turning its host cell cancerous. Dr. Walter Eckhart and his co-workers discovered how polyoma viruses tip the balance in favor of uncontrolled growth. One viral protein, large T antigen, jumpstarts DNA replication, while another, middle T antigen, flips a switch on a cellular enzyme that, in turn, activates middle T itself. The now supercharged middle T incessantly sends “go” signals, pushing cells to divide continuously, thereby causing cancer.
The immune system patrols our body for unwelcome trespassers, and invading pathogens immediately spur it into action. But sometimes, our body walks a fine line between a healthy immune response and jumpstarting the development of cancer. Trying to flush out the culprit behind the furiously dividing cells that characterize a rare type of leukemia, Drs. Batholomew Sefton and Anna Voronova discovered the signaling molecule lck. Remarkably, lck was found to be essential for the normal maturation and activation of T-lymphocytes, a type of white blood cell. Without lck, the body can't produce functional T-lymphocytes, and normally harmless infections become deadly. Turn on lck permanently, though, and it sends T-lymphocytes down the path of leukemia development. Now, Dr. Sefton is trying to uncover the chain of molecular events set in motion by lck that result in the unregulated growth of cells in this cancer.

Telomeres, repetitive sequences of genetic material, protect the ends of linear chromosomes. But each time a cell divides, the telomeres become a little bit shorter until the cell dies. While it had been known that an enzyme called telomerase rebuilds chromosome ends after each cell division, the genes coding for key parts of the enzyme remained elusive. Determined to identify the long-sought-after genes, Dr. Vicki Lundblad and her team launched a large-scale genetic search in baker’s yeast. After swapping crucial information with Dr. Tom Cech, who was hot on telomerase’s heels in another microbe, they succeeded in pinning down the catalytic subunit of telomerase. This subunit is up-regulated in as many as 90 percent of human cancers, allowing them to grow indefinitely by replenishing shortened telomeres. Today, Dr. Lundblad and other researchers continue to probe telomeric proteins, hoping to better understand the development of cancer and the aging process.
"Simply stunning" are the words used to describe the effectiveness of the new drug Herceptin™ that was tailor-made for a particularly aggressive subset of breast cancers – tumors that make too much of the HER2 protein. But nobody understood why Herceptin™ caused severe heart problems in a small percentage of patients. It had been known that, besides its insidious contribution to breast cancer, HER2 also had an important function in healthy brains. But when Dr. Kuo-Fen Lee, who studies brain development, and his team deleted the gene for HER2 in mice, the animals unexpectedly developed fatal cardiac problems, explaining the troublesome side effect. Now, scientists are trying to engineer new generations of drugs that will ameliorate Herceptin™'s deleterious effects on heart function.

Studying brain development may lead to a safer breast cancer drug.

HOSTILE TAKEOVERS

Viruses as a tool to study cells’ first line of defense against turning cancerous

Viruses – little more than protein coats protecting the genetic information inside – reproduce courtesy of host cells. But instead of peaceful cooperation, viral infections resemble hostile takeovers during which the intruders have to outsmart their hosts’ defenses. Dr. Matthew Weitzman and his team discovered that the cellular DNA repair system represents a major hurdle for invading viruses and that viruses employ different strategies to overcome it: Adenovirus, a common respiratory virus, disables the system, while Herpes simplex virus, the cause of cold sores, hijacks the complex for its own purposes. Watching these battles unfold yielded important insights into fundamental cellular mechanisms that are central to preventing cells from turning cancerous. Understanding them may improve the efficiency of gene therapy.
People with Peutz-Jegher syndrome, a rare hereditary disease, face a 15-fold higher risk of developing a malignant cancer than does the rest of the population. The culprit is inherited damage in a gene called LKB1, which is also one of the major genetic mutations behind the most common type of lung cancer. Dr. Reuben Shaw discovered that functional LKB1 activates a metabolic master switch that reduces glucose levels in the blood and puts a damper on cell proliferation. Interestingly, this master switch is also activated in response to exercise and more importantly by metformin, a drug commonly used to treat type 2 diabetes. This raises the tantalizing possibility of killing tumor cells lacking functional LKB1 with something as simple as a drug that’s been used to treat type 2 diabetes for nearly 50 years.

A widely prescribed diabetes drug may kill cancer cells

Exotic snails provide relief for severe chronic pain

Tropical cone snails stun and harpoon their victims with a quick venomous jab before they devour their hapless prey. The injected venom contains a powerful cocktail of toxic peptides, which are small protein-like molecules. Twenty years ago, in collaboration with Dr. Baldomero “Toto” Olivera – the world’s foremost expert on cone snail venom – peptide expert Dr. Jean Rivier synthesized the first cone snail toxin from scratch in his lab. Since then, they have characterized the effects and chemical structure of many more toxins. Already, pharmaceutical companies are tapping the potential of dozens of cone snail peptides to treat disorders including pain, epilepsy, cardiovascular disease, and various neurological disorders. One of these peptides, marketed as Prialt™, which is 1,000 times more potent than morphine, was recently approved by the FDA for chronic, intractable pain suffered by people with cancer, AIDS, injuries, and neuropathic disorders.
Defects in the APC tumor suppressor protein cause 85 percent of all colon cancers, the second leading cancer killer in the U.S. For years, scientists thought they knew why: The healthy version of APC sends another protein, called beta-catenin (ß-catenin) straight to the cellular recycling plant when it is not needed to stimulate cell proliferation. But Dr. Katherine Jones and her team found that APC also ensures that ß-catenin doesn’t go overboard once it has been put to work. After ß-catenin has successfully turned on genes that are involved in cell division, APC pushes ß-catenin off the DNA, and a repressor molecule hunkers down in its place. Mutant APC molecules found in colorectal cancer cells are not only unable to degrade ß-catenin, but are also unable to shut down the activated genes. Identifying the mechanisms that cells use to control their growth is an important step toward advancing our understanding of how cells turn cancerous.
For the last 40 years, the Salk Institute brought together brilliant minds whose vision is to conquer cancer and other diseases through world-class basic research. It has paid off. The Salk Institute is one of only a handful of National Cancer Institutes designated basic cancer research centers, with a long track record of constantly propelling science towards its next breakthrough in basic cancer biology.

In 1975, Dr. Renato Dulbecco received the Nobel Prize for his pioneering studies that gave scientists the first clue to the genetic basis of cancer. Since then, Salk scientists have made big strides in our understanding of the genetic basis and origin of cancer, learned how to manipulate the cancer-causing genes in simple model systems such as fruit flies and tiny roundworms, and laid the groundwork for the discovery of life-saving medicines.

Today, one third of the Salk faculty is searching for answers to cancer-related questions. Every successful step our scientists make in cancer research today could very well benefit you – or someone you love tomorrow.

If you would like to learn more about the cancer research conducted at the Salk Institute or would like to get involved, please call the Institute Relations office at 858.453.4100, ext. 2062 or email Robertson@salk.edu.

Please visit our website at www.salk.edu.

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Where cures begin.