Center for Cancer Research

HORIZONS

Toward a Brighter Future in Cancer Research

NIH〉 NATIONAL CANCER INSTITUTE

CENTER FOR CANCER RESEARCH
The Nation's Cancer Center

As part of the federally funded National Cancer Institute (NCI), the Center for Cancer Research (CCR) is the nation's cancer center. Located in the suburbs of Washington, D.C., our scientists are unlocking the mysteries of cancer and discovering new ways to prevent, diagnose and treat it. The CCR collaborates with academic and commercial partners and advocacy groups across the world in efforts to find treatments and cures for cancer through basic, clinical and translational research. Our physician-researchers translate these discoveries from the lab to the clinic, and we treat thousands of people from around the country every year with novel therapies through our clinical trials program at the National Institutes of Health Clinical Center. For more about our science, our training programs and our clinical trials, visit ccr.cancer.gov.

The **MISSION** of the CCR is to improve the lives of cancer patients by solving important, challenging and neglected problems in cancer research, prevention and patient care through:

- A world-leading basic, translational and clinical research and patient-care program

- An institutional focus on high-risk and long-term projects, unmet needs and pursuit of unexplored ideas

- Leadership and coordination of national disease networks and development of technology resources for the cancer community

- Partnerships with academic institutions, commercial entities and patient advocacy groups

- Training of the next generation of the biomedical workforce

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NOTE FROM THE DIRECTOR

Research is a journey. Every time a basic scientist embarks on a new project or a clinical investigator launches a clinical trial, they set their eyes on an ambitious goal. They venture into the unexplored using expertise and ingenuity to guide them toward their destination, which is often far beyond the horizon of what we know today.

As Nobel Prize-winning physicist Niels Bohr supposedly said, "Prediction is very difficult, especially about the future." Yet, several areas of research that promise new understanding and treatments of cancer are coming into view. Some are fueled by quantum leaps in technology, others by groundbreaking novel conceptual insights into the biology of cancer. All are opportunities for progress against cancer.

In this collection, we highlight several areas of investigation likely to shape future research conducted in CCR. They range from our continued efforts to understand basic mechanisms of cancer to revolutionary new clinical trial designs; from exploration of natural products and RNA for drug discovery to the use of big data to guide cancer prevention, diagnosis and treatment; from the use of cells as drugs to lessons we can learn about common tumors by studying rare cancers; and from the still mysterious questions of what determines the susceptibility of an individual to cancer to the roles of cellular metabolism and microbes in cancer.

The journey to new knowledge and new treatments is often arduous, interrupted by unexpected obstacles and diversions. In CCR and at the NIH Clinical Center, we are ideally positioned to pursue long-term, high-risk projects that explore new directions of research and patient care. What drives us forward is our belief that beyond the distant horizon lie new fundamental discoveries, clinical applications and unexpected new lands of knowledge and opportunity. As we push the boundaries of cancer research, we keep our eyes on the horizon and move forward—relentlessly, creatively, boldly—with the sole purpose of improving the lives of people with cancer.

Tom Misteli
Director, NCI Center for Cancer Research

NATURAL PRODUCTS

More than half of today's chemotherapies are derived from natural sources such as plants or microbes. Despite these successes, most current drug discovery efforts focus on synthetic molecules because they are more compatible with high-throughput screening technologies. New technologies will make it possible to explore the immense richness of chemicals found in natural sources in order to discover tomorrow's nature-derived cancer drugs.

Natural products have given us many important cancer drugs. Paclitaxel (Taxol), important for the treatment of breast, ovarian and other cancers, was discovered in the bark of a Pacific yew tree. Trabectedin (Yondelis), used to treat soft tissue sarcomas, was originally isolated from a sea squirt. And daunorubicin, a chemotherapy for certain blood cancers, was found in soil-dwelling bacteria.

Even some compounds not appropriate for clinical use have inspired researchers to develop closely related molecules that offer benefits to patients. With the vast majority of the earth's biological diversity still unexplored, investigators have only just begun to discover all the clinically useful molecules that nature has engineered.

Standard drug discovery technologies are largely incompatible with the screening of crude extracts from plants, marine organisms and microbes. Natural product extracts have complex physical properties, making them difficult to handle by automated screening platforms.

As a result, many pharmaceutical companies have reduced their natural products discovery programs. However, new groundbreaking technologies make it possible to process natural extracts into partially purified samples that are amenable to modern screening technologies.

CCR is leading this effort in its NCI Program for Natural Products Discovery (NPNPD). At the center of the NPNPD is the NCI Natural Products Repository. This growing collection contains more than 230,000 extracts of plants, microbes, algae and marine invertebrates from 25 countries and is generating more than one million different research-ready, partially purified natural product samples. The NPNPD is the largest and most chemically diverse collection of publicly available natural extracts in the world, and these samples will be sent to screening centers around the globe, greatly enabling the search for active natural products. Once researchers identify a promising extract, the NPNPD researchers use automated chemical techniques to identify and isolate the active compound so that more detailed analyses can quickly get underway.

Nature has generated an astonishing array of molecules with diverse forms and functions, refined by evolution over billions of years. Many of these are extraordinarily efficient and selective for their biological targets. Exploring this untapped potential is an important strategy for expanding our options for treating and preventing cancer.

Caption: Vials containing pre-fractionated natural products in the NCI Natural Products Repository. This automated system will purify over 130,000 crude natural product extracts to produce more than a million samples for screening against cancer and other diseases.

Credit: Barry O'Keefe, NCI Natural Products Repository
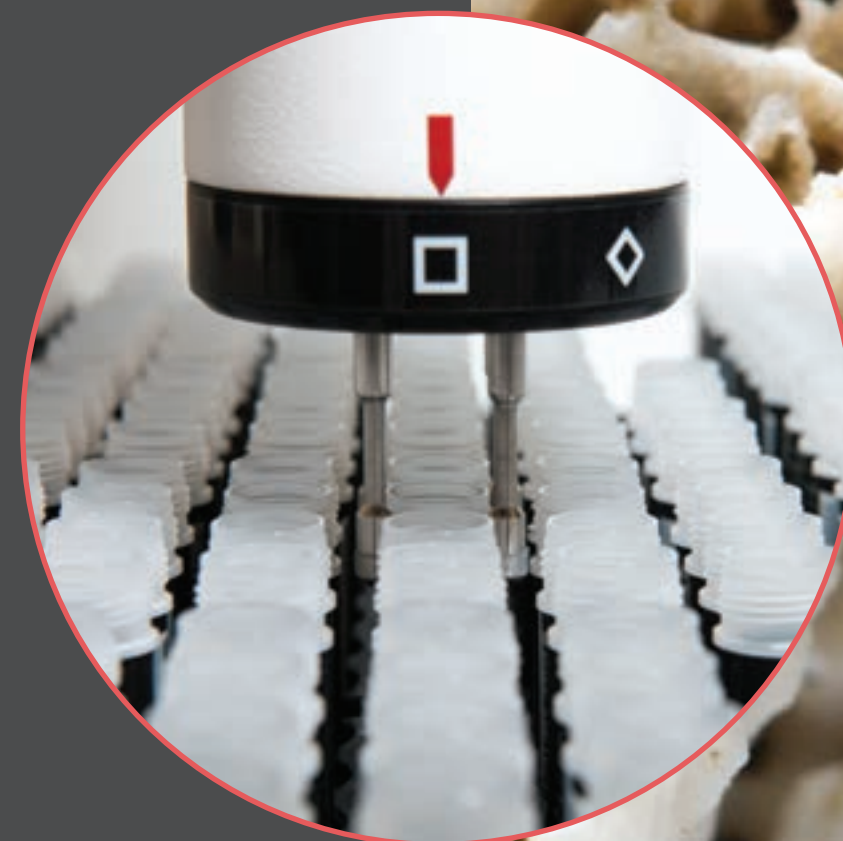
Caption: An automated weighing station in the NCI Natural Products Repository. Purified extract samples are placed in barcoded tubes and weighed prior to storage in an automated repository, which will hold more than one million pre-fractionated natural product samples for screening.

Credit: Barry O'Keefe, NCI Natural Products Repository

CELLS AS CANCER DRUGS

Surgery, radiation, chemotherapy and targeted therapies have been standard treatments for cancer, but they are no longer the only options. A revolutionary wave of cancer treatments that use patients' own cells as drugs will permanently change how we treat the disease.

The general principle behind cell-based therapeutic approaches is to exploit the natural ability of the body's immune system to recognize and neutralize invaders. In cell-based cancer therapy, immune cells that recognize cancer cells are isolated from a patient, genetically engineered to be more powerful and then multiplied before they are reintroduced into the patient to fight the tumor.

The advantages are many. The treatments are patient-specific and use only the patient's own cells, thus avoiding the risk of the body rejecting transplanted cells. Each treatment is customized for a specific type of cancer and importantly, the transferred cells can survive, multiply and continue operating within the patient's body so that only a single therapeutic treatment is needed.

Early results have been dramatic, including the complete remission of advanced metastatic disease in patients given only months to live. As with all therapeutic approaches, side effects can be significant and not all patients seem to benefit, so the quest to minimize toxicity and expand the efficacy of these "living drugs" continues.

One of the earliest approaches to result in cancer remission identified anti-cancer immune cells that had penetrated the environment in and around a patient's tumor. Those cells, known as tumor-infiltrating lymphocytes (TILs), are then multiplied in the lab and reinfused into the patient.

Newer approaches genetically engineer T cells to be more effective. A potentially transformational method, known as CAR T-cell therapy (where CAR stands for the chimeric antigen receptor added to the T cell), recognizes a target on the surface of a cancer cell and destroys the cell. In 2017, the U.S. Food and Drug Administration approved the first two CAR T-cell therapies to treat blood cancers. One, axicabtagene ciloleucel (Yescarta), was initially developed in CCR.

A limitation of CAR T cells is that they recognize only targets found on the surface of a cancer cell. This is proving valuable in cancers of the blood but less so in solid tumors that account for around 90 percent of cancer deaths. To address this issue, innovative new approaches involve engineering a patient's T cells to recognize cancer markers both inside and on the surface of tumor cells to render them effective against a broad range of solid cancers.

In many cancers, it is difficult to identify cancer-specific markers to target or predict which patients will respond to therapy. New approaches to spot potential targets using high-throughput methods to screen cells can expedite the search for targets. Most trials of cell-based therapies have involved small numbers of patients in single institutions around the world, so computational methods that can analyze results across these studies will also accelerate progress.

A different but also promising tactic is to revitalize a patient's cancer-fighting cells by reverting them to a stem cell-like state in the laboratory. It may be possible to coax these stem cells to develop into "younger" anticancer T cells with a greater capacity to flourish inside the body than a patient's own aging immune cells.

All of these cell-based therapies are highly personalized and, as a result, currently require costly and labor-intensive generation of therapeutic cells for each patient. One area for progress will be the streamlining of production methods to more rapidly generate these individually tailored cells. A breakthrough on that front will boost the accessibility of these promising therapies and hopefully will make them the standard of care for many cancer types in years to come.
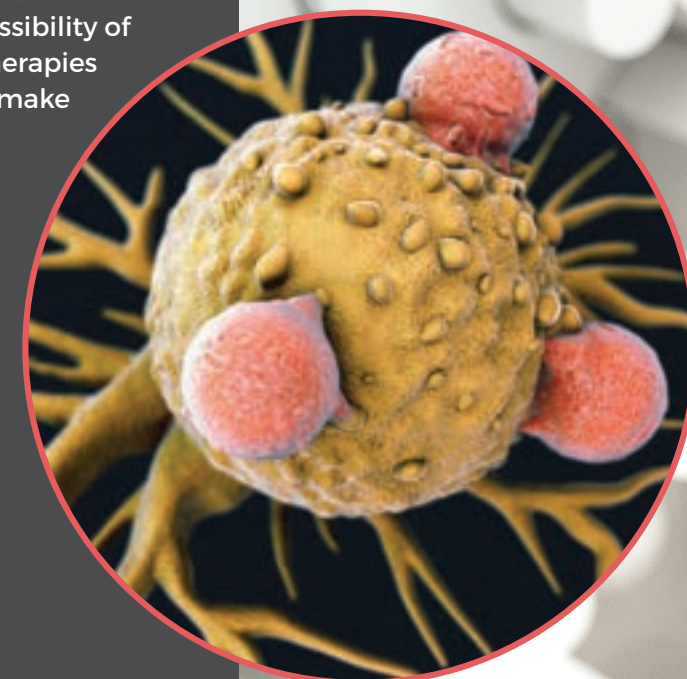
Caption: A colored scanning electron micrograph of T lymphocyte cells (smaller round cells) attached to a cancer cell.

Credit: iStock

THE STUDY OF RARE TUMORS

In the United States, cancers that affect fewer than 40,000 new patients per year are considered rare. Taken alone, each type occurs relatively infrequently, but collectively, rare tumors are not rare at all. In fact, nearly one-third of patients diagnosed with cancer have a rare tumor type. The systematic study of rare tumors will lead to much needed ways to treat patients' tumors and will shed light on how to successfully treat subsets of other more frequently diagnosed cancers.

A major promise of research into rare tumors is that they may expose cancer mechanisms that also exist—but can be difficult to uncover—in subsets of more common tumor types from unexpected drivers of cancerous growth to molecular changes that underlie treatment resistance.

For example, metabolic enzymes called isocitrate dehydrogenases (IDH) were first linked to cancer when mutations in the genes encoding these enzymes were found in rare brain cancers such as glioblastoma. IDH mutations have since been linked to a range of other cancers, including 10 percent of cases of acute myelogenous leukemia, a blood cancer. This discovery in a rare brain tumor advanced the understanding of how changes in cellular metabolism impacts growth regulation and suggested new strategies for targeted therapy for other subsets of more common cancers.

There are other major opportunities in the study of rare tumors. Each case of a common cancer is often very heterogeneous. They may be caused by a wide variety of mutations and driven by different biological pathways in individual patients. In contrast, rare tumors are often more uniform, making it easier to identify the most relevant molecular pathways that either caused or sustain the cancer.

As our understanding of cancer advances, it is becoming evident that even commonly diagnosed cancers can be broken down into multiple subsets, each with their own clinical and biological features. Recognizing these subtypes and understanding their unique behavior will be critical for developing personalized approaches to cancer treatment. Rare tumor research can help, as many of these subsets of common cancers have molecular findings seen in rare cancers.

A different approach to studying rare cancers is to examine the tumors of patients who respond well to treatments that have not been effective for most people. Studying these individuals, known as extraordinary responders, may illuminate biological or lifestyle factors that predict patients' responses to particular treatments.

The primary goal of research on rare tumors—from clinical studies of how rare tumors develop and progress to deep investigations of the biological factors that drive them—will always focus on discovering better treatments to improve outcomes for patients affected by these diseases.

Focused research on these rare diseases will have a far-reaching impact and affect many, leading to breakthroughs in treatment approaches that will improve outcomes for patients with both rare and common forms of cancer.

CCR's ability to focus on unmet needs, its stable, long-term funding and access to the NIH Clinical Center, the world's largest research hospital, allows CCR scientists the unique ability to study rare tumors. Patients with rare tumors come to the Clinical Center from around the world, making it possible to identify new research opportunities and evaluate potential therapies in clinical trials large enough to yield meaningful results. Basic, translational and clinical research capabilities and mechanisms allow CCR to collaborate nimbly with commercial partners. This uniquely positions CCR to help bring new treatments for rare cancers from the lab to the patient.

Caption: Kristy and her daughter, Jane, regularly visit the NIH Clinical Center for Jane's participation in a CCR clinical trial for neurofibromatosis type 1, a rare condition that increases the risk of developing a variety of benign and malignant tumors.

Credit: Brooke Bready, NIH Clinical Center

CLINICAL TRIAL DESIGN AND PATIENT OUTCOMES

Clinical trials have long been vital to advancing how we prevent, diagnose and treat cancer. Traditional clinical trials, however, can be cumbersome and slow. With the application of precision medicine, new concepts in the design of clinical trials will increase the speed and flexibility of clinical trials and the likelihood that a trial will benefit more of the individuals who enroll.

Traditional clinical trials consist of three phases. Phase I first-in-human trials establish a drug's safety and determine the appropriate dose for subsequent testing by slowly increasing the dose administered. Phase II assesses a drug's efficacy. If early trials succeed, an experimental treatment progresses to phase III where trials are randomized to investigate the treatment's safety and efficacy compared to current standard of care. This process can take years and typically requires participation by hundreds or thousands of people.

The promise of new clinical trial approaches rests on the ability to identify patients more likely to benefit from a given therapy based on a detailed molecular profile of their tumor generated by genomic sequencing

and molecular imaging. At a broader level, extensive genomic profiling of tumors is revealing that many common cancers can be classified into unique subtypes, which may respond to different drugs. This increased precision drives the need for more nimble and flexible trial designs that require fewer patients and can more rapidly determine a medication's benefit.

For example, studies like NCI's Molecular Analysis for Therapy Choice (MATCH) are testing drugs in cancers where genomic assays have revealed a particular molecular alteration. Treatments are based on drugs targeted to this mutation regardless of where the cancer originated or how it appears under the microscope. When the molecular target of a therapy in trials for an adult cancer is also present in childhood tumors, there is a mandate to evaluate the agent as safely and quickly as possibly in children who may benefit as well.

Efforts are underway to streamline and meld the three trial phases. Many new trials incorporate phase I/II designs in which an initial group of patients receives escalating doses of the drug until a safe dose is

determined, and additional patients are then treated at this dose. Such approaches require fewer patients to evaluate a new treatment, reducing the time, cost and effort involved in recruiting study participants. This can be particularly valuable for trials of rare cancers that typically have a limited population from which they can recruit.

Today's imaging and molecular analysis technologies have also created opportunities to enrich the data collected once clinical trials are underway. Molecular imaging and biometric sensors, as well as health apps on patients' phones and mobile devices, allow researchers to obtain real-time, objective data to supplement information collected during intermittent clinic visits. Ultrasensitive methods can measure minute changes in tumor volume, for example, and phone apps can request daily input from a patient on levels of pain. Being able to aggregate and share the data generated by these clinical trial outcomes will be critical for facilitating the rational design of future clinical trials.

The ultimate goal of modern clinical trial design is to safely bring greater benefit more rapidly to more patients.

At CCR, we are enhancing the early development and clinical testing of new cancer therapies by closely integrating basic research with clinical science. We are also implementing trial designs that allow as much learning as possible from small groups of patients, which is of critical importance when we test potential new treatments for rare cancers. Our priority is to make clinical studies as powerful and efficient as possible, to get new treatments to patients faster and to ensure they not only extend patients' lives but improve them as well.

Caption: Today's digital technologies, including molecular imaging, biometric sensors and health apps on smart phones, are revolutionizing the way cancer is diagnosed, treated and monitored.

Credit: iStock

MECHANISMS OF CANCER

Decades of discovery have demonstrated that a deep understanding of the fundamental mechanisms of cancer—how it forms, why it persists and what causes it to spread through the body—leads to better outcomes for patients. New areas of basic cancer research, including how each cell differs from others within a tumor, how the environment in which a tumor grows impacts its progress and how well an individual's immune system mounts a defense, will yield improved outcomes for patients.

Now, cancer researchers are using new tools, technologies and ways of thinking to develop an even more sophisticated understanding of cancer mech-anisms. They are exploring subtle var-iations that impact cancer cells' behaviors—not just between different patients or cancer types but even among the different cells that make up an individual tumor. At the same time, researchers are broadening their focus, looking beyond tumors to learn how factors elsewhere in the body impact a patient's disease.

Until now, studies of cancer biology have largely focused on what makes tumor cells different from healthy cells. But it has become clear that not all tumor cells—even within a single tumor—are the same. Only a small fraction of a tumor's cells may have the capacity to divide and sustain the tumor's growth.

This variability has enormous clinical consequences, and we now know that it will be important to understand human cancer on a cell-by-cell basis. Using recently developed methods of high-throughput analysis, researchers can now study the DNA, RNA and proteins of thousands of individual cells to characterize this heterogeneity and investigate how it affects tumor growth, metastasis and patients' response to treatment.

It has also become evident that a tumor's growth depends on more than the makeup of its own cells. The microenvironment in which a tumor grows, as well as the vigor with which the body's immune system recognizes and attacks cancers, are just as critical. A major challenge is to understand the interactions between tumors and their microenvironments. Ultimately, we will need to decode the signals that tumors send to nearby immune cells as well as

define which aspects of a tumor's surroundings help determine whether it stays small and benign or is allowed to grow unchecked and spread.

Although there is still much to learn about the cellular changes that drive cancer, new genomic and computational technologies have greatly accelerated the search. There is now the capacity to characterize and compare thousands of patient tumors, enabling researchers to identify factors that influence cancer risk even if they are rare or when their individual impact is relatively small. Uncovering these factors promises to point us toward important cancer pathways and suggest new opportunities for intervention.

Building on CCR's long-standing strong portfolio of basic research and the ability of CCR principal investigators to freely pursue fundamental questions in biology, our investigators are well positioned to continue elucidating the basic cellular mechanisms that underlie all types of cancer. We are also exploring the mechanisms that drive rare but genetically well-defined tumors, which may serve as model systems to understand more

globally applicable cancer mechanisms. Accelerated by the latest technologies, investigations of basic mechanisms of cancer promise to uncover new and improved diagnostic and therapeutic approaches, just as they have in the past.
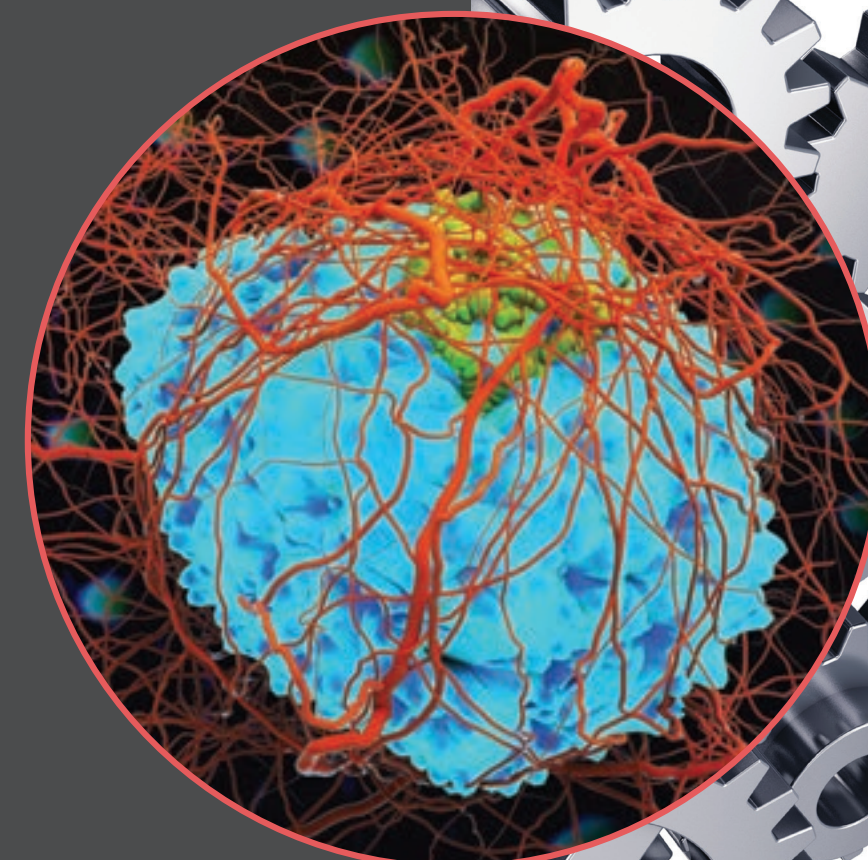
Caption: A cancer cell. New research on how each cell differs from others within a tumor provides a promising avenue for better patient outcomes.

Credit: iStock

RNA BIOLOGY

RNA, once thought of as a simple go-between from DNA to protein, is now recognized as one of biology's most versatile molecules. As such, interrogating the RNA biology of cancer will uncover new diagnostic and treatment strategies.

It is now well appreciated that only a small fraction of RNAs inside human cells encode the genetic instructions for building proteins. A myriad of other types of noncoding RNAs have been implicated in a wide range of functions.

These roles range from providing structural scaffolding, to helping organize DNA, activating signaling molecules, silencing specific genes and boosting gene activities. Many of these species of RNA are important contributors to health and disease.

In cancer, various noncoding RNAs are dysregulated, which in many cases is suspected to drive tumor growth or metastasis. Close correlations have been determined between patient outcomes and levels of certain long noncoding RNAs in their tumors.
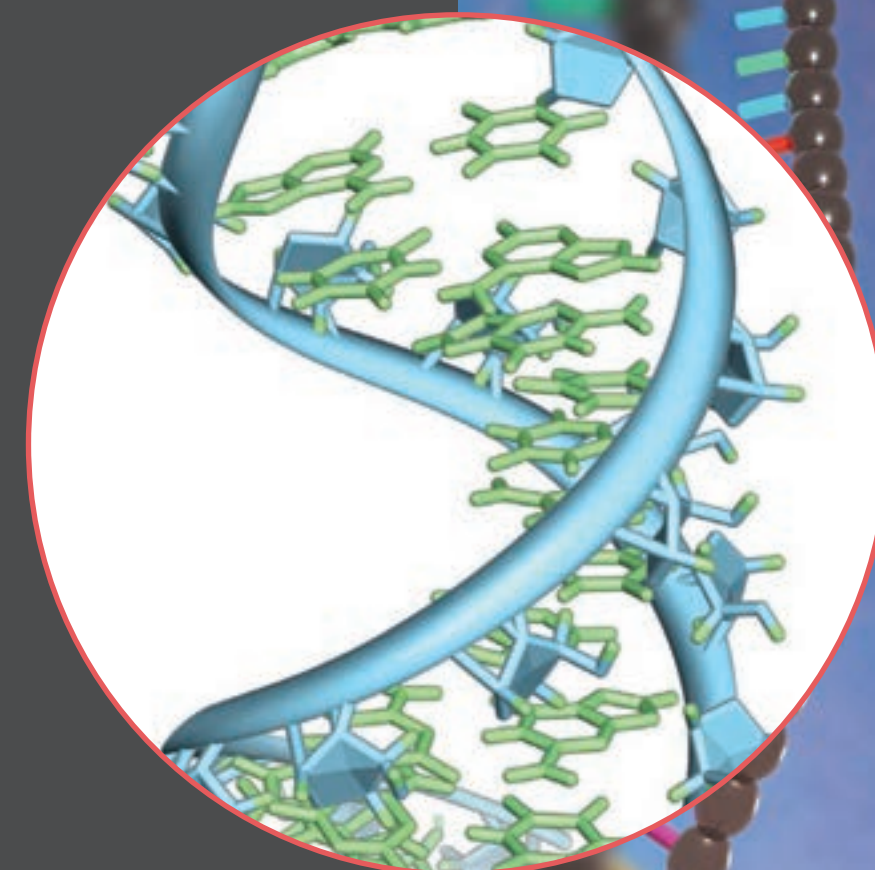
Some noncoding RNAs make their way into the bloodstream, presenting unique opportunities to diagnose disease, inform treatment decisions and monitor patients' response to therapy with a simple blood test. Individual RNAs or RNA profiles may therefore be useful diagnostic tools to help determine the best treatment approach for the individual patient.

As a clearer picture emerges of which RNAs are most relevant to cancer development, it will be possible to use RNAs as potential therapeutic targets. One promising area is the development of short pieces of synthetic RNA as cancer treatments.

These molecules, known as antisense oligonucleotides, can be designed in the laboratory to bind to specific RNAs inside cells and, in doing so, activate or turn off RNAs. In some cases, antisense oligonucleotides can be used to block the production of proteins that are required for certain cancers to grow.

To fully take advantage of RNA-controlled events in the clinic, it will be critical to deepen our knowledge of fundamental RNA biology. New methods of analysis, such as tools to determine how RNA folds into its three-dimensional shapes and how those shapes influence their function, will provide unprecedented insight into RNA behavior, their role in disease and guide us to this new therapeutic frontier.

The CCR RNA Initiative focuses on developing a comprehensive program of cutting-edge research into the roles of RNA and RNA-protein complexes in cancer. It seeks to foster synergistic interactions and cross-disciplinary collaborations among a wide range of RNA scientists and clinicians within and beyond NIH.

Caption: A hairpin loop from a pre-messenger RNA. An RNA hairpin loop is a fold in a strand of RNA which serves as a key building block for many secondary RNA structures.

Credit: Wikimedia Commons

THE HUMAN MICROBIOME IN CANCER

The microbes that crowd our guts, skin and respiratory tracts have a profound impact on how our bodies function in health and disease. The microbiome of trillions of bacteria, fungi and viruses intermingles with each person's cells, influencing human biology in ways we have barely begun to understand. Incorporating the contribution of the microbiome to cancer development and prevention will lead to a more complete understanding of cancer and may shed light on strategies to halt or mitigate those contributions.

This complex community of microbes contains thousands of species and varies enormously from person to person. Its members protect us against pathogens, fine-tune our immune systems, shape how we use nutrients and produce a host of chemicals that impact the functions of our cells.

We have come to realize that the microbiome can also hasten or slow cancer development as well as influence our response to anticancer therapies. Manipulating this intricate ecosystem may one day help us prevent or treat cancer and other diseases.

Advanced genome technologies now make it possible to analyze microbial DNA to characterize communities that live in and on our bodies and how they relate to disease. We know that these communities are not stable because their members change as we alter our diets, spend time in new environments or take a course of antibiotics. Cancer, too, can affect the composition of a person's microbiome. Efforts are underway to determine how factors such as inflammation, tumor development and progression and cancer therapy change a person's microbiome.

With new tools for molecular analysis, we can now extend our studies beyond surveying the microbiome and work toward a deeper understanding of what microbes do and how they interact with other cells. To gain a complete picture of the biological impact of these communities, it will be critical to investigate the genes present in different microbiomes and the vast range of chemicals that their members produce. Such studies will be complemented by work in animal models where investigators can carefully manipulate the composition of the microbiome to explore the mechanisms by which its members influence inflammation, immune activity and other processes. Another priority is to investigate the mechanisms that microbes and human cells use to communicate with one another. Once we understand how these communications work, it may be possible to interrupt or modify them to alter biologicial processes.

Maybe most importantly, a patient's microbiome influences their response to cancer treatment. Researchers already know that a microbiome's composition can modulate both the effectiveness of different therapies as well as their associated side effects. For example, certain types of immunotherapy work best when patients have highly diverse communities of gut microbes. Identifying ways in which the microbiome impacts the response to specific anticancer therapies will require extensive sequencing of microbial DNA and sophisticated bioinformatic analyses. Understanding these relationships is expected to help clinicians identify the best treatment for every patient and may also suggest ways we can modify individuals' microbiomes to improve outcomes.

We cannot be certain of what we will find as we explore the relationship between cancer and the human microbiome. But elucidating its complexity is an immense opportunity that could uncover new aspects of cancer biology and find new ways to improve patient care.
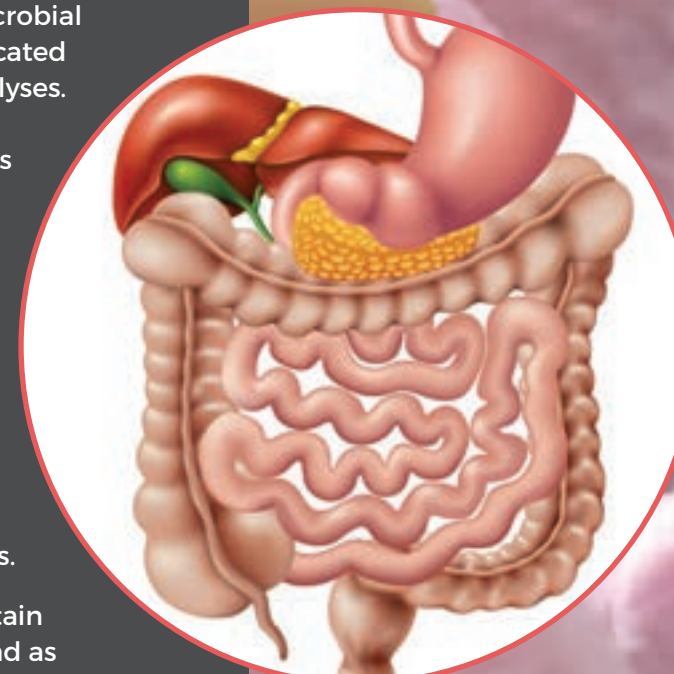
Caption: Scientists have learned that the microbiome, including the gut microbiome, can hasten or slow cancer development and influence responses to cancer treatment.

Credit: iStock

CELL METABOLISM AND CANCER

We have known for nearly a century that the metabolism of cancer cells can differ markedly from healthy cells. For example, cancer cells consume far more glucose to generate energy and to produce materials that support cell division. Until recently, these features were considered just another way cancer cells differ from healthy cells. But it is now becoming clear that these metabolic changes may be one of their driving forces. This insight will open the way to new approaches that treat cancer by disrupting cancer-cell-selective metabolic pathways, resulting in more effective and less toxic drugs as well as more precise ways to diagnose cancer.

The pathways that make up cellular metabolism are complex. Large networks of enzymes work together to convert food into energy and necessary chemical compounds. Cancer cells often abandon the efficient energy-producing pathways used by most cells and shift to alternative strategies that yield less energy but generate more materials needed to build new cells. Although this shift provides a growth advantage to cancer cells, it also represents a vulnerability because rapidly dividing cells can become dependent on these alternative pathways; interfering with them might be a powerful way to thwart tumor growth.
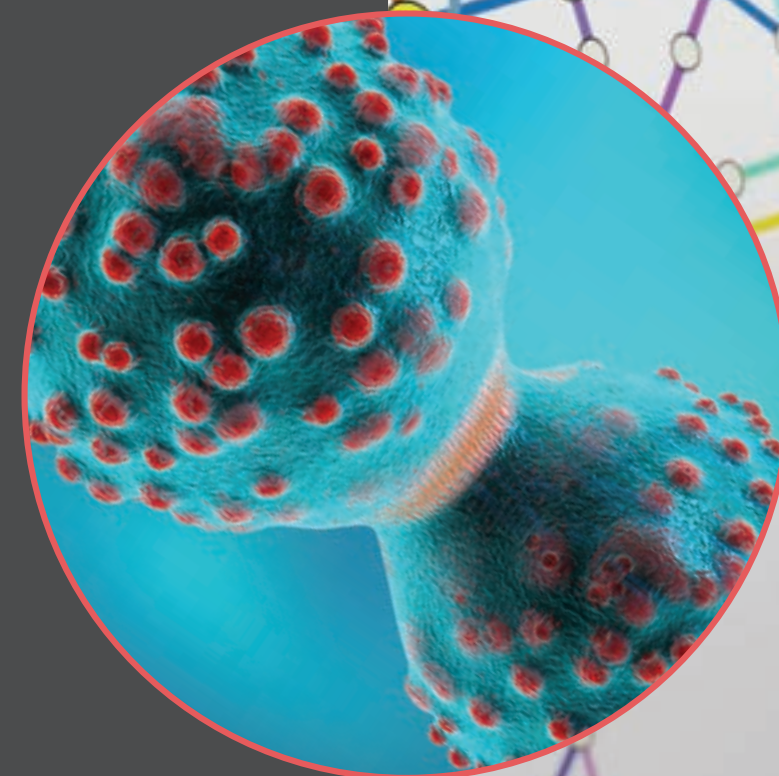
Some genes whose general involvement in cancer were identified long ago are now recognized to influence the way cells take up nutrients, convert food to energy and generate vital biological compounds. On the other hand, previously unsuspected genes and pathways are, in reality, acutely involved in tumor growth and survival. Identifying these culprits is important because they could lead to new targets for therapeutic intervention.

With new technologies that can detect thousands of different metabolites in tissue samples, it is now possible to identify the wide array of chemicals generated by cellular metabolism. These tools uncover how metabolic pathways are disrupted in cancer cells and how subtle changes contribute to tumor growth. Current studies aim to track how metabolism changes as cancer progresses and metastasizes, or as a tumor responds to anti-cancer therapies, especially when acquiring resistance.

Comprehensive elucidation of the metabolic landscape in cancer cells has the potential to guide the development of drugs that target metabolic pathways to deprive cancer cells of the biochemical resources on which they have come to depend. It is also possible that existing drugs that modify metabolism, such as those used to lower cholesterol or treat diabetes, will be useful in treating or preventing cancer.

A clinical goal is to comprehensively catalogue cancer-causing metabolites inside a patient's body and use the information to make treatment decisions. Using sensitive new clinical imaging technology, such as methods developed at the NIH Clinical Center, CCR investigators are beginning to do precisely that. With a deeper understanding of the relationship between cancer and metabolism, this type of imaging might one day be used to rapidly determine how aggressive a patient's tumor is, or to monitor how someone's cancer is responding to treatment.

A first example of the importance of metabolism in cancer is the several metabolic genes discovered in CCR, that, when mutated, increase the risk of kidney cancer. Now it is known that mutations in metabolic genes contribute to a wide range of cancers, including cancers of the brain, prostate, pancreas and lung.

Caption: A three-dimensional illustration of a cancer cell in the process of mitosis.

Credit: iStock

CANCER SUSCEPTIBILITY

What makes one person more likely to get cancer than another? It is known that some habits and environmental exposures predispose people to developing certain cancers, yet not all exposed individuals will develop tumors. Understanding the molecular basis of cancer susceptibility remains one of the holy grails of cancer research and will improve the ability to prevent and treat cancer.

Cancer susceptibility is a complex genetic trait, and few cancers are a result of mutations in a single gene. To tease out the factors that increase risk, it is usually necessary to follow large numbers of people over many years. But the problem has become somewhat more tractable thanks to a combination of cheaper methods to sequence genomes and the development of advanced computational tools.

Advanced tools and methods allow for the detection of subtle differences in the genetic makeup of individuals and help find variations that exacerbate—or mitigate—risk.

Untangling how the environment impacts the risk of cancer is even more daunting than charting the complex effects of our genes. For example, all life on earth must cope with constant exposure to DNA damage from sources such as ultraviolet light from the sun, X-rays and various chemicals, all of which cause mutations. But several research areas promise to uncover the roles of important environmental exposures in the coming years.

To generate a more complete picture of how genetic variation impacts susceptibility, it is important to look beyond cancer cells themselves. Experts need to explore the genes that shape the immune system and

tumor microenvironment to determine which elements permit cancer cells to flourish or help keep them in check. An intriguing example is the potential role of the microbiome, which is a community of microbes that mingle with human cells. The composition of the microbiome differs greatly between individuals and may be one factor that modulates the contribution of the genome to cancer risk for an individual.

The ultimate goal in the area of cancer susceptibility is to both understand the molecular basis of susceptibility and to predict who is most likely to develop certain cancers. There is also a need to understand what the specific risk factors are and which cancers are likely to be most aggressive so that steps can be taken to minimize risk and implement appropriate treatment. Deepening the understanding of genetic and environmental risk factors will also yield important clues into the biological processes that unfold as tumors develop and progress, paving the way toward new interventions.
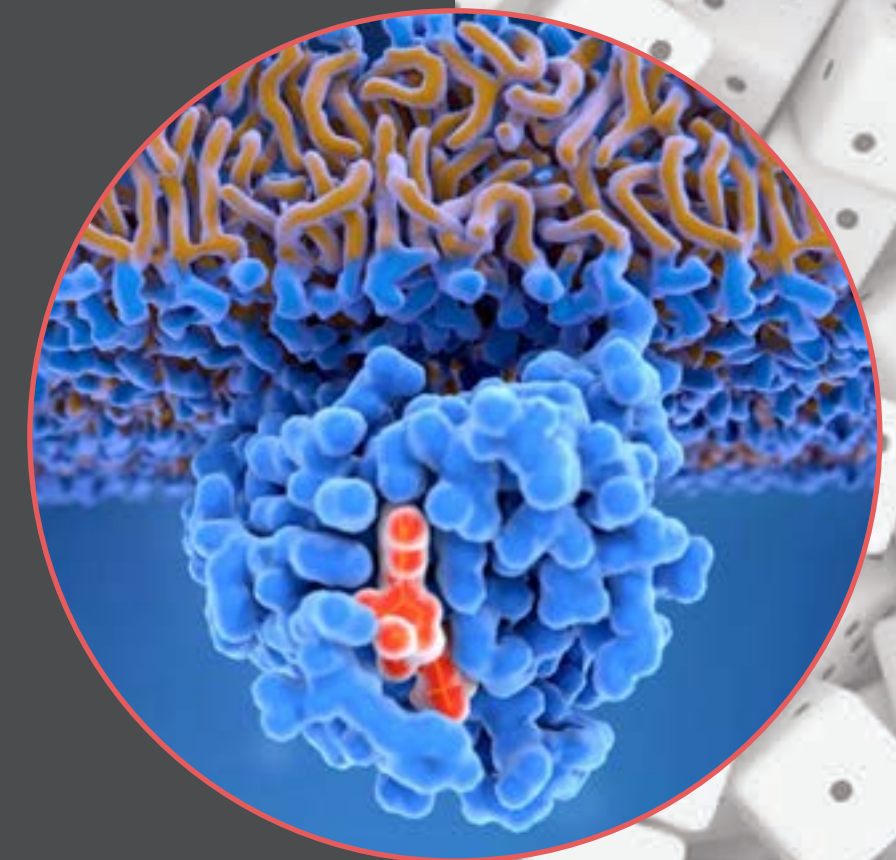
Caption: An activated Ras protein attached to a cell membrane. More than 30 percent of all human cancers are driven by mutations of the *RAS* genes.

Credit: iStock

The National Institutes of Health's *All of Us* Research Program, which is seeking one million or more U.S. participants from all backgrounds, will provide a rich source of data to explore susceptibility factors in a diverse group.

BIG DATA

Modern biomedical research and clinical care generate more data than ever. Information can include genetic, imaging and metabolic data from tens of thousands of patients. It may provide responses to treatment and side effects. These records are creating rich datasets, which can be mined with new artificial intelligence and machine learning tools.

Big data will provide an unprecedented opportunity to understand cancer at every level, from molecular signatures to nationwide statistics, and to help make treatment decisions based on the knowledge distilled from these massive collections.

Once available only to research institutions with extensive data storage and computing capabilities, these datasets are increasingly available to the wider researcher community through repositories such as NCI's Genomic Data Commons, which integrates data from large, collaborative projects such as The Cancer Genome Atlas and the Therapeutically Applicable Research to Generate Effective Therapies (TARGET) initiative.

These repositories provide efficient systems to securely store, share and analyze this information without compromising patient identity. Researchers are encouraged – sometimes required – to add their own results to these collections.

The availability of these public data collections has spurred development of software tools designed to store, process, analyze and visualize large datasets. In turn, this has led to a push to train a new generation of scientists in how to contribute to, and use, these data science assets. As these repositories mature, they will incorporate some of these shared tools for data analysis.

At the forefront of these tools and methodologies are machine learning and artificial intelligence approaches in which computer networks are programmed to rapidly analyze complex biomedical data and find hidden patterns.

For example, in what is known as quantitative imaging, software can detect and quantify abnormal features on a medical image that may be missed by the human eye, leading to an earlier or more accurate diagnosis.

In a research setting, these methods and algorithms are being employed to accurately predict which patients might benefit from a certain treatment based on a review of previous patient genomic data referenced against their responses to treatment.

Another set of digital technologies is enabling patients to contribute data to clinical trials. Biometric sensors and fitness trackers, as well as health apps on patients' phones and mobile devices, allow researchers to obtain real-time reports on items such as pain and activity levels to supplement information collected during intermittent clinic visits.

Finally, in the realm of public health, more sophisticated ways to monitor cancer cases and management on a population level are becoming available.

An improved ability to extract and interpret data tucked into the health records of cancer patients while reliably removing identifiable patient information would do much to speed our ability to measure differences in cancer rates due to changes in cancer screening, therapies and healthcare policies.

These population data would also let us better detect health disparities, assess the outcomes of cancer prevention strategies and better formulate public policy to improve the health of broader populations.

Big data is already transforming cancer research and cancer care—but we have only just begun to understand what the data are telling us. Now, we are building on what we have learned and accelerating the transformation of data into meaningful advances for patients.
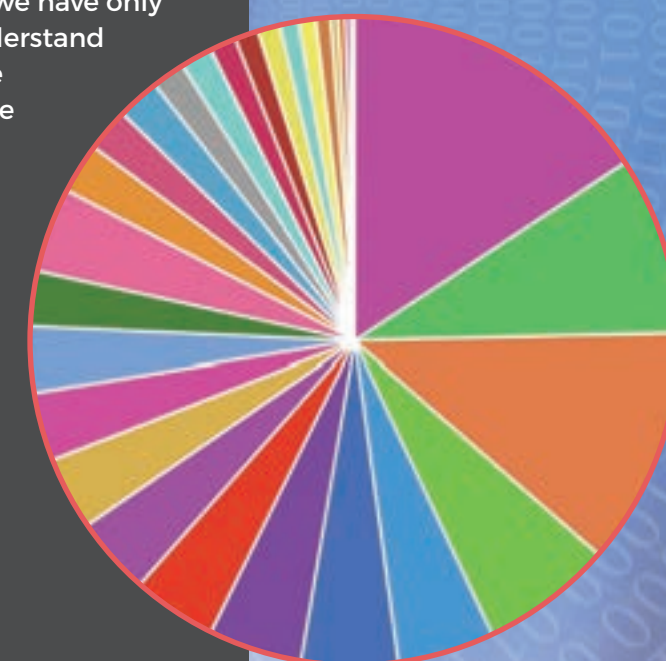
Caption: A pie chart representing data available in the NCI Genomic Data Commons (GDC) categorized by major site of origin. The GDC contains de-identified data from more than 32,000 patients with more than 60 different types of cancer gathered from 40 different projects.

Credit: NCI Genomic Data Commons

CCR RESOURCES

For more information on CCR:

CENTER FOR CANCER RESEARCH
https://ccr.cancer.gov
240-760-6400

CCR CLINICAL TRIALS
https://ccr.cancer.gov/clinical-trials
1-888-624-1937

CCR NEWS
https://ccr.cancer.gov/news

CCR CAREERS
https://ccr.cancer.gov/careers

CCR TRAINING OPPORTUNITIES
https://ccr.cancer.gov/training

CCR MAGAZINES
https://ccr.cancer.gov/news/magazines

*For more information on the programs
mentioned in these stories:*

NATURAL PRODUCTS BRANCH
https://dtp.cancer.gov/organization/npb/introduction.htm
NCINatProdRep@mail.nih.gov

NIH *ALL OF US* RESEARCH PROGRAM
https://allofus.nih.gov

GENOMIC DATA COMMONS
https://gdc.cancer.gov

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