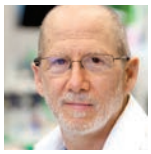
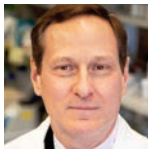
1980s

Our researchers begin to crack the cancer code, revealing it as a disease caused by an accumulation of genetic mistakes. This becomes the paradigm for much of modern cancer research, ushering in the age of molecular cancer biology with new gene-targeted therapies and paving the way for gene-based screening tests for cancer.

Broken Genes

The Mistakes in DNA That Lead to Cancer


VOGELSTEIN


KINZLER

THE DISCOVERIES THAT led the world to understand that cancer is a genetic disease unfolded one by one in the laboratory of **Bert Vogelstein** and **Kenneth Kinzler**.

More than 40 years ago, when they first cracked open the Pandora's box that is cancer, revealing first one and then a series of genetic mistakes responsible for colon cancer, it was a foreign concept. Today, their discoveries have led this lab, and others around the world, to develop genetic tests, screening diagnostics and targeted therapies for colon and other cancers.

"When it comes to cancer genetics, Bert's and Ken's work is on the cutting edge of the cutting edge. They led the world to understand that cancer is a disease of genetic defects, and then led the first laboratory in the world to reveal what those defects are," says Johns Hopkins Kimmel Cancer Center Director **William Nelson**.

The complexity of their genetic discoveries has been likened to finding one two-letter transposition within 20 volumes of *Encyclopedia Britannica* and then figuring out how it got there. Some scientists consider them to be of the magnitude of finding a cause for polio. As transforming as these discoveries have been in the cancer world, they started simply and quietly in 1983 in a converted supermarket on the Johns Hopkins East Baltimore Medical Campus.

THE EARLY DISCOVERIES


BAKER

At the time, very little was known about colon cancer. "The man who is really responsible for advancing the understanding of colon cancer is **Benjamin Baker**," says Vogelstein.

Baker, a Johns Hopkins internist who followed Vogelstein's work, was intrigued by the concept that cancer was caused by genes gone awry. While others were optimistically in search of the magic bullet that would bring down cancer in one fell swoop, Vogelstein's studies were revealing a much more complicated disease process.

A genetic infrastructure unlike anything that had ever been described in human disease was being described. It centered on a delicate balance between cell growth accelerators, called oncogenes, and cell growth brakes, called tumor suppressor genes.

> "THE REVOLUTION IN CANCER RESEARCH CAN BE SUMMED UP IN A SINGLE SENTENCE: CANCER IS, IN ESSENCE, A GENETIC DISEASE."
>
> –BERT VOGELSTEIN

Ushering in the age of molecular biology, Vogelstein, Kinzler and their co-collaborators were among the first to apply it to the study of a human disease, developing the knowledge and tools to look inside the submicroscopic molecules of the cell to reveal those rare, uncorrected errors in our DNA that put the cancer process in motion.

Alterations to these genes, either inherited or acquired throughout life, disrupted the delicate balance, giving an advantage to cell growth. Fundamentally, cancer is a normal cell that does not die. As the immortal cell divides, it eventually reveals itself in the form of a tumor.

While many researchers focused on the cancer, Vogelstein realized very early on that it was what precipitated the cancer that also mattered. He compared it to an iceberg — the cancer was the tip of the iceberg that could be seen, and the benign tumors were the layers beneath the water. He set out to identify the basis of the invisible layers beneath the surface that began forming decades before.

There was much skepticism about his approach.

"Cancers in animals were considered better to study because they were easier to manipulate," says Vogelstein. "That was true in some ways, but our view was this was a human disease, and we wanted to study the real thing."

The first grants Vogelstein submitted were rejected, but he persevered, and the findings that followed uncovered a genetic infrastructure that is now widely accepted to underlie the basis of all human tumor processes.

Using technologies they invented to see inside the cancer cell, they began to unravel the mystery of cancer.

SEARCHING FOR THE ERRANT GENES

As Vogelstein began his quest to uncover the hidden layers of the iceberg, Baker, who liked Vogelstein's visionary approach, convinced his wife's family to donate money from their Clayton Fund to the Vogelstein lab. This seed money, which brought together the Bowel Tumor Working Group, was a turning point in Vogelstein's research.

This collaboration of seasoned clinicians and investigators and young up-and-comers began to shed the first light on the origin of colon cancer and, at the same time, triggered other investigators around the country and the world to look for similar patterns in other cancers.

At first, the discoveries came almost more quickly than they could be sorted out. In 1989, Vogelstein's identification of p53 mutations in colon cancer started a media frenzy as investigators around the country, following the Vogelstein lab's lead, found the same mutation in breast, lung and other cancers. "The p53 gene is the most common gene mutation among all cancers," the reports read.

A public eager for a quick fix pinned their hopes on this discovery as the holy grail of cancer. Vogelstein, his own toughest critic, was the first to dash these hopes. While he felt the discovery was important for advancing the science and technology of gene discovery, he was not looking for an answer in one gene. In fact, his lab's work showed that the p53 alteration was a mutation that occurred late in the cancer process, which led them to the next question. What genetic alterations came before p53?

INHERENT CLUES

Vogelstein hypothesized that colon cancer resulted from a series of genetic alterations that evolved over decades, starting with small clusters of abnormal cells in the lining of the colon, advancing to benign tumors known as polyps, then to a cancerous tumor in the colon, and finally, to where p53 most likely came in, pushing the tumor to its most lethal form, as it spreads outside of the colon to other parts of the body. What Vogelstein wanted to do was identify the whole series of mutations and the order in which they occurred.

He decided to look among the rarest types of colon cancers for the answers — inherited colon cancer syndromes. Although they represented a small percentage of colon cancers, Vogelstein believed the same genetic underpinnings that led certain families to be plagued by an alarmingly high incidence of colon cancer, and typically at a much younger age, would shed light on colon cancers among the general population.

Using technologies they invented to see inside the cancer cell, they began to unravel the mystery of cancer.

Each of us inherits two copies of every gene from our parents, one from our father and one from our mother. In inherited colon cancer syndromes, family members are born with only one good copy of a gene. Subsequent random mutations and assaults from diet and other behaviors knock out the one good copy. The cascade of cellular errors that ultimately results in cancer is put in motion.


HAMILTON

Kinzler, Vogelstein's research partner and co-director of their lab, pathologist **Stanley Hamilton** and other members of the Bowel Tumor Working Group looked for inherited genetic alterations in these hereditary cancers.

The Kinzler-Vogelstein team identified a mutation of the APC gene in familial adenomatous polyposis, a rare, inherited syndrome in which affected people get hundreds of benign tumors known as adenomas, or polyps, in the colon. Further studies showed the same mutation to be the one that jump-starts the cancer process in the nearly 140,000 people within the general population who are diagnosed with colon cancer each year.

Other researchers in the Vogelstein/Kinzler lab were uncovering the genetic culprits of two other inherited colon cancers. In particular, they discovered the genetic and biochemical basis of hereditary non-polyposis colon cancer, which accounts for more than 50% of inherited colon cancer syndromes.

In 1998, the team reported a genetic alteration affecting as many as 400,000 people nationwide — 6% of European descendant Jews (Ashkenazi). Gene testing for cancer was catapulted into mainstream medicine because, along with the discovery of the genes that caused these diseases, Vogelstein, Kinzler and colleagues developed tests that detected the mutations. These tests are now part of the routine management for patients with strong family histories of the disease, and dramatically changed how these patients are diagnosed and treated.

For the first time, clinicians could know which family members had inherited colorectal cancer-causing mutations so that those at risk could be monitored closely for cancer. As important, the tests also revealed family members who did not have the gene mutations, so they could be spared unnecessary screening measures. It was the first example of individualized, or precision, medicine for patients with typical forms of cancers.

A TEST FOR EVERYONE

These finding were key to understanding how cancer originated, and were transforming for families with these hereditary forms, but they represented a small fraction of the cancers. Vogelstein and Kinzler also wanted to develop ways to intercept and prevent the 95% of cancers that occur sporadically among the general population.

They wondered if they could find cancer DNA among colon cells shed and passed in stool. If they could find APC mutations — the mutations that cause normal colon cells to form the benign polyps that occur before cancer — in cells found in stool, they could potentially prevent the cancer from ever occurring.

These studies, first undertaken in 1991 by **David Sidransky**, who later started his own lab using this method to detect cancer-specific DNA in urine, sputum and other body fluids, were moved forward by **Giovanni Traverso** and **Frank Diehl.**

Anne Jennings Krush

Anne Jennings Krush is an unsung hero of cancer research. In 1967, Krush began a research career at Creighton University, working alongside acclaimed cancer genetics expert **Henry Lynch**, a renowned authority in familial predisposition to cancer. During this collaboration, Krush developed an interest in familial colorectal cancer syndromes. In 1973, she came to Johns Hopkins and worked with **Victor McKusick**, continuing her study of hereditary colorectal cancer.

She served as the polyposis registry coordinator, and was a force behind the formation of the Bowel Tumor Working Group, a multidisciplinary team focused on hereditary colon cancer. This interaction initiated her collaboration with leading researchers in the field of cancer genetics, including **Francis Giardiello**, **Bert Vogelstein**, **Stanley Hamilton** and **Gloria Petersen**.

With painstaking attention to detail, she pieced together the medical histories of several hundred families, uncovering what would become the foundation for the Cancer Center's world-renowned discovery of the genetic basis for hereditary colon cancer.

The research led to the first noninvasive genetic screening test for cancer, distributed by Exact Sciences and marketed as Cologuard. The test, which had its origins in the Vogelstein/Kinzler lab, has now been used by millions of people.

Vogelstein and Kinzler developed the test to address the underuse of screening colonoscopy among the general public.

"The stool test is noninvasive and essentially risk-free, and it uncovers the very first genetic event in the colon cancer process," says Kinzler. This mutation could occur years before an actual cancer develops, giving clinicians ample time to cure or even prevent the cancer from occurring, he adds.


SIDRANSKY

CRACKING THE CANCER CODE

Building upon their colorectal cancer discoveries, researchers in the Vogelstein/Kinzler lab applied their methods to other cancers and cracked the genetic codes of more forms of the disease than any other research team in the world. Their work is considered the classic model, the paradigm for much of modern cancer research.

A foundational gift from the Ludwig Foundation allowed them to bring automated gene sequencing equipment to their laboratory, making it possible to simultaneously sequence millions of gene fragments. Research that once took years could now be done in days for a fraction of the cost of earlier studies. This meant an unprecedented, all-encompassing view of precisely what was happening inside the cancer cell was at last possible.

Despite the complexity, in 2006, they began accomplishing something that would have been impossible just a decade earlier. Using advanced technology, the team analyzed more than 30 million base pairs of DNA in a patient's cancer and provided the first ever comprehensive blueprint of cancer — what goes wrong in the cellular instructional manual to cause cancer.

This task of monumental scope took the cancer world by storm, opened new areas of research and, for the first time, presented a full genetic understanding of one of humankind's greatest threats.

With new, faster computing tools to sequence cancer DNA, the team in the Vogelstein/Kinzler lab completed 88 of the first 100 blueprints of human cancers, and inspired similar research in labs around the world.

> "Knowing the road map of cancer is key to attacking it."

The detailed maps of cancer they created provide guides by which scientists can pinpoint characteristics of each person's cancer and tailor therapies and diagnostics to guide treatment — what we call *precision medicine.*

"Knowing the road map of cancer is key to attacking it. Now that we have identified the key gene mutations, we can focus on determining at what point in the cancer process they occur, whether they guide prognosis, and if they might be good targets for prevention or treatment," said Vogelstein.

GENETIC TESTS FOR CANCER

These discoveries provided a detailed schematic for how tumors start and how they become progressively more dangerous as a result of heredity, random alterations or outside cell-damaging exposures that change DNA over the course of up to 30 years.

The last stage of metastasis, when the cancer spreads, and the stage that actually kills people occurs only in the last few years of this 30-year process, according to Vogelstein. Unfortunately, this is when many cancers are diagnosed. By this time, they have acquired so many gene alterations they are often resistant to treatment, he says.

He believed that if the cancers were detected before cancer cells spread to other parts of the body, most patients could be cured with surgery and drug treatment or potentially even surgery alone.

This led researchers in the Vogelstein/Kinzler lab to focus on ways to use their genetic discoveries to detect cancers earlier.

As tumor cells divide, they develop their own blood supply to get the nutrients they need to nourish and grow, and as a result, pieces of the cancer's DNA get carried in the bloodstream, leaving telltale evidence of their existence. The DNA contains the alterations specific to the cancer — the accumulation of errors that occur as normal tissue transforms to evasive, deadly cancer. It's been there all along, floating among a sea of normal cells; scientists had to develop the technology to see it and pull it out.

Next-generation sequencing technologies allowed millions of DNA molecules to be simultaneously and individually analyzed, providing the first opportunity to identify mutations in the bloodstream. However, the technology was fraught with inefficiencies and high error rates that limited their clinical application.

To correct for these sequencing errors, researchers in the Vogelstein/Kinzler lab developed a new technology called SafeSeqS (Safe Sequencing System) in 2011, and then built a better version in 2021 called SaferSeqS (Safer Sequencing System). The technology makes it possible to detect rare mutations in blood efficiently and accurately.

Detecting mutations in blood samples, now known as liquid biopsy, rather than via surgical biopsy provided the potential to detect cancer at its earliest stage.

It ushered in a series of screening tests developed in the Vogelstein/Kinzler lab, including PapSEEK, UroSEEK, CompCyst and CancerSEEK.

PapSEEK could be used on cervical fluid obtained during Pap tests (screening tests for cervical cancer) to detect mutations in 18 genes commonly mutated in endometrial and ovarian cancers. UroSEEK scours urine samples for 11 mutations associated with bladder and other urological cancers. CompCyst finds molecular markers in the fluid of pancreatic cysts to distinguish harmless cysts from those likely to develop into pancreatic cancers.

Sleuthing Out Bladder Cancer

In 1967, when **Hubert Humphrey**, then vice president of the United States under Lyndon B Johnson, sought medical advice for blood in his urine, as many as 12 pathologists examined the cells in the urine. Some thought it was cancer. Others disagreed, and Humphrey was not treated until a few years later, when he developed clear signs of bladder cancer. He died of the disease in 1978.

After learning that Johns Hopkins pathologists had reviewed Humphrey's case in 1967, and that the original slides containing his bladder cells were still in the hospital, pathologist **Ralph Hruban** became intrigued.

He turned to **David Sidransky**, who was working in the cancer genetics lab of Bert Vogelstein and Kenneth Kinzler, researching tests to detect cancer cells in body fluids and secretions. Hruban wanted to put this research to the test and find out if he could prove, once and for all, if Humphrey had bladder cancer in 1967, 10 years before he died from the disease.

In 1994, with Humphrey's widow's permission, the urine specimen was reexamined using Sidranky's test, a genetic probe specific to Humphrey's cancer that would pinpoint the bladder cancer, if it existed, in the 1967 specimen.

Sidransky found mutations of the p53 gene, a common genetic fingerprint of bladder cancer, in 9% of the cells, proving Humphrey had undetected bladder cancer in 1967.

For Sidransky, the most exciting implication of the discovery was looking to the future and how tests like these could be used one day to pick up cancer years before the tumor could be found by normal clinical methods.

It is impossible to know for certain, but if the invasive bladder cancer had been detected earlier, Sidransky speculated, it might have been cured.

"In the not-too-distant future, when people see their doctors, they can provide urine, stool and sputum samples and have them screened for bladder, colon and lung cancers," Sidransky said in 1994.

This science led to the Cologuard stool test for colon cancer, and paved the way for liquid biopsy and the development of gene-based tests, like CancerSEEK, on the horizon.

CancerSEEK is a first-of-its-kind test that screens for eight common cancer types in a single blood test. The cancers the test detects — ovarian, liver, stomach, pancreatic, esophageal, colorectal, lung and breast cancers — account for 60% of cancer deaths, and five of these cancers currently have no screening test. The hope is that the test will detect cancers early when they can be cured.

The test has been licensed by Exact Sciences to continue development as a multicancer screening test for the general population. Quest Diagnostics has licensed the technology to monitor people with cancer for signs of cancer recurrence or progression.

LOOKING TO THE FUTURE

The complexity of cancer stems from the fact that it originates from our own cells. The genetic mutations that mark the genes of cancer cells are the only thing that distinguishes normal cells from cancer cells. However, it is this subtle difference and research spanning three decades that led to one of the most significant advances in cancer treatment.

It started in 1993, when researchers in the Vogelstein/Kinzler lab identified a genetic cause of Lynch syndrome, a hereditary form of colon cancer.

MATCHING CANCER GENES TO TREATMENTS

The genetic discoveries made at the Kimmel Cancer Center over the past 50 years revealed a complex landscape. There are at least 1,000 gene defects in every cancer, making the genetic landscape of tumors very complicated. Although these gene findings opened the door to precision medicine, which makes targeted therapy possible, it requires special expertise to match gene targets to the right therapy. The Johns Hopkins Kimmel Cancer Center Molecular Tumor Board has the tools to address these complexities.

Our experts have learned that not every change in a driver gene is driving the cancer.

"It is important to consider the specific mutation and its implications," says **Valsamo "Elsa" Anagnostou**, who directs the center's Molecular Tumor Board, which was previously directed by former faculty member **Ben Park**. "The informatics tools available that pair mutations with targeted therapies generally do so at the gene level, without consideration of the specific mutation. We can help distinguish genetic alterations driving a cancer from those that are incidental. We evaluate the specific alteration and its implication for cancer growth and metastasis."

More recent research also revealed the importance of co-mutations, something Molecular Tumor Board experts uniquely consider in making recommendations for therapies, including combination therapies.

"Commercially available services are generic, with limited information for less common mutations, and they do not capture co-mutations. Oncologists face a vast volume and variety of generic molecular data that our tumor board can help them navigate," says Anagnostou.

Over the past two years, they saw an increasing rate of matches between gene targets and clinical trials or off-label use of FDA-approved therapies.

Mutations to mismatch repair genes, which correct copying errors when DNA replicates and cells divide, cause high rates of additional mutations and an increased risk of developing colon cancer.

PAPADOPOULOS

Vogelstein, Kinzler and lab member **Nickolas Papadopoulos** developed a test to screen for mismatch repair deficiency/microsatellite instability to allow families with a history of Lynch syndrome to be monitored for development of colon cancer.

Fast forward 20 years. Armed with an understanding of the genetic alterations that are responsible for cancer, the Kinzler- Vogelstein group cooperated with cancer immunology researchers to make an unprecedented suggestion. They suspected that cancers from patients with Lynch Syndrome would be extraordinarily sensitive to a new class of drugs, called immune checkpoint inhibitors, being developed by the cancer immunology group.

The discovery was key to a historic 2017 FDA approval of the immunotherapy drug pembrolizumab across all cancer types for any cancer that contains the mismatch repair deficiency/microsatellite instability genetic defect. It marked the first cancer drug approval based on a specific genetic profile and with no regard to where in the body the cancer started. The research community at large had doubts, leading the researchers to perform the clinical study themselves without the benefit of industry sponsorship.

LE

The clinical trial, led by **Dung Le** and **Luis Diaz**, demonstrated astonishing responses in patients with cancers that had mismatch repair deficiency/microsatellite instability. The historic discovery soon led to the FDA approval of the immunotherapy drug prembrolizumab across all cancer types for any cancer that contains the mismatch repair/microsatellite instability defect. It marked the first cancer drug approval based on a specific genetic profile with no regard to where in the body the cancer started.

> "The history of medicine shows that when a disease is understood, it eventually becomes manageable."

"This illustrates the science of discovery, and how long it can take to fit the pieces together," says Vogelstein. "It is a reflection of the strength and support of research at Johns Hopkins. No other institution had ever done something like this before, discovered the basis for a disease and designed a treatment that obtained FDA approval. This is virtually unique in the history of medicine."

Researchers in the Vogelstein/Kinzler lab continue to contribute to immunotherapy discoveries, focusing on new ways to target specific gene mutations with immunotherapy.

"The history of medicine shows that when a disease is understood, it eventually becomes manageable," says Vogelstein. "This understanding truly has been revolutionary in many other diseases. The next revolution is to take this knowledge we and others have gathered and help patients in ways that could only be imagined before this understanding came about."

Vanessa's Story

In Search of a Miracle

VANESSA WITH HER GRANDSON, ZION

When Vanessa was diagnosed with advanced colon cancer in 2014, just before her 60th birthday, the caring mother and grandmother learned the cancer had already spread to her stomach and liver.

Even after a five-hour surgery and nearly a year of grueling chemotherapy, the cancer continued to grow. Her doctor told her there was nothing left to try.

The news was devastating. Vanessa traveled around the country searching for treatment options.

"I was willing to try anything," she says.

She remembers the day her young grandson, Zion, asked her if she believed in miracles.

She did believe, and she began searching for information. Vanessa came upon the Kimmel Cancer Center's Bloomberg~Kimmel Institute for Cancer Immunotherapy website.

"I grew up on Caroline Street in the shadow of Johns Hopkins. As a little girl, my mother brought me to the Harriet Lane Clinic," she says, as she realized that the help she was searching for might be in her own backyard.

A new immunotherapy, based on more than 30 years of research, was being studied in a clinical trial at the Kimmel Cancer Center. Vanessa prayed it was the miracle she needed.

The new drug, called pembrolizumab, allowed immune cells to see and respond to cancer cells. The first studies did not look promising in colon cancer, but one patient whose cancer responded to the treatment left researchers curious.

MISMATCH REPAIR

The answer, as it turns out, was based in Kimmel Cancer Center genetics research from 1993. Researchers uncovered a gene mutation that allowed DNA copying errors to accumulate, eventually leading to colon cancer in some people.

In 1993, immunotherapy was in its infancy, and researchers had no idea these copying errors could also attract the attention of the immune system.

The large number of mutations caused by this genetic error, known as mismatch repair deficiency/microsatellite instability flagged cancer cells as abnormal. However, when the immune system activated against them, the cancer cells were able to shut down the response through a natural on/off switch of the immune system, called an immune checkpoint.

Pembrolizumab is in a class of drugs known as immune checkpoint inhibitors. It could turn the immune switch back on and unleash the power of the immune system against the cancer.

As Kimmel Cancer Center cancer immunology researchers conferred with cancer genetics researchers, they figured out that the one colon cancer responder had mismatch repair deficiency/microsatellite instability, and in 2013, the clinical trial of the drug was expanded to include any patient with colon cancer whose tumor had mismatch repair deficiency/microsatellite instability.

Vanessa's cancer tested positive for mismatch repair deficiency/microsatellite instability, and she was admitted to the clinical trial of the drug. It was the miracle little Zion had encouraged her to believe in.

THIS WAS DIFFERENT

Pembrolizumab was different than the treatments Vanessa had tried before that made her feel so ill but did nothing to stop her cancer. With this drug, her tumor was melting away, shrinking by 60%.

"During chemotherapy, I felt like I was dying. With immunotherapy, I felt like my body accepted it," she describes.

"My dream was to see my grandchildren grow up," says Vanessa. "Now I'm a great-grandmother. I truly feel like heaven opened up. Each day is a blessing."

Vanessa, who loves to help others, volunteers with the prison ministry in her church and does some catering, providing sandwiches for local police departments, where her stepdaughter is an officer.

She is certain the treatment saved her life. She shares her story to help others.

"I know other African Americans are afraid of clinical trials," says Vanessa. "If just one hears my story, and it changes that person's life, I've made a difference," she says.

The groundbreaking research built upon a 30-year-old discovery, and Vanessa's inspiring story has been the focus of media attention, including an article in *Smithsonian* magazine and in a local TV news segment showing Vanessa speaking at a *Swim Across America* Baltimore event. The organization was the lead donor for the pembrolizumab trial from which Vanessa benefited.

Zion, who just a few years earlier asked his grandmother to believe in miracles, sees her in these news stories and beams proudly, telling Vanessa, "You're a celebrity!"

Vanessa is grateful to her oncologist, **Dung Le**, and her nurse, **Holly Kemberling**.

They were so wonderful to my family and me," says Vanessa. "They explained everything. It was evident their hearts are in it."

Ultimately, the therapy bought her the one thing she most desired — more time with her family.

"I am so thankful. I've seen my grandchildren graduate and go off to college," says Vanessa, who enjoys gathering her family and cooking for them. "Being diagnosed with stage 4 cancer was the hardest journey. I was sad and hopeless. I thought I was going to die, but that didn't happen. I survived."

MILESTONES IN CANCER GENETIC DISCOVERIES

1974: The nuclear matrix is identified as the site for DNA replication, shedding light on cellular changes that cause cancer

1983: Discovery that changes in DNA methylation, now called epigenetic changes, are found in cancers, including early cancers

1984: Discovery that chromosome 11p changes are integral to the development of pediatric kidney cancers called Wilms' tumor

1987: Discovery of GLI genes and their link to brain tumors

1988: A now-classic paper published in the *New England Journal of Medicine* presents the idea that cancers result from the sequential mutations of oncogenes and tumor suppressor genes

1989: Discovery of mutations in the p53 gene in human colorectal cancers, that it is a tumor suppressor gene and that p53 genes are common denominators of most common human tumor types. It is now known that TP53 is the most highly mutated tumor suppressor gene in cancer

1990: Discovery of the biochemical mechanisms through which p53 suppresses tumor development

1991: Discovery of the APC gene, and that inherited mutations in the gene are responsible for the cancer predisposition syndrome called familial adenomatous polyposis (FAP) and that mutations in APC initiate virtually all colorectal tumors, with or without hereditary predisposition

1992: Discovery that genetic alterations, such as mutations, can be found in the stool of people with colorectal cancer, leading to the first genetic test approved by the FDA for detecting early cancers and creating the paradigm for liquid biopsies

1993: Discovery of gene (MSH2) responsible for a major inherited cancer syndrome, hereditary nonpolyposis colorectal cancer (HNPCC), also known as Lynch syndrome and discovery of the biochemical mechanisms through which APC suppresses tumor development

1994: Discovery of mismatch repair genes, such as MLH1, responsible for cases of HNPCC not caused by mutations in MSH2

Discovery of a technique, Serial Analysis of Gene Expression, to evaluate all the genes transcribed in a normal or tumor cell, coining the word "transcriptome"

1992–1999: Discovery of now widely used tests to determine whether patients have inherited mutations responsible for FAP or HNCPCC

1995: *ScienceWatch* names cancer genetics pioneer **Bert Vogelstein** as the most frequently cited scientist in the world in all fields of science

1999: FLT3 gene is cloned and linked to a type of leukemia, with drugs developed to target the mutation along with tests to confirm the drugs hit their genetic target

Discovery of chromosomal instability as a major underlying feature of most cancers

2002: First gene mutation in prostate cancer is discovered

2004: Discovery of mutations in PIK3CA in colon, breast, stomach, brain and other cancers. Later found to be the most highly mutated oncogene in cancer, paving the way for targeted drugs — now widely used — for the treatment of breast cancers with PIK3CA mutations

2006: First analysis of all of the genes in colon and breast cancers, establishing the paradigm for modern cancer genetic research and defining "cancer genome landscapes"

2008–2010: First analysis of all of the genes in pancreas, brain, ovarian and other cancer types

Discovery of the IDH1 and IDH2 genes, establishing the importance of mutations in genes that control metabolism, leading to now widely used drugs that target these mutations in brain tumors and leukemias

2009: The first use of genome-wide sequencing to identify a gene that causes a hereditary disease — in this case, pancreatic cancer

2010: Discovery that the interval from the first, initiating mutation in a tumor cell to the development of a cancer is 20–30 years, providing a broad window for detection and prevention

2011–2018: Discovery of the genetic alterations that drive various types of pancreatic cysts

2012: The genetic driver of hereditary prostate cancer is identified

Resistance mutations are found in blood of patients shortly after treatment, marking cancers predestined to recur

2013–2018: Development of DNA-based tests on urine, saliva and Pap smears that can detect early cancers of the bladder, head and neck, and uterus

2017: Discovery that patients with mutations in the mismatch repair genes MSH2 or MLH1 in their cancers are extraordinarily responsive to treatment with immune checkpoint inhibitors, leading to the first FDA approval of a drug to treat a patient on the basis of the genetic alterations within a tumor, regardless of the tumor type

Study reveals genomic roots of many ovarian tumors is in the fallopian tubes

Discovery of a new type of cancer drug, called MANAbodies, that uses the genetic mistakes inside cancer cells to generate an immune response

2018: Multicancer blood tests are developed and shown to detect relatively early-stage cancers in a noninvasive fashion, laying the foundation for an immense amount of academic and industry research to develop "liquid biopsies" for cancer screening

2019: The largest pancreatic cancer genome-wide association study discovers changes to five new regions in the human genome that may increase the risk of pancreatic cancer

Development of a test that distinguishes precancerous pancreatic cysts that require surgery from harmless benign cysts

2021: Discovery of new immunotherapy approaches for treating people with cancer based on the genetic alterations found in their tumors, such as those in p53

2022: Successful clinical trial shows that DNA shed from early-stage colon cancer into bloodstream can be used to manage patients after surgery

Leaders in Cancer Drug Discovery

SOON AFTER THE Johns Hopkins Kimmel Cancer Center opened its doors in 1977, it became one of the first comprehensive cancer centers to receive a grant to begin clinical trials of new drugs. Our experts quickly earned recognition as they aggressively tested the limits and power of existing drugs, and invented new agents when what we had failed to get the job done.

Today, the combination of drug therapy, radiation therapy and surgery is a mainstay of cancer therapy. However, in 1973, there was no such thing as combined therapies.

"There weren't very many drugs, and the ones we had didn't work well and were very toxic. There was no formal drug development program at that time. There wasn't even much of a solid tumor program," says **Ross Donehower**, one of the Cancer Center's first medical oncologists and a drug discovery researcher. "The Center had three medical oncologists working on solid tumors. The solid tumor program began to grow in the 1980s, and drug development fostered the expansion."


DONEHOWER


COLVIN


ETTINGER


GAILLARD

LAUNCHING DRUG DISCOVERY

Things started to change with **Michael Colvin** and his foundational work in deciphering the activity of the cancer drug cyclophosphamide and how to use it in bone marrow transplant.

Colvin recruited Donehower, who worked with another Center medical oncologist, **David Ettinger**, to win a grant from the National Cancer Institute to conduct clinical trials of new cancer drugs.

Many in the fledgling field of oncology scoffed at the idea of a drug discovery program, and took little notice when the Kimmel Cancer Center earned a grant from the National Cancer Institute for phase I trials of new drugs, Ettinger remembered. The prevailing thought at the time was that viruses were the likely cause of cancer, and antiviral drugs were the only thing worth studying. Although we had wonderful expertise in **Paula Pitha Rowe**, **Nancy** and **Joel Shaper**, and others, who were conducting pioneering research in the study of viruses and cancer, Kimmel Cancer Center researchers did not place artificial boundaries on improving the understanding and treatment of cancer.

"That was what was so special about our center. There was always support and encouragement to be innovative. We take it for granted, but this truly is an amazing place of healing and discovery," said Ettinger.

The drug discovery grant Donehower and Ettinger submitted led to one of the most promising new anticancer drugs of the time, Taxol. It was the first drug Donehower studied.

MOLD, DIRT AND BARK

In the early days of cancer drug discovery, scientists looked everywhere for compounds and chemicals that contained the power to destroy the immortal cancer cell. They collected mold, dirt and plants, and even scraped organisms from the bottom of boats in search of new chemicals and compounds that could attack and kill cancer cells.

Taxol was no exception. It was made from the bark of the Pacific yew tree, and shown by researchers at other medical institutions to be effective against cancer cells.

In 1984, it was heralded as the most promising new drug in the battle against cancer in more than 15 years. However, it might not have made its way to patients if not for Donehower's ingenuity and determination. The problem was that, although the drug was effective against cancer, it was too toxic to give to patients. It caused severe side effects in about one-third of patients, says Donehower.

FIXING TAXOL

The promising drug was headed for abandonment when Donehower worked with Johns Hopkins allergists to develop premedications that allowed Taxol to be safely given to patients.

Donehower, who says he always enjoyed taking on tough problems, was driven by a desire to take care of people who really needed help and could benefit from research rooted in clear-headed thinking and compassion. **Al Owens**, the Center's first director, called it science in human service, he says.

Eric Rowinsky, another recruit of Colvin's, and ovarian cancer expert **Bill McGuire** drew national attention when they began to show in clinical studies that Taxol was effective against ovarian cancer, a cancer type that was in great need of new therapies.

Reporters descended upon the Kimmel Cancer Center when one clinical study showed that 30% of women taking the drug experienced a 50% decrease in tumor size.

McGuire became the national study chair of ongoing trials of Taxol, and Rowinsky worked to improve its effectiveness even further, launching a new clinical trial of the drug in combination with the anticancer drug cisplatin and a white blood cell stimulating growth factor called GCSF. Other clinical studies followed.

EXPANDING THE BENEFIT

Taxol remains a mainstay of cancer therapy, and is now used as a treatment for additional cancers, including breast and lung cancers.

Today, gynecologic cancer expert **Stéphanie Gaillard**, in collaboration with ovarian cancer and drug discovery experts **Deborah Armstrong**, **Ie-Ming Shih** and **Tian-Li Wang**, leads new studies of the drug.

"Taxol is critical in the treatment of gynecologic cancers, including ovarian, uterine and cervical cancers," says Gaillard, director of gynecologic cancer trials and co-director of the developmental therapeutics/phase I clinical trials program.

The drug is typically given in combination with the anticancer drugs carboplatin or cisplatin, and she is working to figure out why some patients' cancers grow resistant to the drug combination.

Gaillard, who studied mechanisms of treatment resistance in ovarian cancer during her fellowship training from 2009 to 2012, is focused on helping patients whose cancers come back after initial therapy.

Although Taxol continues to provide a good response in about 20% of patients, Gaillard wants to see if she and her colleagues can figure out how to expand the benefit to more patients.

Ross Donehower Honored for Training Leadership

In addition to his pioneering work in drug discovery, for the last three decades, **Ross Donehower** served as director of the Medical Oncology and Hematology Fellowship Training Program.

"Every year, I'm amazed by the incredibly talented group of people we have an opportunity to interview for positions in our hematology and oncology fellowship program. They come from a wide variety of backgrounds with varied interests. We provide a robust clinical training that prepares them to treat patients, but we also give them a strong research base. When they leave our program, they are prepared for anything," says Donehower, reflecting on his tenure as fellowship program director.

A reception was held in his honor at the 2023 annual meeting of the American Society of Clinical Oncology.

Kristen Marrone, who was co-director of the fellowship training program, was appointed director.

She identified a protein called SYK that was present at high levels in tumors that have recurred after prior exposure to Taxol. In laboratory studies, cells from recurrent tumors continued to grow, even in the presence of Taxol. However, when Taxol was combined with an SYK inhibitor — a drug that blocks the protein's function — ovarian cancer tumor cell growth was blocked.

Although a SYK inhibitor has been FDA approved for the treatment of an auto-immune condition, it has never been used in combination with Taxol. In 2018, Gaillard launched a Phase 1 study to determine the appropriate dose of the SYK inhibitor, frostation, to use in combination with Taxol for the treatment of platinum-resistant ovarian cancer.

The study team found that the combination of drugs was tolerable to patients and identified a dose to move forward in future studies. While this small study of 27 patients was not large enough to rigorously evaluate the efficacy of the combination, treatment results were promising with partial response (measured as at least 30% tumor reduction) seen in 39% of patients and stable disease in an additional 28% of patients.

"We are encouraged by these results and hope future studies will confirm that this combination is an improvement over what we've seen historically," she says.

Gaillard says new research is aimed at understanding how levels of SYK correlate with response to treatment and how low levels may interfere with response. She is also looking at other cellular factors that might predict response to Taxol.

"It is a long process, but shows how continued work can make an already useful drug more successful," she says.

THE BEST IN THE WORLD

It is studies like these that have earned the Kimmel Cancer Center its reputation as a leader in drug development.

"Our clinical infrastructure grew around drug development," says Donehower. "In the beginning, there was no recognition for drug development, and now we are known for it."

Like Gaillard, a new generation of drug discovery researchers has taken on the charge, including **Michael Carducci** and **Nilofer Azad**, among many others.


CARDUCCI


AZAD

Our experts continue to be among the best in the world at discovering cancer-promoting changes that can be targeted with therapy, finding or developing drugs that promise to go after the cancer target, and developing tests — known as assays — that show whether the drug is having its intended effect on the target.

"We are seeing things happening now we would have never expected in 1973," says Donehower. "Melanoma patients, lung cancer patients, virtually no one back then lived five years. Now, because of targeted drug therapies, immunotherapy and other drug discoveries, these patients are living many years with advanced cancers."

Still, he is not content to rest on prior successes. The bold and adventurous spirit of inquiry remains strong. "We have to continue to look for better drugs and better targets," says Donehower. We must look beyond to the next great discovery."

Janice's Story

The Greatest Gift

IN 1999, WHEN Janice was diagnosed and treated for stage 3 ovarian cancer at a community hospital, her doctor didn't give her much hope. Janice, 38, had three young children: a 12-year-old daughter and 10-year-old twins. She worried that she would not see them grow up, and that led her to seek a second opinion at the Johns Hopkins Kimmel Cancer Center.

"Don't tell me how bad it is. I've heard all of that. Just tell me what you are going to do to fix it."

"Don't tell me how bad it is. I've heard all of that," Janice told Kimmel Cancer ovarian cancer expert and surgeon **Robert Bristow**. "Just tell me what you are going to do to fix it."

Bristow and colleague **Deborah Armstrong**, a medical oncologist and ovarian cancer expert, had no intentions of giving up.

He removed a new ovarian tumor detected on imaging, and referred Janice to Armstrong for treatment with a promising new cancer drug called Taxol.

Taxol was one of the great research discoveries in ovarian cancer in the mid 1980s. It was Kimmel Cancer Center researchers who developed delivery methods that allowed the drug to be tolerated by patients. After a series of clinical trials, it was hailed as the most promising new cancer agent in more than a decade. It is now part of standard therapy for ovarian cancer and other gynecological cancers.

Janice received the drug in 1999 and again in 2001 when her cancer came back. In addition to Taxol, she benefited from a half-century-old method for delivering chemotherapy directly into the abdomen. A seven-year study of more than 400 women, led by Armstrong and reported on in the *New England Journal of Medicine,* found increased survival rates in women with advanced ovarian cancer, which resulted in renewed interest in the abandoned method.

"This method appears to be better at destroying lingering cancer cells," said Armstrong. The findings led to a new recommendation in 2006 by the gynecology oncology group, making the treatment, known as intraperitoneal therapy, standard of care for many women with ovarian cancer.

After three ovarian cancer recurrences, four surgeries and nine years of treatment with Taxol, cisplatin and other drug therapies, Janice has been cancer-free since 2008. Now 62, she is grateful for the science and doctors who saved her life, and she does her part to pay it forward.

She volunteers for Survivors Teaching Students at Johns Hopkins, a program in which cancer survivors speak to third-year medical students to help them better understand the experience of patients with cancer and to prepare them to be better-informed and compassionate doctors. She also participates in the Woman to Woman mentoring program, sharing her experience in navigating ovarian cancer with newly diagnosed women.

She recently was invited to attend the annual conference of the National Ovarian Cancer Coalition, which supports survivors and caregivers and funds ovarian cancer research. Janice had the distinction of being the longest survivor of ovarian cancer there.

She attributes her survival to her Kimmel Cancer Center doctors and the research that led to new treatments.

Janice, who worried in 1999 that she might not live to see her children grow up, has celebrated many milestones with them — high school and college graduations, weddings and the births of five grandchildren.

"They never gave up on me, and I'm alive because of that. It's the greatest gift."

"Knowing there are doctors always looking for new and better cancer drugs gives patients like me such hope," says Janice. "They never gave up on me, and I'm alive because of that. It's the greatest gift."

MILESTONES IN DRUG DISCOVERY

1979: National Cancer Institute grant for new drug development is awarded

1980: Clinical trials of cyclosporin prevent graft versus host disease following bone marrow transplant

1981: Acyclovir proven effective against herpes simplex virus in bone marrow transplant patients

1982: Johns Hopkins is selected by NCI as site for Phase I clinical trials of anticancer drugs

1984: Taxol is refined; it is hailed as most promising new anticancer drug in a decade

1986: Cyclosporin is found to inactivate immune response

1987: Biodegradable, drug-containing wafers implanted at tumor site are approved for clinical trials in brain cancer to get anticancer drugs through the blood-brain barrier

Intravenous BCNU and cisplatin therapy reduces size of glioblastoma and astrocytoma brain cancers

1989: New drug regimen for pediatric acute lymphocytic leukemia moves survival rate from 50% to 90%

Topoisomerase inhibitors induce death of leukemia cells

1992: Sulforaphane, a compound found in cruciferous vegetables, is identified and studied for its ability to block cancer growth

1993: Topoisomerase inhibitors initiate antitumor responses in treatment-resistant cancers

1994: Endothelin 1, a potent blood vessel constrictor linked to heart disease, is associated with advanced prostate cancer

1997: Therapeutic pancreatic cancer vaccine goes to clinical trials

1999: Drugs are developed to target FLT-3, a common mutation in acute myeloid leukemia

2003: High doses of anticancer drug cyclophosphamide are successful against moderate and severe forms of lupus

2004: Phase I trials of therapeutic cervical cancer vaccine begin

2005: Cholesterol-lowering drugs called statins are linked to lower risk of advanced prostate cancer

The drug atrasentan stabilizes the spread of prostate cancer in men who stopped responding to hormone therapy

2006: Half-century-old method of abdominal delivery of chemotherapy is reestablished and improves ovarian cancer survival

2009: Hedgehog inhibitors are studied in basal cell skin cancer and medulloblastoma brain cancer

2010: First therapies targeting epigenetic alterations are tested in clinical trials

2011: Our researchers lead clinical trial of pomegranate extract, given in capsule form, to slow the rise of PSA in patients with prostate cancer

2012: Anti-PD1/PD-L1 immunotherapy drugs restore the immune system's response to cancer cells

2014: BMH-21 is developed to prevent cancer cells from accessing POL-1, a cellular machinery they need to survive

A clinical trial studies anti-parasitic drug mebendazole in glioblastoma brain cancer

2015: Analytical Pharmacology Core tests drugs used in the NCI Experimental Therapeutics Clinical Trials Network

2016: Cancer Chemical and Structural Biology Program is established to accelerate cancer drug discovery

Honokiol, derived from the magnolia, is studied for its ability to slow breast cancer growth

Immunotherapy given before surgery is found to reduce cancer recurrence and extend survival in lung cancer, and leads to similar studies across cancer types

2017: A discovery leads to first FDA approval of a cancer drug across all cancer types when pembrolizumab is approved for all cancers with a genetic alteration called mismatch deficiency/microsatellite instability

2018: Short, intensive bursts of pharmacologic testosterone is used to treat prostate cancer

Novel, low-dose combination of five drugs works against pancreatic cancer

2020: Immunotherapy/chemotherapy combination improves survival for patients with mesothelioma; shows promise as first-line treatment

Phase I trials show epigenetic-targeted/immunotherapy drug combination benefits patients with advanced cancers that have not responded to other therapies

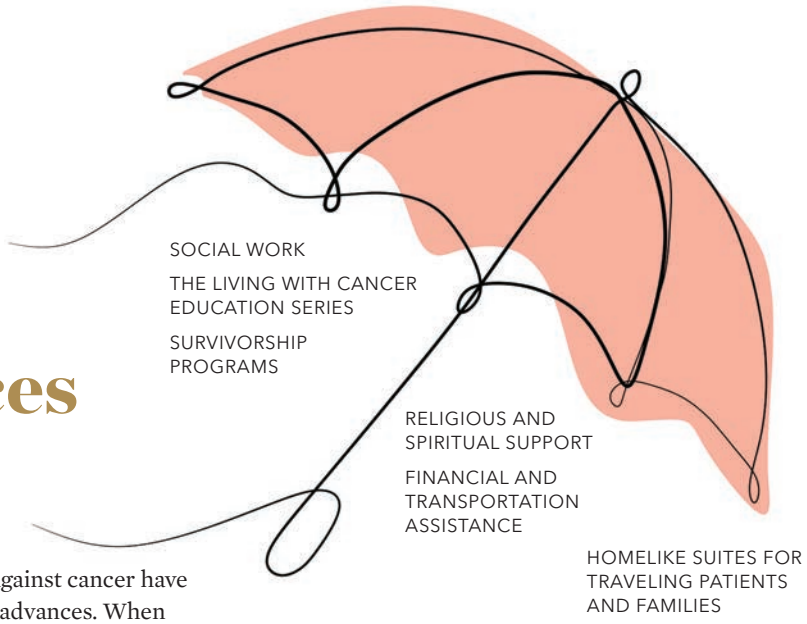
Cabozantinib and immunotherapy drug nivolumab makes curative liver cancer surgery possible for some patients

2021: A vaccine given in combination with two immunotherapy drugs is used to treat rare liver cancer with no standard treatment

2022: Prodrug DRP-104 is developed to release its payload only in tumors, and advances to clinical trials in solid tumors. It is based on an earlier discovery of a drug called DON that cuts cancer cells off from nutrients

Anticancer drug RK-33 is shown to fight SARS-CoV-2, the virus that causes COVID-19

2023: A clinical trial of enoblituzumab is the first that promises antibody-based immunotherapy against prostate cancer



Patient and Family Services

An Umbrella for Supportive Services


KNIGHT


LOSCALZO

As monumental as the therapeutic successes against cancer have been over the past 50 years, so have the social advances. When our Cancer Center first opened its doors in 1977, cancer was taboo and shrouded in fear.

"In those days, if a family member had cancer, families didn't talk about it to many people. The myth was that it was contagious," recalls **Louise Knight**, director of the Duffey Family Patient and Family Services Program. Knight's predecessor, **Matthew Loscalzo**, was director from 1997-2002.

We worked hard to dispel those myths, to be an advocate for patients and families, and to help them through this journey, she says. Today, our patients and their families are very knowledgeable about their disease. They are active participants in their care.

> **"Our Cancer Center is a family place. If someone is struggling, we help them. It is a place of hope."**

Recognizing that patients are more than the disease they are battling, the Cancer Center's Duffey Family Patient and Family Services Program addresses all patient and family needs, and these improvements are as significant as the advances in therapies.

"Our Cancer Center is a family place. If someone is struggling, we help them. It is a place of hope," says Knight.

Patient and Family Services is an umbrella for a breadth of services aimed at supporting patients and families from diagnosis through survivorship: social work; the living with cancer education series; survivorship programs, including an annual day of celebration; financial and transportation assistance; religious and spiritual support; and the Hackerman-Patz Patient and Family Pavilion, which provides homelike suites for patients and families traveling to the Cancer Center for treatment. Two earlier residences, the Joanne Rockwell Memorial House and the Hackerman-Patz House, provided this home away from home until the Pavilion opened in 2008.

Patient and Family Services also hosts the annual Service of Remembrance to offer support and reflection to the families of those who died during the year.

As they work to help others, she can't help but think of the people who make their work possible. "Mrs. Harry J. Duffey was the engine who started this program and her family continues to move us forward. Mrs. Duffey's gifts allowed us to launch the Duffey Pain and Palliative Care Program in 2007," says Knight.

In addition, Paul Reed Smith, whose *One Night, One Show, One Cause* music event, also helps sustain the important work of the Patient and Family Services Program.

"The kindness of so many others, that's what helps support us in our missions. It's really quite beautiful," she says. "We continue to hold true to our mission of caring for patients and families and the full scope of their psychosocial needs. Sometimes that means helping patients with mortgage payments and utilities, providing no-cost counseling to the spouse, providing education about Advance Directives, or helping a family plan for care at home after treatment. I think Mrs. Duffey would be smiling knowing all we have accomplished."

There is a painting that hangs by Knight's desk. It captured her attention several years ago when she visited a consignment shop that supports hospice care. In many ways, it illustrates the mission of Patient and Family Services, she says.

"Everyone who looks at it sees something different," she says of the painting, which shows a path lined by flowers and shrubbery on each side. Where the path leads, she says, is up to the interpretation, imagination and hope of each patient's and family member's journey through cancer diagnosis and treatment. It's different for each one, Knight says, but she and her team are there to help guide patients and families along the path they choose.

PATIENTS AND FAMILIES | ADVANCES

PLANS FOR EXPANSION OF CANCER CENTER ANNOUNCED

Citing overcrowding and increased demand for cancer care and research, the Johns Hopkins Health System announced plans for the construction of a new, $100 million, 88 bed Cancer Center in March 1987. Center Director **Albert Owens** and other Johns Hopkins officials said the existing Center, which opened in 1977, was unable to meet the growing surge of cancer patients. The number of cancer patients coming to Johns Hopkins tripled, and the number of patients under active treatment rose from 6,200 in the 1970s to more than 17,000 in 1986, Owens reported. He added that since its 1977 opening, the Cancer Center operated at capacity. There was also a critical need for additional research space. Owens said that 49 of the 64 full-time faculty had grants totaling more than $11 million, which could support a double amount of research immediately, if space was available.

EARLY TELEMEDICINE AND COMMUNITY OUTREACH

The Cancer Center established collaborative radiation oncology services at Saint Agnes Hospital in Baltimore and Chambersburg Hospital in Pennsylvania in 1989. Patient information from Chambersburg, such as X-rays and charts, was relayed to the Center via computer, fax and video hookup. A telephone and video conference system brought physicians from the facilities together for case review.

DESIGNING NEW THERAPIES FOR BREAST CANCER

Led by **Martin Abeloff**, and later **Nancy Davidson,** Cancer Center clinicians were continually developing innovative therapies to treat all stages of breast cancer. For newly diagnosed patients, our physicians examined the interaction of chemotherapy and several new hormonal therapies to prevent recurrence. They also found a way to effectively administer very high doses of several certain drugs in a timed sequence.

DISCOVERIES IN CANCER DEVELOPMENT

Stephen Baylin, Mack Mabry, Barry Nelkin, Rob Casero and **Andree de Bustros** found that two cancer-promoting oncogenes – c-myc and a mutated form of the ras gene – induced changes in small cell lung cancer and provided a model for studying mechanisms of change in human cancers. In laboratory models of medullary thyroid cancer, they found that the most aggressive tumors lack the protein hormone calcitonin. Inserting genes, such as ras, restored normal calcitonin production. The research provided a model to study the events that disrupt normal cell behavior to promote cancer development.

BEFORE THE HACKERMAN-PATZ PATIENT AND FAMILY PAVILION

Two residential facilities, the Joanne Rockwell Memorial House and the Hackerman-Patz House, opened in the mid 1980s and offered patients and their families a home away from home during treatment. The 20 efficiency apartments just a block from the hospital provided communal dining, garden and living areas, classrooms, counseling programs and physical therapy rooms to create a natural circle of camaraderie and support.

ANTI-NAUSEA TREATMENT FOR PATIENTS WITH CANCER

Noting that control of nausea and vomiting was essential in patients undergoing chemotherapy, **David Ettinger** noted in this 1984 news interview: "Antiemetic (anti-nausea and vomiting) therapy should be instituted before the start of chemotherapy in cancer patients, it should be continuous, and it should be tailored to each patient's special needs."

MILESTONES IN PATIENT AND FAMILY SERVICES

1985: The Cancer Center launches Oncology Social Work Program

1986: The Joanne Rockwell Memorial House opens, providing homelike suites for patients and families traveling to the Cancer Center for treatment

1988: The Hackerman-Patz House opens, increasing the number of homelike suites available to out-of-town patients and families

1990: The Cancer Counseling Center is established with a gift from Mrs. Harry J. Duffey

1992: The first Cancer Survivors Day celebration is held, a collaboration among Baltimore hospitals

1997: The Art of Healing Program starts, infusing art and music into the Center

2003: Oncology social work with Patient and Family Services merge to form the Harry J. Duffey Family Patient and Family Services Department

2007: The Harry J. Duffey Family Pain and Palliative Care Program is established

Johns Hopkins marks social work centennial

2008: The Hackerman-Patz Patient and Family Pavilion opens

2010: The first Service of Remembrance is held