STOCHASTIC MODELS REVEAL THE SPREAD OF DISEASE IN A PANDEMIC OUTBREAK.
Fred Hutchinson Cancer Research
Center’s scientists weave interdisciplinary paths to nurture collaboration and insight. Their scientific endeavors are long and intense, with no shortcuts or guarantees. Fueled by their passion for treatments that offer healing and for preventive steps to circumvent the devastation of cancer, HIV/AIDS and related diseases, they seek answers in the population and at the molecular level. Our researchers strive for breakthrough moments of discovery—discovery for life.

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FRONT COVER: DRESSED IN BRIGHT RED, THE TWO X CHROMOSOMES OF A FEMALE CELL IN A MALE PANCREAS (CENTER LEFT) REVEAL THE PHENOMENON OF MOTHER-CHILD CELL EXCHANGE.
The Hutchinson Center has become one of the world’s premier research institutions thanks to our scientists who have grappled with some of the most challenging questions in the biosciences, and our staff who help bring ideas to fruition.

Over the years, the Center’s researchers have refined treatments for leukemia, lymphoma and other blood diseases. As they have sought to boost survival rates for once-fatal cancers, their research naturally has led into new and unexpected directions.

Today, the Center remains a world leader in cancer research, but we have also expanded our work into other areas, breaking new ground in HIV/AIDS research and other life-threatening diseases.

Consider the research of some of our featured scientists in this annual report. Dr. Richard Nash, an oncologist and specialist in leukemia, hopes that what we have learned from blood cancers and their treatment may some day help people with autoimmune diseases such as systemic and multiple sclerosis.

Dr. Stan Riddell studies autoimmune responses to disease and the role our own T-cells play in fighting cancer. Stan wants to boost the power of the immune system with better defenses by engineering a special kind of T-cell so that it targets tumors more successfully.

Dr. Anne McTiernan’s work has focused international attention on the Center. As a cancer prevention researcher, Anne's detailed studies are showing us how exercise and diet could help reduce many cancers that are caused by obesity and sedentary lifestyles.

These scientists are examples of the exceptional team of researchers here at the Hutchinson Center, people whose passion for their work keeps us focused on the future. With your support, we can ensure that their innovative work stays on the path of discovery.

If you have ever faced a life-threatening diagnosis, or watched a family member, friend or colleague duel cancer, HIV/AIDS or a related disease, you understand why the scientists at Fred Hutchinson Cancer Research Center are working tirelessly to save lives.

Compassion for you and your loved ones is what drives Hutchinson Center scientists and staff to seek a better future.

As you will learn in this annual report, this is an exciting time for scientific research. Technology is playing an increasingly important role in accelerating the pace of discovery—from Drs. Malik and Emerman using computers to explore an ancient retrovirus to Drs. Halloran and Longini using statistical models to study the spread of infectious diseases. The scientists in this report represent the Center’s host of talented investigators, all of whom are seeking answers to challenging questions in daring, new ways. In pursuing the paths of their discoveries, our scientists follow the mission of the Center to eliminate cancer and related diseases.

Contributions like yours are essential to helping the Hutchinson Center sustain our world-class research environment and fund these discoveries. Private donations play an instrumental role in the Center’s ability to remain at the forefront of biomedical research by supporting innovative research that often cannot be funded by government grants alone.

Thank you for sharing my commitment to improving and saving lives and furthering innovative research at Fred Hutchinson Cancer Research Center.

Sally G. Narodick
Chair, Board of Trustees
When we think about deadly viruses, evolutionary biologist Dr. Harmit Malik explains, we need to understand that their complexity and ferocity has been bred through tens of millions of years of struggling against the human race.

“In this genetic conflict, either the host is winning or the virus is winning,” Malik said, pointing to the roughly 8 percent of the human genome that is made up of old retroviruses that we carry inside of us like bits of shrapnel from ancient wars.

Today, we face HIV. It crossed over from chimpanzees to humans within the last 100 years, so far killing 25 million people and infecting twice that many. Why does it kill us and not chimpanzees, which are easily infected by HIV but not sickened by it?

Malik and Dr. Michael Emerman, a molecular biologist, have pondered such questions for a long time. Most recently, their collaboration has yielded important insights into the evolutionary struggle between viruses and humans. Ultimately, they hope their research may lead to new drugs to fight HIV.

In one of their most startling collaborations, their labs used the power of modern computers and DNA technology to assemble a new version of an extinct retrovirus known as Pan troglodytes endogenous retrovirus (PtERV), which infected chimps and gorillas—but not humans—4 million years ago.

By reassembling the retrovirus in such a way that it could reproduce only once, Malik and Emerman found that a human protein known as TRIM5α easily defeated PtERV. Every primate has a version of the TRIM5α protein. In the rhesus monkey, for example, it kills HIV.

Malik and Emerman also modified the human TRIM5α protein to resemble a version present in the ancestors of humans, chimpanzees and gorillas, and found that it no longer protected against the PtERV. By modifying TRIM5α, they also discovered that one version protected against HIV but not PtERV. In another modification, it did the opposite.

Such polar opposites, they agree, are the result of evolution. Because our TRIM5α protein evolved to fight other retroviruses, it likely left us vulnerable to HIV, they say.

Is it possible to reproduce a drug that behaves like a chimp’s TRIM5α does against HIV, or change the human version ever so slightly so it kills HIV? These are the kinds of challenges that Emerman and Malik ponder.

The two agree that studying, and in some cases reconstructing, ancient viruses is not a trivial matter.

In this arms race that’s millions of years old, it pays to understand the enemy, Malik said.
A hard-working member of the immune system, a T-cell is an efficient killer, attacking anything it perceives as an intruder, whether it’s a virus-infected cell, a cancer cell or a bacterium.

But sometimes, a T-cell attacks a friend—and it goes on attacking, unchecked, destroying healthy tissue and creating serious autoimmune diseases such as multiple sclerosis and lupus. Why the immune system goes so very wrong has puzzled researchers for decades.

As many as 80 autoimmune diseases have been identified, and some of them are capable of causing serious complications, even death. One example is systemic sclerosis (also known as scleroderma), a disease without effective treatment. “It’s one of the most frustrating diseases to treat. There’s high mortality and no therapies, and it can hit you in so many ways,” said Dr. Richard Nash.

By training, Nash is an oncologist, a researcher in leukemia and other blood cancers. But thanks to a unique and unexpected insight, he’s now applying his knowledge in whole new ways. Along with colleagues, he’s taking the Hutchinson Center’s pioneering leukemia research and applying it to other diseases, such as systemic sclerosis and MS.

The standard treatment for leukemia and other blood cancers is chemotherapy, radiation and transplantation of bone marrow or blood stem cells. Nash is optimistic the same approach may now help patients with autoimmune diseases.

It has taken some very unlucky patients—a rare few who had both leukemia and systemic sclerosis—to uncover a potential new use for transplantation.

With systemic sclerosis, a patient’s skin becomes very hard, severely limiting movement. When one of these patients received a stem cell transplant for cancer, “we saw evidence of skin improvement. The treatment suggested that the fibrosis of the skin was a reversible condition,” Nash said. “And it appeared to stabilize the organs.”

With transplantation, it may be possible to remove the reactive cells that are triggering the immune system to attack the body. Currently, Nash’s lab is conducting three clinical trials to evaluate the safety and effectiveness of high-dose chemotherapy and stem-cell transplantation for systemic sclerosis and MS.

“For me, that’s part of the excitement of being in this field … we’re doing something different and helping people, and learning about potential new therapies. To be successful in any project, collaboration and teamwork are very important,” he said.
J. Lee Nelson, M.D.
Autoimmunity Researcher/Rheumatologist

DELVING INTO THE AUTOIMMUNE IMPLICATIONS OF MOTHER-CHILD CELL SHARING

It feels like a broken bone that never heals, a constant ache. Pain relievers and powerful steroids may not make a dent in the excruciating pain. Nor do they relieve the swelling and stiffness for many rheumatoid arthritis sufferers. But nature sometimes offers relief: pregnancy. Like a fog lifting, most pregnant rheumatoid arthritis patients experience life without constant pain for the first time in years.

Seeing such transformations made Dr. Lee Nelson yearn for answers. What could make an autoimmune disease like rheumatoid arthritis turn off? The answer may lie in the mother-child cell transfer that happens during pregnancy.

Using the placenta as a corridor, some cells travel between mom and baby, take up guest residence in their hosts, and stick around for decades. Nelson and her interdisciplinary team study this mixing of genetically distinct individuals, known as microchimerism, to identify the good and bad consequences of these foreign cells in autoimmune diseases, transplantation, cancer and pregnancy complications.

Nelson, considered one of the world’s leading researchers in this investigative frontier, has been studying the role that microchimerism plays in the initiation and remission of autoimmune diseases since 1986, the year she began her research career at the Hutchinson Center.

The transferred cells can be found in many human tissues. They are detected by looking for female cells in a male, or male cells in a female, or through DNA analysis. The presence of Y chromosomes in a woman, for example, signifies that she has acquired cells from a male (most likely from a son during pregnancy).

Scientists had assumed that a normal immune system would destroy any maternal cells lingering in a child. That thinking changed when Nelson and her team found maternal cells survived decades later in healthy adults. That work provided evidence for the idea that cells transferred from mother to fetus are stem cells or related cells, capable of becoming any type of cell, since stem cells can divide indefinitely.

She also found maternal cells in the pancreas made insulin, suggesting they may help regenerate the diseased organ in diabetics. This finding suggests that microchimerism might one day be the crux of new therapies if the non-native cells could be coaxed to restore damaged tissues.

“We’re trying to hone in on treatments,” Nelson said. “I would like to help alleviate suffering in some way.”

Nelson also conducted the first study to look at microchimerism in an autoimmune disease. She found evidence for the involvement of adopted fetal cells in scleroderma (also known as systemic sclerosis), a life-threatening illness that makes the skin hard and thick and often attacks internal organs.

Once a lone pioneer in this young field, she said, “This was an interdisciplinary challenge that people had overlooked, and it was ripe for important questions and big leaps forward.”

Thanks to Nelson, many of those questions are being answered.
Mining Genomic Data for Cancer’s Molecular Secrets

Searching for the molecular roots of cancer is akin to looking for the proverbial needle in a haystack. A smaller haystack makes the job a lot easier, which is where Dr. Robert Gentleman comes in. Technology and the need to sift through a deluge of genomic information has transformed biology from a purely lab-based science to an information science as well.

Gentleman, head of the Hutchinson Center’s Herbold Computational Biology Program, creates computing tools to analyze massive amounts of data from biological experiments and uses mathematics and statistics to generate new insights incorporating the existing data. The approach helps researchers understand cancer at its most fundamental level by illuminating which cellular proteins interact and how they work together within a cell. The process also saves both time and money over other lab methods.

A former auto mechanic might seem like an unlikely candidate to become a research scientist. But if you follow Gentleman’s path from Hondas to Harvard to the Hutchinson Center, his trajectory seems perfectly probable. The former grease monkey has a penchant for challenges, so it makes sense that he’d choose a research endeavor that’s moving at breakneck speed. For brilliant young minds, biocomputing is the most challenging field around.

Advances in knowledge and technology have transformed biological research. Just a decade ago, scientists could only analyze the expression of one gene at a time. Technological advances now enable efficient analysis of half a million genes. The new tools enable researchers to uncover novel potential targets for therapies as well as to explore the underlying genetic causes of many human diseases.

There has also been an explosion in the amount of information available about the DNA sequence of the human genome. Consequently, researchers have identified a large number of novel genes within these previously unknown sequences. The challenge currently facing scientists is to find a way to organize and catalog this vast amount of information into a usable form.

“Technology drove enormous data sets, which drove the need for clear, statistical thinking,” Gentleman said.

“We have no true comprehension of cancer on a molecular level yet. We need tools to understand how the genome works and we need to know how things interact. If we’re going to go in and poke something, we better know what the domino effect will be.”

He and his colleagues around the globe collaborate to write free software for the entire scientific community to use. “This is a high-risk area, which is not where commercial software goes,” he said. “We’re only interested in being as close to the edge of scientific investigation as we can be. We share to learn. Real change comes from people working well together.”

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Unraveling vast DNA sequences, written as A-G-T-C codes, requires powerful tools.
When the World Health Organization declared smallpox eradicated in 1980, there was a giddy overconfidence that the deadly struggle against the microbial world was ending.

“There was this feeling that we had won the battle against infectious diseases,” said Dr. Elizabeth Halloran, who studied tropical diseases in the early 1980s, when there was waning interest in the topic.

Halloran was not convinced microbes had been subdued, much less conquered. Nor was Dr. Ira Longini, whose travels through Latin America brought him face to face with tuberculosis, syphilis and other infectious diseases that were presumably under control.

With research funding and drug development for such diseases in full retreat at the time, Halloran and Longini forged paths in the field of biomathematics and biostatistics to study the spread of infectious diseases. Now, as collaborators, they’re among the world’s leaders in the field, their expertise sought widely in the struggle against new and resurgent infectious diseases.

During the last year, they have consulted with federal and state officials and have been consulted by world health organizations to help develop intervention plans to control potential pandemics, such as avian flu.

Today, the threat of a pandemic flu with the potential to kill tens of millions is a top concern of public health officials worldwide. HIV, malaria and tuberculosis kill as many as 6 million people each year. Tuberculosis alone is expected to infect as many as 1 billion people in the next 20 years.

Small as they are, microbes make up 60 percent of the planet’s biomass. With so many microbes out there, “We’re further away than ever from closing the book on infectious diseases,” the Infectious Diseases Society of America declared last year.

It’s within this context that Halloran and Longini collaborate to create mathematical models that predict the spread of disease and simulate intervention strategies to save lives.

Using powerful computers to track the potential path of infectious diseases, the duo believe their mathematical models could help save the lives of hundreds of millions of people, particularly against pandemic flu, which unchecked could spread across the globe in a matter of months.

Mathematical models allow researchers to simulate the spread of disease through different kinds of settings and test different kinds of interventions. In one such model, Longini and Halloran tracked how quickly pandemic flu would move across the United States if nothing were done. In a simulated 60 days, the disease had spread to every corner of the map. The number of dead: tens of millions. They developed other models to help predict which interventions—such as vaccination, keeping children out of schools and asking people to work from home—would most effectively control spread of the disease and save the most lives.

It’s a scary scenario, but Longini and Halloran believe the tools are in place to save the world from disaster. And not just from influenza.

“We hope that the tools we’re developing will be used for all emerging diseases,” Longini said.

“You can’t control disease but you can intervene to save lives,” Halloran said. “You can intervene and change the course of events.”
CANCER KILLERS WITH STAYING POWER

In a perfect world, cancer doesn’t stand a chance of wreaking havoc. Like a soldier guarding the home shores, the immune system gives marching orders to a type of white blood cell known as T-cells to remain vigilant for an invasion of foreign cells, including cancerous ones. When a T-cell recognizes an invader, it initiates a process that targets that cell for destruction.

But cancer is a formidable foe, one that Dr. Stanley Riddell is all too familiar with after more than two decades of waging war against it. “Tumors are very clever and they utilize evasion strategies to limit the effectiveness of the immune response,” he said.

So he’s fortifying the immune system with better weapons: long-lived T-cells specially engineered to seek and destroy cancer.

Through adoptive T-cell therapy, Riddell and his fellow researchers extract white blood cells from a cancer patient and expose them to proteins made in abundance by tumor cells. Scientists then identify the few T-cells that recognize the tumor proteins and stimulate those to divide, generating a billions-strong population of cancer-fighting cells that can be infused back into the patient. Ideally, this unique population of T-cells will find its way to the tumor site and annihilate the cancer cells.

“When you see it work, it is so amazing—the bone marrow just goes from being full of leukemia to being in remission and very large tumors simply melt away,” Riddell said. T-cells, however, have a fatal flaw. They die quickly. And if an immune response isn’t sustained, cancer eventually comes back.

Riddell and his colleagues knew immunity could last a lifetime—that’s how vaccines work. So the researchers reasoned that perhaps they were starting with the wrong T-cells.

They began advanced testing on different types of T-cells and found that one type—central memory cells—had the staying power the scientists were seeking. They now had a sustainable starting point for cancer immunotherapy: T-cells with the capacity to survive.

Riddell’s next step involves drawing blood samples from cancer patients, filtering out their central memory cells and engineering those cells with receptors to target tumors.

The approach holds promise for fighting different types of leukemia, including chemotherapy-resistant acute lymphoblastic leukemia in children, and breast, ovarian and skin cancers. Riddell’s team’s insights may also strengthen the work of University of Washington researchers developing potential breast-cancer vaccines.

“We’re really trying to move immunotherapy with central memory T-cells into the clinic quickly,” Riddell said. “We are excited by the potential for success and believe that this therapy can be applied to several types of cancer.”
We all know that exercise is good for us. But what kind and how much?

As a cancer prevention researcher and pragmatist, Dr. Anne McTiernan has no illusions about most folks’ commitment to exercise. She understands that people want to know exactly what they have to do—and how little they need to do—to reap healthy rewards.

Thanks to McTiernan’s work, some specific answers now exist about the role of exercise and weight loss in reducing the risk of cancer. As director of the Hutchinson Center’s Prevention Center—a state-of-the-art facility for conducting research on exercise and diet—she designs studies with the aim of reducing the 25 percent of cancers caused by excess weight and sedentary lifestyles.

Fewer than one-quarter of Americans get minimum daily exercise, even though regular physical activity reduces body fat, lowers blood pressure, cholesterol, and the risk of diabetes and cancer, and improves bone and joint health, sex drive, deep and memory.

“We have such an epidemic of obesity and lack of exercise, which is one reason I’ve gravitated to exercise and weight control,” McTiernan said. “It’s an area of study that could have a significant impact.”

Exercise trials are uncommon because they’re expensive and difficult to fund. McTiernan’s group is the first to specifically look at the effects increased physical activity and weight loss have on reducing the chance of getting cancer.

Such risk reduction has been difficult to quantify in the past, but McTiernan has been able to definitely gauge impacts by measuring so-called biomarkers in research participants. Among her most important findings, overweight post-menopausal women who exercised for 45 minutes five days a week, whittled away unhealthy belly fat and lowered their estrogen and testosterone levels, hormones that in excess can contribute to cancer. In a different study, women who walked leisurely just one to three hours a week lowered their risk of dying from breast cancer by one-quarter compared to sedentary women; those who walked three to eight hours weekly cut their risk in half. Another study showed that exercise six days a week brought both sexes significant fat loss and a lowered risk of colon cancer in men.

McTiernan’s groundbreaking work has put the Hutchinson Center at the forefront of the field, earning her an invitation to join a federal scientific advisory committee to develop the nation’s first guidelines to focus on physical activity—and the first to recognize the impact of exercise on cancer-risk reduction.

“We’re trying to get specific answers for people: do I need to lose 50 pounds or will 5 percent of my body weight do it? Will exercising 20 minutes a day help?” McTiernan said. “Nothing is guaranteed, but exercise and weight control are like wearing a seat belt. It reduces your risk.”
THE SEEDS OF GREAT DISCOVERIES ARE CONSTANTLY FLOATING AROUND, BUT THEY ONLY TAKE ROOT IN MINDS WELL PREPARED TO RECEIVE THEM.
—JOSEPH HENRY
When research doesn’t turn out the way you expect it to, figure out why. That answer is usually much more interesting than if it had turned out.

—DR. LEE NELSON
Thank you for joining us in our mission to eliminate cancer and related diseases as causes of suffering and death. Private donations like yours are essential for allowing Fred Hutchinson Cancer Research Center to rapidly respond to novel research opportunities that can lead to important medical breakthroughs.

Financial support from our donors enables us to attract and retain the world’s top scientists, provide our researchers with state-of-the-art technology needed to advance their work and launch innovative pilot projects to explore new ways to eliminate cancer and related diseases. Private gifts also leverage significant additional investment by allowing investigators to successfully compete for prestigious foundation grants that do not cover the full cost of research.

The many accomplishments that keep the Hutchinson Center at the forefront of biomedical research could not be achieved without your generous gifts.
At Fred Hutchinson Cancer Research Center, our interdisciplinary teams of world-renowned scientists and humanitarians work together to prevent, diagnose and treat cancer, HIV/AIDS and related diseases. Our researchers, including three Nobel laureates, bring a relentless pursuit and passion for health, knowledge and hope to their work and the world.

With research excellence that spans the full spectrum of cancer research, we are uniquely qualified not only to discover, but to implement lifesaving breakthroughs. To achieve our goal of improving human health around the world, our scientists lead studies in the following areas: Early Detection and Intervention, Immunotherapy, Tumor Research, Fundamental Research, Leukemia and Lymphoma Research, International Research, Prevention Research, and Childhood Cancers.

In addition to our groundbreaking research, we also provide a range of support services for the patients and families who come to the Hutchinson Center for lifesaving treatment. Programs include the Pete Gross House and Hutch School, Cancer Information Service, the Long-Term Follow-Up Program as well as the Fred Hutchinson Cancer Research Center Survivorship Program, part of the LIVESTRONG™ Survivorship Center of Excellence Network, and the Cancer Prevention Clinic located at the Seattle Cancer Care Alliance.
of discovery

“DISCOVERY IS SEEING WHAT EVERYBODY HAS SEEN,
AND THINKING WHAT NOBODY HAS THOUGHT.”

—ALBERT SZEgüGYI

THE EXPLORATORY NATURE OF SCIENTIFIC INVESTIGATION IS DISPLAYED IN DR. MICHAEL EMERMAN’S NOTES.

BACK COVER: STOCHASTIC MODELS REVEAL THE SPREAD OF DISEASE IN A PANDEMIC OUTBREAK.

HIV HIDES IN A DENDRITIC CELL OF THE GENITAL LINING.
Seattle’s reputation as a leader in high technology and biotechnology and the allure of the region’s natural beauty attract the world’s best minds to Fred Hutchinson Cancer Research Center. We draw inspiration from our diverse landscape—from rivers and ocean to mountains and forest. At the Hutchinson Center, we live and breathe a life of science.