NYUPHYSICIAN

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2

EXPLORING THE NEW FRONTIER GENOMICS COMES OF AGE

JAN VILCEK: A MAN OF MANY GIFTS RICHARD TSIEN TO LEAD NEW NEUROSCIENCE INSTITUTE

PLUS

SECRETS OF AGING AND BEHAVIOR

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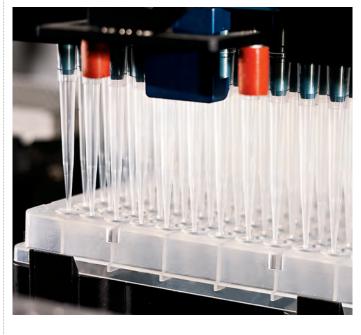
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"WHOLE-GENOME RNAI SCREENING **TECHNOLOGY**

IS OPENING THE WAY TO NEW **DISCOVERIES.**"



TO OUR READERS NYU Physician is available

as an iPad App that you can download free from iTunes.



Transforming Technologies



TEN YEARS AGO THE FIRST DRAFT OF THE human genome was published and, in 2003, the sequencing of the roughly three billion letters of DNA that spell out the genetic code of our species was finally completed at a cost of some \$2.7 billion. It was truly a revolutionary achievement. Since that time, the technology available to sequence DNA and RNA has advanced so rapidly that the same task now would take mere weeks and cost only \$30,000. The ever-faster generating of DNA and other molecular data has created an enormous

* "THIS IS JUST
THE BEGINNING
OF AN ENTIRELY
NEW ERA IN
MEDICINE."

demand for bioinformaticians who can make the best use of this data. In these pages we feature some of the transformative technologies

In these pages we feature some of the transformative technologies at work in recently established core facilities at NYU Langone Medical Center. These facilities offer equipment and expertise that enable scientists and physician researchers to perform experiments designed to probe the biological information contained in the human genome. Until recently the most advanced equipment wasn't widely available to investigators at academic medical centers. By pooling resources and distributing the costs of acquiring and managing new equipment, however, researchers at the Medical Center can now take advantage of the latest technology.

In this issue you will learn about three of our pioneering facilities: the Center for Health Informatics and Bioinformatics (CHIBI), the RNAi Core Facility, and the Genome Technology Center, all of which offer invaluable services. We are justifiably proud of the great investment that the Medical Center has made in acquiring new genomics machines and advanced robotics and in recruiting faculty with the expertise in bioinformatics and health informatics to interpret the flood of data emanating from experiments with this sophisticated equipment. In a very short time, our Center for Health Informatics and Bioinformatics has become one of the world's leading centers of its kind.

I'm sure the investment that we have made today will bear great fruit in the years ahead, when we obtain a fuller understanding of the biological information contained in our own genome and in those of many other organisms. This is just the beginning of an entirely new era in medicine. ◆



A Man of Many Gifts **Q&A** with Dr. Jan T. Vilcek

JANT. VILCEK, MD, PHD, professor of microbiology, and his wife, Marica, recently pledged \$21 million to NYU Langone Medical Center that will help purchase and renovate residence hall space on East 26th Street for students at NYU School of Medicine, create a merit-based full-tuition scholarship fund for medical students, and expand the couple's fellowship fund for students in the Department of Microbiology. For the Vilceks, it was the latest in a series of extraordinary gifts they have made to NYU Langone flowing from royalties they earn from the anti-inflammatory drug Remicade. Used by over a million people worldwide to treat rheumatoid arthritis, Crohn's disease, psoriasis, and other inflammatory disorders, the drug was developed from a monoclonal antibody generated by Dr. Vilcek and his colleague Junming Le, PhD, at NYU Langone.

Dr. Vilcek joined the NYU Langone faculty in 1965 after he and his wife defected from communist Czechoslovakia. In 2005 they announced their intention to donate \$105 million from their future royalties to NYU Langone. NYU Physician recently spoke with Dr. Vilcek at his office in the Smilow Research Center.

NYU PHYSICIAN: You and your wife, Marica, bave pledged over \$100 million to the Medical Center, an unprecedented level of generosity by a faculty member of any institution. Most of the money is devoted to research, but this additional gift of \$21 million mainly supports education-related activities. Why?

DR. VILCEK: My goal in life has never been to become rich. Much of the royalty income from Remicade sales due to me as an NYU faculty member goes to fulfill our 2005 pledge to NYU, but Marica and I still receive significant royalty income. What better way to spend it than to give it back to NYU School of Medicine? I've always considered medical education to be important, and it has become even more so over the last decade.

NYU PHYSICIAN: Why is that?

DR. VILCEK: There is a stage in life—and I think I've reached that stage—when I'm no longer quite as active in research as I once was, yet I feel that I can still do something very useful in medical education.

NYU PHYSICIAN: Why support a residence hall? DR. VILCEK: We lost some good applicants to other schools because the physical condition of our previous residence hall had deteriorated. The new residence hall is so much more comfortable and attractive! Those students who moved from our older facility to the new one are very, very happy. We already have great students, but the

new residence hall will help attract an even better group of students.

NYU PHYSICIAN: Why did you decide to base the scholarships for medical students primarily on merit and not on need?

DR. VILCEK: We decided to base the scholarships primarily on merit because my main goal is to improve the competitiveness of our medical school and attract the most highly qualified and talented students.

NYU PHYSICIAN: Over the last 10 years, you've developed widespread philanthropic interests, including the Vilcek Foundation. What does the Foundation do?

DR. VILCEK: The Foundation recognizes the contributions of immigrants to biomedical science—that's my background—and to the arts, which is my wife's background. Marica studied art history and worked for most of her professional life at the Metropolitan Museum of Art. Our main goal is to raise public awareness about the contributions of immigrants to science and the arts.

NYU PHYSICIAN: What makes you happy?

DR. VILCEK: Well, one thing that makes me happy is to see the Medical Center flourish under Dr. Grossman's leadership. And I'm absolutely delighted that my and my colleagues' research has contributed to this successful new life, so to speak, of the entire medical center. ●



Joel Ernst

Subverting the Immune System

The nefarious TB bacterium's surprising strategy

IT IS AN ALL TOO COMMON SCENARIO THESE DAYS in the developing world: A person is infected by *Mycobacterium tuberculosis*. The body's immune system sends T lymphocytes to search out and destroy the bacteria but some of the intruders escape and take cover in the lungs, where they quietly go about their nefarious business for decades, multiplying and building strength. Finally, once they've mustered a

new army, the bacteria mount a second, more vicious and successful assault. An estimated 2 billion people, nearly one-third of the world's population, are believed to harbor the bacterium that causes TB, a disease that claimed the lives of 1.3 million people in 2008.

Scientists have thought that the bacterium, like most other pathogens that have co-evolved with humans, escapes immune detection by continually changing its appearance so that the defending T cells fail to recognize it. Joel Ernst, MD, director of the division of infectious diseases, the Jeffrey Bergstein Professor of Medicine, and professor of pathology and microbiology, however,

is offering a more audacious, radical explanation. His work suggests that the bacterium may actually subvert T cells, turning them away from their protective task and into allies in destroying a host's lungs and spreading the infection from person to person.

The conclusion sprang from a collaborative study led by Dr. Ernst and Sebastien Gagneux, PhD, of the University of Basel to study the genes that code for the peptides, called epitopes, that T cells recognize and lock onto before trying to blast the bacteria away.

Dr. Ernst and Dr. Gagneux expected to find genetic evidence of the standard shape-shifting maneuver, that is, that the genes across different strains of the bacterium would show variation. The more diverse the genes, the more diverse the epitopes, thus providing the bacteria with an ever-changing set of disguises from T cells.

To their surprise, however, they found the opposite. The research, published in *Nature Genetics*, showed that the genes and their epitopes were extremely stable. Indeed "the [DNA] sequences encoding for T cell epitopes were the most stable, least diverse in the genome," says Dr. Ernst. In addition, he says the bacterium carries a "remarkably high number of known epitopes," 600 versus about 50 for most pathogens.

Taken together, these facts indicate that the bacterium is more likely to be recognized than to be missed by T cells. Thus, says Dr. Ernst, "M. tuberculosis must be benefiting from being recognized by human T cells, and that is absolutely revolutionary." He speculates that after the initial infection, bacteria that survive the first line of defense and lodge in the lungs somehow co-opt the T cells and get them to work to the bacteria's advantage, eventually promoting lung damage and the coughing that transmits the infection to other people.

The new findings have significant implications for developing a vaccine against TB. The usual method is to target the epitope genes and stimulate T cell production, but in this case that may actually exacerbate lung damage and enhance the spread of infection. "What the bacteria want to do is infect, replicate, expand their population, and be transmitted to somebody else," Dr. Ernst emphasizes. "We have to prevent that." •

-GRACIELA FLORES

The battlefield of a lung infected with *M. tuberculosis* (green). At the scene are the immune system's soliders, macrophages and dendritic cells (in red) and CD4+ T cells (in blue).

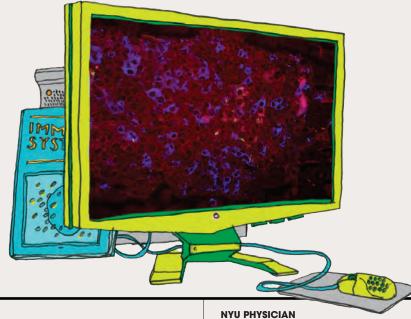


IMAGE COURTESY OF GIRALDINA TREVEJO-NUÑEZ

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MRI of the brain of a patient with a vestibular schwannoma (in red). These slow-growing tumors, the hallmark of neurofibromatosis type 2, engulf the acoustic nerve, typically leading to hearing loss and other problems.

Targeting Auditory Tumors

An NYU Langone Medical Center-initiated clinical trial may open the way to medical treatment

PEOPLE WITH NEUROFIBROMATOSIS TYPE 2 (NF2), a disease characterized by slow-growing tumors on nerves and other tissues in the brain and spinal cord, face an agonizing choice: Watch and wait and risk it all, or undergo multiple surgeries that may very likely incapacitate you one faculty at a time.

That scenario may change for the better if an oral medication that shows early promise in shrinking, or at least arresting the growth of, vestibular schwannomas—the most common NF2 tumors—continues to progress through clinical trials. The drug, called lapatinib, is now undergoing a phase 2 clinical trial at NYU Langone Medical Center, which initiated the study.

"Having taken care of NF2 patients for decades without any effective medical therapies," says Jeffrey Allen, MD, the Otto and Marguerite Manley and Making Headway Foundation Professor of Pediatric Neuro-Oncology, professor of neurology, and a co-investigator on the trial, "I am very excited about the prospect of identifying active drugs against this debilitating disease."

Although it is still early, the investigators are encouraged by the initial response to lapatinib. "Tumors have shrunk in some patients, and several others have remained stable for more than 12 months," says study leader Matthias Karajannis, MD, assistant professor of pediatrics.

NF2 affects about 1 in 25,000 people, according to the Children's Tumor Foundation (CTF). It typically begins in

young adulthood, when the first of many tumors engulf vital structures in the brain and spinal cord. Often, the initial casualty is hearing, because vestibular schwannomas attack the acoustic nerves. Tinnitus, balance problems, facial paralysis, and total hearing loss may follow, depending on the size and location of the growths. The Neurofibromatosis Center at NYU Langone is one of many clinics formed internationally by CTF to create a shared patient registry and trials consortium for NF patients. The Making Headway Foundation is a major sponsor of research and clinical initiatives to fight this disease at NYU Langone.

Dr. Karajannis, a pediatric oncologist who also does basic research in cell signaling, began searching for a medical therapy for NF2 after joining NYU Langone in 2007. In the early 1990s, scientists had linked mutations in a gene called merlin to the growth of NF2 tumors. Subsequent research suggested that when merlin is disabled, cell-surface receptors regulating a variety of cellular processes go haywire, taking the brakes off cell proliferation. Two closely related receptors—epidermal growth factor receptor (EGFR) and epidermal growth factor receptor 2 (ErbB2)—were singled

out as the most likely culprits.

Intrigued by the association between the gene and these receptors, Dr. Karajannis obtained specimens from NYU Langone's tumor bank and in 2008 confirmed that they were indeed overactive in vestibular schwannomas. Fortunately he didn't have to search far for a drug to target these receptors. Lapatinib (brand name Tykerb) was known to inhibit both EGFR and ErbB2; moreover it had already been approved by the FDA in 2007 as part of a combination treatment for metastatic breast cancer.

After further testing in the laboratory, Dr. Karajannis and his colleagues moved directly to a human trial when they received institutional and government approvals. The trial, supported by GlaxoSmithKline, makers of lapatinib, was launched in late 2009. So far, 15 of the 17 trial slots have been filled. Nine patients are continuing on the medication without tumor progression, and three patients have seen their tumors shrink by at least 15 percent in volume.

Encouraged by initial results, the NYU Langone team, along with researchers at Johns Hopkins University, Ohio State University, and the House Ear Institute of Los Angeles, are also enrolling patients on a separate "phase O" trial of lapatinib. Patients who are scheduled to undergo tumor-removal surgery will be asked to take the drug for 10 days preoperatively, and their tumors will be analyzed to further understanding about the drug's effects. • —GARY GOLDENBERG

An Unorthodox Approach to Treating Severe Colitis—Worms?

A case study reveals how worms may heal the intestine

CAN WORMS HELP RELIEVE the symptoms of severe ulcerative colitis? According to a case study of a 35-year-old man from northern California who infected himself, the tentative, stomach-turning answer is yes.

"The idea for treating colitis with worms is not new, but how this therapy might work remains unclear," says P'ng Loke, PhD, assistant professor of medical parasitology, who led the study, published in the December 1, 2010, issue of *Science Translational Medicine*. He says the case study, which analyzed the man's gut tissue when he had active disease and when he was in remission, suggests that infection with a particular parasite "increases or restores mucus production in the colon, providing symptomatic relief."

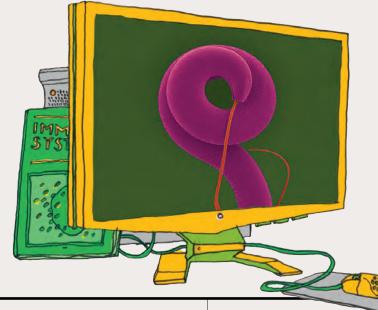
Ulcerative colitis, characterized by open sores or ulcers in the lining of the colon, affects some 600,000 Americans, according to the Crohn's and Colitis Foundation of America. The most common symptoms are abdominal pain and bloody diarrhea. The cause isn't known, but studies point to defects in immune regulation. Disruption of mucus

production is often associated with severe symptoms.

The first clue that worms might be beneficial arose from the observation that most cases of colitis occur in North America and Northern Europe, where helminth (parasitic worm) infections are rare. Yet the disease rarely occurs in Asia, Africa, and Latin America, where worms are common. Some laboratory and clinical tests subsequently supported this observation: Worms suppressed inflammation in animal models of autoimmunity, and helminth therapy helped heal colitis in clinical trials.

Based on these findings, the California man in the case study sought to infect himself with worms after he failed to respond to steroids and feared losing his colon. In late 2004, he ingested 500 eggs of the roundworm *Trichuris trichiura*, which he obtained from Thailand, and

Scanning electron micrograph of a parasitic roundworm of the genus *Trichuris*. Deliberate ingestion of *T. trichiura*, which infects the lower intestine, is reported to relieve the symptoms of ulcerative colitis, apparently by stimulating mucus production in the colon.





three months later swallowed another 1,000 eggs. The worms typically settle in the lower intestine, reaching maturity in about three months. Females can produce thousands of eggs a day, and the worms can live for many years.

Within months, the man's condition improved dramatically, and he remained in remission for almost three years, says Dr. Loke. Curious about his own recovery, and what would happen to him if he relapsed, the man contacted Dr. Loke, an expert in helminth biology, who was then at the University of California, San Francisco. Soon after, the man suffered another bout of severe colitis and decided to reinfect himself with worms; by last year he was in remission. Dr. Loke and his team were able to analyze the man's gut tissue during his relapse and after he was again in remission.

The researchers discovered that when the patient had active disease, a type of immune cell (CD4+ T cell) that produces an inflammatory protein called interleukin-17 abounded. After exposure to the worms, when the disease was in remission, T cells that produce interleukin-22, a protein important in mucosal healing, multiplied. Thus the researchers suspect that to expel the worm, the immune system appears to activate specialized cells that increase mucus production in the entire colon.

"In essence, the worms trigger a big sneeze of the gut, which may have a beneficial side effect for ulcerative colitis," says Dr. Loke, who does not advocate helminth therapy. The problem is that the worms themselves can damage the gut, and, he adds, it is impossible to predict who might be helped and who might be harmed by infection. Studies under way using a worm (*T. suis*) that infects pigs to treat colitis should be less risky, he says. Alas, they will still be stomach turning. •

-GARY GOLDENBERG

IMAGE COURTESY OF C. DENNIS KUNKEL MICROSCOPY, INC

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Boy or Girl?

A genetic switch for determining gender is found

A PERSON'S SEX, IT WOULD SEEM, is a matter of Xs and Ys: Through a biological twist of fate, each of us ends up either female, with two X chromosomes, or male, with one X and one Y. Yet sometimes a child is born with an X and a Y chromosome and develops physically as a female, and her brothers and male cousins may have underdeveloped or ambiguous genitalia.

A new study, led by Harry Ostrer, MD, professor of pediatrics, pathology, and medicine and director of the Human Genetics Program at NYU Langone Medical Center, describes a previously unidentified gene, MAP3K1, that may play a critical role in orchestrating human sexual development. The culmination of nine years of research, the findings, published recently in the American Journal of Human Genetics, could unlock the nuances of the genetic cascade that determines gender.

Since the discovery 20 years ago of a "maleness" gene, SRY, on the Y chromosome, a host of other genderrelated genes have been found. MAP3K1, located on the fifth chromosome, represents a "new molecular switch," says Ostrer, which may "modulate the pathways between male and female development" and hold the key to understanding how these genes are connected.

This discovery, says Alexander Pearlman, PhD, a postdoctoral fellow at NYU Langone Medical Center and the first author of the study, addresses the delicate nature of human sexual development. Even though a person may have the genetic factors associated with being either male or female, he says, "a single base mutation could turn everything the other way."

Researchers unearthed this potent gene by examining individuals with disorders of sexual development (DSDs). These conditions, previously called intersex disorders, affect approximately 1 in 1,000 people and can cause numerous abnormalities.

Dr. Ostrer's team studied one family from France, another from New Zealand, and several individuals with a condition known as 46,XY DSD. Though genetically male, some with the condition developed

as females, and had partially developed ovaries, overdeveloped clitorises, or excessive hair, while others grew up as men and had urethral openings on the underside of their penises, small genitalia, or infertility. By carefully analyzing their DNA, Dr. Ostrer's team and collaborators from France, England, and Australia uncovered several mutations in the MAP3K1 gene and showed that they affected pathways favoring ovarian development.

Dr. Ostrer believes that the discovery will help scientists better understand normal development and provide an avenue for genetic screening, allowing clinicians "to explain a given condition, to identify other families who may be at risk, or to perform prenatal diagnosis." A new

Harry Ostrer

screening technique is already being used in France to identify affected individuals.

"Like it or not, biology is destiny," says Dr. Ostrer. These conditions "influence how people think about themselves and whether they consider themselves male or female." Better scientific understanding, he says, gives affected families peace of mind, providing them an explanation of the cause and helping clarify their options.

Dr. Ostrer plans to set up a national consortium to sequence the entire genome of affected individuals and their families, which he hopes will help researchers identify related genes and eventually develop new therapeutic options for those affected by these conditions. •

— JOSHUA FEBLOWITZ

1970 - Family Identified 2010 - Mutation Found

In 1970 a family with a condition known as 46,XY disorder of sex development was identified. By carefully analyzing the DNA of family members, the mutation responsible for the condition was recently discovered. This mutation results from the replacement of the base A (adenine) by G (guanine).



DELIVERING ON THE PROMISE OF PERSONALIZED MEDICINE

by BRYN NELSON

illustration by JOE MAGEE
photographs by ELIZABETH WEINBERG

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NYU PHYSICIAN
WINTER 2010-2011

IMAGINE A LONG RIBBON OR A STRETCH OF TICKER TAPE TIED INTO AN ELABORATE SERIES OF KNOTS OR BOWS. In the blink of an eye, a protein can likewise assemble within a human cell, transformed from

In the blink of an eye, a protein can likewise assemble within a human cell, transformed from a string of amino acids into a precise combination of knots, turns, coils, spirals, and other shapes that enable it to carry out a specialized task aiding the well-being of the cell. A single wrong fold can destabilize the entire structure, leading to devastating diseases such as cystic fibrosis or Alzheimer's.

The grand challenge of biomedicine is how to convert such biological observations into targeted disease interventions that can correct or prevent such mistakes. But until recently, few tools were available to help researchers delve into the details of how our biological mechanisms really work.

Five years ago, no computer had the power to simulate the thousands of steps required for a ribbon of amino acids to fold into a three-dimensional protein. Today, the fastest supercomputers would need about three years to perform a simulation for each protein. Five years

from now, the best machines might complete the task in little more than a day.

As technology surges forward, gathering raw data is no longer the main barrier to realizing biomedicine's lofty goals. Instead, finding and interpreting the most useful information within the rising flood of data is becoming the overriding problem. The answer, in many cases, may be found within the expanding field of bioinformatics.

Rooted in computer science,
bioinformatics calls upon a diverse range of
other disciplines to help researchers discover
and make the best use of biological and
biomedical observations. Bioinformaticians
repeatedly dive into tidal waves of DNA,
RNA, and protein sequences and into
deep pools of other data detailing the
inner workings of a cell's components. By
highlighting useful signals that point to a
normal or abnormal state, such as unusually
active or inactive genes, researchers can
retrieve pearls of wisdom from the murky depths.

One glittering pearl has been the advancing knowledge of an overabundant protein called HER2/neu. With the help of bioinformatics tools, learning how this protein contributes to aggressive breast cancer has helped clinicians develop effective drugs like Herceptin that kill cancer cells containing excess copies of the protein. At NYU Langone Medical Center, researchers in the new Center for Health Informatics and Bioinformatics (CHIBI) are similarly

using computer-based mathematical strategies, or algorithms, to recognize disease-linked patterns that might otherwise remain hidden.

MAKING PREDICTIONS • CHIBI

researchers are identifying the bits of molecular information that may reveal patterns known as predictive signatures, which assess the risk of diseases like leukemia, psoriasis, and epidemic obesity; pinpoint the best medical studies; and flag websites that promote dubious therapies, among other projects. "It's not a boring place, I can tell you that," says Constantin Aliferis, MD, PhD, associate professor of pathology, who was recruited from Vanderbilt University in 2008 to be CHIBI's founding director. To help get the center off the ground, he brought along three members of his Vanderbilt team, biomedical informatics experts Alexander Statnikov, PhD, Lawrence Fu, PhD, and Yin Aphinyanaphongs, MD, PhD.

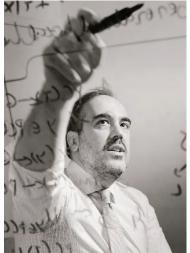
Perhaps the most promising capability of CHIBI researchers and other bioinformaticians is their ability to focus the power of new analytic tools on some of the most challenging issues confronting physicians: the ability to predict the onset or course of disease in a patient. CHIBI researchers have developed several types of algorithms to look for telltale biomarkers within molecular data that reproducibly indicate a patient's health status and can help build predictive models of disease. "You want to learn how to predict events," Dr. Aliferis says. "Who's going to respond to treatments? Who's going to get well, with or without treatment?" Other algorithms suggest which molecular players are causing a disease or condition and which are merely tagging along—essential information for designing drug interventions. All told, he says, more than 2,000 researchers in 50 countries use these and other algorithms created by the center's experts.

Dr. Aliferis counts oil painting and an ancient Greek martial art among his passions, but he is perhaps most animated when talking about CHIBI's many projects and the need to strengthen the scientific rigor of biomedicine. He first became interested in bioinformatics-themed basic research when he entered medical school in 1984. At the time, bioinformatics was just taking off, fueled by new techniques for recombining and sequencing DNA that allowed researchers to extract and compile genetic information more easily. The demand for bioinformaticians increased dramatically with completion of the Human Genome Project in 2003. The mammoth effort assembled the roughly three

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"WHO'S GOING
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WITH OR WITHOUT

TREATMENT?"

1





Dr. Constantin Aliferis, left, director of the Cener for Health Informatics and Bioinformatics (CHIBI). Dr. Stuart Brown, right, head of CHIBI's Sequence Informatics Group.

billion letters of DNA that spell out our genetic inheritance and spurred a gold rush of prospectors eager to find rich veins of information stored in the biological code.

The trend continues with the recent growth of evidence-based medicine, which uses the best scientific evidence to make clinical decisions, and ever-faster methods for generating DNA sequences and other molecular data. "The discovery of meaning is really what science is all about," says Stuart Brown, PhD, an expert in plant molecular biology who serves as a bioinformatics consultant and head of CHIBI's Sequence Informatics Group.

At a recent meeting with fellow researchers, Dr. Brown pointed out that information in the form of RNA or DNA sequences is accumulating so fast that it's now an easily obtained commodity. It took researchers 13 years and some \$2.7 billion to sequence the human genome, a job that would take only a few weeks and \$30,000 today. "As things get cheaper," Dr. Brown says, "more scientists can play," resulting in innovation but also greater need for computational data analysis. CHIBI's specialized ability to help researchers identify patterns in the overflowing pool of data, he contends, offers a "huge growth area" for assisting medical studies.

In one such collaboration with Bruce Cronstein, MD, the Dr. Paul R. Esserman Professor of Medicine, professor of pathology and pharmacology, and co-director of the Clinical and Translational Science Institute, CHIBI scientists are hoping to clarify the cellular mechanism behind keloids. These excessive and often disfiguring scar tissue growths disproportionately afflict people of

African descent. "First, why does that happen?" Dr. Cronstein asks. "Second, can we design a better therapy based upon an understanding of what's happening?" Figuring out how a drug works might provide clues to predict which patients would most benefit from it, thereby personalizing their course of therapy.

To help bring that about, researchers will need to pore over potential differences in the levels of RNA isolated from keloid-associated cells that point to heightened or decreased activity among a subset of our estimated 20,000 to 25,000 genes. Unusually high or low gene expression, compared to normal cells, could implicate genes involved in the condition.

A second project is examining the mechanism behind fatty liver disease, a condition linked to excessive drinking that can eventually lead to life-threatening cirrhosis of the liver. With CHIBI, Dr. Cronstein's lab is scrutinizing the livers of mice exposed to high levels of alcohol. The collaborators are looking at the relative activity of 450 to 500 small RNA pieces, called microRNAs. Past research has pointed to a key role for these molecules in the disease. Preliminary results obtained with the help of Dr. Statnikov, assistant professor of medicine and director of CHIBI's Computational Causal Discovery Laboratory, suggest that 30 to 40 microRNAs may be primary agents of change, perhaps by inhibiting the expression of critical genes.

THE TRANSCRIPTOME • An ambitious joint effort with William L. Carroll, MD, the Julie and Edward J. Minskoff Professor of Pediatrics, professor of pathology, and director of the NYU Cancer Institute, has adopted a similar goal of identifying critical players in the reemergence of childhood leukemia and then discerning which

may offer the best targets for medical interventions. The project is analyzing the entire transcriptome—the full sequence of messenger RNA—from samples at diagnosis and relapse from 10 children with acute lymphoblastic leukemia (the most common form of childhood cancer) to find out hidden pathways responsible for relapse.

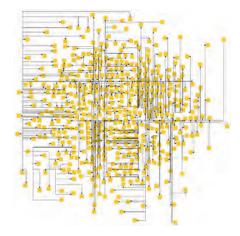
The collaborators sequenced 280 million letters of RNA from the cancerous white blood



Alexander Statnikov

Usir too car sor

Using bioinformatics tools, researchers can visualize and sort highly complex gene interactions. The example to the left illustrates the mapping of a gene regulatory network in which individual genes are represented by yellow boxes linked to many others.





ALTHOUGH
IT'S POSSIBLE
TO GENERATE
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THOSE MOST LIKELY

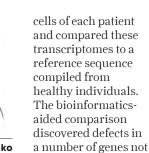
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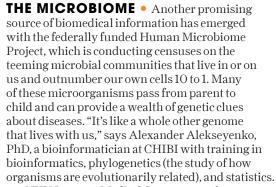


previously linked to

cancer and showed that these key differences in RNA sequences are unique to individual patients. Investigators are now using these observations to identify shared pathways leading to disease.

With technology leading the way, scientists are moving well beyond the genome—the full set of human DNA—to analyze other molecular agents of health and disease. Proteomics, for example, identifies and studies the relative amounts and interactions of our entire collection of proteins. Epigenomics focuses on the physical and chemical modifications to DNA that can activate or deactivate genes.

Together the various disciplines enable researchers to combine layers of information into a complete picture of the disease process, says Jinhua Wang, PhD, research assistant professor of pediatrics, who likens his data-mining task to finding hidden "dark matter" in the genome. Dr. Wang, who comes from a background in computational biology and genomics research, is helping the NYU Cancer Institute integrate multiple sources of clinical and molecular data. "If you look at two-dimensional pictures, you don't have information about the depth," he says. Looking at cancer through multiple layers or different angles may offer a more accurate portrait of its inner workings and root causes.



NYU Langone Medical Center researchers received major funding to study the microbiomes—the entire genetic makeup of specific microbial communities—within the upper gastrointestinal tract and on the skin. As part of the latter project, Martin Blaser, MD, the Frederick H. King Professor of Internal Medicine, professor of microbiology, and

chair of the Department of Medicine, has called upon Dr. Alekseyenko and other CHIBI researchers to help analyze the skin-based microbiome data. Early results have pointed toward a surprising association of several microbes with the skin condition psoriasis.

By comparing the genetic mix of microbes living on patients' psoriatic lesions with unaffected patches of their skin and that of healthy volunteers, the collaborators hope to build the first diagnostic signature of the

disease. "Like any census, it's complicated," Dr. Blaser says. "You could say that we're comparing the census of New York and Chicago, or maybe it's New York and Indianapolis, or New York and Moscow. That's what we're going to find out."

The complex project, he says, would have been impossible without a strong biomedical informatics component. "This is very exciting from my perspective," Dr. Aliferis says of the microbiome census, "because our first results clearly indicate that this technique could be used for diagnostic purposes and could point to previously unidentified microbes that may have a causal role in the disease."

Dr. Blaser has received federal funding for another microbiome project that could establish an unexpected link between gastrointestinal flora and epidemic obesity. Due to changes in the human lifestyle, he hypothesizes, an evolving community of microbes may be fueling obesity by affecting how fat is metabolized, especially among children. As a first step in the project, his team is exposing mice to small doses of antibiotics that alter their composition of gastrointestinal microbes. Although still early in the collaboration with CHIBI, Dr. Blaser says it is already revealing significant differences both in the composition of microbial populations and the ensuing effects on the animals' fat and lean mass.

SELECTING THE BEST DATA • Still.

the successful integration of bioinformatics into medical studies is bringing new challenges. Although it may be possible to generate hundreds or even thousands of molecular signatures that identify those patients most likely to respond to a given treatment based on a genetic profile, which set of markers should researchers use, and are they necessarily any better than others? To resolve the issue, CHIBI scientists have invented a technology designed to scan data sets and extract all signatures that meet two requirements: They must be as diagnostic or predictive as possible based upon the data, and they must be as small in number as possible. The result is a compact catalog of the most significant indicators.

The same general problem confronts researchers trying to sift through the overwhelming hodgepodge of information online.



Alexander Alekseyenko



Jinhua Wang

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Dr. Fu, assistant professor of medicine, and Dr. Aphinyanaphongs. assistant professor of medicine, are using the tools of health informatics to retrieve the most relevant information from existing studies and assessing the overall value of that data. "We focus on trying to help researchers, doctors, and patients search the scientific literature or the web to find the best articles or the best websites," Dr. Fu says. The goal, though, comes with a tricky question, Dr. Aphinyanaphongs says: "Can you teach a machine to recognize quality?"

So far, the answer seems to be yes. A program called EBMSearch, which Dr. Aphinyanaphongs built in his Nashville garage while still at Vanderbilt, analyzes features such as a clinical study's experimental design and ranks the best of the bunch in the public PubMed archive of scientific papers. Researchers can type in search terms, choose the range of publication dates, and decide which aspect of a clinical study to emphasize. "There is a pyramid of evidence, and when a field matures and conclusive evidence is finally available, only the top of the pyramid really matters for medical decision making," Dr. Aliferis says. "It consists of well-designed clinical trials and syntheses of the literature."

Another popular way to assess a study's value is to count the citations it receives in subsequent papers. But that method works only for older studies, Dr. Fu says, because newer ones simply haven't had enough time to amass citations. His solution: He designed the first computer model to predict successfully which papers will receive the most citations in the future, a tool that should likewise help researchers and physicians quickly find the most important papers. The model also incorporates agreed-upon signposts of good studies

and accounts for factors such as the track record of the scientific journal and other papers by the same authors.

To highlight less-than-reliable information, Dr. Aphinyanaphongs is developing a public health tool to help consumers steer clear of dubious websites touting unproven and even dangerous therapies. With no reliable filter now to sort good websites from bad, desperate patients can fall prey to commercial sites that pitch "miracle" cures and bogus treatments.

For a pilot study, Dr. Aphinyanaphongs is using key words as red flags to predict whether advertised cancer treatments are simply too good to be true. With health informatics tools guiding him, Dr. Aphinyanaphongs has found several traits shared by sites investigated so far. "The language of a site that's trying to cure your cancer is a very nonscientific, pie-in-the-sky language," he says, with words like "Nobel," "discovered," "amazing," "cure," and "orthodox" frequently used.

Although still a work in progress, the algorithm has performed better than a simple Google rank and another online tool called The Quackometer in predicting unreliable sites. Purveyors of dodgy therapies could try to game the system by avoiding words identified as signatures of quackery, of course, but Dr. Aphinyanaphongs says wording that is muted to avoid detection may fail to entice new consumers.

Ultimately Dr. Aliferis believes that well-designed and carefully vetted bioinformatics and health informatics tools must become routine features of biomedical research for the field to deliver on its many promises. Several CHIBI projects and services may simplify that task, including a user-friendly search program called

Find a Researcher that could help foster more in-house collaborations. Another tool helps medical investigators choose the best available software for recognizing patterns. "They can take a look at what's under the hood of different software packages," Dr. Cronstein says. "This will make a huge difference in our ability to analyze data."

In turn, the push to fully integrate bioinformatics into biomedicine may help redirect the incoming flood of information into the clinical channels that make the biggest impact in saving and improving lives.



Lawrence Fu



Yin Aphinyanaphongs

al This figure shows multiple runs of DNA sequencing from the white blood cells of a single leukemia patient, compared to the standard reference sequence from the Human Genome Projects."

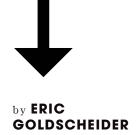
This figure shows multiple runs of DNA sequencing from the Human Genome Projects of South Proj

the standard reference sequence from the Human Genome Project (shown in white). The position labeled "R" indicates a potential cancer-linked mutation. Some of the white blood cells have this change while others do not, perhaps reflecting a mix of normal and cancerous white blood cells in the sample selected for sequencing.



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INTERACTION PATTERNS

THAT MAY FORETELL

THE STORY OF LIFE.

illustration by
JOE MAGEE
photographs by
ELIZABETH WEINBERG

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DIVING DEEP INTO THE GENOME



AT THE GENOME TECHNOLOGY CENTER AT NYU LANGONE MEDICAL CENTER,

the latest technology, called next-generation sequencing, offers unparalleled views of the human genome and the genomes of other organisms, enabling scientists to begin to understand how cells function and evolve. On another level, it provides a more effective and efficient means of finding mutations in genes. "Mutations are the proverbial needle in the haystack," says Jiri Zavadil, PhD, assistant professor of pathology, who directs the Genome Technology Center. "Now we can deconstruct the haystack. This is an example of the unprecedented power of deep sequencing. It is really revolutionary."

Identifying sequences of A, T, G, and C (the nitrogen bases adenine, thymine, guanine, and cytosine, the four-letter alphabet of DNA) is at the heart of genomics. Next-generation sequencing, commonly referred to as deep sequencing, enables the recording of an enormous number of reactions with a high degree of accuracy based on certain chemical characteristics of each base.

The highly anticipated sequencers of the near future are expected to generate 10 times more data. "The field is moving so fast that yesterday is the olden days," says Jane Carlton, PhD,



The Illumina Genome Analyzer Ilx, above, is one of the next-generation sequencers in the Genome Technology Center.

associate professor of medical parasitology and director of genomics who chairs the faculty advisory board of the Genome Technology Center.

Another tool offered at the Genome Technology Center is called a microarray, which allows researchers to search a biological sample rapidly for known base sequences.

The complexity involved in capturing, storing, and manipulating the huge amounts of data the high-

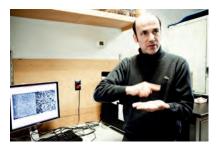
throughput technologies yield demands collaboration among scientists with specialized skills. "You have to put together this holy triangle of IT [information technology] people, bioinformaticists, and biologists," Dr. Carlton says. "But in the end genomics is still just a tool really. It's not the be-all and the end-all, it's the biological questions that keep driving what we do."

Taken together, deep sequencing and other technologies are now helping scientists understand the big picture, to connect how genes influence cellular activity, to compare patterns of gene expression in healthy versus diseased cells, and analyze the interactions of gene products under varying conditions over time.

Here are some examples of research resulting from collaborations between NYU Langone Medical Center investigators and the Genome Technology Center. **JANE CARLTON** • Several years ago, Dr. Carlton sequenced the sexually transmitted human pathogen *Trichomonas vaginalis*, which latches onto the lining of the urogenital tract, destroying epithelial cells and increasing susceptibility to HIV, the virus that causes AIDS; she is now leading a team to sequence the genomes of four more parasites using the next-generation sequencing equipment at the Genome Technology Center. Such so-called



Dr. Carlton



Dr. Zavadil

de novo sequencing is a crucial first step in generating data for future investigations aimed at seeing how similarities and differences between genomes translate into observable phenotypes—traits, behaviors, or properties. Intriguingly, the new sequencing techniques also allow scientists to capture genetic information from communities of organisms, an approach called metagenomics that Dr. Carlton is also using to study microbial interactions in the urogenital tract. "Metagenomics is really powerful because not only do we get to find out about that particular organism, but we can also see what are all the other friends and foes in terms of microbes that it has in that particular environment," says Dr. Carlton. This multidimensional swath of information can yield clues about how organisms interact with each other or even how they may have co-evolved.

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ROBERT SCHNEIDER •

Robert Schneider, PhD, the Albert B. Sabin Professor of Microbiology and Molecular Pathogenesis, professor of radiation oncology, and associate director of Translational Research and co-program leader of the Breast Cancer Research Program at the NYU Cancer Institute, is looking for patterns of small pieces of regulatory RNAs known as microRNAs within breast tumors, as well as in the surrounding healthy tissue. Specific microRNAs and patterns of microRNA expression may help predict whether breast cancer is likely to spread. The equipment at the Genome Technology Center enables him and his team to address the question of which cancers are likely to remain in the breast and which are likely to metastasize. The answer has implications for patients whose underlying resilience would be damaged by unnecessary treatment, as well as for overburdened healthcare systems globally where cancer care is still considered a luxury, says Dr. Schneider. Because of scarce resources in many poor countries, doctors often can't provide treatment to patients most in need. Genomics-based diagnostics, he says, may offer them the ability to focus their resources more rationally in order to do the most good.



Dr. Schneider

PhD, chair of the Department of Environmental Medicine and professor of environmental medicine and pharmacology, wanted to find out if gene expression in healthy cells transformed in his laboratory into cancer cells differed depending on which known carcinogens they were exposed to. "One very interesting thing we found is that if we take human bronchial epithelial cells and

MAX COSTA • Max Costa,



Dr. Costo

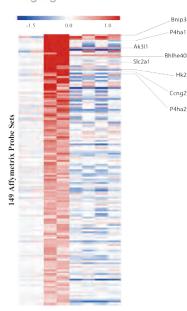
make them into cancer cells with chromium, all the resulting cancer cells have the same gene expression pattern," says Dr. Costa. "But if they were transformed by nickel, it's a completely different pattern." This kind of information can eventually give physicians an important diagnostic tool. Studies he is able to do with next-generation sequencing technology in collaboration with the Genome Technology Center, he adds, "allow us to understand which factors interact with individual genes in response to environmental stressors."

DAVID ZAGZAG • David Zagzag, MD, PhD, professor of pathology and neurosurgery and chief of the Division of Neuropathology, studies the development of blood vessels—or angiogenesis—in brain tumors. A strategy to fight the growth of cancer is to inhibit blood flow to malignant cells in order to cut off their nutrient supply, which also curtails their access to oxygen. Curiously, the gliomas he studies actually do better in a low oxygen, or hypoxic, environment, which undermines the full effectiveness of treatments that inhibit blood vessel formation.

Dr. Zagzag turned to genomics to understand a transcription factor called HIF-1α associated with cells' response to low oxygen. (Transcription factors are proteins that latch onto sequences of DNA, thereby regulating the activity of genes, and Dr. Zagzag first reported on the presence of HIF-1α nearly a decade ago.) Last June his team published a paper in the journal *Molecular* Cancer, which used microarray analysis to measure gene expression in cancer cells engineered to be deficient in HIF- 1α . His findings help elucidate how the factor influences the invasive potential of those cells, providing a piece of a puzzle that cancer researchers are putting together about gliomas. •



Dr. Zagzag



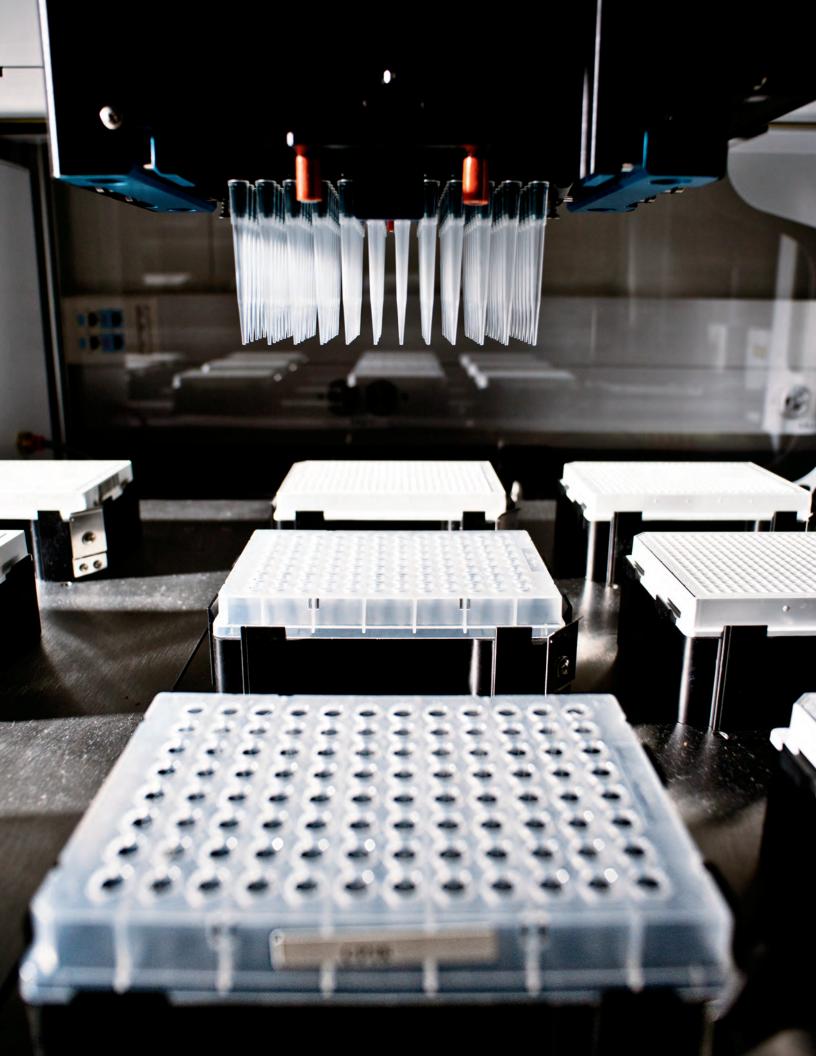
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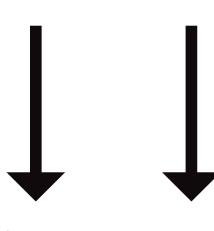
4 matched metastases LEFT: Expression patterns of microRNAs within breast tumors may be useful to assess the likelihood that a breast cancer might metastasize. Locally advanced breast cancers that spread five years after treatment showed a similar pattern to matched cases of metastatic cancer.

"THE FIELD IS MOVING SO FAST

THAT
YESTERDAY
IS THE OLDEN
DAYS."

ABOVE: The heat map identifies changing patterns of gene expression induced by low oxygen in brain tumor cells that are dependent on a key regulatory gene, HIF-1 α





DAN FERBER

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photographs by **RENÉ PEREZ**

ZEROING

RNAI, A POWERFUL
NEW TOOL, IS HELPING
RESEARCHERS
RAPIDLY DISCOVER
THE FUNCTION OF
THOUSANDS OF GENES.

LEFT: A liquid-handling robot in the RNAi laboratory at WU Langone Medical Center. This type of automated equipment enables analysis of the entire human genome in a matter of weeks or months rather than years.

FOR DECADES, RNA HAD BEEN THOUGHT TO ACT AS DNA'S LIEUTENANT, DUTIFULLY CARRYING OUT THE COMMANDER'S INSTRUCTIONS TO MANUFACTURE PROTEINS IN THE CELL. BUT RECENTLY, THAT THINKING HAS CHANGED, AND SCIENTISTS HAVE DISCOVERED THAT THERE ARE A MULTITUDE OF RNA COUSINS RUNNING AROUND IN OUR CELLS THAT PLAY CRITICAL ROLES IN HUMAN HEALTH. ONE OF THESE MOLECULES, SMALL INTERFERING RNA (RNAI), IS THE FOUNDATION FOR A POWERFUL TOOL THAT CAN RAPIDLY SCREEN WHOLE GENOMES TO IDENTIFY GENES INVOLVED IN A HOST OF SPECIFIC BIOLOGICAL PROCESSES.

Ramanuj DasGupta, PhD, assistant professor of pharmacology, is director of the RNAi Core Facility, a state-of-the-art laboratory at NYU Langone Medical Center that opened in 2008. Here researchers can simultaneously test the function of thousands of genes, using an array of advanced robotics, automated microscopes, and other highly specialized equipment. This new technology can help untangle complex biological pathways like those that lead to cancer or to the proper development of tissues and those that keep infectious microbes from invading our tissues.

"The amazing thing is that you can systematically and comprehensively query the function of each and every gene in the genome in a matter of weeks. It is also highly cost-effective," Dr. DasGupta says.

A UNIQUE RESOURCE

RNAi screening is based on the Nobel Prize–winning discovery that when fragments of double-stranded RNA are introduced into animals or cells in culture, they effectively suppress the expression of the corresponding gene by destroying its complementary messenger RNA. This form of RNA carries messages from DNA in the cell's nucleus to the cytoplasm, where proteins are made.

The need for an automated screening tool has never been greater. Although genomicists have cracked the human genome and decoded that of the roundworm, fruit fly, mouse, and other organisms, the function of thousands of genes remains unknown. And the old method of determining gene function—shutting down a gene and then observing what happens to the mutated cells or organism—is inordinately laborious and time consuming.

The RNAi Core Facility funds three full-time staff, including assistant director Chi Yun, PhD, who maintains RNAi libraries for organisms commonly studied by biologists, such as humans, mice, fruit flies, and roundworms. She also coordinates the work flow for the variety of whole-genome screens that are currently being performed at the facility. The lab is open to researchers everywhere, providing they agree to share their data with the scientific community.

Dr. DasGupta himself has employed RNAi to probe a crucial cellular signaling pathway—called the Wnt pathway—that regulates many aspects of development and disease. A malfunctioning Wnt pathway can lead to devastating birth defects or a variety of cancers. The pathway is complex and its regulation only partially understood, and whole-genome RNAi screening technology provides Dr. DasGupta and others in the field the means to identify novel modulators of this pathway.

To identify them, he took a modified version of a firefly gene and engineered it into fruit fly cells so that they glowed when the Wnt pathway was activated. He mixed tiny samples of those cells with about 22,000 double-stranded RNAs, each corresponding to a potential gene in the fruit fly genome. By focusing on samples



Dr. Yun

that glowed much more or less than usual, Dr. DasGupta identified 148 novel genes that seemed to regulate the Wnt pathway; later studies demonstrated that some of them actually did so. More than half have human equivalents, and 21 had been linked to human disease, the researchers reported in *Science* in 2005 and *Genome Biology* in 2007.

Dr. DasGupta's team reported in the journal *PLoS One* in 2009 that they had used an RNAi screen to pinpoint a previously unresearched protein, dBili, that turns off a master switch of this critical pathway in fruit flies, zebrafish, and cultured human cells. And Foster Gonsalves, PhD, a postdoctoral fellow in the lab, further exploited this tool in a novel strategy of integrating RNAi with chemical genetic screens to identify three small molecules that could be the basis for innovative therapies for colorectal cancer and other diseases associated with misregulated Wnt signaling.

SCREENING FOR SURPRISE

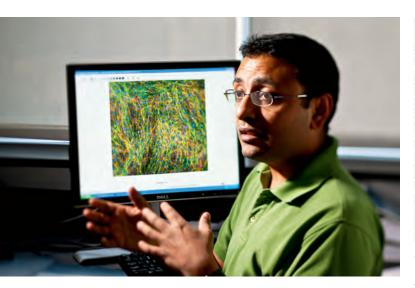
To find essential genes, researchers need a cell-based assay—a way to quickly detect the cellular process they're examining—that can be used on the RNAi-screening lab's automated "assay-detection" equipment. A number of researchers at NYU Langone Medical Center have used such assays to find a particular gene.

Michael Garabedian, PhD, professor of microbiology and urology, in collaboration with Susan Logan, PhD, associate professor of urology and pharmacology, worked with the RNAi facility staff to develop a screen that could identify potential targets for new and better drugs for prostate cancer. Current

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drugs stem the action of male hormones, androgens, but they chemically castrate the patient, sometimes causing hot flashes, fatigue, sexual dysfunction, and other serious side effects. Cancer cells also frequently become resistant to these drugs. Drs. Garabedian and Logan wanted to use RNAi to find new ways to block the androgen receptor, which turns on genes in the nucleus in response to testosterone. Such an approach, they reasoned, might lead to therapies with fewer side effects and lessen the likelihood of resistance.

The screen identified 80 genes that alter the activity of the



Dr. DasGupta

androgen receptor. Some were known, and others were newly identified. Blocking one of these genes stopped the growth of laboratory-cultured cells from late-stage prostate cancer patients who no longer responded to conventional therapy. "This is the kind of target gene that we were looking for," Dr. Garabedian says.

E. Jane Hubbard, PhD, associate professor of pathology, is using RNAi screens to better understand the genes and proteins that make cells proliferate in normal development and in cancer. She works on a soil-dwelling roundworm called *Caenorbabditis*

elegans that serves as a model because it shares many fundamental features with other organisms, it is easy to manipulate at the molecular level, and its cells can be tracked precisely under a microscope. Importantly, RNA interference is triggered when the worm eats bacteria engineered to produce a specific double-stranded RNA.

Dr. Hubbard knew that tumors can develop from malfunctions in genes that direct immature cells called stem cells to develop into mature tissue or in genes that direct cells to multiply. She "...YOU CAN
SYSTEMATICALLY
AND
COMPREHENSIVELY
QUERY THE
FUNCTION OF
EACH AND
EVERY GENE IN
THE GENOME IN
A MATTER OF
WEEKS."

developed a sophisticated but counterintuitive test in which tiny stem-cell-like tumors form in the roundworm's developing gonad, but only when RNAi blocks genes that spur cells to overgrow earlier in development. Then, using techniques developed by Fabio Piano, PhD, director of the NYU Center for Genomics and Systems Biology, she and her laboratory team mixed an RNAi that targeted each of the worm's 18,000 genes.

Some of the RNAi experiments obstructed the cell's response to an insulin-like protein, they reported in the journal *Development* in 2010, offering clues about how nutrition might



The RNAi screen above reveals genes that alter the activity of the androgen receptor, which turns on genes in the nucleus in response to testosterone. Each circle represents a well that contained an RNAi corresponding to a gene in the cell. Red wells indicate the presence of genes that inhibited the receptor, while purple and blue wells reveal genes that helped it function.

affect tumor growth. "The real beauty of RNAi is that you can screen the library fast," Dr. Hubbard says. "Unlike conventional genetic screens, you know right away which gene is responsible. If you get an interesting hit, you go with it."

And Jennifer Philips, MD, PhD, assistant professor of medicine, pathology, and microbiology, uses RNAi screens to identify human genes that make tissues vulnerable to *Mycobacterium tuberculosis*. The results of her initial screen, published in *Science* in 2005, identified 86 genes that promote bacterial infection in fruit fly cells. Some belong to a cellular pathway called ESCRT (endosomal sorting complex required for transport), which serves as a guide to the cell's recycling center, the lysosome.

In 2008 she and her colleagues reported in the *Proceedings* of the National Academy of Sciences that ESCRT proteins also steer mycobacteria to the lysosome in mammalian cells. More recently they identified a protein from TB bacteria that interacts with the ESCRT machinery; she suspects this interaction may help the TB bug survive in human macrophages. (In humans, TB bacteria evade normal immune defenses by hiding out in macrophages.) "Without RNAi screening, the role of that machinery would never have been identified. No one who works on TB would have thought to look at it," Dr. Philips says.

The appeal of the work lies in the unbiased nature of RNAi screens; you never know what you may get, Dr. DasGupta says. With a clever genetic test, RNAi screens routinely open up the door to years of new discoveries. "You're really limited only by your imagination," he says. •

A worker of the jumping ant Harpegnathos saltator with sickle-shaped mandibles and large eyes used for hunting prey. Illustration based on a photograph by Jürgen Liebig.



by JOSIE GLAUSIUSZ

- illustration by EMILY COOPER
- photograph by SASHA NIALLA



AN ANT COLONY IS A MONARCHY RULED BY A LONG-LIVED, EGG-LAYING QUEEN SERVED BY SCURRYING, SEX-SACRIFICING FEMALE WORKERS AND SHORT-LIVED, EXPENDABLE MALES. SOMETIMES THE REGIME IS OVERTHROWN—THE QUEEN DIES,

and workers battle to replace her, forming a powerful oligarchy of now-fertile pseudoqueens. Such is the world inhabited by Jerdon's jumping ant, or *Harpegnathos saltator*, a primitive species hailing from south India that preys on small insects.

Not all ant societies conform to these rules however. The wood-boring, territorial Florida carpenter ant, or *Camponotus floridanus*, lives in large complex colonies dominated by an egglaying queen, with day-to-day tasks performed by two infertile female worker castes: majors that guard the nest and minors that scavenge food. When the queen dies, so does the colony.

Autocratic insect empires may seem of interest only to entomologists, but these two ant species are poised to reveal secrets of human development, aging, and behavior, thanks to the work of Danny Reinberg, PhD, professor of biochemistry, and his colleagues. The Chilean-born Dr. Reinberg is an expert in the burgeoning field of epigenetics, alterations in gene activity that do not involve mutations to DNA, but are determined instead by molecular "tags" that latch onto genes, turning them on or off, or directing them to shout or to murmur. These changes are typically inherited when cells divide.

Dr. Reinberg, a Howard Hughes Medical Institute investigator who has co-edited an authoritative textbook on epigenetics, has spent 30 years studying how genes are expressed in cells and ultimately translated into proteins, the building blocks of life. Most significantly, he has discovered some of the key enzymes that control access to DNA in its cellular form, where it is curled tightly around proteins called histones in a complex called chromatin. This access is crucial to the development of specific cell types during embryonic development. A liver cell, which shares the exact same DNA with every other cell in the body, becomes a liver cell and gives rise only to liver cells because certain areas of that cell's DNA are exposed and expressed.

In the course of his research, "I started reading about epigenetics, and I got fascinated," Dr. Reinberg says. To truly understand how this process controls development and behavior, he realized he needed to study a whole organism. And that's when he hit upon ants.

THE NEED FOR A MODEL • The idea arose during a long conversation with Shelley Berger, PhD, a fellow expert on epigenetics, on a traffic-choked bus ride to a conference outside Mexico City five years ago. A biologist at the University of Pennsylvania, Dr. Berger had recently returned from Costa Rica, where she had observed fungus-farming leaf-cutter ants. The two agreed on the need for a model organism in which an identical genome gives rise to individuals of varying form and behavior. The honeybee was one option—a draft version of its genome had been sequenced in 2006—but bees are difficult to handle,

they sting, they fly, and their queens mate multiple times, making it difficult to analyze gene inheritance.

Ants are perfect, the researchers thought, not only because they do not sting, but because different castes within the same colony, the queen and the workers, carry identical genes, yet give rise to individuals of differing size, behavior, and fertility. Clearly, some other mechanism—diet or pheromones,

for example—must influence the expression of individual genes and overall development of individuals. What's more, both the Florida carpenter ant and Jerdon's jumping ant are already well studied. Jürgen Liebig, a behavioral ecologist at Arizona State University in Tempe, spent years investigating social behavior and chemical communication in these two species. In 2008 Drs. Reinberg, Berger, and Liebig received a generous grant from the Howard Hughes Medical Institute to sequence the genomes of the two ant species; they published their results in the August 27, 2010, issue of *Science*.

EPIGENETIC TAGS • Understanding epigenetic alterations has been compared to reading a book. Once printed, the text—the genes or DNA—will always remain the same. But a reader may interpret the text differently, depending on the emotions he or she experiences while reading it or comments scribbled in the margins by previous readers. The classic view of genetics is that mutations in DNA, or changes in gene sequence, are passed on to future generations. By contrast, epigenetic tags that turn individual genes on or off make no fundamental change to the underlying DNA, just as readers' wisecracks in a book's margins may alter later interpretation, but not the basic text. In order to understand epigenetic alterations in the ants, the research team first had to "print out" the original text, or genome, of these species—the first social insects, after honeybees, to have their genomes sequenced.

The project began with the arrival of 10 packages of frozen ants from Dr. Liebig's lab. Then the team crushed the ants in liquid nitrogen using a mortar and pestle and extracted DNA from each caste in both species—for the carpenter ants, the queen, major and minor workers, and males; for the jumping ants, the pseudoqueens (also known as gamergates), workers, and males. (Removing the queen from a jumping ant colony triggers the development of gamergates.) They shipped the DNA to the Beijing Genomics Institute in Shenzhen, China,

where scientists chopped it up and sequenced the DNA with the aid of highthroughput genome analyzer machines. They then analyzed the results.

Some findings were straightforward, says Roberto Bonasio, PhD, a postdoctoral fellow in Dr. Reinberg's lab who is supported by a fellowship from The Helen Hay Whitney Foundation. The ant species share about 33 percent of their genes with humans, while 20 percent of them are unique. The carpenter ant has 17,064 genes and the jumping ant has 18,564. The researchers, however, were just as interested in epigenetic changes, since

UNDERSTANDING EPIGENETIC ALTERATIONS

HAS BEEN
COMPARED
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A BOOK.

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Dr. Danny Reinberg (left) and Dr. Roberto Bonasio are investigating the role of epigenetics in brain function and behavior.

it's clear that these must influence behavior, such as the jumping ants' switch from workers to pseudoqueens, resulting in both extended life span (queens typically live at least five times longer than workers) and a sudden ability to lay eggs. So the team also looked at the RNA levels in different ant castes, an indicator of which genes were being expressed.

Two enzymes were overexpressed in the jumping ant pseudoqueens, telomerase and SIRT1, which are both involved in aging, Dr. Reinberg says. In addition, the switch from worker to pseudoqueen brought about major changes in the biosynthetic pathways for complex chemicals involved in communication and social behavior. Dr. Reinberg also found intriguing chemical differences in the brains of the major and minor carpenter ant workers: The levels of certain neuronal receptors—the docking stations for neurotransmitters in the ants' brains—varied. This observation suggests that these variations may influence behavior in the castes.

Brain function in ants as well as in humans may also be affected by another epigenetic tag—DNA methylation. This is a common type of clamp comprising a methyl group, a carbon atom with three hydrogen atoms (CH₃) that locks onto a gene, typically preventing its transcription into RNA, which in turn directs the construction of proteins. DNA methylation may be influenced by the outside environment. For example, in one fascinating 2004 study, rat pups whose mothers spent more time grooming them showed a specific pattern of methylation in the brain and were less anxious and more resilient to stress. In humans, abnormal methylation has been associated

with neurological disorders such as Rett Syndrome, which is characterized by severe language difficulties and lack of social engagement. Curiously, Dr. Reinberg and colleagues found that DNA methylation levels were lower in the primitive jumping ants than in the more socially sophisticated and rigidly organized carpenter ants.

CLINICAL APPLICATIONS • The role of epigenetics in brain function and behavior is "a fascinating question," says molecular biologist Vincenzo Pirrotta, PhD, of Rutgers University, who calls Dr. Reinberg "perfectly positioned" to do this research in ants. "His work on epigenetics has been going on for many, many years, and he has made many major contributions," Dr. Pirrotta says. "Now the question is how to go about applying that kind of expertise to try to understand how epigenetics works in the nervous system."

Understanding epigenetic changes may also be key to curing diseases—an area of intense focus for Dr. Reinberg, who two years ago started a new company, Constellation Pharmaceuticals. The company aims to develop novel drugs that combat miscues in epigenetic control of gene expression that can lead to cancer, autoimmune diseases, or mental retardation. It's already known, for example, that DNA methylation can silence certain tumor suppressor genes and lead to rampant cell division and cancer metastasis.

"I cannot predict what is going to happen," Dr. Reinberg says. "But as long as the dedication to this kind of basic research continues, I am sure that the clinical applications will follow." ●

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Faculty News



Dr. Joseph McCarthy



Dr. Benard Dreyer



Dr. Rochelle Hirschhorn

School Honors Three Masters and One Major Benefactor at Dean's Honors Day

On October 6, 2010, the School of Medicine honored three of its most distinguished faculty members for embodying outstanding lifetime achievement in the three missions of NYU Langone Medical Center: patient care, research, and education. In ceremonies highlighting the School's annual Dean's Honors Day, Dean and CEO Robert

I. Grossman, MD, cited the trio for their "powerful intellect, sustained effort, steadfast achievement, and greatness of spirit."

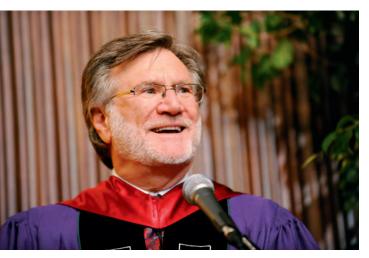
Dean's Honors Day, established in 2002 to recognize faculty advancement and achievement over the previous year, added in 2007 the special categories of Master Clinician, Master Educator, and Master Researcher to honor those deserving of such distinction. This year, Joseph McCarthy, MD, the Lawrence D. Bell Professor of Plastic Surgery and director of NYU Langone Medical Center's Institute of Reconstructive Plastic Surgery, was named Master Clinician. Benard Dreyer, MD ('70), professor of pediatrics, was recognized as Master Educator, and Rochelle Hirschhorn, MD ('57), professor emerita of medicine, cell biology, and pediatrics, was honored as Master Researcher.

Dean Grossman lauded Dr. McCarthy as "a trailblazer who has revolutionized craniofacial surgery." In his 35-year career at the Medical Center, Dr. McCarthy has specialized in reconstructive plastic surgery of the face. He developed the concept of craniofacial distraction and also introduced surgical reconstruction of the face as early as infancy to avoid or ameliorate future psychosocial problems.

Dr. Dreyer was cited as "one of the nation's premier experts in health literacy and a revered mentor who has shaped countless careers." Over a 34-year career at the Medical Center, he has been a leader in developing the pediatrics curriculum for students and fellows. He has also taken a leadership role in his field outside the Medical Center and was recently voted president-elect of the American Pediatric Association.

Dr. Hirschhorn, a member of the School of Medicine community since graduating in 1957, was described as "a pioneer in genetics, conducting seminal work on enzyme deficiencies and gene mutation." Her major work concerned the enzyme adenosine deaminase (ADA) and its role in immune cells, which led to an understanding of the role of ADA and its deficiency in individuals with impaired immune systems. •

Dr. Robert Berne, executive vice president for health; Kenneth G. Langone, chair of NYU Langone's Board of Trustees; and Dr. Robert I. Grossman, dean and CEO of NYU Langone Medical Center.



Dr. Steven B. Abramson, senior vice president and vice dean for Education, Faculty and Academic Affairs.

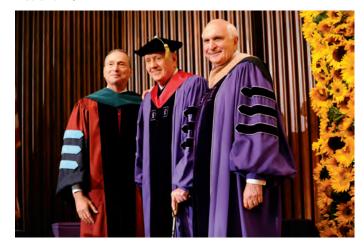


Some of the faculty members who attended the ninth annual Dean's Honors Day.

THE GIANTS AMONG US

THE VALENTINE MOTT FOUNDER'S AWARD, named for the father of modern surgery and co-founder of NYU School of Medicine, is bestowed upon those who have shown exceptional support for NYU Langone Medical Center's medical program. This year, the award went to Thomas S. Murphy, Sr., who served as the Medical Center's chairman of the board from 1984 through 1997. The former chairman and CEO of Capital Cities/ ABC Inc., Mr. Murphy has been a member of NYU Langone's Board of Trustees since 1972. He is also a member of the Urology Research Program Advisory Board, an honorary alumnus of NYU School of Medicine, and a life trustee and honorary vice chair of New York University. Together with his late wife, Suzanne, he endowed the Thomas and Suzanne Murphy Professorship in Neuroscience and has also generously supported the Medical Center's biomolecular research program, Centers of Excellence, Trustee Annual Fund, and expansion of Tisch Hospital's Emergency Department.

"This day is about pausing to recognize the giants among us," said Dean Grossman, "and Thomas Murphy is a giant if ever there was one." \bullet

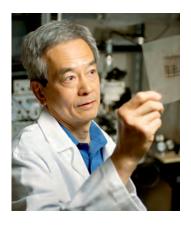


Thomas S. Murphy, Sr. (center), recipient of the Valentine Mott Founder's Award, with Dean Grossman and Kenneth Langone.



Dr. Anthony J. Grieco, associate dean for Alumni Relations, led the faculty procession on Dean's Honors Day.

Faculty News



Dr. Tsien Named Director of New Neuroscience Institute

RICHARD W. TSIEN, DPHIL, an internationally renowned scientist, has been appointed director of the recently established Neuroscience Institute and the first Druckenmiller Professor of Neuroscience, effective January 2012. Dr. Tsien—a member of both the National Academy of Sciences and the Institute of Medicine and a former Rhodes Scholar—joins NYU Langone from Stanford University, where he currently serves as the George D. Smith Professor of Molecular and Genetic Medicine in the Department

of Molecular and Cellular Physiology.

In 2009, NYU Langone Medical Center received a \$100 million gift from the Druckenmiller Foundation to establish a state-of-the-art neuroscience institute and to provide for the recruitment and support of the highest caliber neuroscientists. Dr. Tsien's appointment reinforces NYU Langone's existing strengths and will enable it to become a leader in translational neuroscience.

At Stanford, Dr. Tsien was the founding chair of the Department of Molecular and Cellular Physiology. He helped establish the Stanford Brain Research Center and served as its co-director from 2000 through 2005. He also served a 10-year term as director at Stanford's Silvio Conte Center for Neuroscience Research. Dr. Tsien studies how synapses contribute to neuronal computation and network function in both healthy and diseased brains. His research, supported by the NIH and private foundations, has contributed substantially to understanding how neurotransmitters, drugs, and molecular alterations regulate calcium channels.

Born in China, Dr. Tsien came to the United States as a child and later received both undergraduate and graduate degrees in electrical engineering from the Massachusetts Institute of Technology. He was then named a Rhodes Scholar, graduating with his doctorate in biophysics from Oxford University, England. He subsequently joined the faculty at Yale University School of Medicine and served there for nearly two decades before moving to Stanford. ullet

DR. OPPENHEIM RECEIVES LIFETIME MENTOR AWARD

JOEL D. OPPENHEIM, PhD, senior associate dean for Biomedical Sciences, professor of microbiology, and director of the Sackler Institute of Graduate Medical Studies at NYU School of Medicine, was recently awarded the 2010 Lifetime Mentor Award of the American Association for the Advancement of Sciences.

The award honors an individual who has demonstrated extraordinary leadership in increasing the participation of underrepresented groups in the science and engineering fields. It especially recognizes an individual who has mentored significant numbers of these students to the completion of doctoral degrees.

Since becoming director in 1994 of the Sackler Institute, Dr. Oppenheim has built

its doctoral program in the biological sciences into a model of diversity. Approximately 15 percent of Sackler's PhD graduates belong to underrepresented minorities—African Americans, Native Americans, Hispanic Americans, as well as individuals with disabilities or from economically disadvantaged backgrounds—compared to only 7 percent to 8 percent of bioscience PhDs awarded nationwide.

Dr. Oppenheim has been a member of the NYU faculty for 37 years. ullet



MEDICAL CENTER JOINS WITH PATH MALARIA VACCINE INITIATIVE

NYU LANGONE MEDICAL CENTER is
working with the PATH Malaria
Vaccine Initiative and Merck to
develop a vaccine to prevent the malaria
parasite from entering the human liver.

Researchers from the three organizations will evaluate a vaccine approach that targets a novel part of a major surface protein on the malaria parasite. Malaria is estimated to kill nearly 900,000 people each year with the majority of deaths occurring in children under the age of five in sub-Saharan Africa.

The circumsporozoite protein (CSP), identified in the early 1980s by Drs. Ruth and Victor Nussenzweig and Dr. Jerome Vanderberg at NYU Langone Medical Center, is the basis for many of the vaccines now in development. Blocking a critical function of the protein may prevent invasion of the malaria parasite into the liver, an essential step in causing malaria.

"We think we can improve the way subunit vaccines are designed by strategically targeting this critical protein function," notes Elizabeth Nardin, PhD, professor in the Department of Medical Parasitology at NYU Langone



Medical Center. "Other vaccine approaches targeting CSP have required extremely high levels of antibody, which are difficult to elicit and to maintain. This approach has the potential to address that problem."

Although this vaccine approach is being tested primarily for use in children younger than one year of age, researchers believe it could be used to help prevent disease in all populations.

PATH Malaria Vaccine Initiative (MVI) was established at PATH in 1999 through an initial grant from the Bill & Melinda Gates Foundation. Merck is one of the world's largest pharmaceutical companies, operating in more than 140 countries.

Plastic Surgery Becomes a Department

The Plastic Surgery Service at NYU Langone Medical Center, one of the largest in the United States and internationally renowned for leadership in congenital facial surgery, microsurgery, breast

reconstruction, and aesthetic surgery, has been elevated to the status of a full academic department.

Joseph McCarthy, MD, the Lawrence D. Bell Professor of Plastic Surgery who was honored as Master Clinician at last year's Dean's Honors Day (see page 26), will serve as the department's first chair. Dr. McCarthy has provided

leadership as director of both the division of plastic surgery and the Institute of Reconstructive Plastic Surgery at NYU Langone for the past 30 years. Hospital and at Bellevue Hospital Center, the School of Medicine's primary teaching affiliate, the Institute's faculty annually perform more than 2,500 and 1,300 surgical procedures, respectively.

In addition to the clinical expertise of its faculty, the department is well known for its outstanding training programs. Its six-year residency program for plastic surgery (with 24 residents) is rated as one of the most competitive in the United

States.

The department also pioneered post residency fellowships in craniofacial surgery, microsurgery, hand surgery, and aesthetic surgery.
Graduates of these training programs have assumed the chairs of plastic surgery in over 20 universities worldwide.

The department's clinical and research efforts have been made possible in large part by generous support

from the National Foundation for Facial Reconstruction, which helped to found the department's Institute of Reconstructive Surgery in 1955; the Foundation has provided nearly \$50 million since the Institute's inception. The Foundation recently gave the Institute a \$4 million grant toward the design and construction of a new state-of-the-art clinical facility. •



DR. NUDLER RECEIVES 2010 BLAVATNIK AWARD

Evgeny Nudler, PhD, the Julie Wilson Anderson Professor of Biochemistry, was awarded the New York
Academy of Science's prestigious 2010
Blavatnik Award for Young Scientists for his highly innovative, distinguished, and interdisciplinary achievements in science and research. The award includes \$25,000 in unrestricted funds, which is provided to support promising scientists early in their careers.

Currently Dr. Nudler and 12 members of his research team are involved in numerous studies in diverse fields. In September 2009, Dr. Nudler published a breakthrough study in *Science* that revealed how dangerous bacteria such as *Staphylococcus aureus* and *Bacillus anthracis*, the causative agent of anthrax, can thwart antibiotics.

A separate project under his guidance is investigating the mechanism for the critical cellular process of transcription, which creates RNA templates for protein production. His lab has discovered RNA molecules, dubbed riboswitches, that can control gene expression by directly sensing the presence of various metabolites.

Another research effort is focusing on protective cell components known as heat shock proteins, and the lab has identified the main factors that spur production of these proteins in response to stress. Finally, a project on aging, funded in part by Timur Artemyev, is examining how bacteria can affect the lifespan of the roundworm Caenorhabditis elegans.



DR. SHAH NOMINATED COMMISSIONER OF STATE HEALTH DEPARTMENT

Nirav R. Shah, MD, MPH, assistant professor of medicine at NYU Langone Medical Center, has been selected by New York State Governor Andrew M. Cuomo to serve as the new commissioner of the state's Department of Health. Dr. Shah's expertise in using systems-based methods to improve patient outcomes and electronic health records and other means to improve the effectiveness and efficiency of care



will serve him well in his new position. He is "a nationally recognized thought leader in the very methods needed to transition to the future of lower-cost, more patient-centered health care," according to the announcement by Governor Cuomo. A native of Buffalo, Dr. Shah received his undergraduate education at Harvard University and his MD and MPH degrees from the Yale University School of Medicine. He has published more than 90 peer-reviewed articles and received over \$4.5 million in research funding.

A Pioneering Cardiothoracic Surgeon

Rosalyn Scott, MD, recalls the challenges of academic medicine and motherhood.

IN 1977 ROSALYN SCOTT, MD ('74), became the first African American woman in the country to start residency training in cardiothoracic surgery. During the interview at Boston University School of Medicine, the department head offered her the job if she could start that July. Although she had a toddler at home and had just learned that she was pregnant again, and had still to complete her general surgery residency, she took the job for a very practical

reason: "I didn't want to lose this opportunity." Later she found out that if her boss had known she was pregnant, he would not have hired her.

"It was not so hard to do surgery when you are nine months pregnant," Dr. Scott admits. "It turned out that the chair of surgery was equally rotund," she adds with a wry smile. "People asked if I could reach the operating table. I told them that Dr. Williams could and I didn't think I would ever be as large as Dr. Williams. I could always borrow his scrubs if necessary!"

Dr. Scott had her baby, finished her training, and went on to the University of Texas Medical School in Houston as an assistant professor of surgery. In 1983 she joined the University of California, Los Angeles, and the Charles R. Drew University of Medicine and Science, where she spent most of her career as

chief of the division of cardiothoracic and vascular surgery.

At a recent interview, in dark slacks and a bright coral-red jacket, umber beads at her throat, dark hair cropped short, Dr. Scott recalled the challenges of motherhood as a surgery resident and then later as an academic surgeon, when life was never predictable. "When my girls were young, I'd never say no, but I'd always say, 'Let's have a fallback plan.'"

A consummate diplomat, Dr. Scott will not comment about the demeanor of her colleagues when she was first starting out,



NYU PHYSICIAN WINTER 2010-2011



At NYU Langone, nearly half of new surgical faculty are women. Since becoming interimchair of the Department of Surgery in 2005, now-Chair H. Leon Pachter, MD, has recruited 39 new faculty members, 18 of whom are women, shown surrounding him in a recent photo.

except to say that there was a lot more "throwing of instruments" back then. Colleagues describe Dr. Scott—a founding member of both the Association of Black Cardiovascular and Thoracic Surgeons and the Society of Black Academic Surgeons—as a fearless and thoughtful leader in a profession dominated by men.

"I thought, here's this field, heart surgery, which is absolutely male dominated, and she stands out in a second as being completely different and wonderfully creative, and always wise beyond her years," says Peter Greene, MD, of Johns Hopkins School of Medicine, who got to know Dr. Scott in the mid-1980s through the Society for Thoracic Surgeons, when they were both young heart surgeons.

"SHE'S U

"SHE'S

One of those she guided was trauma and critical care surgeon Anthony Charles, MD, a Nigerian native, who, when Dr. Scott took him under her wing, had just arrived in Los Angeles from the United Kingdom. "She facilitated my whole academic career. She was incredible," says Dr. Charles, now an assistant professor of surgery at the University of North Carolina at Chapel Hill School of Medicine.

When Dr. Charles started his job search, Dr. Scott told him, "I think you should look at North Carolina. I'm going to call up the chair and tell him you're coming." At the time Dr. Charles wasn't even considering North Carolina. "I already had two other job offers," Dr. Charles says with a laugh. "But she was right."

A native of Newark, New Jersey, and the only child in a family of medical professionals, Dr. Scott always knew she

wanted to be a physician. Her uncle, Arthur Falls, MD, was a thoracic surgeon, who, in the 1920s, worked at Provident Hospital in Chicago, the only hospital in the city that accepted African American physicians and patients. He later became president of that hospital. Her father, Roy Proctor, DDS, had gone to dental school at New York University College of Dentistry. "I'd always heard about NYU," she says. He was 48 when she was born and had his first heart attack when she was in the third grade. But he lived long enough to see her go to medical school, urging her to become a heart surgeon because he believed that it was a good niche for his daughter.

"SHE'S USED TO GOING INTO A FIELD LIKE CARDIOTHORACIC SURGERY, WHICH IS VERY OLD SCHOOL

AND NOT DIVERSE, AND BEING COMFORTABLE THERE HERSELF AND GUIDING IT ALONG A BETTER PATH."

Before attending NYU School of Medicine, Dr. Scott majored in chemistry at Rensselaer Polytechnic Institute in Troy, New York. "There were 5,000 men on campus and about 100 women," she says. "I started in the first class that had a place for women to stay on campus. Now there's a female president who is African American."

Despite the increasing numbers of women in many medical fields cardiothoracic surgery remains an almost exclusively male club. In 2009 women made up only 3.3 percent of the membership of the Society of Thoracic Surgeons. "I think it is clear that women have had a harder time in the field than men, though opportunities are a little better now," Dr. Scott says. "Until you're 20 to 30 percent of a field, you're at a disadvantage." African American women cardiothoracic surgeons are rarer still, with fewer than a dozen working in the U.S. today. continued on page 32

KEITH KRASINSKI, MD

KEITH KRASINSKI, MD, professor of pediatrics and environmental medicine, died October 2, 2010, after a two-year struggle with an especially aggressive type of skin cancer. He was 61 years old. Dr. Krasinski dedicated his career to caring for children infected with HIV and to preventing transmission of the virus from mothers to their newborns. In 1999, as a result of his groundbreaking work with Assemblywoman Nettie Mayersohn of Queens, the state of New York established a screening program to detect newborns at risk for HIV and offer treatment to mothers and babies.

"Keith really fought hard for the legalization of routine testing of newborns," says his longtime colleague and friend Robert Holzman, MD, professor emeritus of medicine. Early in the AIDS epidemic, privacy concerns limited the testing of mothers and babies at risk, leaving many of them untreated. "So it was not a popular position," Dr. Holzman says, "but he saw what was needed and worked very hard in the



political process to achieve it."

A native of suburban Chicago, Dr. Krasinski joined NYU School of Medicine in 1981. He earned his MD from the

University of Illinois School of Medicine and completed a pediatric residency and an infectious disease fellowship at the Children's Hospital at the University of Texas Southwestern Medical School, In 1991, he co-founded and served as director of the Lower New York Consortium. a Ryan White and New York AIDS Institute-funded network of providers in lower Manhattan and Staten Island that offered coordinated care and access to clinical trials for HIV-infected women, children, youth, and their families. A member of the New York State AIDS Advisory Council, he helped establish guidelines for the care and prevention of pediatric AIDS. In 1997, he became director of NYU School of Medicine's Institutional Review Board, which monitors research ethics, a position he held for 10 years. For 25 years he served as deputy hospital epidemiologist for Bellevue Hospital Center, assuming the top post after Dr. Holzman retired in 2007.

Dr. Krasinski is survived by his wife, Debra, and three daughters, Katie, Annie, and Stephanie. ●

A PIONEERING CARDIOTHORACIC SURGEON

continued from page 31

Remarkably, Dr. Scott never viewed her gender or her race as impediments. "That's not to say I'm naive about it. But if you put that in front of everything you say or do, you probably become pretty paralyzed. You just have to go do the best you can do."

Two years ago she left California to take the positions of chief of surgery at the Dayton VA Medical Center and professor of surgery at Wright State University Boonshoft School of Medicine in Ohio. Today, as part of a nationwide team designing the most advanced medical simulation center yet for the national Veterans Affairs in Orlando, Florida, Dr. Scott directs the Dayton VA Medical Center's simulation center and is designing

the renovations for a 17,000-square-foot center at the VA, where she is also associate chief of staff for medical education. She also has a faculty appointment in the College of Engineering and Computer Science at Wright State.

Besides the robotic "patients," much has changed in medical education since her own training in the 1970s. "Today, here in our [surgery] residency program, we're very female friendly," she says. "We have three or four babies a year."

Indeed, she argues that surgery is really women's work. "Surgery is an exercise in perfection and compulsion," she said in the 1999 short documentary *Women Are Surgeons*, produced by the National Institutes of Health Office of Science

Education. "Basically, I think cutting and sewing should be a woman's profession. It was really, to me, a natural extension of what women do anyway. Men have to learn how to cut and sew."

Married to businessman Clarence Scott, Dr. Scott has two daughters, one of whom is a lawyer in California; the other recently finished a postdoctoral fellowship in public health at the University of North Carolina at Chapel Hill and now works at the U.S. Health Resources and Services Administration in Washington, D.C.

What career advice did she give her own adult daughters? "I told them they should do whatever they wanted to do, but make sure they get terminal degrees in their field!" • —AUBIN TYLER

NYU PHYSICIAN WINTER 2010-2011

The Gift of a Lifetime

elping others is life's driving force for Eugene Kalnitsky, MD,'54, a retired physician and air force officer, and his wife, Linda, a former teacher and coordinator of volunteers for local Florida charities.

Eugene completed his medical degree and residency in internal medicine at NYU School of Medicine. He was especially affected by his classes with Samuel Standard, MD, who opened Eugene's eyes to the value of patient-centered care.





Linda Kalnitsky and Eugene Kalnitsky, MD, `54

With the compassion they have shown throughout their lives, and in gratitude for Eugene's medical education, Eugene and Linda made the gift of a lifetime through a charitable annuity.

Legacies like theirs help transform the future of medicine.

You, too, can make a difference at NYU Langone.

To learn more about how to create your own legacy, please contact Marilyn Van Houten at 212.404.3656 or email her at marilyn.vanhouten@nyumc.org.



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