To combat mood disorders, a new professorship and seminal research

Hope Furth and her husband John, of the Yale College Class of ’52, are passionate about advancing understanding of developing brains because of their devotion to children’s causes and excitement about emerging science. But their strongest motivation is even closer to home.

Searching for information that would help two of their grandchildren with special needs, they met the School of Medicine’s Hilary Blumberg, M.D., professor of psychiatry, of diagnostic radiology, and in the Child Study Center, and director of Yale’s Mood Disorders Research Program. “We were terribly impressed by the research that she’s doing,” said John Furth. “Hilary is looking for answers to the questions that most concern us: What is the cause of very serious mental and emotional problems in children? And how do we develop effective treatments?”

In December the Furths created the John and Hope Furth Professorship of Psychiatric Neuroscience with a $3 million gift. Blumberg has been named the inaugural Furth Professor. “This is a partnership between people with a passion for knowledge and a belief that it can improve lives,” said Robert J. Alpern, M.D., dean and Ensign Professor of Medicine. “The Furths’ vision advances neurodevelopmental psychiatry and promises to make a tremendous difference for people with mood disorders.”

Researchers like Blumberg have brought psychiatry to a “transitional moment,” said John H. Krystal, M.D., the Robert L. McNeill Jr. Professor of Translational Research and director of Yale’s Mood Disorders Research Program. “The Furths have created a new professorship and endowed chair that will help shape the future of this field.”

Building a legacy of support for science

In supporting neuroscience, a five-generation Yale family honors a patriarch

Asked to reflect on the life and career of her husband, Pat Klingenstein smiles warmly. “John has always been his own man, speaking his mind, and following his own path wherever it has led. And, I’m proud to say, that path has led to a career of real significance.” In talking about John Klingenstein, now 86, Pat gets to the heart of a man whose influence on medical science has been undeniable.

Inspired by his grandfather Frederick Adler, an 1891 graduate of Yale College, and an uncle, Milton Steinbach, of the Class of 1924, Klingenstein graduated from Yale College in 1950 as an engineering major. For more than three decades, he worked alongside his brother Frederick, Yale College ’53, who later succeeded Joseph as CEO of diagnostic radiology at Yale-New Haven’s Musculoskeletal Center. And in July, Jean-François (Jeff) Geschwind, M.D., an internationally known radiologist and a recognized leader in the field of liver cancer, joins the faculty as chair of the Department of Diagnostic Radiology at the School of Medicine and chief of diagnostic radiology at Yale-New Haven Hospital (YNHH).

Geschwind comes to Yale from The Johns Hopkins University (JHU) School of Medicine, where he was vice chair of its Russell H. Morgan Department of Radiology. “I’m proud to say that John Klingenstein (second from left) held by Pietro De Camilli (right) honoring John Klingenstein (second from left). Also pictured are Dean Robert Alpern (left) and John’s wife, Patricia Klingenstein.

The School of Medicine has been a beneficiary of the Klingenstein family’s support of medical science for more than three decades. The family’s most recent gift supports an endowed chair held by Pietro De Camilli (right) honoring John Klingenstein (second from left). Also pictured are Dean Robert Alpern (left) and John’s wife, Patricia Klingenstein.

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In supporting neuroscience, a five-generation Yale family honors a patriarch

As a partner for many years, he worked alongside his brother Frederick, Yale College ’53, who later succeeded Joseph as CEO of diagnostic radiology at Yale-New Haven’s Musculoskeletal Center.

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To support research on developing brains, Hope and John Furth have endowed a new professorship in psychiatric neuroscience.
A commitment to care, basic science

Clinical trial access means better patient care and more clinical research

Early cancer drugs killed indiscriminately, going after the body’s healthy cells as relentlessly as its cancerous ones. Today, hundreds of anticancer drugs target the specific genetic mutations that drive cancer. Pinpointing those mutations and pairing patients with targeted drugs has become standard at Salkow Cancer Hospital at Yale-New Haven, thanks in large part to the work of Thomas J. Lynch Jr., M.D., and Jonathan Sackler Professor of Medicine.

According to the National Cancer Institute (NCI), nearly 41 percent of Americans will be diagnosed with cancer in their lifetimes. Growing up in New Jersey as the son of a hematologist, Lynch says, “I knew even as a kid that I wanted to make [addressing] that my life calling.” Lynch returned to Yale in 2009 as director of Yale Cancer Center (YCC) and physician-in-chief at Salkow Hospital. He has overseen the standardization of molecular profiling in cancer patients, the establishment of an early drug development unit, and the re-designation of YCC as a comprehensive cancer center by the NCI.

Lynch is also committed to advancing treatment by improving patients’ access to clinical trials. Today YCC has more than 200 open clinical trials, and Lynch has established Salkow Care Centers around Connecticut to bring greater access to patients. Citing progress made in breast cancer and melanoma outcomes, he hopes these trials will someday lead to cures. “It’s a daunting challenge,” Lynch says, “but unless we make that goal, we’re never going to get there.”

Endocrinologist honored with Leffell Prize praises his staff first

Silvio Inzucchi, M.D., professor of medicine and medical director of the Yale Diabetes Center, is the 2015 recipient of the David J. Leffell Prize, an award given to individuals who demonstrate high ethical practice and individual commitment to excellence in patient care.

Inzucchi is director of the Yale Affiliated Hospitals Program and associate chief for clinical affairs in the Section of Endocrinology. He received his medical degree from Harvard Medical School and completed an residency and internship in internal medicine and a postdoctoral fellowship in metabolism at Yale-New Haven Hospital.

The Leffell Prize was established in 2008 with a gift from David J. Leffell, M.D., the David P. Smith recipient of the David J. Leffell Prize. He is the 2015 Sackler Professor of Medicine at the School of Medicine and the School of Management, has been named the nation’s 38th surgeon general.

Murthy was officially sworn in by Health and Human Services Secretary Sylvia Mathews Burwell in December. “I applaud the Senate for confirming Vivek Murthy to be our country’s next Surgeon General,” said President Barack Obama in a White House statement. “As ‘America’s Doctor,’ Vivek will hit the ground running to make sure every American has the information they need to keep themselves and their families safe.”

After graduating Yale, Murthy co-founded two organizations and joined the national leadership of the Smoke Free Schools Campaign. He is an attending physician and an instructor in medicine at Harvard Medical School. Howard P. Forman, M.D., professor of diagnostic radiology and director of the Cancer Center, co-founded TrialNetworks, an online platform for coordinating clinical trials, which was acquired by DrugDev in 2014. In the lead-up to the Affordable Care Act, he served as president and co-founder of Doctors for America, which works to provide the healthcare access to the general public.

Murthy, the first Yale alumnus to serve as U.S. Surgeon General, completed his residency in internal medicine at Boston’s Brigham and Women’s Hospital. He is an attending physician and an instructor in medicine at Harvard Medical School. Howard P. Forman, M.D., professor of diagnostic radiology and director of the Cancer Center, co-founded TrialNetworks, an online platform for coordinating clinical trials, which was acquired by DrugDev in 2014. In the lead-up to the Affordable Care Act, he served as president and co-founder of Doctors for America, which works to provide the healthcare access to the general public.

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Knocking the wind out of lung disease

State-of-the-art research programs and an emphasis on bioinformatics are pushing pulmonary research at Yale forward

The January unveiling of President Obama's Precision Medicine Initiative in the White House was able to identify which treatments will be most effective for which patients—highlights the increasing importance of personalized medicine today. But while physicians and scientists have made strides in tailoring treatments to patients with cancer and diseases caused by mutations in a single gene, similar advances in other diseases have lagged behind.

Members of the School of Medicine's Section of Pulmonary, Critical Care and Sleep Medicine (PCCSM) are changing that paradigm. By applying high-throughput RNA sequencing technologies and genomic methods to the study and treatment of chronic lung diseases like pulmonary fibrosis and asthma, they are unraveling the underlying mechanisms of these illnesses and developing targeted approaches to help them.

Pulmonary fibrosis is a respiratory disease in which uncontrolled scarring damages the lungs and impairs breathing. Patients typically survive three to five years after being diagnosed, but as with many diseases, how well they can do vary widely. Until recently, doctors had nothing to offer in the way of treatment short of a lung transplant.

Research by Naftali Kaminski, M.D., the Boehringer Ingelheim Pharmaceuticals, Inc. Professor of Medicine and chief of PCCSM, has shed light on the disease, revealing that it is an active process of destruction and rebuilding with many pathways. Kaminski's approach to developing personalized treatment has focused on analyzing gene expression in pulmonary fibrosis to help predict which patients progress more quickly. His lab identified a family of microRNAs—small RNA molecules which do not code for proteins but instead regulate which genes are turned on and off—that are changed in patients with pulmonary fibrosis.

Last year he showed that supplementing mice with a molecule that mimics miR-29a, a microRNA decreased in fibrosis, not only blocked fibrosis but could potentially reverse it. With a new five-year, $7.1 million Centers for Advanced Diagnostics and Experimental Therapeutics (CADET) grant from the National Heart, Lung and Blood Institute (NHLBI), Kaminski's team is taking its findings to the next level. Awarded last July, the grant is enabling the team to develop the evidence needed to support the use of miR-29 mimics as FDA-approved drugs.

They will evaluate miR-29 as a therapeutic agent for pulmonary fibrosis in humans and identify biomarkers to show which patients will benefit from the treatment. "The aim in five years is to have both a molecule [for drug development] and a target population," he said.

Kaminski’s passion for pursuing personalized medicine is shared across his section by colleagues both junior and senior. Working in the Kaminski lab, Jose Herzao-Maya, M.D., is using microRNAs to identify a gene expression signature in the blood of patients with pulmonary fibrosis that indicated which patients’ disease would likely progress more quickly. Such information could be useful in light of two drugs recently approved by the U.S. Food and Drug Administration that can slow disease progression.

"We think that the use of gene expression profiles in the blood of patients with pulmonary fibrosis may be helpful to actually get these patients on the drugs faster and to predict when lung transplants will be needed," Herzao-Maya says. Geoffrey L. Chupp, M.D., associate professor of medicine, uses an approach similar to Kaminski’s to treat asthma patients. He developed a system for collecting sputum that provides a window into the lung. After isolating cells from the airway and analyzing the gene expression of those cells, he has identified three sub-groups of patients whose genetic profiles correlate with the severity of their disease. He has also identified a gene expression signature in the blood that he has validated in both adult and pediatric asthma patients.

"In asthma there's a revolution of [therapeutic] biologics coming down the pipeline," says Chupp, also director of the Yale Center for Asthma and Airways Disease and the Pulmonary Function Laboratory at Yale-New Haven Hospital. He and his colleagues are conducting more than a dozen clinical trials to study these biologics—antibody-based therapies that bind to specific targets—and identify which therapies work best in which patients. Chupp is also the recipient of an NHLBI-funded CADET grant that he is using to develop a biologic that binds to and blocks VLA-4, a protein that is typically elevated in those with severe asthma.

Kaminski and Chupp are co-directors of the Center for Precision Pulmonary Medicine (P2MED), a new program that houses genomic technology and expertise within PCCSM. Technology alone cannot, of course, provide the kinds of insight required for precision medicine. "The idea is to create a skilled critical mass of pulmonary physicians—scientists who are well versed in clinical medicine, as well as in genomics, bioinformatics and computational biology—the trade tools of precision medicine" Kaminski says.

Genetic analysis generates a massive amount of data—what scientists call “big data”—that require expertise to decipher, a process central to developing personalized treatments. "When you look at outcome data you can gain some insights, but you don't know exactly why some patients are responding while others are not," says Xiting Yan, Ph.D., assistant professor of medicine and director of the P2MED Data Analysis and Bioinformatics Hub. "Big data can provide hints about why and how patients respond to a drug."

"Big data can provide hints about why and how patients respond to a drug."

— Xiting Yan

Members of the School of Medicine's Section of Pulmonary, Critical Care and Sleep Medicine (PCCSM) include (from top left) Jose Herzao-Maya, Argyrios Tzouvelekis, Tony Woolard, Geoffrey Chupp, Milica Vuk-mirovic, Vera Nezgovorova, Farida Ahangari, Qing Liu, Adrian Wyllie, Keji Sakamoto, Giuseppe Delulio, and Chief of PCCSM Naftali Kaminski.
In 2007 Geschwind was promoted to faculty. 

He completed an internship and residency in orthopaedics and a fellowship in orthopaedic oncology, both at Mayo Graduate School of Medicine. At her Mayo practice, O’Connor treated orthopaedic oncology patients and adults needing complex reconstructive surgeries for degenerative joint diseases. She is co-investigator on a pilot study to determine if injecting a patient’s stem cells into his or her knee joint will slow the progression of arthritic changes. Similar to Yale Cancer Center, the new Musculoskeletal Center will coordinate interdepartmental clinical and research programs at the medical school and hospital. As a clinical and research center, it brings together specialists in orthopaedics, neurosurgery, neurology, rehabilitation, biomedical engineering, and other specialties to provide a wide range of services, including joint replacement, pain management, and advanced treatment for arthritis, spine disorders, multiple sclerosis, Parkinson disease, and other conditions.

“Mary O’Connor and Jeff Geschwind bring extraordinary strengths and track records to the medical school,” said Robert J. Alpern, M.D., dean and Ensign Professor of Medicine. “I look forward to the growth of these programs under their leadership.”

OUT & ABOUT

November 17
The New Haven Mental Health Outreach for Mothers (MOMS) Partnership held a press conference at the Stop & Shop supermarket on Whalley Avenue to announce an expansion following a new $3.7 million federal grant. Under the direction of Megan V. Smith, Ph.D. (left), assistant professor of psychiatry, the project has provided mental health services to 3,000 low-income single mothers in New Haven.

December 9
A celebration of the election of W. Mark Saltzman, Ph.D., Goizueta Foundation Professor of Chemical and Biomedical Engineering, to the Institute of Medicine was held in the medical school’s Historical Library. Pictured are (from left) Dean and Ensign Professor of Medicine Robert J. Alpern, M.D.; Saltzman, who is also chair of the Department of Biomedical Engineering, and T. Kyle Vanderlick, Ph.D., dean of the School of Engineering and Applied Science and the Thomas E. Golden Jr. Professor of Chemical and Environmental Engineering.

March 20
Each spring, medical students across the country eagerly await Match Day when students receive word of acceptance in residency training programs. 1. Jennifer Guo (left) and Ruth Wang’oudou. 2. Emily Thomas (left) and classmate Jennifer Quon. 3. (From left) Auguste H. Fortin VI, M.D., MPH, associate professor of medicine; Marcella Nunez-Smith, M.D., MHS, associate professor of medicine and of epidemiology and public health and director of the Equity Research and Innovation Center (ERIC); Teri-Ann M. Thompson, Ph.D., associate research scientist, and Damaris Faustine, coordinator for ERIC. 4. Serene Chen and Daniel Hart, M.D., a resident in emergency medicine.

September 11
A gathering marked the establishment of The Daniel Jordan Fiddle Foundation Adult Autism Research Fund by the medical school’s Child Study Center (CSC) and The Daniel Jordan Fiddle Foundation (TDJFF) to support research projects related to adults living with autism spectrum disorders. (From left) Roger J. Jou, M.D., Ph.D., assistant clinical professor in the CSC; Linda J. Walder, J.D., founder and executive director of TDJFF; Kevin Pelphrey, Ph.D., Harris Family Professor of Child Psychiatry in the CSC and professor of psychology, Fred R. Volkmar, M.D., Irving B. Harris professor in the CSC and professor of pediatrics, psychiatry, and psychology, and Frederick J. Fiddle, founder and treasurer of TDJFF.
**The anatomy of autoimmune disease**

By analyzing data from dozens of genomic studies, a team of scientists zeroes in on the molecular links among related diseases

What do diabetes, Crohn’s disease, psoriasis, and multiple sclerosis have in common? From the outside, not much: they affect different organs and have vastly different symptoms. But each is an autoimmune disease, and new research, identifying genes and cell types responsible for such diseases, reveals just how much they have in common.

“What we showed is that, to some extent, autoimmune diseases are one fundamental entity with many variations,” says David A. Hafler, M.D., chair and the William S. and Lois Stiles Edgerly Professor of Neurology, professor of immunobiology, and a senior author of the paper.

In all autoimmune diseases, the body’s immune system gangs up on a person’s own cells. If the immune system attacks skin cells, the redness and itching of psoriasis can result; if it attacks pancreas cells, type 1 diabetes; if it turns against cells lining the intestines, ulcerative colitis or Crohn’s disease. As a whole, autoimmune diseases—which affect an estimated 50 million Americans—are tricky to treat, and their causes are poorly understood.

Previous research on individual autoimmune diseases have used genome-wide association studies (GWAS) to narrow down which areas of DNA within the human genome are linked to disease. But the areas of the genome identified in GWAS can contain many genes.

Hafler and his colleagues at the Broad Institute of MIT and Harvard wanted to home in on specific genes linked to autoimmune diseases. To do so, they analyzed 19 previous GWAS studies, spanning 21 different diseases, using new software and data analysis techniques. Says Hafler, “We went from a large region of DNA that’s implicated in a disease to the precise gene change that’s likely responsible. I call this a post-GWAS understanding of disease.”

By mapping certain molecular features within these areas, the team discovered that many autoimmune diseases aren’t caused by variations in genes that encode proteins, but by changes to “enhancers,” elements in the DNA that can turn on nearby genes. If an enhancer is altered, a whole slew of genes it controls can be flipped on or off at once. In the case of many autoimmune diseases, the scientists reported February 19 in the journal *Nature*, the affected enhancers go on to affect immune genes. And, they found, many genes overlapped between diseases—affecting both Crohn’s disease and rheumatoid arthritis, for example.

But the team didn’t stop with the identification of genes and enhancers associated with the autoimmune diseases. Next, they studied which cell types each genetic change was active in. “If you have a genetic change in a region where the DNA is tightly wound up, that change is unlikely to make a difference to that particular cell,” Hafler explains. But in other cells, the DNA containing the genetic variant could be more “open” and thus accessible for DNA transcription, suggesting that the variant is influencing the cell’s function.

Some findings were expected: the DNA regions linked to ulcerative colitis, for instance, were activated in immune cells and mucosal cells lining the digestive system. But others were more surprising—the genetic variants associated with multiple sclerosis seemed to be inactive in brain cells, only making a difference in immune cells themselves.

“What this work does is provide, for the first time, a landscape as to how genetic variants are causing autoimmune disease,” Hafler says. “That landscape—the molecular events and cell types involved—is a critical step in understanding disease.”

While that step of pinpointing important genes and cell types requires more refinement to more fully reveal the cause of autoimmune diseases, it does pave the way toward drugs that can block the immune system from its unwarranted attack, Hafler says. It also shows just how effective new techniques can be at moving from GWAS results to specific genetic changes that cause disease. And that, he says, is useful for studying not only autoimmune disease, but everything from heart disease and Alzheimer’s to cancer.

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**Yale’s partnership with Johnson & Johnson promotes data sharing**

In January 2014, the Yale Open Data Access (YODA) Project began a collaboration with Johnson & Johnson to establish an independent process promoting data sharing. Since then the YODA Project has fielded more than a dozen requests for clinical data from researchers and played a key role in pushing the clinical research field toward a more open way of operating.

Part of Yale’s Center for Outcomes Research and Evaluation (CORE), the YODA Project began in 2011 with the mission of promoting scientific inquiry and lowering barriers to data access. The partnership with Johnson & Johnson gives the YODA Project all decision-making authority over the release of the company’s pharmaceutical clinical trial data. The idea is to make this data available to researchers who can put it to good use. But there is also a larger aim, says Joseph S. Ross, M.D., M.H.S., co-director of the YODA Project: “We’re trying to create a paradigm shift in the way clinical research is done,” Ross says. “It’s about honoring the commitment the patients have made to research, [and] about making sure all of the evidence that could potentially inform a decision about whether a patient should use or a physician should prescribe a given therapy is available.”

Investigators requesting data must submit a research proposal to the YODA Project. The application and review process is key to the idea of promoting responsible research, says Ross, also associate professor of medicine and assistant professor of public health. Studies have found that up to half of all clinical data are never published —data that could move medicine forward. The YODA Project aims to shift this paradigm, and to take decision-making power about data sharing “out of the hands of these large companies that had a major investment in what happens with the data,” Ross says. In January of this year, on the same day that Johnson & Johnson announced it expanded its collaboration with the YODA Project to include data from clinical trials of medical devices, a committee of the Institute of Medicine (IOM) called on stakeholders in the medical research process to “foster a culture where data sharing is the expected norm.” The committee recommended that all stakeholders in clinical trials commit to “responsible strategies aimed at... // Sharing (page 7)
Several other organizations,“ says Daniel Greif, Sandia National Laboratories, "because we wanted a partner with a prominent track record that is known

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Hormones such as insulin and growth factors mediate their many physiological responses by activating a family of proteins known as tyrosine kinases. Because of their roles as “drivers” of many cancers, tyrosine kinases have become a favorite target within the field of personalized cancer therapy: as of today, 20 cancer drugs targeting them have now been approved by the FDA. Yale’s Joseph Schlessinger, Ph.D., chair and the William H. Prusoff Professor of Pharmacology, has researched the underpinnings of these enzymes for more than three decades.

The work of Schlessinger and two colleagues has garnered them the 2015 Frontiers of Knowledge Award in Biomedicine from the Madrid-based Fundación BBVA. Schlessinger shares the award, which carries a €400,000 cash prize, with Tony Hunter, Ph.D., of the Salk Institute, and Charles L. Sawyer, M.D., of Memorial Sloan Kettering Cancer Center. According to the Fundation’s awards panel, they helped blaze the “path that led to the development of a new class of successful cancer drugs.” For his part, Schlessinger identified how receptor tyrosine kinases are activated, how mutations in receptor tyrosine kinases cause cancer, and how tyrosine kinases can be blocked to treat cancer. He elucidated a mechanism, known as receptor dimerization, that explains how receptor tyrosine kinases are activated when a molecule binds at the cell surface. “We found a mechanism for information flow from outside the cell to the interior of the cell, and how this mechanism was hijacked by cancer,” Schlessinger says. “We also uncovered the way these signaling pathways operated, and it became clear that if we developed inhibitors we could have drugs to treat cancer.”

Schlessinger, also director of the Yale Cancer Biology Institute, has had an exceptional record of research “that reflects a creative experimental approach, spanning molecular, genetic, and structural studies to explore fundamental and important questions in biomedical science,” said Dean and Ensign Professor of Medicine Robert J. Alperton, M.D. “He then translated these discoveries into the development of Food-approved drugs through companies that he founded, Sugen, Plexxikon, and Kollanet.”

Schlessinger notes that while most drugs in the new class of targeted therapies cannot be considered cures, “they do extend by months, years, and sometimes even decades the survival of complicated disease, and the challenge now is how to overcome resistance.”

In 1979 the field experienced a breakthrough with the discovery of the tyrosine kinase that enables the cell to produce its environment. Ligon, a seminal paper, opens a specific door in the cell membrane and induces a cascade of signals that work to regulate cell proliferation and other processes. The work of the three scientists has shown how aberrant tyrosine phosphorylation enables some cancers and other diseases.

Schlessinger sits on the editorial boards of leading journals such as *Environ, Cell, and Molecular Cell*. He is a member of the National Academy of Sciences, the National Academy of Medicine, the American Academy of Arts and Sciences, and the European Molecular Biology Organization. In 2001, the Institute for Scientific Information listed him among the top 30 most cited scientists of the 1990s.

**Chair of pharmacology honored by Spanish foundation**

Hilary Blumberg

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**Hormones such as insulin and growth factors mediate their many physiological responses by activating a family of proteins known as tyrosine kinases. Because of their roles as “drivers” of many cancers, tyrosine kinases have become a favorite target within the field of personalized cancer therapy:** as of today, 20 cancer drugs targeting them have now been approved by the FDA. Yale’s Joseph Schlessinger, Ph.D., chair and the William H. Prusoff Professor of Pharmacology, has researched the underpinnings of these enzymes for more than three decades.

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