Morgan Huse (right) with research technician Niels Bantilan.

Summary

A glimpse into the minds of three young faculty members: immunologist Morgan Huse, biostatistician Ronglai Shen, and medical oncologist Diane Reidy-Lagunes.

For more than a century, Memorial Sloan Kettering has been improving and extending the lives of cancer patients through pioneering research, an undertaking that would run dry without the fuel provided by innovative minds. Here, we steal a glimpse into the minds of three of the Center's young faculty members: Morgan Huse, of the Sloan Kettering Institute's Immunology Program; Ronglai Shen, of Memorial Sloan Kettering's Department of Epidemiology and Biostatistics; and Diane Reidy-Lagunes, of the Department of Medicine.

Immunologist MORGAN HUSE has been hooked on biochemistry since his college years. “I’ve always been taken with the idea that we are all aggregates of tiny protein machines,” he says. “Nowadays this notion might seem somewhat old-fashioned, but I don’t seem to be getting over it.”

Yet the way he and his colleagues are studying cell signaling — processes that allow a cell to receive and respond to molecular messages in its environment — is anything but old-fashioned. The lab uses a combination of newfangled techniques such as protein engineering and videomicroscopy to probe some of the immune system’s best-kept secrets.

Currently, Dr. Huse and colleagues are studying cell signaling in cytotoxic T cells and natural killer (NK) cells, two immune cell types that share the ability to recognize and kill foreign invaders — such as virally infected cells or cancer cells — while leaving the body’s normal cells and tissues unharmed.

“The mechanisms that enable T cells or NK cells to selectively destroy their targets are not well understood,” Dr. Huse notes. “In my lab, unraveling these mechanisms boils down to visualizing a single immune cell as it responds to various signals in the second-to-minute timescale.”

Research in his lab also boils down to investigating the rapid effects some signaling events have on cell polarization, a process in which a cell reshapes its basic structures to establish a direction — a “front” and a “back” end.

For example, a cytotoxic T cell can kill a tumor cell it has encountered by attaching to the tumor cell and releasing toxic substances. When the two cells connect, the T cell receives signals through receptors on its surface that cause it to adjust its orientation so that it can release toxins exclusively toward the tumor cell — seemingly in an effort to avoid killing normal cells that might exist nearby.

To investigate such events, which occur very rapidly, the investigators have developed experimental tricks that allow them to manipulate and visualize signal transduction processes in individual cells under the microscope. For example, using a protein engineering approach called photocaging, they can induce T cells to undergo polarization by exposing the cells to a flash of ultraviolet light.

Dr. Huse offers an analogy: “Visualizing cell-signaling events in immune cells is like trying to film a toddler doing something. The moment you focus the camera, your toddler will already have wandered off to do something else.” However, in the context of cell-signaling studies, protein engineering makes it possible to control the behavior of immune cells so that they do the right thing at the right time, he explains.

“The immune system is tuned with tremendous precision,” he continues. “If we better understood the processes that bring about this fine-tuning, we could ultimately develop more-sophisticated ways to manipulate these processes in the clinic and thereby fine-tune our therapeutic approaches.” For example, in cancer patients who receive bone marrow transplants from donors, it might be possible to harness the beneficial anticancer activities of NK cells and T cells while curbing side effects that potentially could result in dangerous immune complications.

When he joined Memorial Sloan Kettering in 2007, Dr. Huse was relatively new to the field of immunology, which he entered as a postdoctoral fellow working in the laboratory of Mark Davis at Stanford University. Prior to Stanford, he earned his PhD degree in structural biology from The Rockefeller University under the mentorship of John Kuriyan.

“What I most admire about John and Mark is their passion for science in its broadest sense,” Dr. Huse notes. “They taught me that borders between disciplines can and should be crossed, and that what really matters is being a good scientist — whether you call yourself a structural biologist, an immunologist, a gene hunter, or anything else.”

Biostatistician RONGLAI SHEN was raised on a university campus in Shanghai. Her mother, a professor of chemical engineering, influenced her decision to become a scientist.

Ronglai Shen (right) conferring with biostatistician Venkatraman Seshan, one of her collaborators.

“My mother never told me what to do with my life, but her dedication in pursuing an academic career was a great source of inspiration for me,” Dr. Shen says. Her second role model was Jianxiong Wu, a mid-20th-century physicist nicknamed “the Chinese Marie Curie,” whose biography Dr. Shen read in college, enthralled.

In 1999, Dr. Shen moved to the United States for her graduate training in biology at the University of Michigan. There, she investigated genetic events that may cause developmental defects in the roots of *Arabidopsis thaliana*, a small flowering plant.

“Under the microscope, this peculiar root patterning is incredibly beautiful,” she recalls. “The way we studied its genetics — by mapping one gene at a time in an extensively studied model system — was elegant, and yet so different from the cancer genome research I’m doing today.”

A few years into Dr. Shen’s graduate work, the complete sequence of the human genome became available.

“I was fascinated with this breakthrough and its implications,” Dr. Shen says. “Genome-wide experiments were generating terabytes of information. Such high-dimensional data couldn’t just be recorded on a piece of paper, the way I was doing my lab experiments. Instead, statistical and computational tools were needed to process all this information, and to draw conclusions from the results.”

Her fascination motivated her to earn her PhD degree in biostatistics, which is the science behind the design and analysis of biological and clinical studies. Since 2007, when Dr. Shen joined Memorial Sloan Kettering, much of her research has been focused on The Cancer Genome Atlas (TCGA), a landmark effort to catalogue genomic alterations in more than 20 types of cancer. Memorial Sloan Kettering is one of seven institutions across the country selected by the National Cancer Institute to develop new tools that help researchers process and analyze TCGA data.

“Scientists are taking cancer genomes apart into millions of pieces, creating a map of everything that might go wrong genetically in cancer,” Dr. Shen explains. “From that, we are developing modern statistical tools to extract clues that can guide researchers to search for new therapeutic targets.”

In the human genome, things can go wrong in a number of ways simultaneously. The activity or function of genes may be warped by changes in the DNA sequence as well as by epigenetic changes, which leave the genetic code unchanged but modify the structure of molecules that surround DNA.

In collaboration with cancer biologists and clinicians at Memorial Sloan Kettering, Dr. Shen has developed a mathematical tool that facilitates tumor subtype discovery — studies aimed at classifying patients into disease subtypes based on genomic abnormalities that are clinically or therapeutically relevant. Such investigations, which have been conducted in several cancer types including prostate cancer and glioblastoma brain tumors, could accelerate the development of personalized therapies and diagnostics.

A public resource, Dr. Shen’s model, called iCluster, integrates all types of genomic aberrations measured in a set of patient samples —including both genetic and epigenetic changes. “Using statistical learning techniques, iCluster sifts through this data searching for genes that have been altered in multiple ways,” Dr. Shen explains. She and her colleagues are positing that such genes are likely to play key roles in tumor growth and metastasis, because, as she puts it, “if a tumor needs to take control over certain genes to thrive, it will find many ways of manipulating those genes.

“Unless we approach genomic data with a guiding hypothesis, we won’t be very successful in finding useful information,” she adds. “Essentially, we would be looking for needles in a haystack.”

For medical oncologist DIANE REIDY-LAGUNES, translational medicine is a perfect union of her two vocations. “I’m so impressed by the wonderful things laboratory scientists are doing for cancer patients,” she says. “Yet I’ve always felt that my place is more toward the bedside than the lab bench.”

She zealously keeps up with progress in many research areas and works closely with basic scientists as well as with other clinicians. “As physicians, we need to be fluent in the language of science and stay alert to every opportunity that might allow us to improve treatment strategies for our patients,” she notes.

Dr. Reidy specializes in the treatment of neuroendocrine tumors — a fairly uncommon group of diseases that can arise in many different organs, most commonly in those of the gastrointestinal tract — as well as in the treatment of colorectal and pancreas cancers. When not seeing patients, she is spearheading the Center’s efforts to build an extensive neuroendocrine tumor research program.

Diane Reidy-Lagunes (right) with hospitalist Chhavi Kumar on rounds.

Neuroendocrine tumors tend to be slow growing, but are nonetheless difficult to diagnose and treat. “Many of our patients can do very well for a long period of time,” she says. “However, others may have a more aggressive disease course.” To determine what type of disease a patient has, doctors currently use biopsy — a procedure in which a small piece of cancer tissue is taken out and examined under the microscope.

“Biopsy only gives us one ’snapshot’ of tissue and, therefore, may not represent what is going on in all of a patient’s tumors,” Dr. Reidy explains. Together with her colleagues in Memorial Sloan Kettering’s Department of Radiology, she is exploring whether an emerging imaging technique called diffusion MRI, which provides information about the random motion of water molecules within tumors and other tissues, could facilitate the diagnosis of neuroendocrine tumors. “We hope diffusion MRI tests, which can be done in conjunction with a regular MRI scan, might help us determine which patients are likely to do well with gentle intervention and which may require more-aggressive treatment,” she adds.

In addition, Dr. Reidy runs several clinical trials focused on neuroendocrine tumors and is working with biologists at Memorial Sloan Kettering and Weill Cornell Medical College to develop new targeted therapies and prognostic tools for these tumors — for instance, by exploring the safety and effectiveness of potential new drugs in mouse tumor models.

“We are trying very hard to better our therapies,” she affirms. “Today, treatment options for neuroendocrine patients with metastatic disease are very limited. But as we’re learning more about these tumors, we may eventually get to a point where we can distinguish those patients who are likely to do well from those who are not, and develop safe and effective treatments that are vested to each patient’s type of disease,” she says.

“My patients are my motivation,” she says. “When people are diagnosed with advanced disease for which there currently is no cure, my colleagues and I do everything we can to extend their lives and give them the best possible quality of life. Escorting such patients on their journeys is a huge honor — and a constant reminder of how much we have left to learn.”

She is also inspired by her colleague and mentor, medical oncologist Leonard Saltz, who she says “has immense talent, and a contagious enthusiasm for patient care, clinical trials, and drug development.” Dr. Reidy trained with Dr. Saltz as a medical fellow and served as chief medical fellow at Memorial Sloan Kettering. She earned her medical degree from the SUNY Downstate College of Medicine and completed her residency and chief residency training at Mount Sinai Medical Center.

“One thing I’ve learned since joining the Memorial Sloan Kettering faculty [in 2008] is that people here are not just exceptionally good at what they do. They are also genuinely kind,” Dr. Reidy notes. “And having such outstanding colleagues is extremely valuable given the way we work — always as a comprehensive team.”

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