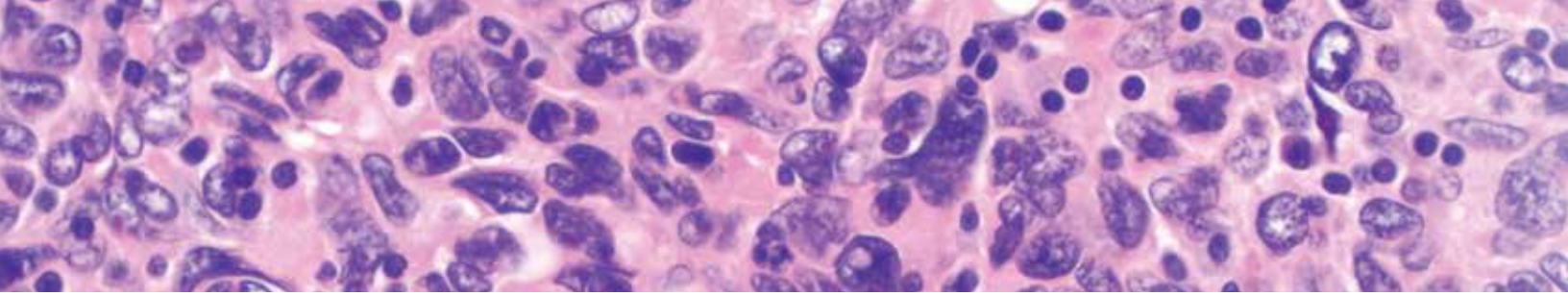


SCIENCE FICTION *Comes to Life*

BY RENÉE GEARHART LEVY

Sarcoma is a rare and aggressive cancer that can occur in soft tissue and bone, affecting both children and adults. Sarcomas are classified into several groups, with more than 50 different subtypes. Historically, treatment options have been limited to surgery, with or without radiation, followed by chemotherapy. There are only a few drugs currently available for patients with sarcoma; the overall survival for metastatic disease is 11 to 20 months. But the advent of DNA sequencing technologies is opening new frontiers, allowing doctors and scientists to study genetic alterations causing these tumors and develop targeted therapies tailored specifically to their cancer.

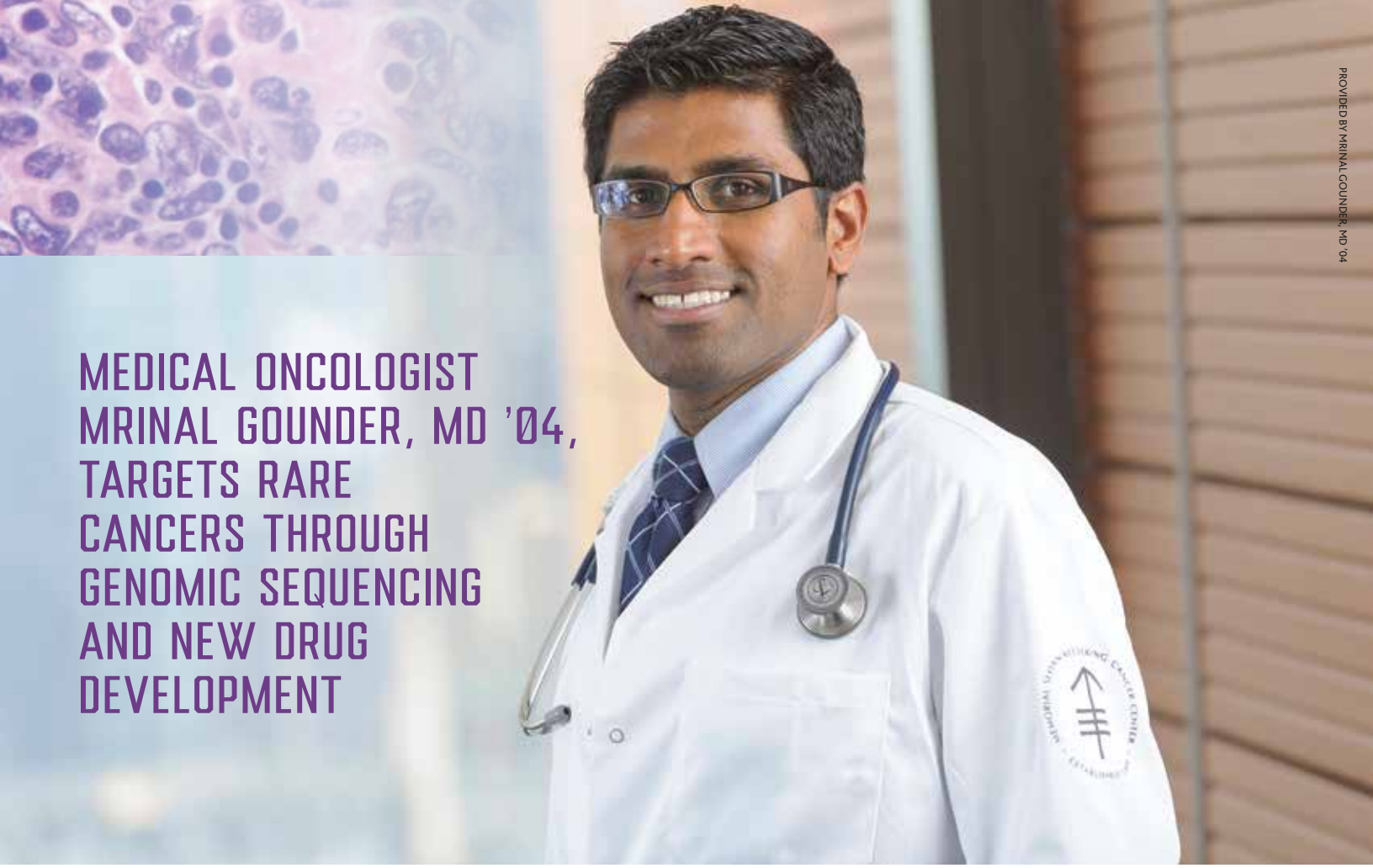
"We are now able to do extraordinarily sophisticated analysis at a genetic and molecular level of a patient's tumor sample or blood specimen to find out what is driving that tumor. This is something that I thought of as science fiction as a medical student and now its reality," says Mrinal Gounder, MD '04, a medical oncologist specializing in sarcoma and other rare cancers at Memorial Sloan Kettering Cancer Center in New York City.

Personalized medicine—the use of an individual's genetic profile to help guide medical decisions—has shown great promise in identifying effective treatments for patients with certain types of cancer. In 2000, a type of sarcoma called Gastrointestinal Stromal Tumors (GIST) was the first solid tumor to have targeted therapy based on mutations on a gene for KIT when the drug imatinib, which was also being developed in leukemias, was noted to also inhibit KIT, a driver gene in GIST. Imatinib in GIST became the proof of concept for personalized medicine in solid tumors, and thus, heralded a revolution in oncology.

Working with a team of sarcoma experts in medicine, surgery, radiation, pathology, and cancer biology at Memorial Sloan Kettering, Dr. Gounder is attempting to unravel the complexity of each type of sarcoma and develop new drugs in order to move away from the "one size fits all" paradigm.

"There are many exciting new gene-targeting drugs out there–existing drugs that have shown good results for people with other rare cancers, as well as promising new drugs now in clinical trials that might be very beneficial for some sarcoma patients," he says.

Gounder is an attending physician in Memorial Sloan Kettering's Phase I Clinical Trials program and lead investigator on several clinical trials in his division. His own research focuses on discovering and developing new compounds that are more effective in treating solid tumors while being less toxic for the patient, as well as leading the movement to expand the knowledge base on sarcoma.



PROVIDED BY MRINAL GOUNDER, MD '04

MEDICAL ONCOLOGIST MRINAL GOUNDER, MD '04, TARGETS RARE CANCERS THROUGH GENOMIC SEQUENCING AND NEW DRUG DEVELOPMENT

Using a sophisticated DNA sequencer, Gounder is investigating the genetic mutations driving different types of sarcoma. At the 2017 American Society of Clinical Oncology Conference, Gounder and colleagues presented results from a study investigating the impact of next-generation sequencing in discovering diagnostic criteria and therapeutic treatments for both soft-tissue sarcoma and bone sarcoma. Their work identified more than 60,000 mutations, including germline mutations of known and novel genes, results suggesting that next-generation sequencing may play a pivotal role in diagnosis and treatment selection.

Foremost, the data can be used to match patients to clinical trials that treat cancer based on a specific genetic mutation, regardless of where in the body the cancer originated. Finding the genomic cause of the tumor may give a patient a new frontier to battle cancer when standard therapies are unsuccessful or toxic.

"There are many different mutations and gene signatures associated with sarcoma, and we suspect they play a very important role in understanding a patient's disease," says Gounder. "We are now left with the task of validating these findings in prospective studies. This is the essence of precision medicine."

The son of an endocrinologist and a scientist, Gounder got hooked on translational research as an undergraduate biochemistry major at SUNY Binghamton. He was a research assistant in an insect lab doing molecular biology and spent two years at Harvard Medical School conducting research on gene therapy of brain tumors. "I observed physicians who were seeing patients in the morning and then spending the afternoon in the lab on research, trying to move the needle forward," he recalls. "That back and forth was exciting."

He says he approached his medical studies at Upstate Medical University with an open mind. "Every time I was in rotation, I was seduced by that field and how individual attendings talked with passion about what they did. I remember spending a summer working with Dr. Mantosh Dewan on schizophrenia, and I was convinced that I was heading into the field of psychiatry" he says.

Ultimately, he felt there was no area with greater potential for impact than oncology. The Human Genome Project was underway. "There was an explosion of understanding and drug development," says Gounder, who says he was influenced by David Duggan, MD '79, Bernard Poiesz, MD, and John Wright, MD. "By the time I was writing my essay to apply for internal

"It's bench to bedside and bedside to bench. More and more, the human body has become the lab. Historically, things would happen in the lab and then many years later move to the patient, but now, it happens much faster. We've found that the best thing you can study is that one patient sitting in front of you."

—MRINAL GOUNDER, MD '04

medicine residency, it was crystal clear I was heading for oncology," he says.

During his intern year at Northwestern University, Gounder treated a patient who had large sarcoma in his pelvis resulting in an amputation. "He was a young man in his 20s with a young family. He'd lost his leg and the pain management was very difficult. He'd had several rounds of chemotherapy and there was nothing left; basically, he transitioned to hospice," Gounder says. "That kind of haunted me."

He'd intended to focus on pancreatic cancer during his residency at Memorial Sloan Kettering Cancer Center, but after making a connection with two attendings that were sarcoma specialists, his direction was sealed.

When he joined the faculty of Memorial Sloan Kettering in 2009, Gounder says sarcoma treatment was still "the wild, wild west."

"The standard treatment was surgery—removing the tumor if you could, or amputation, possibly radiation, and then chemotherapy," he says.

The revolution has occurred only in the last seven or eight years, fueled by advances in genetic sequencing that began almost 2 decades ago.

"What was primarily being done in the lab has moved into the clinic. We now routinely offer a patient the option to do tumor genetic sequencing of approximately 500 or more genes in the clinic. Clinic is now the new lab," says Gounder, who, given his background in molecular biology and genetics, got involved early on.

Sarcomas comprise only one percent of adult cancer diagnoses, making them one of the rarest forms of cancer. Even among this small group, there is broad tumor heterogeneity, making even the diagnosis of sarcoma quite challenging.

DNA sequencing has changed that as well. "We've moved away from using what you see under the microscope to making a diagnosis at a molecular level," says Gounder. "We've gone from one in 10 patients getting the wrong diagnosis to patients getting the most precise diagnosis, which in itself is a huge leap forward."

One of the challenges of working with rare diseases is the low number of patients to draw comparable information from. Gounder is currently working on a paper for *Nature Medicine* compiling information learned from 8,000 sarcoma patients worldwide who have had genetic sequencing for sarcoma. "There is truly going to be a paradigm shift in thinking about how to treat a sarcoma patient," he says.

But sarcoma isn't his sole purview. Gounder is part of Memorial Sloan Kettering's Early Drug Development Center, where he sees cancer patients who have failed standard care and need to move on to an experimental therapy.

"We take very promising new drugs developed in the laboratory and evaluate their safety and efficacy in cancer patients," he says.

Gounder focuses his efforts on rare cancers, which he views as a huge unmet need. "Many of them are generally very neglected, are poorly studied from a biological perspective, and are not considered profitable in terms of drug development by pharmaceutical companies because of the low number of patients," he says.

Despite the challenges, Gounder has seen his efforts pay off. To study desmoid tumors—a locally aggressive sarcoma—Gounder aligned with patient advocacy groups internationally and was able to complete the first Phase 3 randomized, global study, something other experts had said would be impossible.

There is no standard of care for desmoid tumors, which can be locally aggressive and painful. In a phase 3 clinical trial, Gounder found that a drug called sorafenib stopped progression of desmoid tumors for two years in 80 percent of patients who completed treatment, a significant increase in progression-free survival compared with the placebo. The results were published last

year in the *New England Journal of Medicine* and Gounder hopes will lead to drug approval by the FDA. The study was named as one of the top Advances of the Year for 2018 by the American Society of Clinical Oncology.

Gounder says there's no division between the various aspects of his work. "Everything is sort of tied to everything else," he says. He sees patients two days a week—one day, patients with non-sarcoma rare cancers, where his focus is on early drug development; the other, sarcoma patients, who receive the gamut of care, depending on the stage of treatment they are in.

Many of these patients undergo surgery and chemotherapy. Others need experimental treatment and will undergo genetic sequencing. Sometimes, he will replicate a patient's tumor in mice to test the efficacy of various drugs. "If something works, we bring it back to the patient," he says.

Gounder's remaining time is focused on research efforts: writing and managing protocols, talking with pharmaceutical companies, managing his research staff, and collaborating with other lab directors. "It's bench to bedside and bedside to bench," he says. "More and more, the human body has become the lab. Historically, things would happen in the lab and then many years later move to the patient, but now, it happens much faster. We've found that we can leapfrog our knowledge by just carefully studying that one patient sitting in front of you, something I remember Sara Greithlein, MD, telling me at Upstate."

Gounder says his primary goal in pursuing oncology was to help cancer patients through the development of new drugs. "That's what drives me," he says, "to find a cure."

But it takes a village, from the clinical researchers, to the laboratory scientists, to the patient advocacy groups, the pharmaceutical companies, and most importantly, the patients who agree to participate in clinical trials. Over 10 years, he's led or been part of teams on several drugs that have received FDA approval and gone to market and believes he will see half a dozen more entering the market soon—seeds planted a decade ago that are just now beginning to mature.

"We all want to make a difference," says Gounder, "to improve on the status quo." ■

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