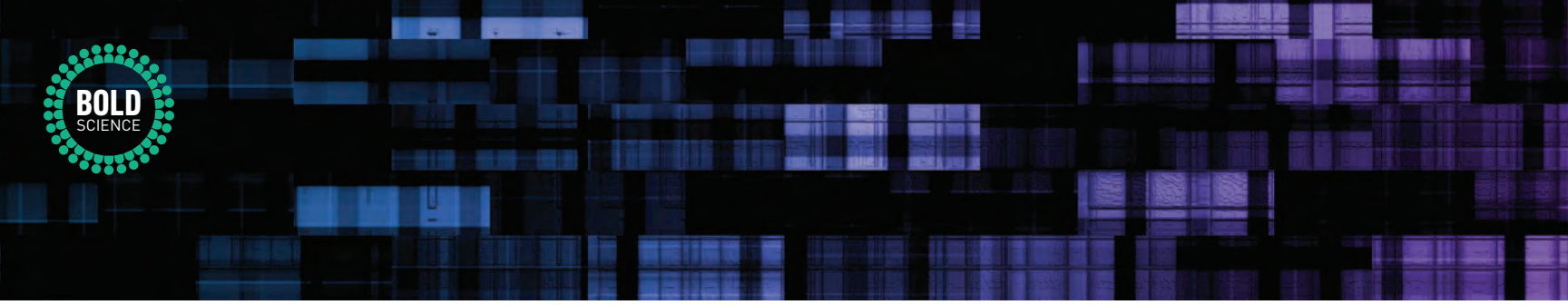


BOLD SCIENCE

CRACKING TH

When you're diagnosed with late-stage, drug-resistant multiple myeloma, hospice is often a next step. That step was what one New York City-based artist faced when a novel collaboration between scientists and clinicians at Mount Sinai enabled him to change course.

Despite major advancements in multiple myeloma over the past few decades—the approval of new drug therapies, the advent of stem cell transplants (including autologous transplants), the introduction of CAR T-cell therapy—the median life expectancy from the time that a patient is diagnosed with this blood cancer is a mere five and a half years, says Sundar Jagannath, MD, Director of The Tisch Cancer Institute's Multiple Myeloma Program and Professor, Medicine, Hematology and Medical Oncology. Most patients spend those years cycling between periods of remission and relapse. As clones of the original cancer mutate and proliferate, current treatment fails and other options must be explored—quickly. After a relapse, multiple myeloma can advance within weeks or even days.

Older patients tend to succumb most rapidly. They're usually too frail for stem cell transplants and CAR T-cell therapy and don't qualify for the majority of large clinical trials. That was the case for the NYC-based artist, who hoped to live a few more months so he could finish some of his artwork that had been lingering in storage. That didn't seem likely—until he enrolled in a pilot study at Mount Sinai that entailed analyzing his tumor DNA and RNA so he could be matched with a drug that was FDA-approved for an entirely different type of cancer.

TESTING A NEW APPROACH

Samir Parekh, MD, Associate Professor of Medicine, Hematology and Medical Oncology and of Oncological Sciences, was tired of watching patients jump from treatment to treatment without any clear reasoning behind it. "Right now 50 to 60 percent of patients are getting drugs that they don't respond to and potentially getting toxicity without the benefits," he says. "As a physician-scientist, I wanted to bring a little more biology into how patients are given appropriate treatment, including patients who aren't eligible for big clinical trials," he says.

At many other institutions, oncologists like Dr. Parekh are encouraged to stay in their lanes, but at Mount Sinai experts do not work in silos; clinicians are encouraged to foster relationships with scientists to uncover innovative solutions. In this instance, Dr. Parekh, who has a background in computational biology, turned to Joel Dudley, PhD, Mount Sinai Professor in Biomedical Data Science and Director of the Institute for Next Generation Healthcare. Dr. Dudley, who was recently appointed Executive Vice President for Precision Health for the Mount Sinai Health System, is an expert at RNA sequencing and machine learning, a type of artificial intelligence in which complex data analysis is automated.

While analyzing tumor DNA and using the results to guide treatment decisions has proved effective for treating patients with a growing number of cancers, multiple myeloma has not been among them because it's so heterogeneous. "When we do a higher-resolution genetic analysis, we realize that although cells may look alike, they can actually be very different," Dr. Parekh explains. Factoring in RNA, the messenger that instructs cells about how to express proteins, would provide more insight into what's driving a specific patient's cancer. That information could then theoretically be used to identify similarities between

Photos by Andrew Lichtenstein

E CODE

Using Genomics and Machine Learning to Treat Multiple Myeloma

BY BARBARA BRODY

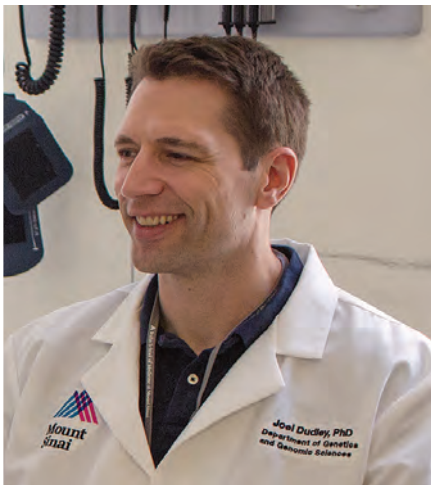
> **As a physician-scientist, I wanted to bring a little more biology into how patients are given appropriate treatment, including patients who aren't eligible for big clinical trials.**
>
> SAMIR PAREKH, MD

it and certain types of breast cancer, melanoma, or another seemingly unrelated cancer. If a match could be made, a myeloma patient might be able to tap into a treatment that was already FDA-approved for another cancer. He and Dr. Dudley set out to make that happen.

To crunch the vast amount of data needed to execute such a plan, the Institute for Next Generation Healthcare had to first create a dedicated server, nicknamed CRUSHER, and a specialized software program, named DAPHNI. They then enrolled 64 patients who had exhausted FDA-approved options for myeloma and were expected to survive only six months. Tumor genomic DNA and RNA were obtained from the patients' bone marrow aspirates, and the samples underwent extensive sequencing (including whole-exome sequencing and targeted sequencing) before the data was run through the DAPHNI software.

This methodology enabled the research team, which included several other Mount Sinai scientists and clinicians like Dr. Jagannath, to obtain more precise information

Joel Dudley, PhD



on the genetics of multiple myeloma in individual patients than ever before. "The mutation alone is not the full story," says Dr. Jagannath. "We are looking at the pathway activation, and through RNA sequencing we can tell if the mutation is meaningful or not. That's where this proprietary algorithm becomes a big help."

Using the machine-learning software, researchers generated treatment recommendations for 63 of the 64 participants in their initial study, which was published in August 2018 in *JCO Precision Oncology*. Twenty-six patients implemented one or more of the suggested treatments, and 16 patients went into remission (for a median duration of 131 days). The above-mentioned artist went into remission for a full year and completed several of his paintings, though he ultimately passed away after having a heart attack.

NEXT STEPS: ACCURACY AND SPEED

With the preliminary trial now complete, Dr. Parekh and his colleagues are focused on refining the technology and patient-flow process for accuracy as well as speed. Obtaining the required patient samples, sequencing DNA and RNA, and running the DAPHNI software to generate drug matches can take a few months, and many multiple myeloma patients can't afford to wait that long. "We want to have an impact on more patients and make this something anyone walking in through the door can take advantage of," says Dr. Parekh.

To that end, everyone who comes into Mount Sinai's multiple myeloma program now has the option of getting this RNA sequencing done. The plan is to input data from about 1,000 patients into DAPHNI, then choose a few hundred to participate in a larger clinical trial that will start in the fall.

In addition to analyzing RNA expression and DNA mutations, the researchers plan to hone in on the specific clones that seem to play a crucial role in the progression of this disease. "We're actually mapping the surrounding cells, not just the cancer," says Dr. Jagannath. "We want to know about the cancer cells, but also about the milieu in which they're growing. Cancer cells are like terrorists; why do [the surrounding cells] tolerate them?"

While potential drug matches for each patient are being identified and vetted, the scientists plan to simultaneously treat a small piece of the tumor in the lab with one or more drugs they believe hold promise for a given patient. The goal: delivering personalized treatments much faster.

Although the results from the forthcoming trial likely won't be available to the public for a few years, providing the best possible care right now is what continues to drive the Mount Sinai team. "This is bench-to-bedside medicine," says Dr. Jagannath. For patients, "it's immediately applicable."

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>
> SUNDAR JAGANNATH, MD