Jean Sanger, Ph.D., and Joseph Sanger, Ph.D., '68:

SOCIAL SCIENCE

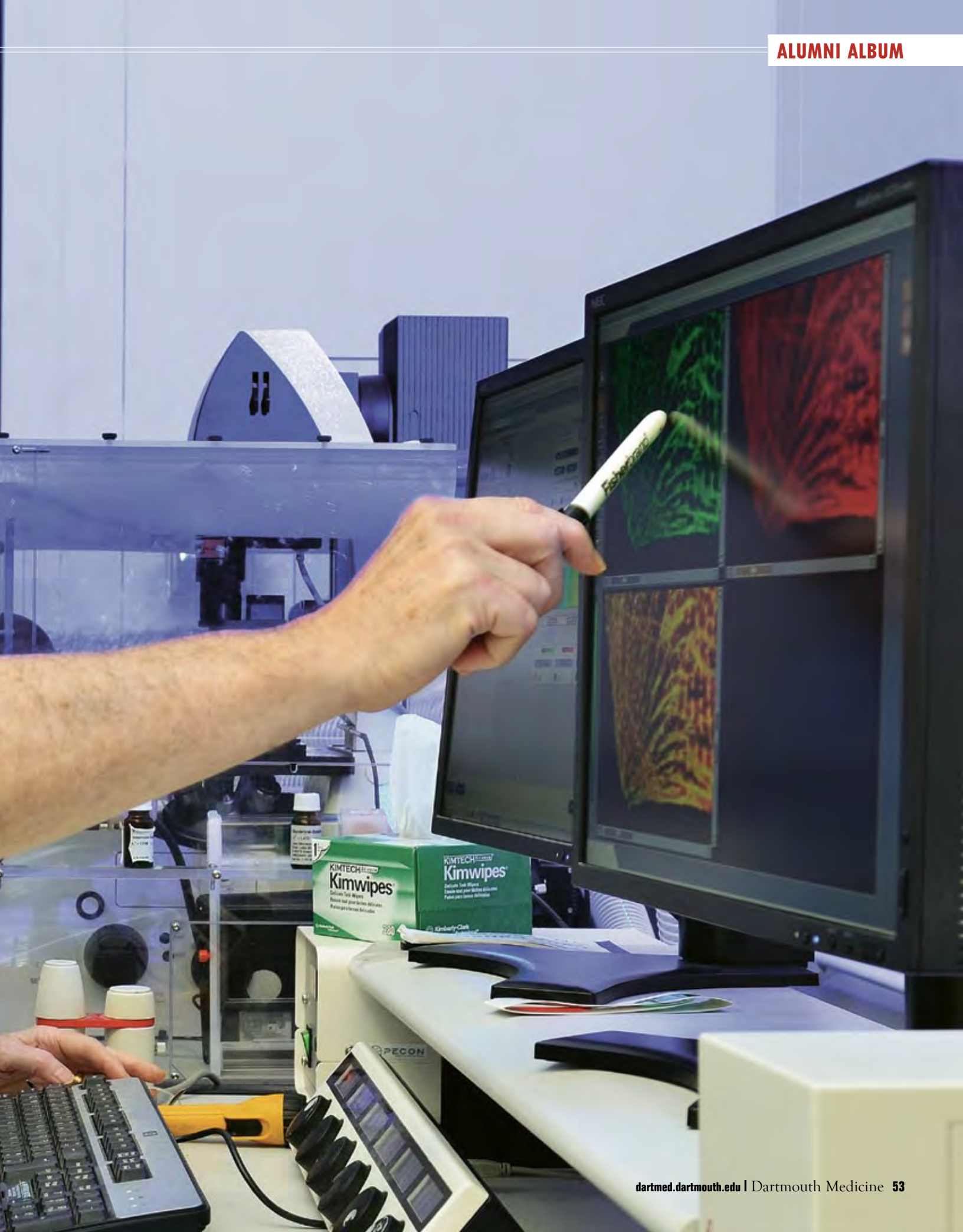
BY ALEXANDER GELFAND

TWO MEMBERS OF THE CLASS OF 1968, JEAN AND JOSEPH SANGER, BOTH GRADUATES OF THE PH.D. PROGRAM, HAVE FOUND THAT STRONG RELATIONSHIPS—INCLUDING THEIR OWN—HAVE BEEN THE KEY TO SUCCESS IN RESEARCH.

Anyone seeking to refute the myth of the lone scientist—that white-coated figure toiling in utter isolation in the laboratory—need look no further than the husband-and-wife team of Joseph and Jean Sanger.

In a discussion of their life in science, Joe and Jean spend little time reviewing their list of accomplishments, as impressive as it is (between the two of them, they have published more than 150 journal articles, been awarded millions of dollars in research grants, and used their expertise in fluorescence microscopy to advance our understanding of everything from cell division to the strategies employed by bacterial pathogens).

Instead, the Sangers emphasize the relationships they have enjoyed, and which have nurtured and sustained them. Science, as they describe it, is a social endeavor. That thread runs through their recollections of their time at Dartmouth, their decades-long tenure at the University of Pennsylvania, and their more recent appointments at the State University of New York Upstate Medical Center, where both are professors of cell and developmental biology and Joe is chair of the department.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The story of how they first met as undergraduates in 1961 neatly captures the warp and weft of their life together as both personal partners and professional colleagues. So, too, does the way they tell it.

"We met at a chemistry lecture," Jean recalls. "Joe knows the exact title."

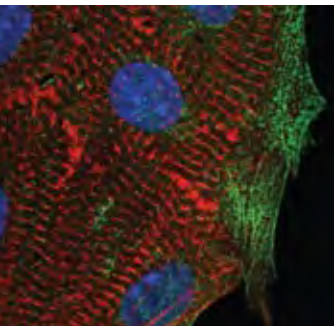
"I don't know if I know the exact title," Joe demurs, before warming to the topic. "It was on how life might have arrived on Earth via meteorites. And that idea is still current in popular thought!"

"But not *accepted*," Jean adds, a sardonic edge to her voice.

"Well . . ."

That same affectionately bantering tone also characterizes their discussions of other scientific topics, such as their own work on green fluorescent protein (GFP). This protein exists naturally in a species of jellyfish, but scientists use it to illuminate many facets of cellular dynamics in other organisms. The gene that expresses GFP can be linked to the DNA that encodes a protein of interest to a researcher. When the GFP-linked DNA is introduced into a cell, the protein it encodes will be fluorescent and visible in that cell and its progeny. This approach allows the behavior of GFP-tagged proteins to be observed in living cells.

The Sangers were among the first to use GFP to demonstrate how myofibrils, the basic units of muscle fibers, are assembled, and to elucidate how the bacterium *Listeria monocytogenes* and pathogenic strains of the bacterium *Escherichia coli* hijack the production of muscle-like proteins inside infected cells to spread the infections to neighboring cells—breakthroughs that were reported in 1997 in the *New York Times*.



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Before the advent of GFP, however, Joe and Jean relied on the more laborious process of injecting live cells with purified muscle proteins coupled to fluorescent dyes. A question about how they conducted research in those early, pre-GFP days elicits an exchange not unlike the earlier one.

"Well, you used the dyes that have been around for a long time," Joe says. "Like FITC."

"Fluorescein," Jean murmurs, unpacking the acronym for fluorescein isothiocyanate.

"Fluorescein," Joe echoes.

"Rhodamine," Jean offers, almost in a whisper.

"Rhodamine," Joe replies. "My favorite. . . . What was my favorite at the time?"

"I don't know."

"It had to be lissamine rhodamine. I loved that dye."

They prompt each other, fill in gaps in one another's memories, and finish each other's sentences, just as they might if they were talking about their two sons, or recounting the story of how they met. But then, what would you expect from two people who have been married for nearly 50 years and have conducted research together for nearly 40?

The Sangers have lived through several revolutionary periods in cell biology. In the early 1960s, the cytoskeleton, that network of protein filaments inside the cell that makes possible everything from basic cellular locomotion to muscle-fiber contraction, was just beginning to yield its secrets to electron microscopy. In the 1970s, improved techniques for attaching fluorescent labels to proteins generated fresh insights into cell structure and protein function. In the 1980s, advances in imaging techniques and computers further improved scientists' ability to visualize the dynamic inner workings of cells. And in the 1990s, GFP opened up a whole new world of possibilities that researchers continue to explore.

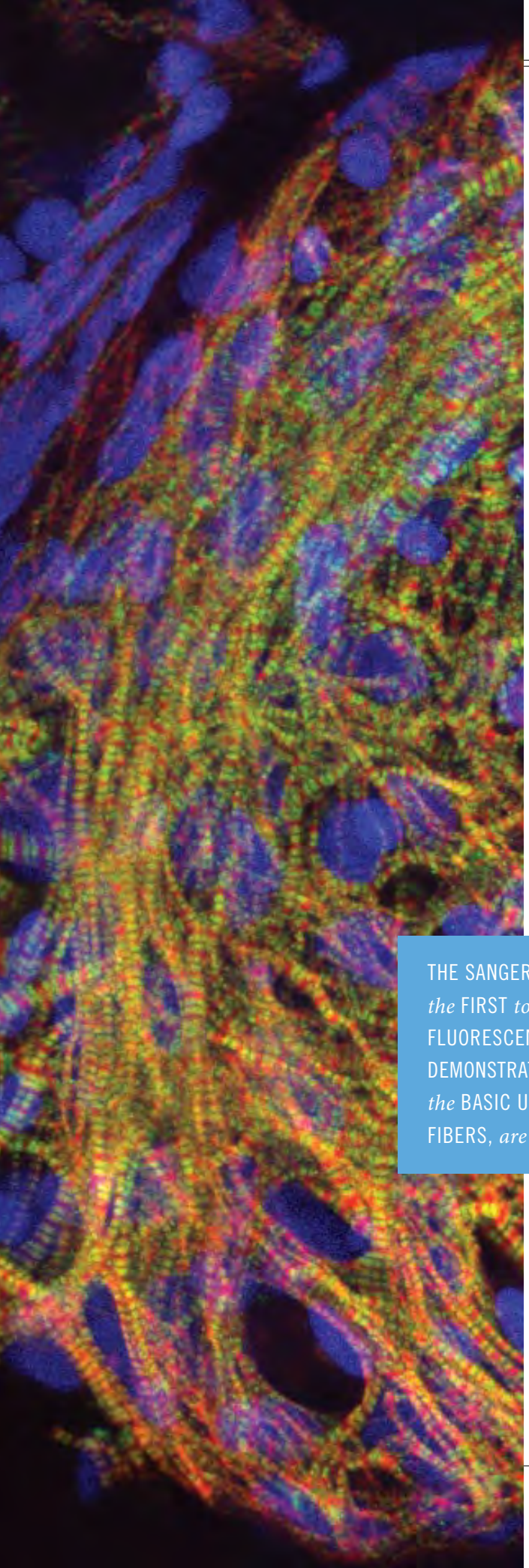
From their early studies of the cytoskeleton, through their investigations into myofibril assembly using fluorescent-dye-labeled proteins, to their more recent work using GFP-linked proteins to illuminate myofibril formation and dynamics, the Sangers have contributed to the many advances made over the course of these tumultuous decades. Their studies of *Listeria* and *E. coli* helped explain the mechanisms by which those pathogens manipulate the machinery of infected cells to their own advantage, while their research into the assembly and dynamics of myofibrils, stress fibers, and cleavage furrows in both muscle and non-muscle cells represents the kind of basic science that could one day lead to novel therapies for muscle-related disorders.

For example, much of their work has focused on actin and myosin, the proteins that permit muscle contraction as well as the movement and division of non-muscle cells. Determining how these proteins function is essential not only to understanding the fundamental workings of cells, but also to understanding the mechanics of abnormal muscle development—and thus to discovering the origins of muscle-related disorders ranging from muscular dystrophy to cardiac disease.

"Often, it's not known what leads to these diseases," says Joe. "You can have a mutation in one amino acid that leads to an enlarged heart—hypertrophy—and you can have a mutation just three amino acids away that leads to a thin-walled heart—a dilated myopathy—and you don't know why."

The two are currently joint principal investigators on a grant from the National Institutes of Health to investigate the differences between mutated and wild-type muscle proteins—work that might one day help prevent and treat muscle-related disorders.

It's easy to trace the Sangers' professional history by mapping out their scientific contributions over the years, sketching the chronology of



their insights and innovations. But they, themselves, refer to more personal reference points.

The year they were married, Joe was in his third year as part of the first cohort of students in the graduate program in molecular biology at Dartmouth; Jean was in her second year as part of the second cohort. The elder of their two sons, John, was born in 1965, when both were still knee-deep in grad school and learning the finer points of microscopy from Shinya Inoué, a pioneering cell biologist who was then chair of the cytology department. The couple lived in the town of Lyme, a short commute from Hanover, and were in desperate need of child care. Fortunately, their landlady and her husband volunteered to watch their toddler while Joe and Jean worked in the lab. "That really was a big thing in making the start of our career work," says Jean.

Soon after, Inoué left for the University of Pennsylvania. Coincidentally, Joe and Jean also moved to Penn in 1968, and they quickly rekindled their relationship with their old mentor. "Whenever we needed to borrow equipment, I could just walk over from the medical school to the biology building," says Joe.

Most of their summers during the 1970s, meanwhile, were spent at the Bermuda Biological Station for Research (now the Bermuda Institute of Ocean Sciences) in St. George's, Bermuda, an idyllic setting where John and his younger brother Matthew could snorkel in pristine waters. Or at least, they could whenever they weren't busy printing photographic negatives for their parents, whose work on cell division in sea urchins would lead to their first coauthored paper. "We made it clear to them that this was a paying job, and we expected first-class work," recalls Joe, laughing.

In the 1980s and 1990s, the Sangers began spending their summers at the Marine Biological Laboratory in Woods Hole, Mass., a hotbed of scientific research. There, John and Matthew attended the Children's School of Science, while Jean and Joe conducted research, renewed connections with old friends and colleagues like Inoué, and soaked up the latest developments in their field. It was at Woods Hole that Joe first learned about GFP from Douglas Prasher, the man who cloned the GFP gene.

And during the 1970s and 1980s, Joe often left his lab at Penn to coach his sons' soccer teams in the afternoon, returning later in the evening to finish his work.

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"I approached coaching the way I did science," says Joe, who once stole away from a meeting of the American Society of Cell Biology in St. Louis, Mo., long a center for North American soccer, to diagram plays at local matches for use back in Pennsylvania. "I have a little cup at home that says 'Championship Coach,'" he says. "I've always been very proud of that."

It's a rare admission of pride. When discussing their research, Joe and Jean invariably emphasize the contributions of others, a tendency that lends a human element, and occasionally a hint of poignancy, to even the most technical subjects. Ask them about their investigations of the vitamin D-binding protein, for example, and talk will quickly turn from the role that the protein plays in preventing blood clots to a remembrance of the late John Haddad, the endocrinologist who first drew them to the topic—and who died of a heart attack on his way to a medical conference in 1997, shortly after the three had discussed writing another paper together.

The unifying theme in all of their reminiscences, whether of work or of family life, is of connection and community; a reminder that in the lab, as in life more generally, no one operates alone.

"Everything we've done," says Jean, "has been part of a bigger picture."