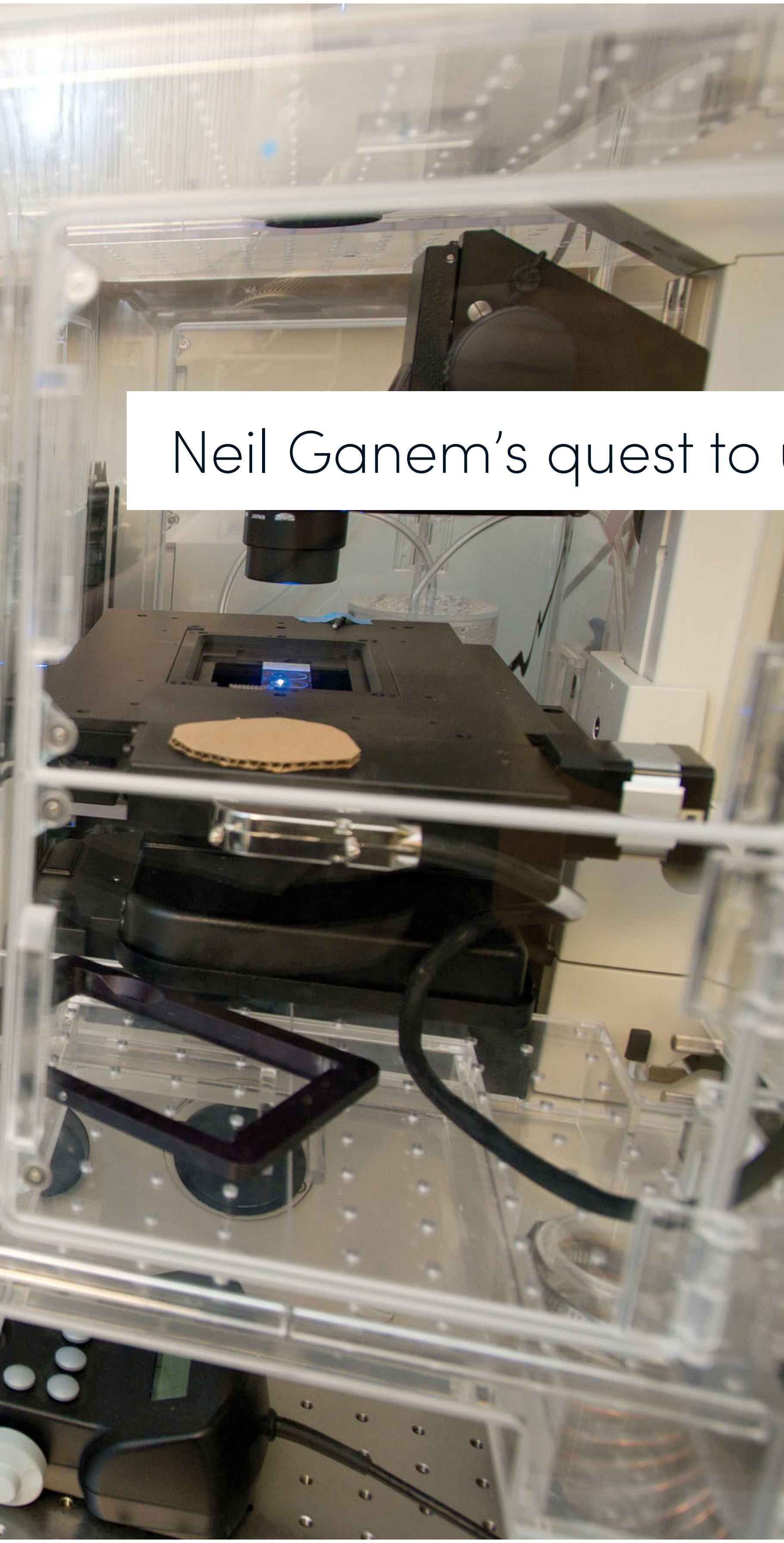
Every Cell Has a Story

Biologist Neil Ganem captures stunning images of cells and asks questions no one has thought to ask. "It's just amazing what's there to be seen," he says.

BY BARBARA MORAN



Neil Ganem's quest to understand cancer, by unraveling the mysteries of cell division

Photographs by Cydney Scott

THERE COMES a defining moment for many scientists that divides their lives into before, and after. Neil Ganem remembers that moment. He was a PhD candidate at Dartmouth's Geisel School of Medicine, with a vague idea of studying "some sort of neuroscience." He thought it might be Parkinson's disease, which had killed his father. But then came Duane Compton's black-and-white movie.

Compton, a Dartmouth professor of biochemistry and interim dean of the medical school, has studied cell division for more than 20 years. In particular, he studies chromosome segregation—how cells separate their DNA into two equal heaps before dividing into two daughter cells. "We want to know how this works so well in normal cells, how they segregate so perfectly every time they divide," Compton says. Each fall, he presents his research to aspiring Dartmouth PhDs, starting with a simple movie of cell division. "It was just one cell," recalls Ganem. "You could see the nucleus, and then you could see all the chromosomes. You could see them all move around, line up perfectly, and then suddenly that one cell pinched into two."

The process of cell division takes about 20 minutes.

If the cell senses something amiss, it self-destructs.

The movie mesmerized him. Then Compton spoke. "Why do we study this?" he asked the assembled students. "Cancer. Cancer is just a disease of cell division gone wrong."

"And that's all he said," Ganem says. "And that's all I needed. I was hooked."

Since that day in 2000, Ganem, a BU School of Medicine assistant professor of pharmacology and experimental therapeutics, has tackled cancer in his own unique way: by capturing stunning images of cell division, examining them with a critical eye, and asking questions that nobody had asked before. His work has upended our understanding of how cells become cancerous, earning the 37-year-old scientist influential articles in *Cell* and *Nature*, as well as many grants, awards, and accolades. These include the Smith Family Foundation Award for Excellence in Biomedical Research, the Melanoma Research Alliance's Jackie King Young Investigator Award, and the Searle Scholar Award, given to the country's most promising young chemistry and biology researchers.

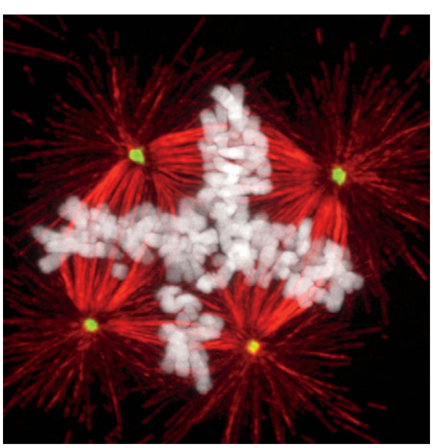
"He has the ability to identify big, broad questions, express them in a simple way, then proceed logically with testing his hypotheses. That's a rare talent," says David Farb, a MED professor and chair of pharmacology and experimental therapeutics. "His research is a way to open up new avenues for treating cancer, and he does it in a beautiful and rigorous way."

Cell Division Gone Bad

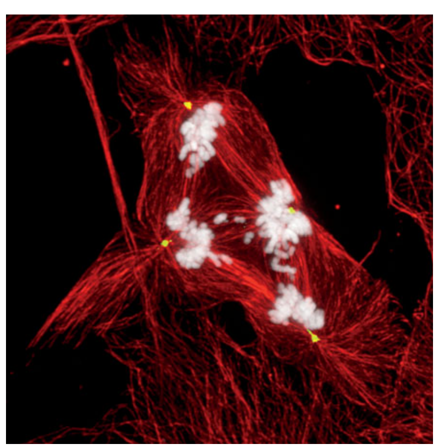
Cell division, when all goes well, is breathtaking. It starts when the DNA in the cell's nucleus, usually a scramble of stretched-out spaghetti, duplicates itself, then coils into tightly packed structures shaped more like stubby macaroni. Matching pairs of macaroni join at the middle with a little nub of protein, forming the familiar X-shaped chromosomes.

Meanwhile, two tiny structures called centrosomes migrate to the poles of the cell. Then the mind-blowing part happens: the centrosomes at either pole grow tiny tubes called microtubules that reach toward the center of the cell, building long spindles that attach to the center of each chromosome. It's sort of like spearfishing, with the centrosomes as fishermen casting multiple lines that hook the waiting chromosomes. When all the chromosomes are hooked, they line up in the middle of the cell. Then—one, two, three, presto—the centrosomes pull them apart, the cell pinches down the middle, and you now have two identical daughter cells.

The whole process, start to finish, takes about 20 minutes and is so complicated and choreographed that most people—even experienced cell biologists—are astonished that it all works. But it does work, most of the time, because the cell has built-in checkpoints along the way. If the cell senses something amiss—like too many chromosomes in a cell or not enough—it self-destructs. Cancer happens when the self-destruct mechanisms stop working and mutant cells that should die do not. Instead, they keep dividing, out of control. Most anticancer drugs target this characteristic, attacking all the rapidly



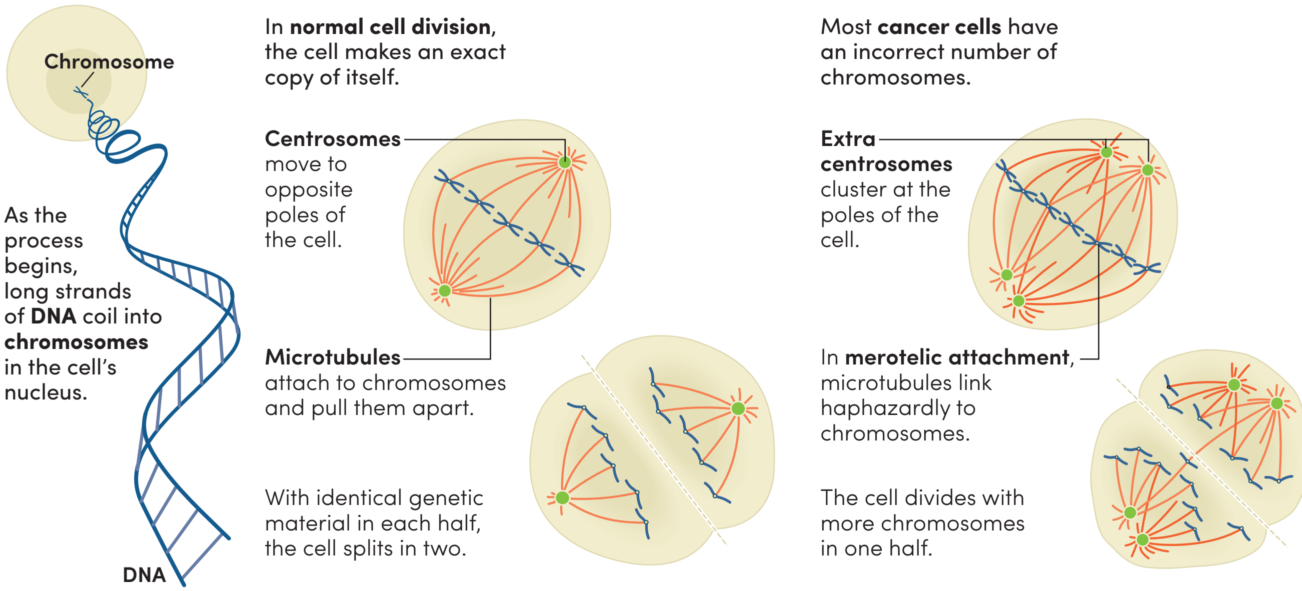
When cells divide incorrectly, it can lead to cell death or cancer. During cell division, centrosomes—seen here as yellow-green dots—attach to chromosomes—the white blobs—and pull them apart. Normal cells have two centrosomes; cancer cells often have four.



COURTESY OF NEIL GANEM

Scientists assumed that the extra centrosomes led to four abnormal daughter cells, which then give rise to tumors. But Ganem found that the four daughter cells self-destructed before becoming cancerous and that another mechanism led to cancer.

Breaking bad: Cell division in cancer cells



dividing cells in the body. This kills cancer cells, but also destroys healthy hair follicles, skin cells, and the lining of the mouth and gut, leading to painful and dangerous side effects.

"The cancer problem is so hard to crack because it's not like a foreign bacteria invading our cells. It's a deregulation of the cell's normal machinery," says Compton. "It's not easy to figure out how to stop cancer without stopping everything else. It's hard to find its Achilles' heel."

Almost all tumors have an incorrect number of chromosomes, a condition called aneuploidy—"that's one of the hallmarks of cancer," says Ganem. Understanding aneuploidy is a leading area for cancer research; the oddly numbered chromosomes make cancer cells stand out, offering possible ways to attack them selectively. The idea appealed to Ganem, who joined Compton's lab and began to study the nitty-gritty details of how chromosomes move into daughter cells. He focused on proteins called kinesins, which help build and dismantle the spindles. Sometimes kinesins go wild, building abnormal spindles, which can connect to chromosomes incorrectly and pull too many into a daughter cell. He studied the process through high-resolution imaging, taking pictures of spindles attaching to individual chromosomes.

Ganem calls himself a visual person, preferring books to podcasts and microscopy to mental math. His mother, a grade school science teacher, bought him a microscope when he was a young boy, "one of the best gifts I ever got," he says. "It came with a bunch of cover slips and empty slides, so I spent a ton of time out in the backyard just finding stuff, putting it on there, and looking at it." Squashed bugs, spit, money—he grabbed everything in reach and studied it under the scope, marveling at the fine details of everyday objects, like the tiny creatures swimming in a drop of pond water. "It's just amazing what's there to be seen," he says. And he's never stopped looking.

"When I put a cell on a microscope and watch it move with my own two eyes, I understand it better," he says. "Now that I can see how it's moving—jeez, now I have an idea about why it's moving incorrectly. As you watch it, the ideas just come—at least come to me—a lot easier."

In Compton's lab Ganem met his future wife, Amity Manning, now an assistant professor of biology and biotechnology at Worcester Polytechnic Institute. "The imaging was a big draw for both of us," Manning says. "You can interpret numbers, but when you can also see the results, it has that much more power. Plus you're looking at things nobody has seen before. It's like being a space explorer, but the other way around."

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Visions of Dividing Cells

The live-cell images Ganem produced at Dartmouth allowed him to explain how two novel kinesins help assemble spindles and move chromosomes, and he made several important discoveries detailing how deregulation of these kinesins contributes to aneuploidy and cancer. He carried this background with him to Harvard in 2006, for

DIAGRAM BY ED WIEDERER

Ganem's 2009 cover story in *Nature* is the most cited paper on centrosomes in the last 10 years. His insight "put together all the different pieces and related them in a way nobody else had," says Ganem's mentor, Duane Compton.

a postdoctoral fellowship under David Pellman, a professor of cell biology and the Margaret M. Dyson Professor of Pediatric Oncology at Harvard Medical School and principal investigator, pediatric oncology, at Dana-Farber Cancer Institute. "Neil had been studying the basic mechanics of cell division and was starting to think more about cancer," says Pellman, who appreciated the "sparkle of intellect" he saw in the young scientist. "He came to my lab to make the connection between basic cell biology and cancer biology."

Nearly all cancer cells, in addition to their myriad other problems, have extra centrosomes—those spearfishermen at the poles that cast out the microtubules and pull chromosomes apart. Most scientists assumed that the extra centrosomes formed three or four poles in a dividing cell, leading to three or four abnormal daughter cells, instead of two healthy ones. Those abnormal daughter cells then gave rise to tumors. Or so everyone thought. The idea seemed plausible, but Pellman and Ganem weren't so sure it was true.

"We wanted to pick apart what was going on," Pellman says. "We thought that centrosomes played a role, but every cancer cell—like every unhappy family from Tolstoy—has its own unique story. Lots of strange things go on in a cancer cell, and it's hard to tease apart the centrosomes' role."

So Ganem got on the microscope and got to work, watching thousands of cancer cells with extra poles divide, and then tracking their daughter cells to see if they survived. Nobody had ever done this before, partly because the technology hadn't existed. The work relied on a new microscope with a cell incubator attached, which allowed Ganem to follow the fates of dividing cells over several days. It also required grit. "This was really tedious, boring work," he says. "It gave me motion sickness." At night, visions of dividing cells swam through his mind, keeping him awake.

Ganem's work led to a discovery that turned the conventional wisdom on its head. He found that the multipolar divisions did sometimes lead to three or four daughter cells with abnormal numbers of chromosomes. But those mutant daughter cells always died, never becoming tumors as expected. "So basically that idea was just wrong," he says.

Peering at the cells, what Ganem saw instead was that many of the cancer cells had four centrosomes, appearing as if they would divide into four abnormal daughter cells. But the ones that became cancer didn't do this. Instead, they clustered the extra centrosomes at two poles and divided into two daughters. Scientists had seen this before, but Ganem discovered that cancer cells did this most of the time. He discovered something else as well: exactly what those clustered centrosomes were doing and how it led to cancer. Because the extra centrosomes sent out extra microtubules, they hooked chromosomes every which way and reeled them in willy-nilly—a process called merotelic attachment. The daughters survived, but their rate of chromosome missegregation skyrocketed. This mechanism is now widely accepted as the major underlying cause of chromosome missegregation in human cancer cells.

"Neil made the connection between the centrosomes and merotelic attachment," says Pellman. "He had the insight. He realized the significance and made it work." Ganem published the results in a 2009 cover story in *Nature.* The article is the most cited paper on centrosomes in the last 10 years—an indication of its significance in the field—and the most cited paper ever to come out of Pellman's lab. Ganem says that he'll "probably be doing science for the next 40 years, and I'll likely never make a discovery as important as this one."

Pellman disagrees.

"I know Neil very well. He's creative; he has interesting ideas and insight. He's a rigorous scientist and his own strongest critic," he says. "He's the guy who's going to get the right answer."

A Gene Called Hippo

Ganem looks much younger than his 37 years, with a round boyish face and a wide smile. He's enthusiastic and cheerful, with an aw-shucks demeanor and office décor consisting mostly of photos of his three young sons and their artwork, like the brightly painted rocks propping open his door. So it's a bit surprising to hear his colleagues and mentors list his defining qualities as intensity, intellectual ferocity, and scientific rigor.

"He's naturally very optimistic, but when it comes to science, there's something intrinsically skeptical about him," says Manning. "That's what makes him check all the data and make sure all the controls are in place before moving forward."

Ganem and Manning juggle dual science careers and raising their children. Ganem spends much of his free time trying to re-create the best parts of his New Hampshire boyhood for his kids—tromping around the woods, reading Dr. Seuss, playing basketball. Manning says her husband also builds lots of LEGO cars and trucks with the boys, an especially appealing pastime for Ganem. "It's very visual," she says. "You have these little building blocks and you put one section together, then you put the bigger sections together, and then you get to see the final product. It's like that in the lab. You build your understanding little by little until you see the final picture."

> Ganem hopes his research will lead to therapies that target abnormal tetraploid cells while leaving healthy cells alone.

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That is one of Ganem's greatest gifts as a scientist, according to Compton: puzzling together disparate pieces of information into a coherent whole. "When I saw what Neil did with that 2009 *Nature* paper, I said, 'Aha!'" recalls Compton. "It was his insight that put together all the different pieces and related them in a way nobody else had done before."

At Boston University, Ganem continues to build on the work he began at Dartmouth and Harvard, now focusing on tetraploid cancer cells—those with four sets of chromosomes instead of two. When tetraploid cells divide, they can lead to cancer.

"If you look at any solid tumor—doesn't matter if it's from the brain, from the lung, from the breast, from the pancreas—and you count the number of chromosomes in each cell, the numbers will vary, depending on the cancer," he says. "But at least half, if not more, will have a near tetraploid number."

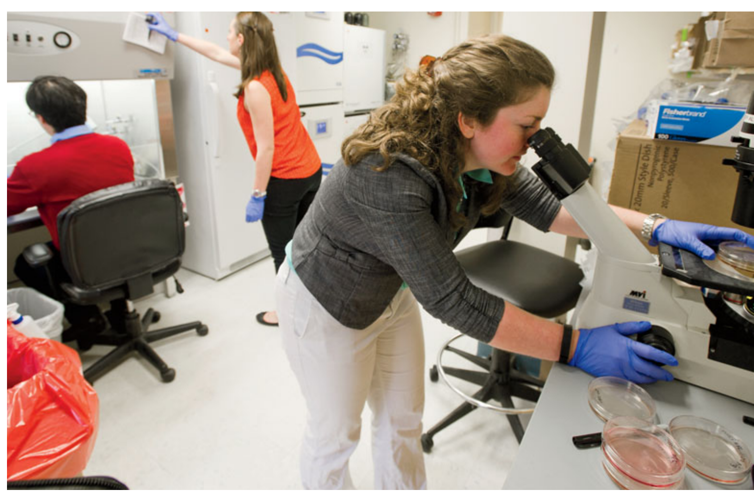
Usually when a tetraploid cell forms, it never divides again. Ganem wondered why. "Some tumor suppression mechanism kicks in and just shuts down the whole thing," he says. "I was really curious about this. I wanted to know: what is stopping tetraploid cells from proliferating?"

After several years of examining, purifying, and screening tetraploid cells, he found an answer: the Hippo pathway, a cascade of cell signals that control the size of organs in animals. First discovered in fruit flies, the name comes from a gene called Hippo—yes, as in hippopotamus. When mutated, it causes the unfortunate flies to grow monstrous eyes or wings.

Ganem and his colleagues discovered that the Hippo pathway regulates not only organ size, but also the growth of individual cells. Most tetraploid cells, because they are simply too big, turn on the Hippo pathway and self-destruct. Cancer cells, Ganem found, turn off the pathway, and keep growing and dividing despite their already enormous size.

He hopes that this line of research, published in 2014 in the journal *Cell*, may point the way to new cancer therapies that target abnormal tetraploid cells while leaving healthy cells alone. This remains the Holy Grail of cancer therapy. Although as president, Richard Nixon memorably declared a war on cancer in 1971, the disease has proven an intractable enemy, killing more than 1,500 people in the United States every day. Ganem's research may someday put a dent in that statistic.

"Our long-term goal is to identify new ways to specifically kill cells with an abnormal number of chromosomes, while sparing the normal cells from which they originated," he says. "To do that, we first need to identify what makes cells with too many or too few chromosomes unique. And taking a good, hard look at them under the microscope is a good place to start."



Amanda Bolgioni, a PhD candidate in Ganem's lab, prepares human cells for experiments and imaging. Ganem wants to identify what makes cells with too many or too few chromosomes unique.