Duane Compton, Ph.D.: An upbeat tempo

By Amos Esty

Cell division is often described as a dance. If that description fits, then one big problem is that all too often tumor cells display a disastrous sense of rhythm. DMS biochemist Duane Compton, Ph.D., is trying to change that.

The dance of cell division never stops—at any given moment, tens of millions of cells in a person's body are undergoing the process of dividing into two "daughter" cells. During that process, each of a person's 46 chromosomes is duplicated, and then those chromosomes are divided equally among the daughter cells. But sometimes one of the copies ends up in the wrong cell, leaving one daughter cell with too many chromosomes and one with too few. When that happens in a normal human cell, the loss or gain of a chromosome usually leads to the death of the cell. It's a steep price for one misstep.

Grew up: Suburbs of Detroit, Mich.

Education: University of Oklahoma '84 (B.S. in microbiology and chemistry); University of Texas '88 (Ph.D.)

Training: Postdoctoral fellowship at Johns Hopkins

Role model: His father. "I wish I could do half the stuff he knows how to do," Compton says.

Hobbies: Snowboarding, learning to play the guitar, and rooting for the University of Oklahoma football team

Origin of his interest in science: "I've always sort of liked digging around in things. When I was a kid I took clocks apart. I never put them back together, but I took them apart to find out what was inside. . . . I've been a tinkerer for a long time."

"Seeing how much Duane loved doing the research and loved mentoring students . . . had a huge influence."

But tumors usually already have any number of genetic mutations, Compton explains. As a result, the mechanisms of a normal cell—the ones that put an end to the dance if a chromosome missegregates—don't work in tumor cells, leaving them free to dance on, even with an abnormal number of chromosomes. And that complicates efforts to treat cancer. For example, a chemotherapy treatment may work well against tumor cells for a time. But then chromosome missegregation changes the genetic makeup of those cells, helping them to develop resistance to the treatment. In effect, it's a form of rapid natural selection. Missegregation of a single chromosome can change the number of copies a cell has of hundreds or even thousands of genes, potentially changing how the cell reacts to drugs. "You're constantly shuffling the deck," Compton says. "For some of those cells, the chromosomal content will be a bad situation in that environment. But for other cells it will be a good change and be selected for, and that will allow for the evolution of the tumor."

Compton has been at DMS since 1993, and in that time he has made a number of contributions to the study of chromosome segregation in tumor cells—and how to prevent it. Perhaps most significantly, he made discoveries that changed the understanding of the causes of chromosome missegregation.

During cell division, the duplicate pairs of chromosomes line up in the center of the cell. It had been thought that the problem was one of timing—that cancer cells were dividing before all the chromosomes were lined up. But Compton, working with graduate students in his lab, realized that the real explanation was more complex. When the chromosomes line up, they attach to thin filaments that extend from either side of the cell. What should happen is that half of the chromosomes attach to filaments from one end of the cell, and the other half attach to filaments from the other end. Then, as the cell divides, the filaments from each end pull half of the chromosomes into each of the daughter cells. But Compton showed that in tumor cells, one copy of a chromosome will often become attached to filaments from both sides of the cell. When the cell divides, that chromosome is pulled in both directions and sometimes will end up in the wrong cell.

Compton also found that two proteins can correct improper attachments between a filament and a chromosome. But in tumor cells, those proteins often fail to carry out their duties, allowing the missegregation to proceed.

By manipulating levels of those proteins, Compton came up with two possible solutions to problems with this part of the dance of cell division. Adding just the right amount of the proteins stabilizes tumor cells, helping their chromosomes to segregate correctly. Adding too much of the proteins can prevent tumor cells from growing and dividing further. So Compton can either teach the tumor cells the proper steps or kick them off the dance floor altogether. "We now understand how to take an unstable tumor cell and make it stable, and that's pretty powerful," he says. "We can make them faithful in how they segregate those chromosomes."

Now Compton is using this knowledge to learn more about the implications of chromosome instability. "We now have the ability to turn [chromosome instability] on and off at our command," he says. Doing so can shed light on how missegregation affects drug resistance and the growth rate of tumors.

Graduate students played important roles in these discoveries, which is not surprising given Compton's reputation as a strong mentor for young scientists. Sarah Thompson, Ph.D., was a graduate stu-

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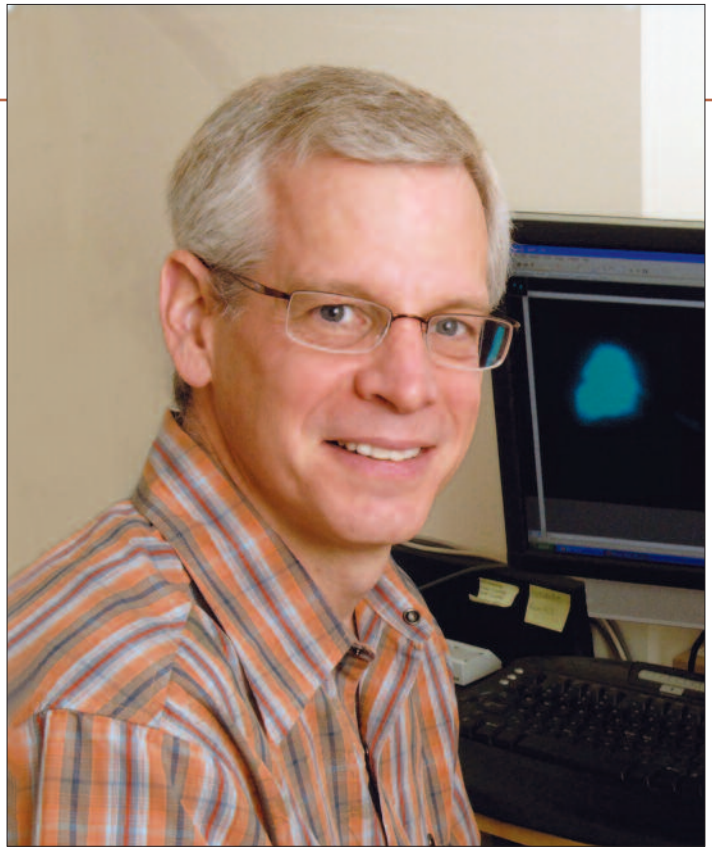
For a WEB EXTRA with a video showing the division of tumor cells, see dartmed.dartmouth.edu/sp11/we01.



JON GILBERT FOX

Compton calls himself "an eternal optimist." His graduate students term him "a great mentor." And DMS recently named him senior associate dean for research.

dent in Compton's lab from 2005 to 2010, and she appreciates the effort he put into helping her and other students succeed. "He was a great advisor," she says. "His office door was always open, and you could go in to ask him questions anytime."

Amity Manning, Ph.D., another product of Compton's lab, agrees with Thompson. "He's a great mentor," she says. "Even now I still contact him with questions and for advice, and he's still great about that."

Both Manning and Thompson have continued to work in academic science as postdoctoral fellows—Manning at Massachusetts General Hospital and Thompson at the University of Manchester in the United Kingdom. "Before I joined his lab I wasn't really sure what I wanted to do after grad school," Thompson says. "But somewhere along the way, seeing how much Duane loved doing the research and loved mentoring students, it definitely motivated me to want to have my own lab someday. . . . I think he had a huge influence on the direction my career is going."

Compton says he has been fortunate to have great graduate students, and he adds that mentoring and teaching have always been priorities for him. "It's a joy to watch them grow and mature as they proceed through their training, and I still keep in contact with almost all of them," he says. "It's sort of a lifelong relationship."

Both Thompson and Manning say Compton always seemed upbeat, something that may result from the pleasure Compton takes in his work. "I wouldn't be doing it if I didn't enjoy it," he says. He believes that despite the difficulties of succeeding in academic science, it is possible. "I don't know anyone in graduate school who doesn't at some point think about quitting, because it's really hard," he says. But, he adds, "I'm an eternal optimist, so I think if you're very dedicated and you have very good ideas, you will succeed in this business."

After years of doing just that in his own lab, Compton is now taking on a new role that he hopes will lead to the growth of research at DMS generally. Since January, he has been the senior associate dean for research, a brand new position at DMS.

Compton says he had to think before accepting the position, because it's important to him to maintain his own research. But he felt the opportunity was too good to pass up. "I think it's a way to have a real impact," he says. "The overall mission basically boils down to resource allocation. Where are you going to hire faculty? Where are you going to put resources to build programs? How is space going to be allocated for those programs?"

He notes that DMS already has a strong research program, but he thinks it could be stronger. He would also like to see the research that's carried out at DMS get more attention. "There are so many good investigators here," he says. "Outside of our Upper Valley here, I don't think people appreciate how much good science goes on at Dartmouth."

Compton acknowledges that Dartmouth Medical School is smaller than some institutions, but he says that's one of the things he likes about it. "I like the fact that you can know a lot of people here," he says.

But as much as Compton enjoys his work, he also likes Dartmouth for the opportunities it affords outside the office and the lab. He's a snowboarder and often hits the slopes at the Dartmouth Skiway, which is not far from his home in Lyme, N.H.

Ever the scientist, however, Compton also pursues a more cerebral hobby. "I'm learning how to play the guitar," he says. "I discovered that I sort of need to learn new things every few years. . . . So a few years ago, I was like, I want to know how to play the guitar." He has long loved jazz, so naturally he decided to learn jazz guitar.

Still, it is science that gets Compton most excited. He remains amazed by new findings, whether in biochemistry or related fields. And despite taking on new roles, he remains committed to spending time in the lab continuing to investigate the dance of cell division, to try to make tumor cells dance in a more orderly fashion. "At the heart of many cancers is genome instability," he says. "So it's the general principle of instability in the genome that I think is a key event we have to get our heads around."

And he remains a strong believer in the capacity of scientific research to solve such problems. "The more knowledge we get," he says, "the more we understand about what's going on." ■