Larry Norton

Terrorist Cells

Larry Norton is pushing a radical new theory of how cancer spreads—and how to cure it.

By Robert Langreth

LARRY NORTON SEES some of the toughest cases as deputy physician-in-chief for breast cancer at Memorial Sloan-Kettering Cancer Center. He has access to the most advanced imaging machines, the best surgeons and numerous new tumor-fighting drugs. But often the fancy technology helps only temporarily. Sometimes a big tumor will shrink dramatically during chemotherapy. Then all of a sudden it comes back in seven or eight locations simultaneously.

Norton thinks adding more mathematics to the crude science of cancer therapy will help. He says that oncologists need to spend much more time devising and analyzing equations that describe how fast tumors grow, how quickly cancer cells develop resistance to therapy and how often they spread to other organs. By taking such a quantitative approach, researchers may be able to create drug combinations that are far more effective than the ones now in use. "I have a suspicion that we are using almost all the cancer drugs in the wrong way," he says. "For all I know, we may be able to cure cancer with existing agents."

His strategy is unusual among cancer researchers, who have tended to focus on identifying cancer-causing genes rather than writing differential equations to describe the rate of tumor spread. Yet adding a dose of numbers has already led to important changes in breast cancer treatment. The math of tumor growth led to the discovery that just changing the frequency of chemo treatments can boost their effect significantly.

In the future Norton's theorizing may lead to new classes of drugs. Researchers have always assumed tumors grow from the inside out. His latest theory, developed in collaboration with Sloan-Kettering biologist Joan Massagué, asserts that tumors grow more like big clusters of weeds. They are constantly shedding cells into the circulatory system. Some of the cells form new tumors in distant places. But other wayward cells come back to reseed the original tumor, making it grow faster. It's like hardened terrorists returning to their home villages after being radicalized abroad and recruiting even more terrorists, says Massagué, who in December showed that the self-seeding process happens in laboratory mice. If this model works in humans, it will open up new avenues for treatment. It suggests that to cure cancer, doctors need to come up with drugs that stop the seeding process. These drugs may be different from the current crop of drugs, which are designed to kill fast-dividing cells.

Among other mysteries, self-seeding may explain why tumors

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sometimes regrow in the same location after being surgically removed: not necessarily because surgeons failed to remove part of the original tumor but because some itinerant cancer cells returned later to their original home to start a new tumor in the same place.

Norton, 62, got a degree in psychology from the University of Rochester, then an M.D. from Columbia University. For a while during college he thought he would make a career as a saxophonist and percussionist. The remnant of that dream is a vibraphone in his office in Memorial's new 16-story breast cancer center.

Ever since he was a fellow at the National Cancer Institute in the 1970s he has been trying to come up with mathematical laws that describe tumor growth. He treated a lymphoma patient whose tumor shrank rapidly during chemotherapy. A year later the cancer returned worse than ever. The speed with which the tumor grew back didn't jibe with the prevailing notion that most tumors grew in a simple exponential fashion.

Working with NCI statistician Richard Simon, Norton came up with a new model of tumor growth based on the work of the 19th-century mathematician Benjamin Gompertz. The concept (which other researchers proposed in the 1960s) holds that tumor growth generally follows an S-shape curve. Microscopic tumors below a certain threshold barely grow at all. Small tumors grow exponentially, but the rate of growth slows dramatically as tumors get bigger, until it reaches a plateau. A corollary of this: The faster you shrink a tumor with chemo, the quicker it will grow back if you haven't killed it all.

Based on these rates of growth, Norton argued that giving the same total dose of chemotherapy over a shorter period of time would boost the cure rate by limiting the time tumors could regrow between treatments. The concept got a skeptical reaction initially. "People said it was a total waste of time," he recalls. It took decades before Norton was able to prove his theory. But in 2002 a giant government trial showed that giving chemotherapy every two weeks instead of every three lowered the risk of breast cancer recurrence by 26% over three years, even though the two groups got the same cumulative dose.

Today Norton's "dose-dense" regimen is common practice for certain breast cancer patients at high risk of relapse after surgery. Timing adjustments are also showing promise in other tumor types. Last October a Japanese trial found that ovarian cancer patients lived longer if they received smaller doses of chemotherapy weekly rather than getting larger doses every three weeks, according to results published in *The Lancet*.

"Larry has been one of the real thinkers in this area," says Yale University professor and former NCI head Vincent DeVita. But designing better treatment schedules doesn't get as much credit as the glamorous business of inventing drugs.

Norton's latest theory about how tumors grow is derived from Massagué's pioneering research. It is consistent with Gompertz's growth curves and ties together two essential features of cancer that researchers had long considered separate—cell growth and metastasis.

Joan Massagué showed killer cells can return to their original home.

Their collaboration started five years ago, when Massagué called Norton and shared a startling finding that was emerging from his laboratory. Massagué was studying how tumors spread from an organ such as the breast to the lungs, brain and other faraway places. He took human breast tumor cells, implanted them in mice and waited for metastases to occur. He analyzed cells that had metastasized to see what genes were overactive. None of the genes implicated in the spread of cancer to distant organs had to do with excessive cell division, it turned out. Instead, they all related to the ability to infiltrate and adapt to new environments.

The finding seemed to contradict doctors' impression that the fastest-growing tumors are also the most likely to spread. Pondering how to reconcile the two ideas, Norton and Massagué theorized that tumor cells released into the bloodstream sometimes are attracted back to the original tumor and help it expand.

Self-seeding may explain why large tumors tend to grow (in percentage terms) more slowly than small tumors: It could be that growth is a function of surface area rather than volume. Tumors that are efficient seeders may kill people by promoting the seeding process, not because they have a higher exponential growth rate.

It took Massagué four years of work to prove that self-seeding occurs in laboratory mice. Now comes the tricky part: coming up with drugs that block tumor seeding. Massagué and Norton have identified four genes involved in seeding and are testing for drugs to block them. Convincing drug companies to go along could be difficult; it's easier to see whether a drug shrinks tumors than to see whether it stops evil cells from spreading. But Norton believes that doing this hard work may be the key to a cure. **F**

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