MEDICINE

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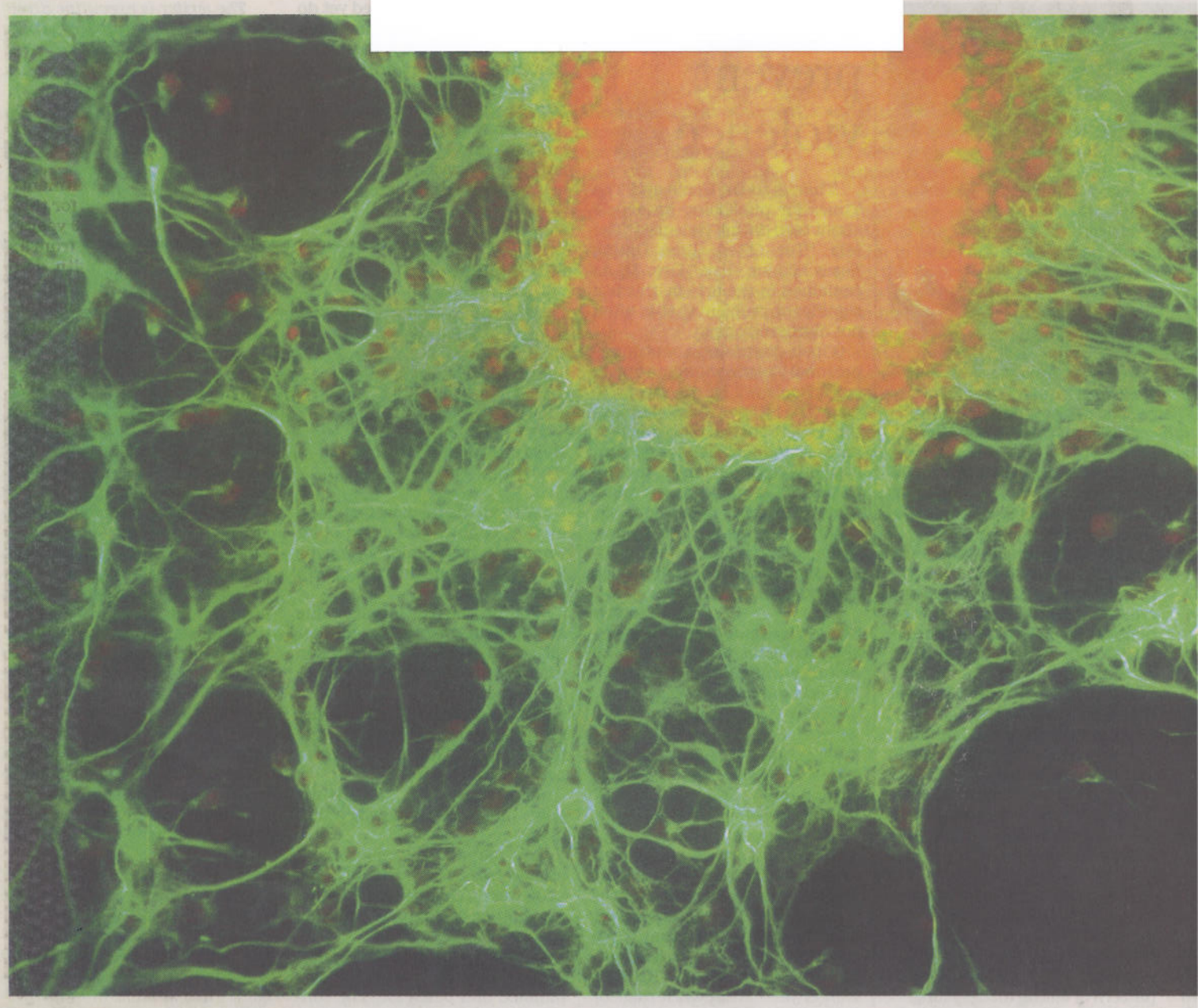

ROOT CAUSE? *Scientists hope that if drugs are designed to kill or disable "cancer stem cells" like this one, they could eradicate the tumor.*

IN THE LAB

War on cancer shifts

A few deadly cells in a tumor may drive the disease. Different drugs could be key to winning the battle.

By Chandra Shekhar
Special to The Times

In the decades since President Nixon's 1971 declaration of war on cancer, scientists have made great progress in their battle against many cancers, such as childhood leukemia, testicular cancer and Hodgkin's disease.

But progress against most other types of cancer has been less dramatic, according to National Cancer Institute statistics. The percentage of women with late-stage breast cancer who die within five years of diagnosis is still about the same — nearly 70%. And the story is similar with other deadly cancers, such as those of the lung, prostate and colon. Better screening and prevention have reduced the risk of dying from them, but once they take firm hold, the most aggressive therapy often fails.

Researchers believe they now understand why this happens. In focusing their efforts on trying to shrink tumors, cancer treatments may be missing a vital target.

Mounting evidence points to a handful of special cells within a tumor as the true culprits that trigger the disease and cause it to recur and spread. These so-called cancer stem cells seem to act like the more-familiar adult or embryonic stem cells in their ability to renew themselves while churning out cells of other types. What's worse, they may be more resistant than the bulk of the tumor cells to traditional cancer therapy.

With that growing knowledge comes a new approach to fighting cancer. Scientists hope that if they redesign drugs to specifically kill or disable the cancer stem cells, they could stop the cancer for good. Shrinking the tumor could come later.

This insight has triggered a race to develop a new generation of cancer drugs, some of which are already in human trials. "We are on the verge of a new era in cancer medicine where we target not the bulk of the tumor but its seeds," says Dr. Owen Witte, head of the Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research at UCLA. "We can then definitively treat the tumor instead of continuously suppressing its growth."

The idea that cancer originates from malignant stem cells has been around since the 19th century, when scientists observed that tumor tissue resembled embryo tissue under a microscope. Concrete evidence had to wait for recent advances in biotechnology such as ways to rapidly scan the activity of thousands of genes and techniques for breeding rodents with specific gene mutations.

Armed with these modern tools, in 1994 a research team led by John Dick, a senior scientist at the Toronto General Research Institute in Ontario, studied the effects of injecting human leukemia cells into mice lacking an immune system. "We found that only one cell in a million had the ability to initiate leukemia," Dick says.

Cancer stem cells rare

These rare, cancer-initiating cells displayed special molecules, or markers, on their surface that distinguished them from other leukemia cells. Furthermore, they were similar in certain ways to normal stem cells found in the body. "These leukemic stem cells are a caricature of normal development," Dick says. They resemble stem cells but give rise to tumor cells instead of healthy tissue.

Researchers have now implicated stem-like cells in many other types of cancer. In 2003, a team of researchers at the University of Michigan at Ann Arbor found that only about 1% to 10% of breast cancer cells had the ability to form new tumors. When injected into a mouse, as few as 200 of these distinctive cells were enough to form a tumor. Yet even 20,000 of the other tumor cells failed to form one when injected.

"Only a small fraction of the cells in a tumor drive the cancer," says Dr. Max Wicha, professor of internal medicine and a member of the research team. "The rest are dead-end cells."

A similar pattern has been found in brain, prostate and colon cancers, as well as other solid tumors. Wicha suspects that cancer stem cells in different tumor types may turn out to have common features. "A treatment that works against one type of cancer stem cell may work against other types as well," he says.

If a single, universal malignant stem cell type exists, it would be an attractive target for cancer therapy. But some researchers say that care is needed in interpreting the findings, which are mostly based on injecting human tumor cells into mice and other animals. Dr. Richard Hill, professor of medical biophysics at the University of Toronto, says this method might not be identifying cancer stem cells, but be identifying human cells that are able, for some reason, to survive in the alien mouse environment.

Hill also thinks it may be hard to pinpoint and eradicate the subpopulation of cells responsible for perpetuating cancer in humans. "There may be many such cell types," he says. "Targeting them is going to be more problematic than we think."

Many other questions remain — such as whether the "dead-end" tumor cells can turn into cancer stem cells and where, within the tumor, those cancer stem cells lurk. Scientists also don't know if drugs that kill cancer stem cells would also kill normal stem cells, possibly causing toxicity. "This is a very exciting development," Hill says. "But we don't want to be in a mode where hype exceeds reality."

Several drugs based on the stem cell model of cancer are being developed. Some target specific markers on cancer stem cells and kill the cells using toxic molecules. Others aim to paralyze the cells by blocking the biochemical processes they use to renew themselves. A third category tries to force the cells to mature, or "differentiate," into less harmful tumor cells.

A hunt for new therapies

More than 50 research groups and nearly 20 small companies are on the hunt for such therapies, says John Bates, an analyst with the UK-based consultancy company BioPharm Reports who published a report on the topic last year. Bates says big pharmaceutical firms are also interested in the concept of cancer stem cells but may want to see more results before investing in it. "In the meantime, small companies appear to be picking up the baton and running with it," he says.

One company to take this approach is New York-based Stemline Therapeutics. One of the company's drugs couples a cell-killing toxin with a molecule that homes in on a variety of blood cancer cells. When tested on mice, the drug proved effective in killing leukemia stem cells while sparing normal stem cells. It is now in early human trials to test for safety, says company Chief Executive Dr. Ivan Bergstein.

Another leukemia remedy poised to enter human trials comes from the lab of Dr. Craig Jordan of the University of Rochester Medical Center in New York state. Based on a chemical from the feverfew plant, the drug causes leukemia stem cells to undergo a kind of programmed death, known as apoptosis.

In studies on leukemia cells grown in the lab, the drug proved toxic to leukemia cells, including cancer stem cells, but nearly harmless to normal blood cells. The drug also showed anti-leukemia stem cell activity in dogs, Jordan says.

Similar treatments developed by other researchers for blood, brain, breast and colon cancers may also soon enter clinical trials.

Jordan cautions that most of the work so far on cancer stem cells has been in the laboratory and may have a long way to go before benefiting patients. "As yet, very little has happened that has clinical relevance," he says. "But we are right on the cusp of making the transition."

A cell's 'neighborhood' might make it go bad

By Chandra Shekhar
Special to The Times

The realization that cancers may be driven by stem cells isn't the only new concept in oncology. Scientists are also taking a closer look at the role of the "neighborhood" in which a cell resides — its microenvironment.

"A healthy or unhealthy microenvironment may determine if a stem cell is normal or cancerous," says Mark LaBarge, a postdoctoral fellow in life sciences at the Lawrence Berkeley National Laboratory.

Every cell, be it normal or cancerous, lies among a multitude of other cells, attached to a support structure known as the extracellular matrix. The space outside of a cell teems with a variety of chemicals. Studies offer intriguing clues to the role of this chemical-rich microenvironment in cancer.

In the 1980s, experiments with chickens showed that an embryo carrying a so-called oncogene — a genetic mutation associated with cancer — could develop into a normal, cancer-free adult bird. When cells from the bird were cultured in the lab, however, they quickly turned cancerous. And if such a bird was wounded, a tumor developed at the site of the injury.

These and similar findings suggest that oncogenes alone can't form tumors — a microenvironment marred by wounding, swelling, aging, or other causes may also play a part. The findings also suggest, conversely, that a healthy microenvironment may act to suppress tumors.

LaBarge and his colleagues are testing the idea further by comparing the response of normal human breast stem cells and mutated, cancer-prone breast stem cells to different microenvironments. (They've created a variety of microenvironments in the lab using combinations of proteins present in breast tissue.)

A microenvironment link to cancer may explain why many Japanese women who were in puberty during the nuclear attacks on Hiroshima and Nagasaki went on to develop breast cancer 20 to 30 years later, LaBarge says. The radiation fallout would have damaged the victims' breast stem cells, which would have turned cancerous as the breast microenvironment deteriorated with age. "Mutated stem cells may very well be the root of cancer," LaBarge says. "But we don't think they turn nasty until something goes wrong with the microenvironment."

Many compounds that affect the tumor microenvironment have shown promise in treating cancer. The drug bevacizumab (Avastin), which starves tumors by blocking the formation of blood vessels in them, was approved in 2004 for treating some types of colon and lung cancers. Nonsteroidal anti-inflammatory drugs such as aspirin also seem to protect against colon cancer when given in large doses. A type of chemical called bisphosphonate that binds to bone tissue may prevent breast, prostate and other tumors from spreading to the bones. These and various other compounds are in human trials.