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Screening Could Lead to More Potent Cancer Drugs

By [NICHOLAS WADE](#)

Researchers have discovered a way to identify drugs that can specifically attack and kill [cancer stem cells](#), a finding that could lead to a new generation of anticancer medicines and a new strategy of treatment.

Many researchers believe that [tumor](#) growth is driven by cancerous stem cells that, for reasons not understood, are highly resistant to standard treatments. [Chemotherapy](#) agents may kill off 99 percent of cells in a tumor, but the stem cells that remain can make the cancer recur, the theory holds, or spread to other tissues to cause new cancers. Stem cells, unlike mature cells, can constantly renew themselves and are thought to be the source of cancers when, through mutations in their DNA, they throw off their natural restraints.

A practical test of this theory has been difficult because cancer stem cells are hard to recognize and have proved elusive targets. But a team at the [Broad Institute](#), a [Harvard-M.I.T.](#) collaborative for genomics research, has devised a way of screening for drugs that attack cancer stem cells but leave ordinary cells unharmed.

Cancer stem cells are hard to maintain in sufficient numbers, but the Broad Institute team devised a genetic manipulation to keep [breast cancer](#) stem cells trapped in the stem cell state.

The team, led by Piyush B. Gupta, screened 16,000 chemicals, including all known chemotherapeutic agents approved by the [Food and Drug Administration](#). The team reported in the Thursday issue of [Cell](#) that 32 of the chemicals selectively went after cancer stem cells. These particular chemicals may or may not make good drugs, but the screening system proves, the researchers say, that it is possible to single out cancer stem cells with drugs that leave ordinary cells alone. Only one of the 32 chemicals is approved as a drug for cancer.

Another approach to concentrating on cancer stem cells, based on the use of [antibodies](#), was reported this month by [OncoMed Pharmaceuticals](#), a company founded by Dr. Max Wicha and [Michael F. Clarke](#), a Stanford researcher who in 2003 discovered cancer stem cells in breast [tumors](#).

If effective drugs against cancer stem cells can be developed, one obvious strategy would be to use them in combination with standard chemotherapeutic agents, so that all types of cells in a tumor could be attacked. That way, cancer would be attacked as [AIDS](#) is now — with a cocktail of chemicals that blocks all escape paths. Both the AIDS virus and cancer cells can change DNA to dodge an effective drug, but are thought to perish if confronted with many drugs at once.

Standard chemotherapy is effective because the chemicals are applied in such large doses that they kill all cells. But this approach is stressful for the patient.

“You could probably lower the doses considerably with a combination of drugs that attacked specific types of cell,” Dr. Gupta said.

[Eric S. Lander](#), director of the Broad Institute, said: “If we make a drug that kills 99.9 percent of the cells in a tumor but fails to kill the 0.1 percent, that is the real problem. It’s a pyrrhic victory.”

Dr. Lander said that given the new screening system and the idea of using combinations of drugs against cancer, there was “a potential for a real renaissance in cancer therapeutics.”

“We have not been able to do that yet with cancer,” he added, “but if we could, it’s a numbers game, and we win.”

The cancer stem cell theory has been thrust into the spotlight in recent years with the discovery of stem cells in many types of solid tumors, including those of the breast, brain, prostate, colon and pancreas. This month, a Stanford team led by Irving Weissman reported finding the stem cells of [bladder cancer](#).

But the theory is not without critics.

“The cancer stem cell hypothesis has in the past year been challenged on many fronts,” said Bert Vogelstein, a leading cancer geneticist at [Johns Hopkins University](#). “For example, a paper on melanomas last year showed that 100 percent of [melanoma](#) cancer cells were cancer stem cells.”

If many of a tumor’s cells are stem cells, then existing chemotherapy agents are clearly killing them, Dr. Vogelstein said, and the cancer stem cell theory is not an effective guide to finding new drugs.

The theory has also aroused opposition because, in its extreme, it implies that standard chemotherapy goes after the wrong targets and is ineffective.

“It’s the most amazing polarity that I’ve seen,” Dr. Clarke, the Stanford researcher, said of the debate over stem cells among cancer researchers. “It’s like two religions fighting.”

Some advocates of the idea believe that to dissolve tumors, it would be necessary to go after only cancer stem cells, if such drugs existed. But the Broad Institute team and others take the view that a combination of drugs attacking each of the types of cells in a tumor would be best.

One reason for using a combination of drugs is the suspicion that mature cancer cells may be able to convert themselves back into stem cells, a route that is apparently prohibited to normal mature cells.

“The possibility is that the nonstem cells in a tumor may regenerate de novo new stem cells,” said Robert Weinberg, a leading cancer biologist at M.I.T. and, a co-author with Dr. Lander of the Cell report. “If one had ways of treating both the stem cells and the nonstem cells, then the de novo generation of stem cells would be dealt with.”

The basic insight of the cancer stem cell theory is that there is a hierarchy of cells in a tumor, with the stem cells at the top generating the mature cells that are the majority. Most researchers accept that this is a good description of leukemias because Gleevec, a highly effective drug for [chronic myelogenous leukemia](#), does not kill stem cells, and the leukemia returns if the treatment is stopped.

But with solid tumors, Dr. Vogelstein said, “the jury is out.” If stem cells are common in solid tumors, not just a small resistant reservoir of cells, “then there’s no difference between the stem cells and the bulk cancer — so a screen for drugs to kill melanoma cells is by definition also going to kill the melanoma’s cancer stem cells.”

Still, in Dr. Vogelstein’s view, the Broad Institute’s new screening method is important whether or not the cancer

stem cell theory is correct. “Because most of the compounds in use now clearly aren’t doing the job we’d all like,” he said, “then novel methods for screening could be extremely valuable.”

The Broad Institute researchers hope that pharmaceutical companies will use their screening method to begin to develop drugs against cancer stem cells.

This article has been revised to reflect the following correction:

Correction: September 3, 2009

An article on Aug. 14 about drugs to attack cancer stem cells referred imprecisely to the founding of OncoMed Pharmaceuticals, a pioneer of such drugs. While Dr. Michael F. Clarke started the firm, he did not do so alone; Dr. Max Wicha was a co-founder.

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