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Scientists discover bladder cancer stem cell

BY KRISTA CONGER

Researchers at Stanford's School of Medicine have identified the first human bladder cancer stem cell and revealed how it works to escape the body's natural defenses.

"This is first time we've found this 'don't eat me signal' in a stem cell of a solid cancer," said [Irving Weissman](#), MD, the Virginia & D.K. Ludwig Professor for Clinical Investigation in Cancer Research at the medical school. "We're now moving as fast as we can to look at other tumors to see if this is a universal strategy of all or most cancer stem cells." If so, the signal may be a valuable therapeutic target for many types of cancers.

Weissman, who directs Stanford's [Stem Cell Biology and Regenerative Medicine Institute](#), is also a member of Stanford's [Cancer Center](#). He is the senior author of the work, published in the *Proceedings of the National Academy of Sciences* on Aug. 3. His laboratory recently published two studies in the journal *Cell* showing that human leukemia stem cells use the same protective molecular signature on their surface to evade cells called macrophages that engulf and destroy sick or cancerous cells.



Irving Weissman

Like queen bees, cancer stem cells are constantly replenishing their "hive" of tumor cells. Therapies that kill off the workers might reduce the size of the tumor and the symptoms of the disease, but will ultimately be unsuccessful unless they also eliminate the stem cells working behind the scenes.

Support for the current research came from a gift from Jim and Carolyn Pride. In 2002, the couple attended a talk by Weissman in which he discussed the then-emerging idea of cancer stem cells. Jim Pride, who had been diagnosed with bladder cancer, approached Weissman after the talk and offered to sponsor a post-doctoral fellow — Keith Syson Chan, PhD — to investigate whether there was a bladder cancer stem cell.

"The whole concept of cancer stem cells is that they are often resistant to current therapies," said Chan, who is the first author of the work, "and, at least in the case of bladder cancer, they drive the progression of the disease." Identifying and following these cells may be one way to monitor tumor status, the researchers feel, and targeting the cells for destruction may be a good way to eradicate the cancer. Although Pride lost his life to the disease in 2004, his gift launched the experiments necessary to obtain NIH funding for the project.

There are two main types of bladder cancer: one that invades the muscle around the bladder and metastasizes to other organs, and another that remains confined to the bladder lining. Unlike the more-treatable non-invasive cancer — which comprises about 70 percent of bladder cancers — the invasive form is largely incurable. Although about 15 percent of non-invasive cancers eventually become invasive, there is no current diagnostic method that can predict which will progress.



Chan used breast cancer stem cell markers to identify a subpopulation of human bladder cancer cells with stem cell qualities: The cells formed tumors when transplanted into mice with compromised immune systems. He then looked to see which genes were more highly expressed in these cells than in other bladder cancer cells from the same tumor. He found that most, but not all, non-invasive bladder cancers expressed lower levels of these genes than did invasive cancers. Further research showed that the anomalous non-invasive cancers with higher levels of gene expression behaved more aggressively: About 80 percent recurred within 25 months of initial diagnosis, whereas only about 20 percent of the low-expressing tumors did so.

"The fact that we were able to pull out the subpopulation of these cancers that will become invasive is an important step in identifying those that will be more dangerous," said Chan. "It may be possible to follow the progress of the tumor by analyzing the expression levels of these genes."

Chan found particularly interesting one gene, which encodes a cell-surface molecule called CD47. He knew from previous research in Weissman's lab that CD47 works to prevent leukemia cells from being engulfed by macrophages by binding to a molecule on the surface of the macrophage. Blocking this interaction with an antibody specific for CD47 allows the macrophages to swallow the leukemia cells. When he tried a similar experiment with the bladder cancer stem cells in a test tube, the same thing happened — human macrophages began to destroy the cancer cells.

"Leukemia is totally different from the kind of epithelial cancer we see in the bladder," said Chan, "so it was very exciting to see that these two kinds of cancer stem cells use a similar mechanism to escape

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the macrophages. It's also very interesting to find that macrophages seem to be playing such a major role in cancer progression."

The researchers are now investigating whether CD47 is expressed at high levels on other cancer stem cells and pondering ways to help circulating macrophages better infiltrate solid tumors — always with an eye towards therapy.

"Jim knew our research results would be too late for him," said Weissman, who visited Pride in the hospital before he died, "but he hoped that they would help others."

In addition to Weissman and Chan, other Stanford collaborators on the paper include post-doctoral fellow Inigo Espinosa, MD; graduate student Mark Chao; post-doctoral fellow David Wong, PhD; senior research associate Laurie Ailles, PhD; post-doctoral fellow Max Diehn, MD, PhD; professor of urology [Joseph Presti](#), MD; associate professor of dermatology [Howard Chang](#), MD, PhD; professor of pathology [Matt van de Rijn](#), MD, PhD; and professor of urology [Linda Shortliffe](#), MD.

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