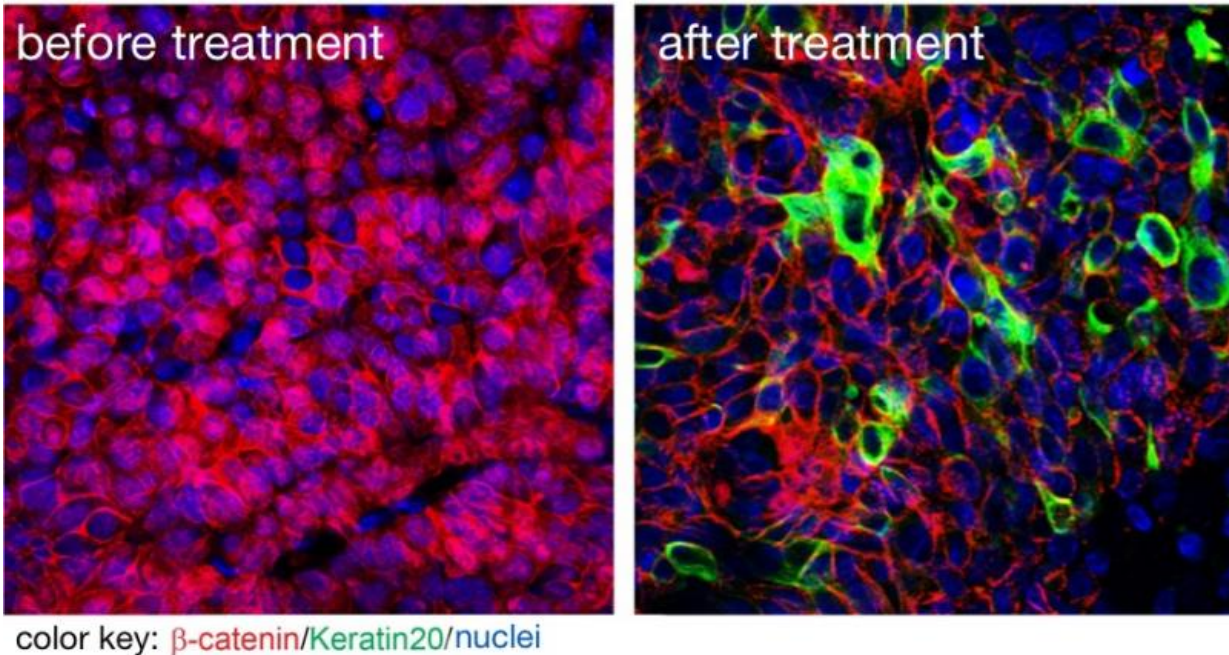


# Hacking the programs of cancer stem cells

January 25 2016, by Russ Hodge

---



A new inhibitor suppresses tumor growth and cancer stem cells. The image on the left shows beta catenin (red) in cell nuclei indicating that these are cancer stem cells. The image on the right shows that the new substance successfully removed beta catenin from the nuclei. Credit: Picture by Liang Fang for the MDC

All of the cells in a tumor are the offspring of a single, aberrant cell, but they are not all alike. Only a few retain the capacity of the original cell to create an entire tumor. Such cancer stem cells can migrate to other tissues and become fatal metastases. To fully cure a patient's cancer, it is

crucial to find and eliminate all of these cells because any that escape can regenerate the tumor and trigger its spread through the body.

Liang Fang and his colleagues in Walter Birchmeier's group, working with the Screening Unit and Medicinal Chemistry Group of the FMP and the campus company EPO, have now discovered a molecule that interrupts biochemical signals essential for the survival of tumor [cells](#) called Wnt-addicted [cancer stem cells](#). The discovery is the product of an approach known as "rational drug design," targeting specific molecules based on a thorough understanding of the biology of a disease and the biochemical signals that support it. The work appeared ahead of print in the online edition of *Cancer Research*.

A main challenge for any cancer therapy is the need to eliminate tumor cells without damaging their healthy neighbors. Since cancer arises from the body's own tissues, it is difficult to find a therapeutic approach that can distinguish these cells. And even if a drug overcomes this hurdle, it may not work against cancer stem cells, whose biochemistry is subtly different than that of the majority of cells in a tumor.

Liang Fang and his colleagues took advantage of years of research carried out by Birchmeier's lab on the biochemistry of cancer-related signaling within cells. Much of their work has been devoted to unraveling a molecular network called the Wnt signaling pathway, which plays an essential role in healthy embryonic development. In adults the system helps maintain the structure and integrity of tissues. Its activity must be carefully controlled, but in many cancers the system is switched on inappropriately. Tumor cells hijack it to promote their uncontrolled growth and survival and the migrations seen in metastases.

Wnt is named for a group of secretory proteins. Like most pathways, the Wnt system is normally activated when a Wnt molecule is secreted, binds to receptors on neighboring cells, and triggers a chain of

biochemical signaling within them. The chemical message is passed from molecule to molecule until it activates a transcription complex that can enter the nucleus and switch on genes. This causes the cell to produce RNAs and proteins in response to the environmental stimulus. In cancer, signaling can become independent from such stimuli, through mutations in oncogenes and [tumor suppressor genes](#) "downstream" in the Wnt pathway, which become activated all the time although they have not received a signal.

Many drugs have their effects by preventing receptors from receiving signals. This strategy wouldn't work in the case of cancers involving Wnt because the defects occur later in the pathway. It's at these points downstream that scientists hope to find suitable targets for an intervention, which will only disrupt the signal in [defective cells](#).

In the current study Liang Fang and his colleagues focused on a component of the Wnt pathway called beta-catenin. "In the absence of an environmental signal, beta-catenin is locked out of the cell nucleus," Birchmeier says. "It is linked to a complex of proteins that ultimately break it down. External signals can release it from this 'destruction complex,' and it travels to the cell nucleus."

There beta-catenin binds to transcription factors such as the protein TCF4, and in combination the molecules activate specific target genes. Over the past few years Birchmeier's lab and others have shown that cancer stem cells require continual stimulation via this pathway to survive and maintain the properties that make them so dangerous.

It might be possible, the scientists reasoned, to interrupt the interaction between beta-catenin and TCF4 with a drug. Contacts between two proteins are normally very difficult to destabilize with the small molecules that make up drugs. Proteins usually bind over large areas of their surfaces, which means that a comparatively small obstacle won't

prevent the interaction.

But the crucial points of contact between beta-catenin and TCF4 appeared to be small "hotspots" which suggested that an inhibitor might block it. Liang Fang took the problem to the campus Screening Unit and Medicinal Chemistry group, a partnership between the MDC and FMP. The facility has high-throughput technology platforms and a "library" of tens of thousands of substances that scientists use to search for inhibitors.

Jens von Kries, the head of the Screening facility, is a former member of Birchmeier's lab. He was already thoroughly acquainted with the beta-catenin story: in the mid-1990s he had participated in the discovery that the molecule binds to a range of transcription factors, including TCF4.

"From the beginning this looked like an ideal problem for the unit," Jens says. "It would have been much harder to interfere with other beta-catenin interactions that cover large surfaces – imagine trying to displace an elephant by putting a pea on the ground."

To find an inhibitor, the scientists used technologies called AlphaScreens and ELISAs. The latter involved mounting TCF4 molecules on plastic surfaces in tiny plates, then adding beta-catenin and compounds from the library, one by one. If the substance interfered with the interaction, the two molecules would bind at a low rate. The screens turned up a compound they called LF3 that strongly inhibited binding. Martin Neuenschwander and Edgar Specker, scientists in the Screening Unit and Medicinal Chemistry group, repeated the experiment with 10 chemically similar compounds; again LF3 turned out to be the most potent inhibitor.

This demonstrated the effect under pure, "test tube" conditions – would it also work in cells? Liang developed a line of cells using a fluorescent "reporter" that would indicate whether beta-catenin and TCF4 managed

to bind. LF3 was equally effective at preventing their interactions in cells.

The next step was to determine whether the compound would have any effect on the properties of [tumor cells](#). They discovered that LF3 blocked several crucial features: it interrupted the cell cycle, preventing them from replicating, and strongly reduced their ability to migrate. LF3 didn't seem to affect [healthy cells](#) at all.

All of these were promising signs, but a final test remained to be carried out. The scientists turned to the company EPO, a campus-based spin-off of the MDC, to develop lines of mice with tumors derived from human colon cancer stem cells. The company specializes in creating mouse models from individual patients' tumors, then testing the animals with a battery of known drugs in hopes of finding one that will effectively combat a specific case of cancer. In this case, all the animals developed tumors, even when injected with a relatively small number of enriched cancer cells.

The animals were then treated with LF3. "We observed a strong reduction of tumor growth," Walter Birchmeier says. "What remained of the tumors seemed to be devoid of cancer [stem cells](#) – LF3 seemed to be powerfully triggering these cells to differentiate into benign tissue. At the same time, no signaling systems other than Wnt were disturbed. All of these factors make LF3 very promising to further develop as a lead compound, aiming for therapies that target human tumors whose growth and survival depend on Wnt signaling."

**More information:** Fang L, Zhu Q, Neuenschwander M, Specker E, Wulf-Goldenberg A, Weis WI, von Kries JP, Birchmeier W. A small-molecule antagonist of the  $\beta$ -catenin/TCF4 interaction blocks the self-renewal of cancer stem cells and suppresses tumorigenesis. *Cancer Res.* 2015 Dec 8. pii: canres.1519.2015.

Provided by Helmholtz Association of German Research Centres

Citation: Hacking the programs of cancer stem cells (2016, January 25) retrieved 26 April 2024 from <https://medicalxpress.com/news/2016-01-hacking-cancer-stem-cells.html>

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.