

One-two punch knocks cancer cells out

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A classic boxing move, the "one-two punch," could also be effective against cancer: a left jab knocks cancer cells senseless, quickly followed by a right hook that knocks them out altogether. Researchers at the Netherlands Cancer Institute have shown that cancer cells are vulnerable to this kind of approach. "This is a beautiful, universal principle, that could be used for all forms of cancer." On October 2nd, the researchers publish their results in *Nature*.



Many combinations of cancer medicines could theoretically work very well together, but in practice these combinations are too toxic for the body to withstand. The researcher René Bernards has devised a possible alternative: the 'one-two punch," named after the effective combination of two quick successive punches in boxing. "The first medicine creates a weakness in the cancer cell and the second deals a merciless blow to the weakened cell. So while the two medicines are not given simultaneously, you still get the benefit of their synergetic effect."

Sleeping cells

At the Netherlands Cancer Institute, Bernards and his colleagues investigated whether this worked. As the cancer cell's weak spot they chose a well-known cell reaction to stress: <u>senescence</u>. Under stressful circumstances ordinary body cells can put themselves into a kind of sleep mode. They do so, for instance, if their DNA is damaged. This is useful, because they then stop proliferating and the body's own immune system can clear them up.

In the laboratory Bernards and his colleagues found a way to bring this about in liver cancer cells. This was doubly useful: The cells stopped proliferating, and they had a vulnerability that could be exploited, since the researchers also discovered a way to knock out the 'sleeping' cells. Working with liver cancer cells, the researchers finally identified a combination of medicines that had good results in mice (see box).

Exploiting a weakness

"The great thing about this approach is that it could work for a wide range of tumor types," says Bernards. "In principle, senescence can be induced in all kinds of tumors." Provided you know how, and how you then deal the sleeping cells a death blow. Bernards recently founded a



company, Oncosence, which is entirely devoted to identifying substances that induce senescence in cancer cells and other substances that kill these specific cells. The second 'punch' is essential. "It seems that senescent cancer cells can actually encourage tumor growth and metastasis if the immune system, or a therapy, does not remove them."

The idea of the "one-two punch" arose out of earlier research in which researchers at the Netherlands Cancer Institute exploited a weak point in resistant skin <u>cancer cells</u> in order to destroy them. "The principle of exploiting a weakness was one we wanted to apply more widely, and we identified senescence as a universal response that could be used in this way." Having been awarded a substantial grant by the European Research Council, the research group is now searching for different ways to induce senescence in <u>cancer cells</u>.

More information: Cun Wang et al. Inducing and exploiting vulnerabilities for the treatment of liver cancer, *Nature* (2019). <u>DOI:</u> 10.1038/s41586-019-1607-3

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