Study shows low-dose chemotherapy regimens could prevent tumor recurrence in some cancers

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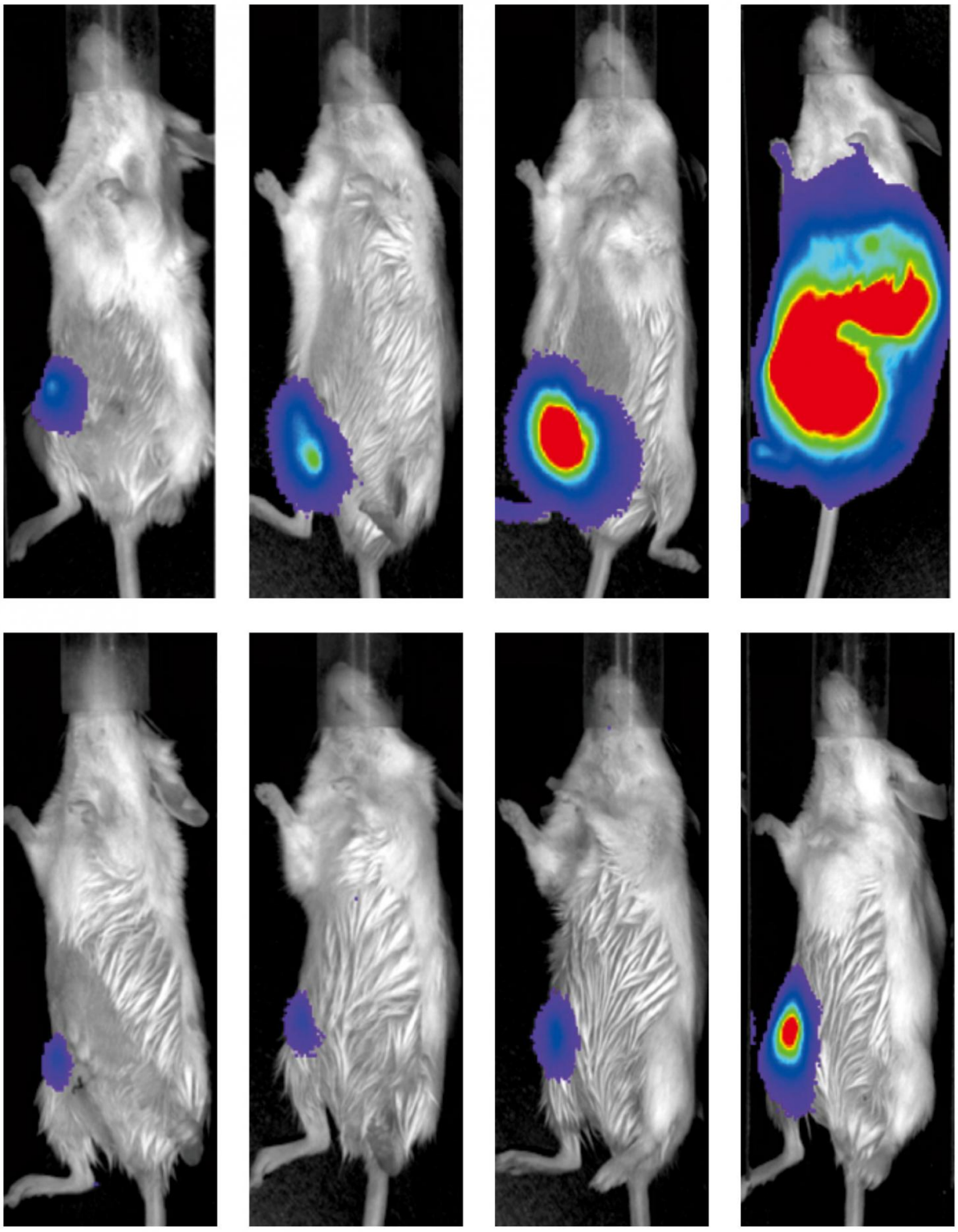

Bioluminescence imaging shows that tumors associated with fibroblasts treated with the maximum tolerated dose of doxorubicin (top) grow larger over time

than tumors associated with fibroblasts treated with frequent, low doses of the same drug (bottom). Credit: Chan et al., 2016

Conventional, high-dose chemotherapy treatments can cause the fibroblast cells surrounding tumors to secrete proteins that promote the tumors' recurrence in more aggressive forms, researchers at Taipei Medical University and the National Institute of Cancer Research in Taiwan and University of California, San Francisco, have discovered. Frequent, low-dose chemotherapy regimens avoid this effect and may therefore be more effective at treating certain types of breast and pancreatic cancer, according to the murine study "Metronomic chemotherapy prevents therapy-induced stromal activation and induction of tumor-initiating cells," which will be published online November 23 in *The Journal of Experimental Medicine*.

Chemotherapy drugs are usually administered to cancer patients every few weeks at a high "maximum tolerated" dose. Though this approach kills the majority of tumor cells, it often spares a small number of tumor-initiating cells (TICs) that subsequently give rise to new tumors. Moreover, these recurring tumors are often more aggressive and able to metastasize to other tissues, in part because high doses of chemotherapy drugs also affect cells in the stromal tissue that surrounds tumors, including immune cells and blood vessel endothelial cells.

Kelvin Tsai at Taipei Medical University and Valerie Weaver at the University of California, San Francisco, decided to investigate the effect of chemotherapy on fibroblasts, a major component of the stroma in desmoplastic tumors such as breast cancer and pancreatic ductal adenocarcinoma.

The researchers found that, in response to the maximum tolerated doses

of several commonly used chemotherapy drugs, breast cancer-associated fibroblasts secrete large amounts of cell signaling proteins called ELR+ chemokines. These proteins promoted tumor growth and metastasis in mice by converting neighboring cancer cells into TICs, stimulating the formation of blood vessels within the tumor and enhancing the recruitment of immune cells called macrophages.

Recent studies have suggested that treating patients with low doses of chemotherapy drugs at more frequent, even daily, intervals may be more effective than traditional chemotherapeutic approaches. Tsai and colleagues found that such "low-dose metronomic" regimens did not induce the production of ELR+ chemokines by cancer-associated fibroblasts. This, in turn, reduced the fibroblasts' ability to promote TIC formation, blood vessel growth, and macrophage recruitment.

Mice with breast cancer or pancreatic ductal adenocarcinoma therefore responded better to low-dose metronomic chemotherapy, surviving longer than mice treated with the maximum tolerated dose. "Our results lend support to the emerging paradigm that stroma-derived signals contribute to tumor pathology," Tsai says. "They also suggest that low-dose metronomic chemotherapy or targeting the chemokine signaling mediated by chemo-treated fibroblasts may improve the therapeutic outcome in desmoplastic cancers."

More information: Chan et al. 2016. *J. Exp. Med.* DOI: 10.1084/jem.20151665

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