

Dogs inhale immunotherapy to test lung cancer treatment

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A protein that the body naturally produces could become an important new immunotherapy drug in the cache of cancer-fighting tools available to oncologists. UC Davis cancer researchers for both companion dogs and humans joined scientists from other institutions to study a new approach that triggers the body's defense mechanisms, its T-cells and natural killer (NK) cells, to respond and destroy cancer.

Surgical oncologist Robert J. Canter with UC Davis Comprehensive Cancer Center and canine oncologist Robert B. Rebhun with the UC Davis School of Veterinary Medicine are corresponding authors for a study just published in the *Journal for ImmunoTherapy of Cancer*.

In the first-of-its-kind Phase 1 clinical trial, 21 pet dogs of various breeds that had metastatic lung disease resulting from osteosarcoma or melanoma were treated with protein interleukin-15 (IL-15). Although previously recognized for immunotherapy properties, IL-15 has undergone few [human clinical trials](#) because of toxicity risks associated with concentrated doses.

"No one previously had administered IL-15 as an inhaled treatment in dogs to deliver it directly to the site of the cancer. We came up with that idea as a means of reducing exposure to the rest of the body, in order to improve the benefit-risk ratio, to improve the immune stimulating effects, and to reduce toxicity," Canter explained. "In this study, we used interleukin-15 to reinvigorate the immune system to make it recognize the [cancer cells](#) that had evaded the immune system and eliminate them."

The research shows that amplified concentrations of IL-15 can stimulate immune system defenses against some types of cancers in dogs. IL-15 is one of several types of cytokines—substances that have signaling and regulating functions in [immune system](#) activity.

"As part of our comparative oncology research, we are strong advocates of clinical trials in companion dogs, especially for immunotherapy, as a way to speed bench-to-bedside translation," said Canter, who is chief of the UC Davis Division of Surgical Oncology and co-director of the comparative oncology training program at UC Davis. "The cancers that afflict dogs, including sarcomas, [brain tumors](#), lymphoma and melanoma, are incredibly similar to cancers that humans develop." For instance, osteosarcoma and melanoma that develop elsewhere in the body commonly spread to the lung, in dogs as well as humans.

Methodology

In the study, conducted between October 2018 and December 2020, the dogs inhaled a mist containing IL-15 twice daily. Doses were increased over time, to help determine not only effectiveness, but also tolerable levels and the ceilings above which toxicity would result. Dogs exhibited significant responses within 14 days after they began inhaling the IL-15 mist.

Tumors shrank dramatically in two dogs in the

study, including one that went into complete remission for more than a year. Cancer that had been growing rapidly in five other dogs stabilized for several months. "Our overall response rate, the clinical benefit rate, was close to 40%," Canter said.

For that and other reasons, additional studies are needed, noted Rebhun, a professor in the UC Davis School of Veterinary Medicine's Department of Surgical and Radiological Sciences.

"The inhaled IL-15 responses that we've seen in dogs are better than prior human studies, but clinical benefit is seen in less than half of the dogs. Using IL-15 in people has led to potentially favorable immune responses but has not yielded good tumor responses. This indicates that combining IL-15 with other immunotherapies may result in additive or synergistic responses," said Rebhun, who holds the Maxine Adler Endowed Chair in Oncology and is the associate director of the cancer program in the Center for Companion Animal Health.

Key findings

In his view, the study yielded two significant findings: the therapy was well tolerated, and even a short two-week course of inhaled IL-15 could lead to sustained suppression of advanced and diffuse metastatic cancer. Both he and Canter noted that in eventual clinical application, IL-15 likely would be used not as a standalone therapy, but as a reinforcement in combination with other treatments.

"All of the canine patients in this study had advanced metastatic cancer, and the majority already had received prior chemotherapy, radiation therapy and, in some cases, immunotherapy. Studies are ongoing now to see whether we can predict which patients might respond to this therapy based on properties of the tumor or the patient's immune status," Rebhun said.

"This may help us identify patients that might respond to this therapy, as well as help us understand how to potentially combine other immunotherapies to improve response rates. We are grateful to the extremely dedicated clients who sought any and all possible care for their pets,

and even elected to enroll them in this study, and even delivered the inhaled IL-15 to their dogs at home—in hopes that it could benefit their dog, other dogs, or possibly even people with advanced metastatic cancer," Rebhun said.

More information: Robert B Redhun et al, Inhaled Recombinant Human IL-15 in Dogs with Naturally Occurring Pulmonary Metastases from Osteosarcoma or Melanoma: A Phase 1 Study of Clinical Activity and Correlates of Response, *Journal for ImmunoTherapy of Cancer* (2022). DOI: [10.1136/jitc-2022.004493](https://doi.org/10.1136/jitc-2022.004493). jitc.bmj.com/content/10/6/e004493

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