

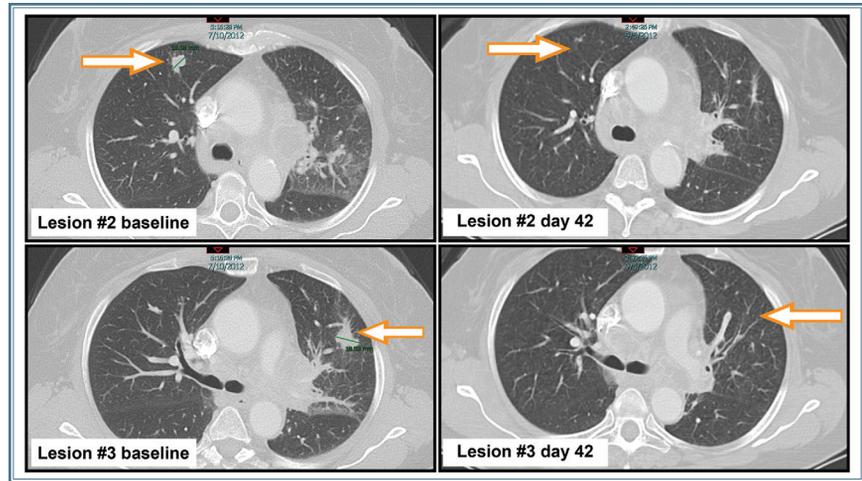
# A New Immunotherapy Makes Its Clinical Debut

*A first-in-human trial of the cytokine IL-15 in metastatic cancer spurs new research.*

There comes a moment in therapeutic development when the preclinical studies are compelling and the next step is a first-in-human study. For Thomas Waldmann, M.D., Co-Chief of CCR's Lymphoid Malignancies Branch, and Kevin Conlon, M.D., Staff Clinician in the Branch, and colleagues, that moment arrived four years ago in their development of interleukin-15 (IL-15) as an immunotherapy. Published earlier this year in the *Journal of Clinical Oncology*, the results of their phase 1, dose-escalation trial encourage the team to continue their efforts with further clinical studies.

Waldmann co-discovered the cytokine in the mid-1990s (see "IL-15 Prepares for Its Clinical Debut," *CCR connections* Vol. 5, No. 2). Like IL-2, which was developed by Steven Rosenberg, M.D., Ph.D., Chief of CCR's Surgery Branch, as the first effective immunotherapy for human cancers (see "Immunotherapy's First Cure," *CCR connections* Vol. 8, No. 1), IL-15 shares an ability to stimulate the attack dogs of the immune system: natural killer (NK) and CD8+ T cells. Unlike IL-2, it does not simultaneously activate regulatory or suppressor T cells, cause activation-induced cell death in the immune system, or induce a capillary leak syndrome in animal models. This difference has made IL-15 an attractive lead for therapeutic development.

To secure enough clinical-grade IL-15 for a human trial, Waldmann, Conlon, and their team turned to NCI's Biological Resources Branch, which used the bacteria *Escherichia coli* to produce recombinant human IL-15. After preclinical toxicology testing of bolus injections in non-human primates revealed no causes



Computed tomography (CT) chest images of a melanoma patient before treatment with recombinant human interleukin-15 (rhIL-15) and 42 days after treatment. Orange arrows indicate lung metastases.

for concern, the team commenced their trial and ultimately recruited 18 adult patients with metastatic malignant melanoma and metastatic renal cell cancer.

As hoped, IL-15 therapy led to increased counts of circulating NK cells and T cells, in particular,  $\gamma/\delta$  and CD8+ memory T cells. By studying the dynamics of the cell counts, the researchers were able to develop a model of cellular activation after IL-15 infusion: immediate redistribution of cells out of circulation, followed by hyperproliferation and subsequent hypoproliferation until a baseline was achieved.

However, acute side effects from bolus administration of IL-15 led to increased levels of multiple cytokines and accompanying clinical toxicities including fever, chills, rigors, and blood pressure changes. The researchers concluded that they could not safely control the clinical toxicities produced by such intense dosing and are currently investigating alternative dosing strategies. After more preclinical testing, the researchers are beginning

a new dose-escalation trial, using continuous intravenous infusions to avoid localized high concentrations. They have also joined with the Cancer Immunotherapy Trials Network to begin a phase 1 trial of IL-15 administered subcutaneously.

"Our study clearly shows that IL-15 activates NK cells, monocytes,  $\gamma/\delta$ , and memory CD8+ T cells, which should augment the patient's own immune response to the tumors," said Conlon. "Hopefully, with new dosing strategies, we can reduce the toxicity and increase the expansion of lymphoid populations and thereby improve the antitumor effects of IL-15 in patients with metastatic malignancy."

*To learn more about Dr. Waldmann's research, please visit his CCR website at <https://ccr.cancer.gov/thomas-a-waldmann>.*

*To learn more about Dr. Conlon's clinical research, please visit his CCR website at <https://ccr.cancer.gov/kevin-c-conlon>.*

Image: T. Waldmann, CCR