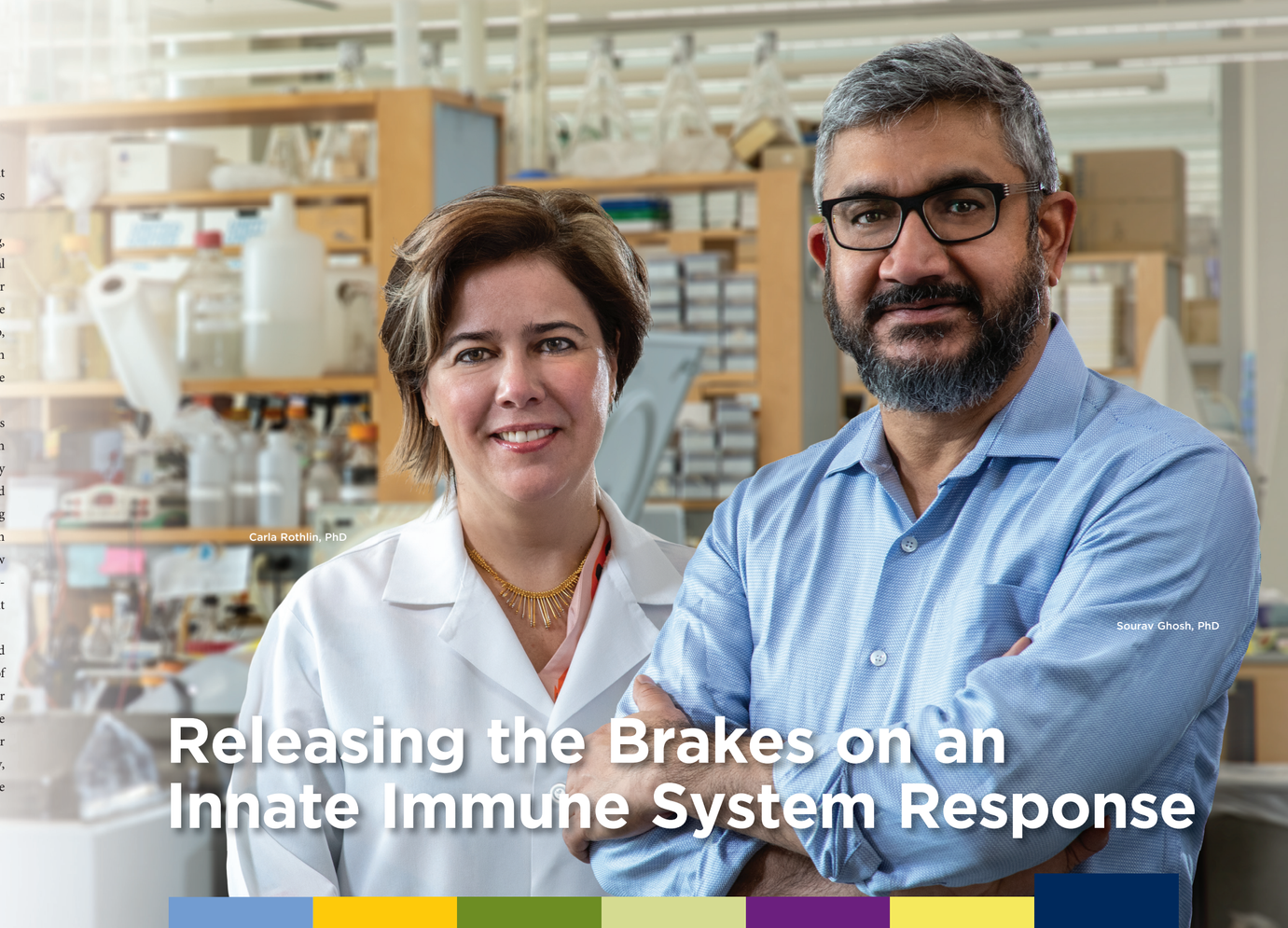
Releasing the Brakes on an Innate Immune System Response



Our bodies have two immune systems: the innate one we are born with that is capable of inducing a rapid immune response; and the adaptive one, which is prompted into action by the innate immune system. The innate immune system detects an intruder and sends out a first line of defense, and directs the adaptive immune system to create a more specific and nimble response.

Cancer can proliferate when the immune system fails to destroy cancerous cells. Tumors can, for example, neutralize pathways that lead to the production of T-cells, a type of white blood cell the body creates that forms part of the adaptive immune system and can attack cancer.

And while checkpoint inhibitor drugs, a newer class of cancer treatments, can block this type of cancer defensive move, they don't always work. In fact, only 15 to 20 percent of patients respond to the drugs, and they are not effective on some cancers at all, including types of brain, breast, ovarian, pancreatic, and colon cancers.

Instead of relying solely on the adaptive immune system to sustain an on the ground defense, two Yale Cancer Center scientists have gone upstream. Their research focuses on Tyro3, Axl, and MerTK, a group of receptor tyrosine kinases collectively known as TAM, which together play a key role in regulating the innate immune system.

Together, they are testing small molecule drugs to "release the brakes," explained Sourav Ghosh, PhD, Associate Professor of Neurology and Pharmacology, which allows the innate immune system to direct T-cells themselves and boost the effectiveness of checkpoint inhibitor drugs.

"If you inhibit the TAMs, you release the brake on the innate immune system response, and mount a much stronger response to the cancer," added Carla Rothlin, PhD, Dorys McConnell Duberg Professor of Immunobiology and Pharmacology and Howard Hughes Medical Institute Faculty Scholar. Going straight to the innate immune system skips the war between cancer's defenses and adaptive immune system responses.

When the innate immune system detects an invader, like a virus, it creates a range of responses, including natural killer (NK) cells, which are a blunt force, front line attack, and dendritic cells, which direct the adaptive immune system to spring into action and create specific responses. One of those responses are T-cells to go after that specific intruder and also establish an immunological memory to respond to a recurrence.

"The adaptive immune system is more precise and focused," said Dr. Ghosh.

Normally, TAMs inhibit some inflammation of an immune system response. While that is good if you don't want a papercut on your finger to flare out of control while the body repairs the wound, it's not always good when it comes to attacking cancers.

Small molecule inhibitors or biologics to inhibit the inhibitors could break the brakes and allow the innate immune system to get T-cells where they need to go. "Our hope is that by targeting the innate immune system, you can get T-cells to come to the tumor and engage them," said Dr. Ghosh. "We are trying to make the immune system trainers better."

That means tumors that are now considered "cold" or T-cell excluded "may be where we see the most effect of this immune system blockade if the immune system is a little bit on hyperdrive and then engage the T-cells to go to tumors unphased by checkpoint blockers," he added.

The pair is currently working with Sarah Goldberg, MD, MPH, Associate Professor of Medicine (Medical Oncology), on launching a clinical trial for the TAM inhibitor sitravatinib, to determine if, when combined with the checkpoint inhibitor immunotherapy drug pembrolizumab, it can provoke a better immune system response. They plan to enroll 70 patients from Smilow Cancer Hospital and one other hospital site in the trial.

"Pembrolizumab is one of the standard treatment options for patients with advanced non-small cell lung cancer with PD-L1 expression of at least one percent, but unfortunately many patients will not benefit from this treatment," said Dr. Goldberg. It's only about 15 percent effective in treating advanced non-small cell lung cancer. Based on Drs. Rothlin and Ghosh's findings, Dr. Goldberg and oncology fellow Emily Collier, MD, believe that "targeting certain characteristics in the tumor microenvironment with sitravatinib might make the immunotherapy work even better."

Dr. Rothlin said that even though this discovery could lead to cancer treatments, that's not the primary focus of their work. "We study how you regulate how much your immune system responds, and how long your immune system responds," Dr. Rothlin said, which leads to a better understanding of how our bodies work and yes, potentially, help cancer patients for whom current treatments have failed. "That's the beauty of basic science," she said.