Breaking Down Silos: Colorado University Program Casts a Wide Net for Lung Cancer Research

CU Cancer Center's TORI helps expand promising work on other cancers into the lung cancer space through funding and collaboration.

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Some of the University of Colorado Cancer Center's foremost scientists are investigating ways to apply their groundbreaking research in various fields to lung cancer with funding and collaborative support from the cancer center's Thoracic Oncology Research Initiative (TORI).

Among them is Diana Cittelly, PhD, an associate professor in the CU Department of Pathology whose research focuses on the mechanisms that allow breast cancer cells to spread, or metastasize, to the brain. With TORI support, she is also investigating ways to thwart the spread of lung cancer to the brain.

And Zhirui Wang, PhD, a professor in the CU Department of Surgery, whose expertise is to develop diphtheria toxin-based recombinant immunotoxins — artificial proteins that combine a toxin with a targeting agent — to treat cancers. One immunotoxin developed by Wang and his colleagues, called bivalent CD47 immunotoxin, has shown promise as a targeted therapy for a type of leukemia. TORI is now backing his research into using the bivalent CD47 immunotoxin against lung cancer.

Launched in 2015, TORI aims to foster a collaborative approach to basic, translational, and clinical lung cancer research drawing on a variety of disciplines and approaches.

Together with TORI

"TORI is not just a research initiative. We are a community of innovators across cancer disciplines committed to making a tangible difference in the fight against thoracic cancers," says Sharon Pine, PhD, a CU Division of Medical Oncology professor who has been TORI's director since July 2022.

Collaboration across departments "has always been one of TORI's strengths," Pine says. "By supporting faculty in surgery and pathology, alongside others, our commitment to breaking down

silos and fostering a campus-wide effort to advance thoracic oncology research has been exemplified time and again."

Lung cancer has been a longtime area of expertise at the CU Cancer Center, and the team continues to look for new diverse approaches to fight cancer and collaborate across the center.

"Fresh ideas and innovative approaches are exactly what we are harnessing to push boundaries in lung cancer research," Pine says. "These researchers with expertise in other cancer types bring a wealth of expertise that will elevate our work and strengthen the lung cancer progress at our cancer center."

→ Sharon Pine, PhD, Studies the Role of Sox9 in Lung Cancer

Blocking cancer's spread

In her TORI-supported research, Cittelly is investigating entrectinib, a medication (branded as Rozlytrek) approved to treat patients with non-small cell lung cancer that has metastasized to other parts of the body, when the cancer is caused by overexpression of tropomyosin receptor kinase (TRK) proteins, which are found on nerve cells and are involved in signaling pathways that control cell growth.

Cittelly seeks to learn whether entrectinib is effective at preventing or decreasing progression of lung cancer metastases to the brain in tumors that express normal levels of TRK protein but are susceptible to overactivation of this protein in the brain microenvironment.

She also is working to better understand how lung cancer cells adapt to the brain's tumor microenvironment – the ecosystem of cells, blood vessels, and molecules surrounding a tumor – and acquire resistance to a family of targeted cancer drugs known as tyrosine kinase inhibitors (TKIs).

→ Diana Cittelly, PhD, Named Co-leader of Tumor Host Interactions Program

"In the context of breast cancer spreading to the brain, we have shown in the past that when cancer cells get to the brain, they can utilize signals that are normal to brain signaling and development for their benefit," Cittelly says. Pilot funding from TORI "allowed us to investigate whether similar mechanisms take place in the lung cancer space," she says.

She notes that entrectinib and other TKI drugs "are only used right now in a very small subpopulation of lung cancer patients" with brain metastasis. Her initial work shows that entrectinib could be helpful for a larger subset of patients.

'Do not eat me'

Wang's previous research points to the bivalent CD47 immunotoxin as an effective potential

targeted therapy for T-cell acute lymphoblastic leukemia, an aggressive cancer mainly in children, and as “a promising and safe therapeutic drug candidate” for various other cancers with a type of protein on the surface of cancer cells called CD47 that helps the cells evade the immune system.

As Wang puts it, CD47 sends out a “do not eat me” signal to immune cells that might otherwise attack the cancer. His team has demonstrated that the toxicity of bivalent CD47 immunotoxin is much lower than other CD47-based monoclonal antibody therapies.

CD47 is overexpressed on lung cancer cells, so in his TORI-supported work, Wang is assessing the bivalent CD47 immunotoxin as a potential lung cancer treatment, “especially for patients with relapsed/refractory lung cancer who frequently have very limited options for the next line of treatment” after initial chemotherapy or surgical treatment.

He adds: “These pilot studies will be expanded in future studies to determine which patient subgroup might benefit most from the bivalent CD47 immunotoxin, and if combinations with chemotherapy or targeted therapies would be most effective.”

→ After Lung Cancer Clinical Trial, Betty and Bill Moren Give Back as Patient Advocates for TORI

Next-level science

Wang describes TORI as “like a small family with good collaboration, and Dr. Pine’s leadership is very strong and supportive. If we have difficulties, she will try to help us find the resources to make this kind of project run smoothly.”

In her initial TORI project, Cittelly collaborated with top CU Cancer Center lung cancer experts D. Ross Camidge, MD, PhD; and Raphael Nemenoff, PhD.

“I was very hesitant for the longest time to go into the lung cancer space, because I felt it was not my area of expertise,” she says. “The TORI program has helped me create collaborations with experts in the biology of lung cancer. I provide my expertise in brain metastasis and they provide their feedback so we can model the disease in the right way. That’s something I couldn’t have done if it wasn’t for the support from TORI. Having a team that provides different expertise is key to taking science to the next level.”

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