

# Is There a Way to Boost Immunotherapy Response?

American Cancer Society grant will fund new analysis of how advanced melanoma evades the immune system

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Immunotherapy has joined surgery, radiation and chemotherapy as one of the major pillars of cancer treatment, one that sometimes results in lifelong protection against a cancer ever coming back.

This approach — which coaxes the body’s immune system into “seeing” cloaked cancer cells again — includes [cellular immunotherapies](#) like CAR T cells, immune [checkpoint inhibitors](#) and [antibody-drug conjugates](#), therapies that have worked remarkably well for a small group of patients, with response rates of [37% in melanoma](#) and higher in select colorectal cancers.

But for most patients — including many diagnosed with these “responsive” cancers, as well as those with pancreatic, uterine or germ cell tumors — immunotherapy has not made a difference.

“While melanoma or MSI-high colorectal patients [that is, patients with tumors with high levels of [microsatellite instability](#)] have the best chance of responding to these treatments, a large proportion of patients even in these responsive indications don’t benefit,” said Fred Hutch Cancer Center’s [Kevin Barry, PhD](#), a molecular biologist whose [lab](#) focuses on the workings of the immune system.

“Our immune system protects against cancer, and the new immunotherapies work by re-activating the immune system to kill cancer and, in some cases, essentially cure patients,” he said. “But the immune system can be overrun by cancer. Only around 30% of patients respond to this type of treatment. Even in melanoma where we see the most promise of these drugs, we have work to do.”

Barry will soon launch into that work thanks to a \$270,000, two-year grant from the American Cancer Society. With it, he’ll investigate new ways to boost immunotherapy responses in metastatic (or advanced) melanoma patients by exploring how the tumor microenvironment helps cancer cells evade our innate immune system.

“We plan to study and define the mechanisms that control the innate immune system within the

tumor and how they are harnessed by cancer to block protective immune responses,” he said.

His goal? To identify novel pathways that regulate these protective immune responses to cancer that can then be exploited via new therapies that coax the immune system back into destroying cancer cells, improving patient responses and prolonging patient lives.

## How the immune system fights cancer

The innate immune system — which each of us is born with — is the first line of defense against infection and disease, including cancer.

“The innate immune system has two major roles,” Barry said. “The first is to initiate disease control and the second is to activate and shape the sterilizing immune response, that is, the immune response that kills cancer.”

Innate immunity, he said, lays the foundation for protective immune responses; innate immunity has also been shown to control patient survival and responses to current FDA-approved immunotherapies.

“Together, these findings make the innate immune system an exciting target for new immunotherapies,” Barry said. “Our aim is to define the mechanisms that control innate immune responses to melanoma.”

Cancer avoids detection through a process called tumor immune evasion, hijacking the body’s mechanisms that exist to protect it from attacking its own healthy cells.

“In order to develop immunotherapies that fully harness the power of the immune system to fight cancer, it’s imperative to understand how tumors evade the immune system,” Barry said.

Examples of tumor immune evasion include immune cell exclusion, reduced recruitment of immune cells to the tumor, the production of immunosuppressive cytokines and tumor cell down-regulation of neoantigen expression, he said.

With the ACS grant, Barry and his team will focus on a novel form of tumor immune evasion that blocks protective immune responses through the activity of a specific innate immune cell in the tumor, the type 2 conventional dendritic cells, or cDC2.

Conventional dendritic cells, or cDCs, are specialized immune cells found in tissues that are exposed to the environment — think skin, lungs and gut mucosa. There, they act as sentinels, capturing antigens like viruses, bacteria or cancer cells and presenting them to T cells to initiate the adaptive immune response. As the main antigen presenting cells, cDCs basically act as a bridge between the innate and the adaptive immune system. Through them, the body learns to recognize, destroy, and “remember,” or *adapt*, to specific pathogens or bacteria.

This category of dendritic cells have two types, cDC1s and cDC2s, but only cDC1s have been

studied adequately, “due to their ability to efficiently induce CD8 T cells and their ability to be manipulated genetically,” Barry wrote in his proposal, adding that “tumor-induced cDC1 dysfunction is a form of immune evasion, resulting in reduced anti-tumor CD8 T-cell responses and reduced protection from cancer.”

But cDC2 dysfunction in the tumor is less well-defined, he said. Ditto for its role when it comes to shaping anti-tumor CD8 T-cell responses.

Barry’s research will attempt to fully investigate how innate immune dendritic cells shape adaptive immune responses. Specific aims are to develop models to test the effects of cDC2 priming on T-cell function in vivo (in living preclinical models) and determine how the phenotypes and spatial organization of cDCs shape CD8 T-cell responses in human metastatic melanoma.

“These studies will provide a novel understanding of the regulation of CD8 T-cell responses in cancer and will allow us to begin to develop treatments to disrupt the tolerogenic, or immune tolerant, role of cDC2s in cancer,” he said.

“A significant output of our studies will be the future development of novel immunotherapies that work in concert with existing treatments to enhance survival of patients with primary and metastatic cancers.”

### Why study this in melanoma?

Barry chose to conduct research on melanoma — the most dangerous form of skin cancer — because it was one of the first cancers on which immunotherapy was used.

“Melanoma has the longest history with immunotherapy,” Barry said. “But we believe that what we learn from studying dendritic cells in melanoma will translate to other solid tumors, as well.”

Earlier research, he said, suggests the pathways found in melanoma hold true across other types of cancers.

“We don’t know if it will be true for all solid tumors,” he said. “But it will be true for at least some other solid tumor indications.”

Barry is one of three Fred Hutch researchers to receive 2026 awards from the American Cancer Society. Other awardees include epidemiologist [Trang VoPham, PhD, MPH, MS](#), and clinical researcher and oncologist [Kate Markey, MBBS, PhD](#).

The American Cancer Society’s mission is to improve the lives of people with cancer and their families through advocacy, research and patient support, to ensure everyone has an opportunity to prevent, detect, treat and survive cancer.

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