

Rallying the troops of the immune system to fight cancer ^[1]

Discovery ^[2]

In tumors, there's an epic battle going on between cancer cells and immune cells, which act as the body's natural defense against disease. Cancer cells fend off attack by releasing signals that bind to immune cells and keep them dormant. The goal of a new class of drugs called checkpoint inhibitors is to cripple this defense system and unleash the body's cancer-fighting army.

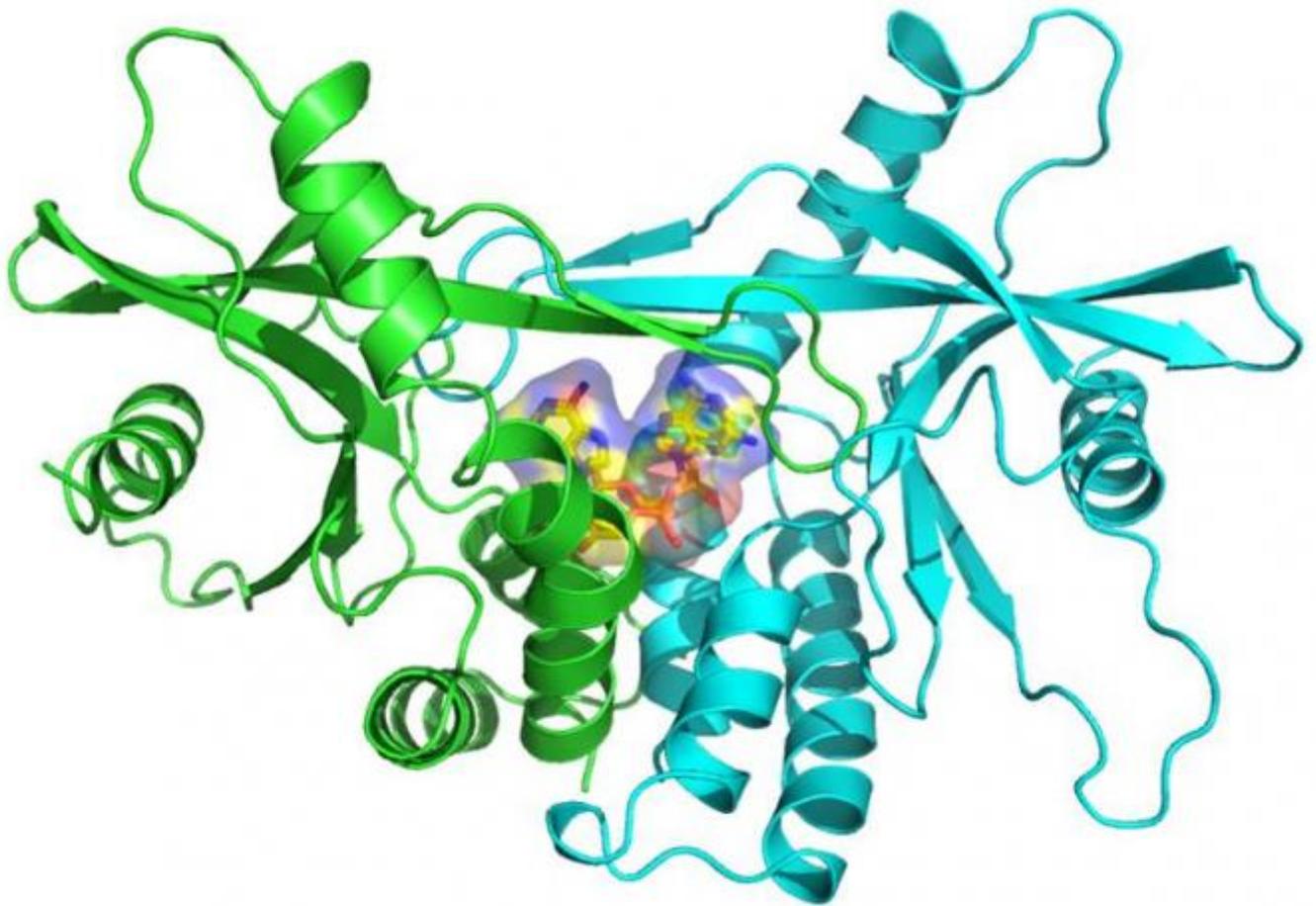
While checkpoint inhibitors are proving powerful in clinical trials, their effectiveness so far has been limited to select tumor types. They seem to work better in tumors that have already been infiltrated by key immune cells called lymphocytes. In [these tumors](#) ^[3], the immune system already recognizes cancer cells as the enemy, so it's deployed forces to the site of the invasion. Checkpoint inhibitors simply issue the command to attack. But other tumors are trickier. The immune system does not yet recognize the cancer cells as dangerous, so it doesn't train or deploy soldiers.

A new collaboration between Aduro Biotech and Novartis has the potential to extend the usefulness of checkpoint inhibitors—and other immunotherapies—beyond the existing subset of tumors. It focuses on a molecular pathway called STING (stimulator of interferon genes), which rallies the troops of the immune system. In preclinical models, STING agonists flood tumors with cancer-fighting forces, and the response is dramatic.

“In animal models, STING agonists induce a complete elimination of the tumor,” says Glenn Dranoff, [Global Head of Immuno-oncology at NIBR](#) ^[4]. “When these animals are challenged again with the same tumor, the immune system blocks the tumor from being reestablished.”

This indicates that the immune system has been alerted centrally. It's deployed cells throughout the body to kill any similar cancers. So STING activation is akin to “vaccinating” the body against the tumor.

STING was discovered relatively recently, [in 2008](#) ^[5], but researchers have already uncovered many details about how it operates. It's a transmembrane protein that bridges the innate and adaptive immune systems, activating several distinct signaling pathways. It triggers, for example, the production of interferons that orchestrate innate immune responses. It also transforms dendritic cells into messengers that recruit, activate, and induce the proliferation of T cells that target specific “invaders.”



Researchers at the Genomics Institute of the Novartis Research Foundation study what happens at the molecular level to STING when a natural signal called cGAMP (shown between the green and blue) binds and activates it. Image: Christian Lee/GNF Structural Biology Team

STING is activated by intracellular signals, specifically cyclic dinucleotides, which are produced when double stranded DNA is detected in the wrong place, a hallmark of viral infection. Aduro has altered cyclic dinucleotides to make them more potent and stable than the natural versions, creating drug candidates. Working in mice, Aduro scientists injected their cyclic dinucleotides into tumors, generating substantial immune responses that might be capable of providing long-lasting protection against further cancer growth and metastasis. The goal is to test the same direct injection approach in patients.

In parallel, Novartis scientists have been working to identify small molecule agonists of STING. They've conducted massive chemical screens to discover low molecular weight compounds that can travel through the cell membrane and activate the human version of the protein. Teams are now working to characterize and optimize the hits. They're using a combination of biophysical methods—such as NMR spectroscopy and X-ray crystallography—together with mutagenesis to establish where exactly these compounds interact with STING.

“Beyond the low molecular weight compound campaign, we bring complementary chemistry and assays to the collaboration that could aid the cyclic dinucleotide work,” says Jeff McKenna, a senior investigator in Global Discovery Chemistry at NIBR.

Together, scientists at Aduro and Novartis will move the cyclic dinucleotides and small molecules toward the clinic.

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[1] <https://www.novartis.com/stories/discovery/rallying-troops-immune-system-fight-cancer>

[2] <https://www.novartis.com/stories/discovery>

[3] <https://www.novartis.com/news/media-library/renal-cell-carcinoma-rcc-fact-sheet>

[4] <https://www.novartis.com/content/part-3-multidisciplinary-care-net>

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