Understanding the immune system's 'big eater': New insights into macrophage behavior in cancer therapy

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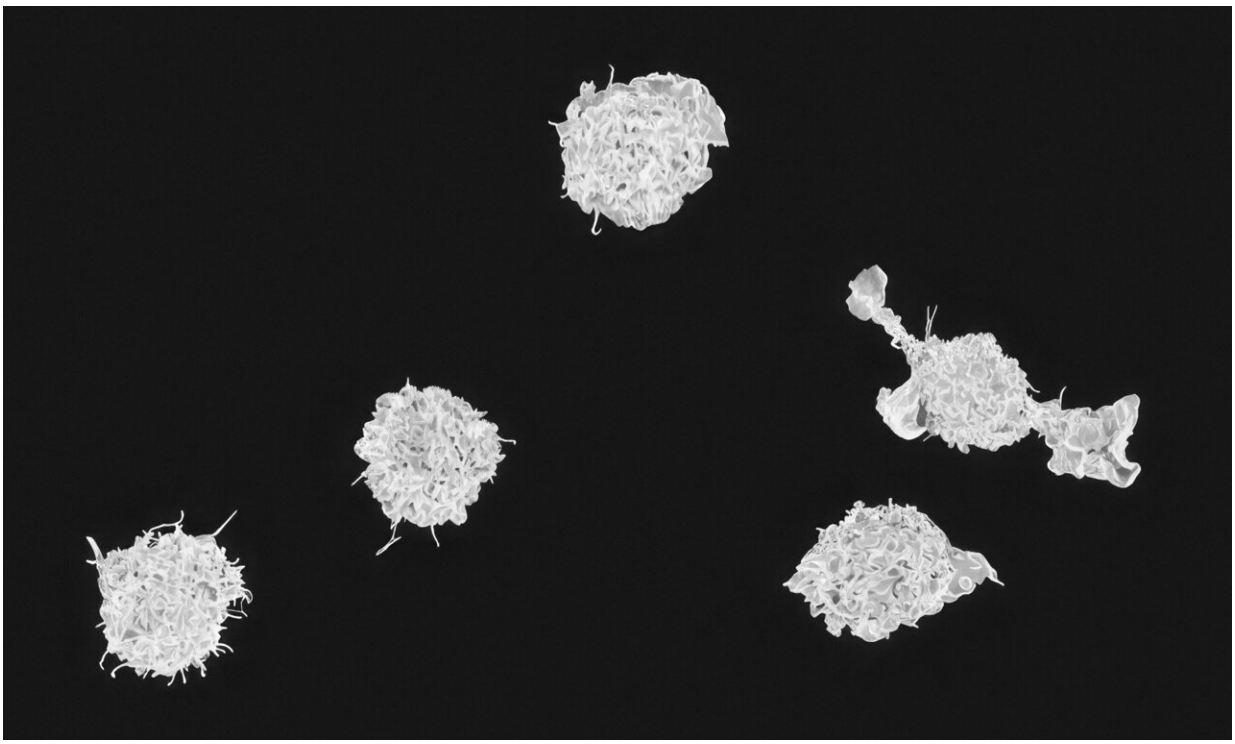

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Do you want the bad news, good news or better news? The bad news is that cancer continues to be the second leading cause of death in the United States, trailing heart disease. The good news is that overall cancer

mortality rates have been steadily decreasing over the last 20 or so years.

The better news is that researchers from South Dakota State University are slowly chipping away at the universally dreaded disease in hopes of improving treatments and eventually seeing better health outcomes.

A new study from SDSU's Department of Chemistry, Biochemistry and Physics, led by professor Adam Hoppe, shows a greater understanding of macrophages—one of the immune system's key tools in defeating cancer cells—through the application of one of the oldest and most viable cancer treatments on the market, rituximab.

The study, titled "Antibody surface mobility amplifies Fc gammaR signaling via Arp2/3 during phagocytosis," was published in the *Biophysical Journal*.

"What we are finding out is that some cancer treatments don't work for certain types of cancer and certain types of people," Hoppe said. "What we are trying to do is better understand how these treatments work within the body so we can make them more effective and with less side effects."

Hoppe, director of SDSU's Center of Biomedical Research Excellence (COBRE), has focused his—and his lab's—research efforts on better understanding macrophages, which means "big eater" in Greek. While these immune cells play a variety of roles in the body, they are, in terms of cancer research, one of the most crucial cells in helping the body eliminate disease. However, there is much to learn about their fundamental characteristics and functions.

Since starting at SDSU in 2008, Hoppe's work has slowly but surely chipped away at the vast, unknown nature of macrophage functionality in defeating cancerous cells.

Brady Fischer is a doctoral candidate who conducts research in the Adam Hoppe Lab. He graduated from Augustana College in 2017 with a degree in biochemistry. During his childhood, Fischer's mother was diagnosed with thyroid cancer. While she is now in remission, her diagnosis prompted Fischer to pursue a graduate degree focused on cancer research. One thing led to another, and he joined the Adam Hoppe Lab in summer 2021.

Now, with nearly three years of research experience, Fischer has played a pivotal role in some of the latest research findings from the Adam Hoppe Lab.

"This research focused on a treatment specifically for B cell cancers, like lymphoma," Fischer said. "Rituximab is usually the first line of treatment after a diagnosis. It does a great job of putting people into remission, but it has an issue: it never fully cures the body of the disease. One of things we are looking at is how the treatment works within the body so we can understand why it fails."

Rituximab is a cancer drug known as a monoclonal antibody, which targets proteins—specifically, a protein called CD20 found on B cells—on the surface of cancer cells. The drug was first approved for use in 1997.

When antibodies attach to cancerous cells, macrophages are able to identify them. Macrophages are found throughout the body, and when they identify something that isn't supposed to be there, they engulf and eliminate the cell, cellular debris or foreign substance through a process called phagocytosis.

"The macrophages' main job in the body is simply eating things that shouldn't be there," Fischer said. "For this research, we wanted to know the fundamentals of how it does that and how it can be applied to

immunotherapies for cancer treatments."

One of the key findings from this research is that when macrophage identify antibodies on the surface of a cancer cell, they don't immediately begin phagocytosis. Instead, they first rearrange the antibodies on the surface of the cancer cell before moving into phagocytosis. As Fischer explains, early evidence shows that rearranging the antibodies allows the macrophages to better engulf the cancerous cell. However, this particular piece of information needs to be further explored.

"When the macrophages are able to rearrange and restructure, they seem to do a little bit better," Fischer said.

Another key finding from this research was discerning how macrophages decide to engulf a cell.

There are two models for how researchers explain the decision-making process of the macrophage: the "zipper model" and the "trigger model." In this work, the researchers homed in on the trigger model, which is described as a "threshold of signal the macrophage needs" to make a decision. Once the signal threshold is reached, the macrophage will decide to absorb the cell, and much like pulling a trigger, it will shoot, wrap around and then swallow the cell.

"When the macrophage is able to rearrange the drug on the target cell, it's able to amplify the signal threshold," Fischer said. "The ability to amplify that signal makes it easier for the macrophage to decide to eat the target cell and destroy it."

Overall, the clustering of the targeted drug by the macrophages does increase signal threshold strength, an important finding that will help researchers better understand both macrophages and the targeted drug,

rituximab. But as Hoppe notes, the decision-making process of the macrophage may be even more complex than either the zipper or trigger model, which leads his lab into its next stage of research—gaining an even deeper understanding of this process.

"We will basically take this research one step deeper, more or less taking a look 'under the hood,'" Fischer said. "What happens (at the molecular level) when macrophages rearrange the drug? It seems to be helping. Why is it helping? Why is that a good thing? Understanding those questions is the next step."

Fischer is midway through his graduate studies. After earning his doctorate, he hopes to become a professor.

More information: Seongwan Jo et al, Antibody surface mobility amplifies FcγR signaling via Arp2/3 during phagocytosis, *Biophysical Journal* (2024). DOI: 10.1016/j.bpj.2024.01.036

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