# Spinning, magnetic micro-robots help researchers probe immune cell recognition

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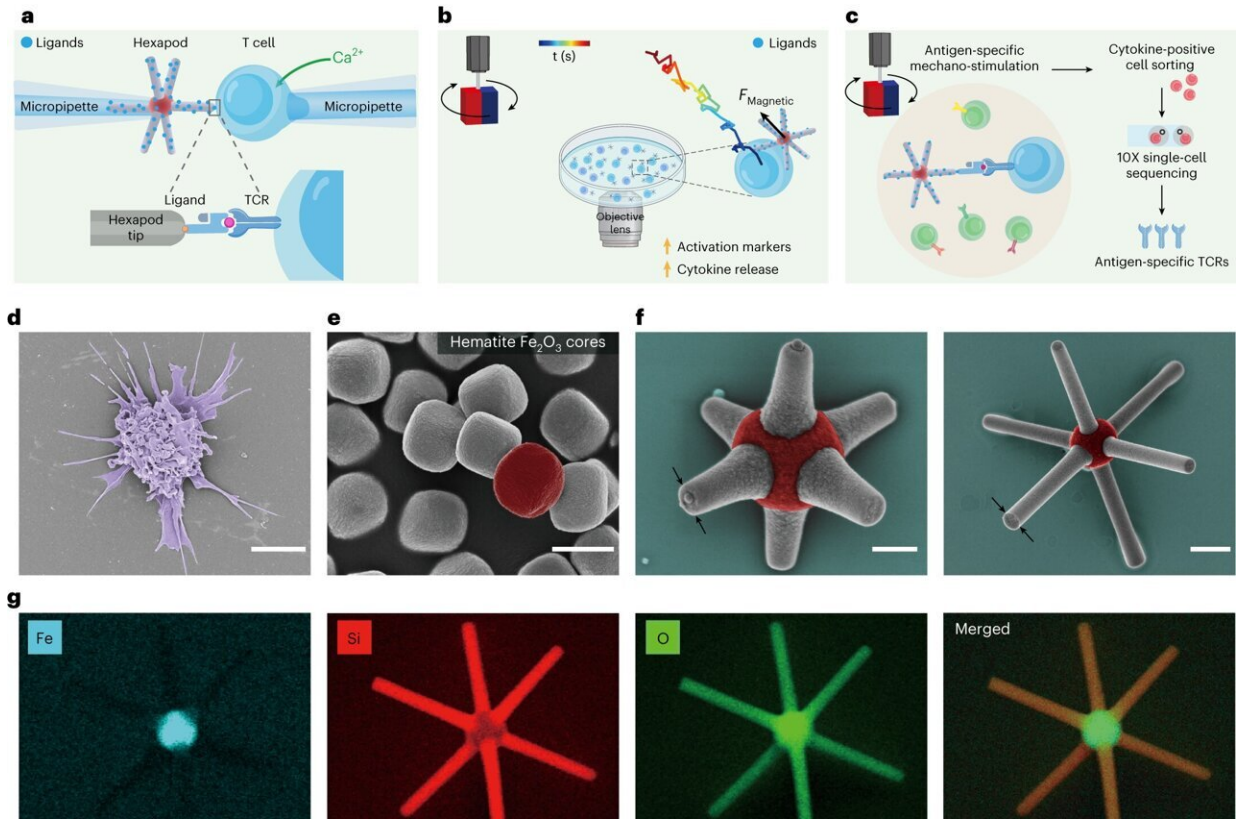


Hexapod-enabled molecular level interrogation of T-cell recognition. Credit: *Nature Methods* (2024). DOI: 10.1038/s41592-023-02165-7

Researchers at the Pritzker School of Molecular Engineering and the Department of Chemistry at the University of Chicago have engineered

tiny, spinning micro-robots that bind to immune cells to probe their function. The robot, or "hexapod," gives scientists a new, highly adaptable way to study immune cells and to aid in the design of immunotherapies against cancer, infection, or autoimmune diseases.

Each hexapod robot has six arms containing molecules that might be recognized as foreign by the immune system—such as protein fragments from a tumor, virus, or bacterium. Researchers can use the hexapods to scan large collections of immune cells and discover which immune cells bind the foreign molecules of interest and how the hexapods' movements impact that binding.

"Numerous aspects of which immune cells and how immune molecules sense pathogens remain uncharted territory, and now we have this new tool to help us understand the molecular interactions," said Jun Huang, associate professor of molecular engineering at Pritzker Molecular Engineering and co-senior author of the new paper, published in *Nature Methods*.

"Scientists often use biomaterials to study and manipulate the immune system, but we've developed a way to use inorganic materials, which is an incredibly unexplored area," said Bozhi Tian, professor of chemistry and the other co-senior author. "The benefit of these materials is that we can change their properties in many more ways."

## A 'T cell' in a haystack

T cells are a type of white blood cell responsible for recognizing foreign pathogens that have been processed by dendritic cells—immune cells with long branching arms that capture pathogens and display bits of the pathogens' molecules on their surface. There are trillions of distinct T cells in a person's body, each one with a different T cell receptor that is finely tuned to recognize a pathogenic molecule (antigen) on a dendritic

cell.

Researchers who want to boost the immune system's power to fight a particular antigen often want to know what T cell recognizes that pathogen. But finding the exact match among the trillions of T cells is like finding a needle in a haystack.

"People have developed ways to do this, but they mostly rely on whether a T cell receptor binds an antigen," said Xiaodan Huang, one of the co-first authors of the paper. "Since some T cell receptors can bind to an antigen without then provoking a strong immune response in the cell, we knew this wasn't a perfect proxy."

Previous platforms to study T cells also couldn't mimic the role of physical force in the interaction between dendritic cells and T cell receptors; they generally relied on isolated antigens that don't behave like a living dendritic cell.

## A robotic dendritic cell

To overcome these challenges, the researchers designed a minuscule robotic mimic for a dendritic cell. The bot has a central, spinning magnetic core and six arms made of silicon dioxide (the compound that most sand is composed of) to which antigens can be attached.

Tian and Huang's lab groups used known antigen-T cell receptor pairs to test the effectiveness of the hexapod. They put copies of the antigen on all six legs and then immersed the hexapod in mixtures of T cells. Even when the matching T cell was present in small quantities amidst many other T cells, the hexapods bound only the correct cell.

"We were incredibly happy with how well the system worked," said Lingyuan Meng, one of the co-first authors of the paper. "The fact that it

could pick out the right T cells with such a high accuracy exceeded our expectations."

In addition, the research team showed that they could analyze the resulting immune response in the T cells that bound to the hexapod. For instance, when two different T cells bound to the hexapod, they could determine which led to stronger immune activity. The group also found that the force exerted by the spinning hexapod led to stronger immune responses than when the same T cells bound to static antigens.

"We'd now like to begin applying this to other antigens, including those from human cancers and pathogens," said Huang. "There are a lot of questions, both basic scientific questions and clinically relevant ones, that can be explored using these hexapods."

For instance, the hexapods could be used to identify the T cells that most strongly react to certain antigens.

**More information:** Xiaodan Huang et al, Multimodal probing of T-cell recognition with hexapod heterostructures, *Nature Methods* (2024). DOI: 10.1038/s41592-023-02165-7

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