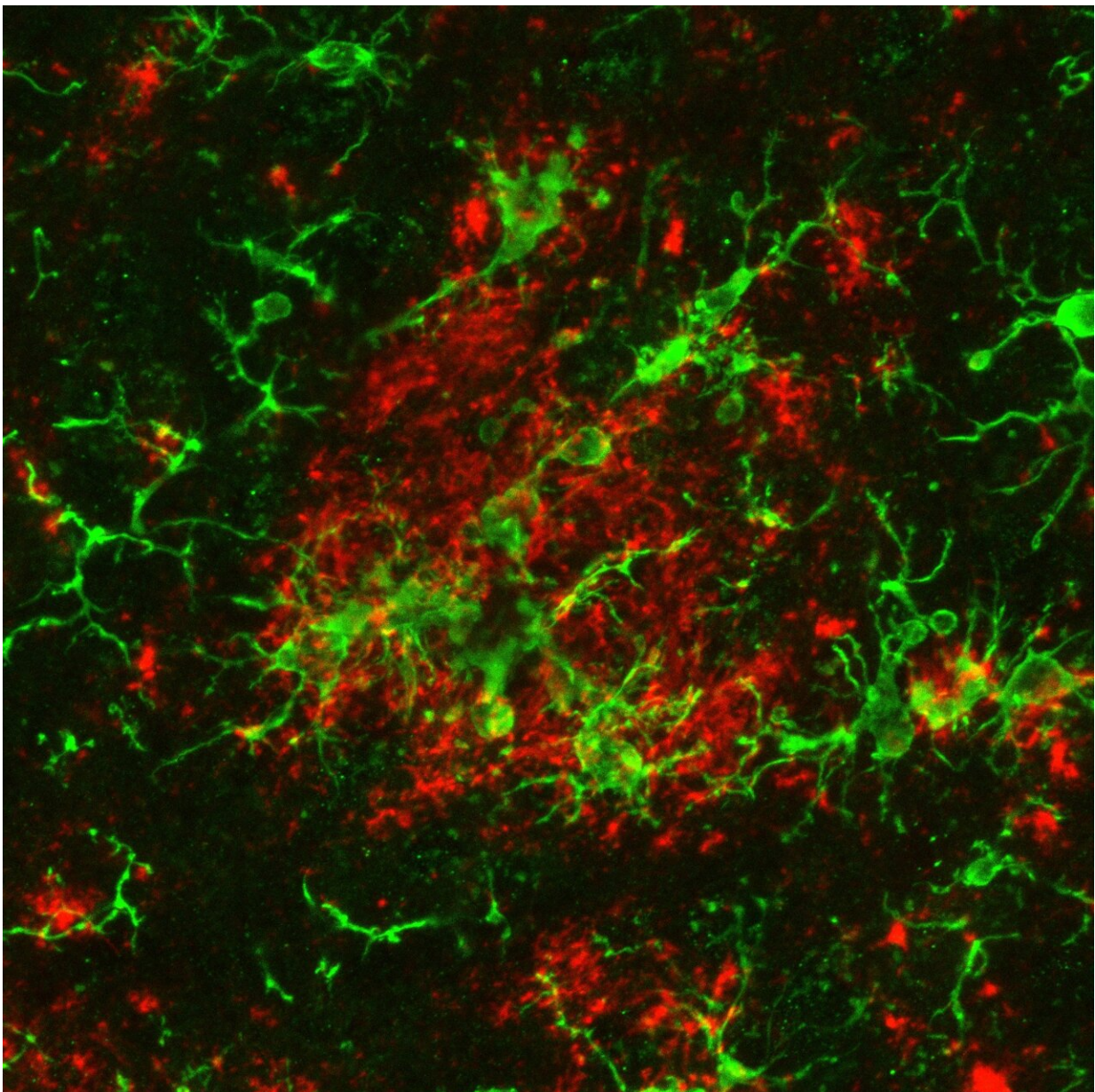


Study shows new way to spur brain immune cells to clear toxic waste linked to Alzheimer's disease

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An image of brain immune cells called microglia (green) clustering around a build-up of toxic beta amyloid (red). Credit: LKCMedicine/NTU Singapore

A newly discovered "energy switch" in the immune cells of the brain may lead to the development of drugs for Alzheimer's disease, the most common form of dementia.

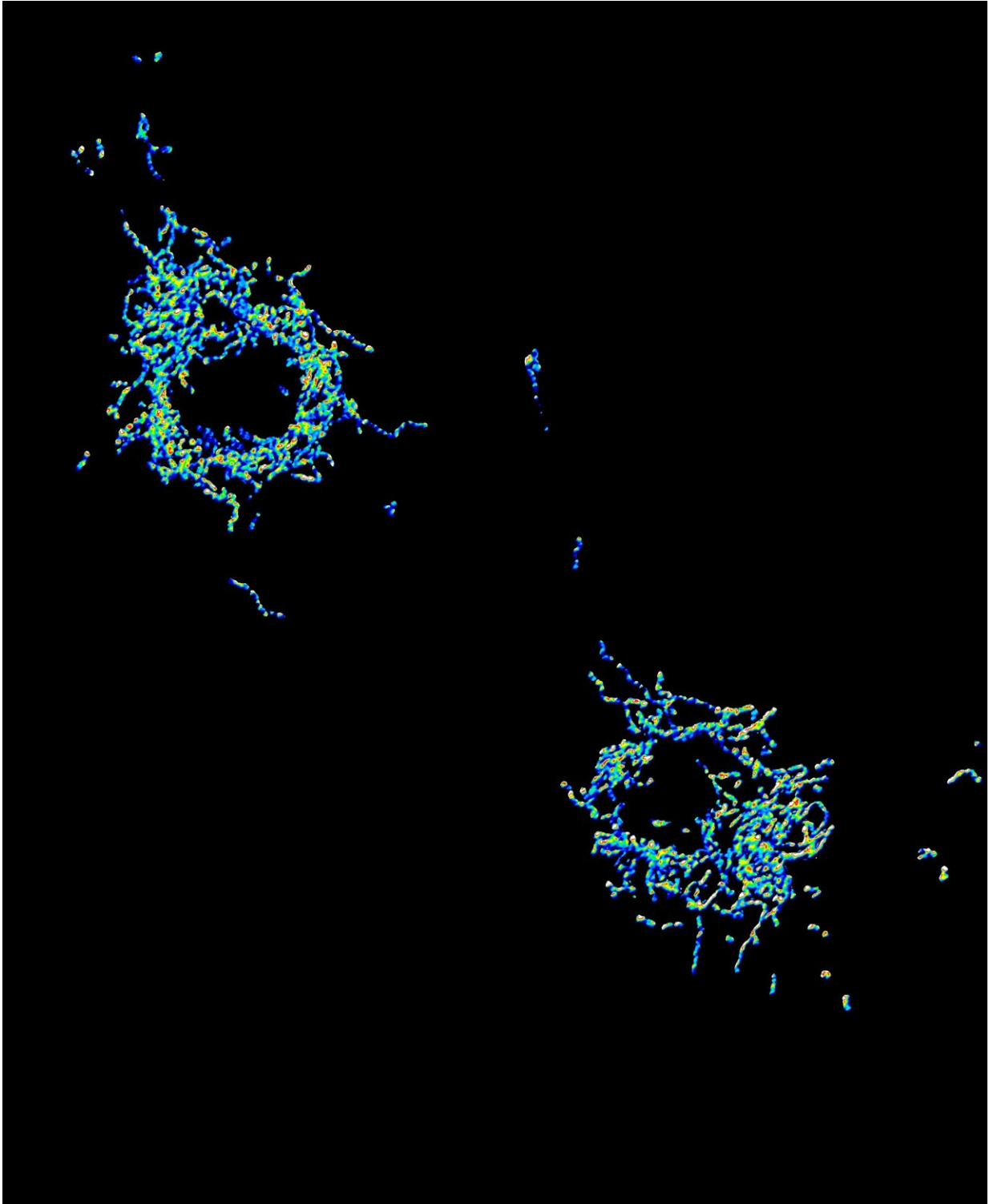
Nanyang Technological University, Singapore (NTU Singapore) scientists discovered that after blocking and turning off this "switch," brain [immune cells](#) called [microglia](#) were able to remove toxic proteins that can build up and lead to Alzheimer's disease.

Microglia tend to be damaged in people with the disease, which makes them less capable of clearing cellular toxic waste. To restore the clean-up function, the scientists "switched off" their inefficient metabolism by preventing a key enzyme from attaching to energy-generating parts of the immune cells.

The findings from lab experiments set the stage for developing drugs that can specifically target metabolism in brain immune cells in order to treat Alzheimer's disease, which contributes to 60% to 70% of all dementia cases globally. The World Health Organization estimates that 78 million people worldwide will have dementia by 2030.

Such drugs are of high interest in health care. While there are ways to treat the symptoms of Alzheimer's disease, there are currently no definitive cures for the condition, which tends to affect the elderly and impairs people's ability to think.

The researchers' findings, which were published in *Proceedings of the National Academy of Sciences* in February 2023, are in line with one of the goals of the NTU 2025 strategic plan to respond to the needs and challenges of healthy living and aging.



An image showing the sugar metabolizing enzyme, hexokinase-2 (multi-colored heatmap), stuck all over the mitochondria of brain immune cells called microglia. Mitochondria are the power stations of cells. Credit:

Cracking a metabolism puzzle

The findings of the researchers, led by Nanyang Assistant Professor Anna Barron from NTU's Lee Kong Chian School of Medicine, stem from their work investigating the function of a biomolecule called the translocator protein, which is found in energy-generating parts of immune cells and which is widely used in [clinical research](#) to track inflammation.

Asst Prof Barron's group had previously shown that drugs that activated this protein led to less toxic waste build-up in the brain, which improved the condition of mice with Alzheimer's disease. But how this worked was not clear.

The team cracked the puzzle with their latest experiments on cells from mice with Alzheimer's. Their work revealed that the translocator protein is critical for the microglia immune cells of the brain to generate their own energy.

Microglia perform the important function of "gobbling up" and removing beta amyloid, a toxic protein whose build-up in the brain causes damage and death to nerve cells, resulting in Alzheimer's disease. To do their job properly and remove the toxic waste, the immune cells need a lot of energy.

The research team showed that without the translocator protein, microglia from mice with Alzheimer's had an energy problem and could not remove the beta amyloid, which resulted in the disease worsening in the mice.

"We found that microglia lacking the translocator protein resembled damaged microglia observed in aging and Alzheimer's disease," said Asst Prof Barron. "These damaged microglia inefficiently produced energy and could not clean up toxic waste in mice with Alzheimer's disease."



A team of Nanyang Technological University, Singapore scientists discovered a "metabolic switch" in brain immune cells that could be targeted as a potential treatment for Alzheimer's disease. Credit: NTU Singapore

The experiments also demonstrated that when the translocator protein is absent, an enzyme called hexokinase-2, which metabolizes sugar, kicks into action in microglia to compensate. The enzyme promotes an inefficient way for cells to produce energy. What was surprising was that hexokinase-2 became activated when it stuck to the energy-generating

parts of cells called mitochondria.

The researchers found that hexokinase-2 was also activated in microglia when exposed to more toxic forms of beta amyloid, just as happens in Alzheimer's disease. The scientists believe this finding helps to partly explain how microglia fail in patients with Alzheimer's disease and when people age.

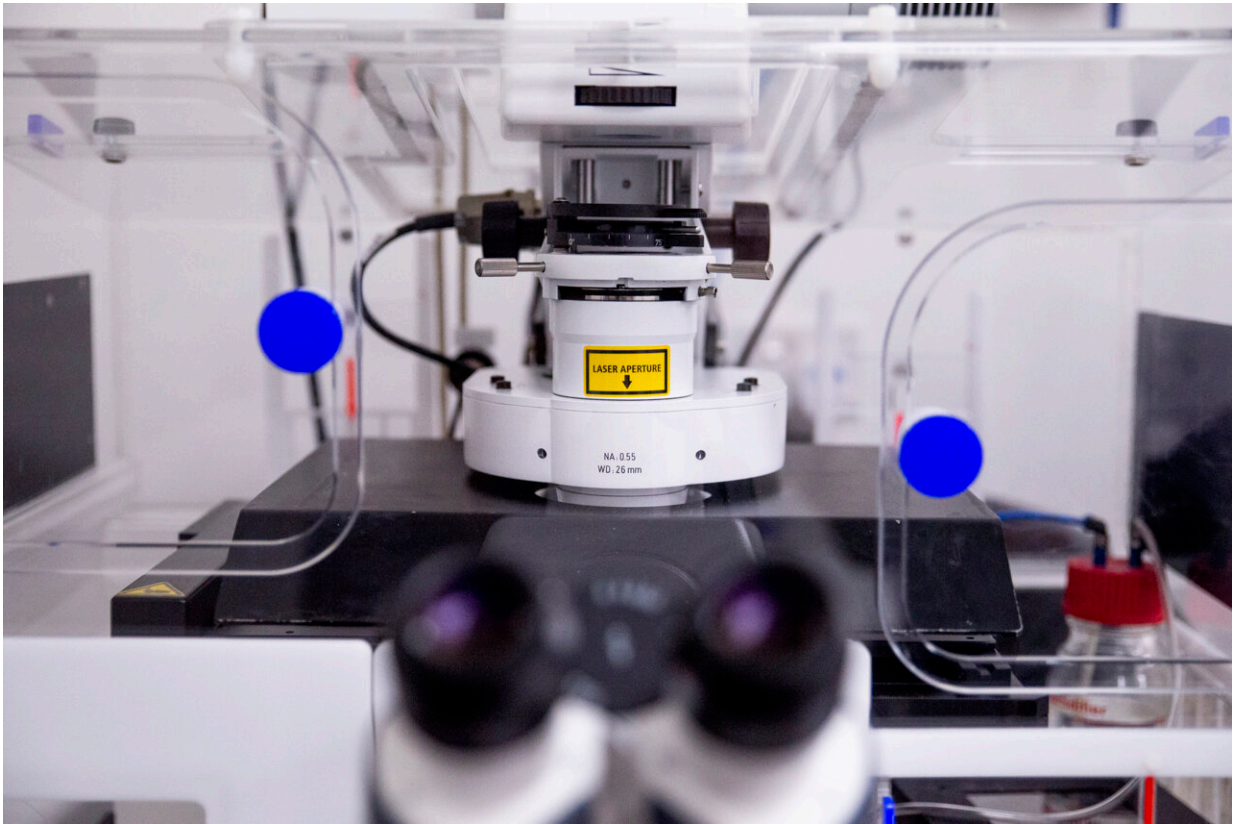
To manipulate the enzyme's role in microglia energy production, the NTU researchers developed a light-activated tool. Their tool involves shining [blue light](#) onto a genetically modified version of the hexokinase-2 enzyme to "switch off" one of its functions.

When this happens, it blocks the enzyme's ability to stick to the energy-generating parts of the microglia and forces the cells to stop relying on an inefficient method of energy production. Experimental results showed that this improves their ability to clear beta amyloid by nearly 20 percent.

However, if hexokinase-2's sticking ability is not blocked and its function is disrupted by simply inactivating the enzyme, it does not help the microglia to clear away waste. This insight provides a critical clue for future drug targets.

Targeted drug development

Asst Prof Barron said that her team's findings provide a basis for them to develop drugs that can act specifically on the metabolism of immune cells in the brain to treat Alzheimer's disease.



The super-resolution microscope used by the Nanyang Technological University, Singapore scientists to observe experiments they did which led to the discovery of a "metabolic switch" in brain immune cells that could be targeted as a potential treatment for Alzheimer's disease. Credit: NTU Singapore

For instance, drugs could be developed to prompt the brain's microglia to produce energy more efficiently and thus clear toxic beta amyloid proteins to protect against Alzheimer's disease.

Such drugs could target the hexokinase-2 enzyme, which is found in the brain's microglia at high levels in people with Alzheimer's disease.

The team expects targeted drugs for Alzheimer's disease to be an improvement over those drugs being studied now that do not specifically

zero in on metabolism in brain microglia cells.

Dr. Yeo Tianrong, a senior consultant neurologist at Singapore's National Neuroscience Institute who was not involved in the research, said that Asst Prof Barron and her team were able to gain new insights to piece together the puzzle of energy generation that is needed for microglia to remove beta amyloid in the brain.

"Importantly, they found that the displacement of hexokinase-2 led to improved energy production and enhanced the microglia's ability to get rid of beta amyloid. This is of significance as the strategy of hexokinase-2 displacement represents a potential therapeutic target for improved beta amyloid removal by the microglia," said Dr. Yeo.

"The study by Asst Prof Barron's team highlights the possibility that, one day, we can harness the intrinsic capability of microglia to mop up toxic [beta amyloid](#) by re-configuring their energy generating framework," he added.



From left: Research fellow Dr Wong Jia Hui, Nanyang Asst Prof Anna Barron, and final year PhD student Ms Lai Kei Onn from Nanyang Technological University, Singapore's Lee Kong Chian School of Medicine. They are part of the NTU team that discovered a "metabolic switch" in brain immune cells that could be targeted as a potential treatment for Alzheimer's disease. Credit: NTU Singapore

Future research that the team is planning includes experiments in mice to verify that what they observed in cells can be replicated in animals, where physiological conditions may have an unexpected impact on the results.

The approach of controlling metabolism in microglia using the light-activated tool will also prove useful in studying how energy production

works in cells for other diseases and conditions, including diabetes and obesity.

"This tool gives us a way to understand how metabolism contributes to diseases. Historically, this has been hard to study because most approaches to control metabolism are irreversible, lead to toxicity or cannot target cells of interest. However, our tool allows us to control [energy](#) processes in specific cells in a reversible way that also doesn't kill the cells being studied," said Asst Prof Barron.

More information: Lauren H. Fairley et al, Mitochondrial control of microglial phagocytosis by the translocator protein and hexokinase 2 in Alzheimer's disease, *Proceedings of the National Academy of Sciences* (2023). [DOI: 10.1073/pnas.2209177120](https://doi.org/10.1073/pnas.2209177120)

Provided by Nanyang Technological University

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