Nuclei-free cells prove utility in delivering therapeutics to diseased tissues

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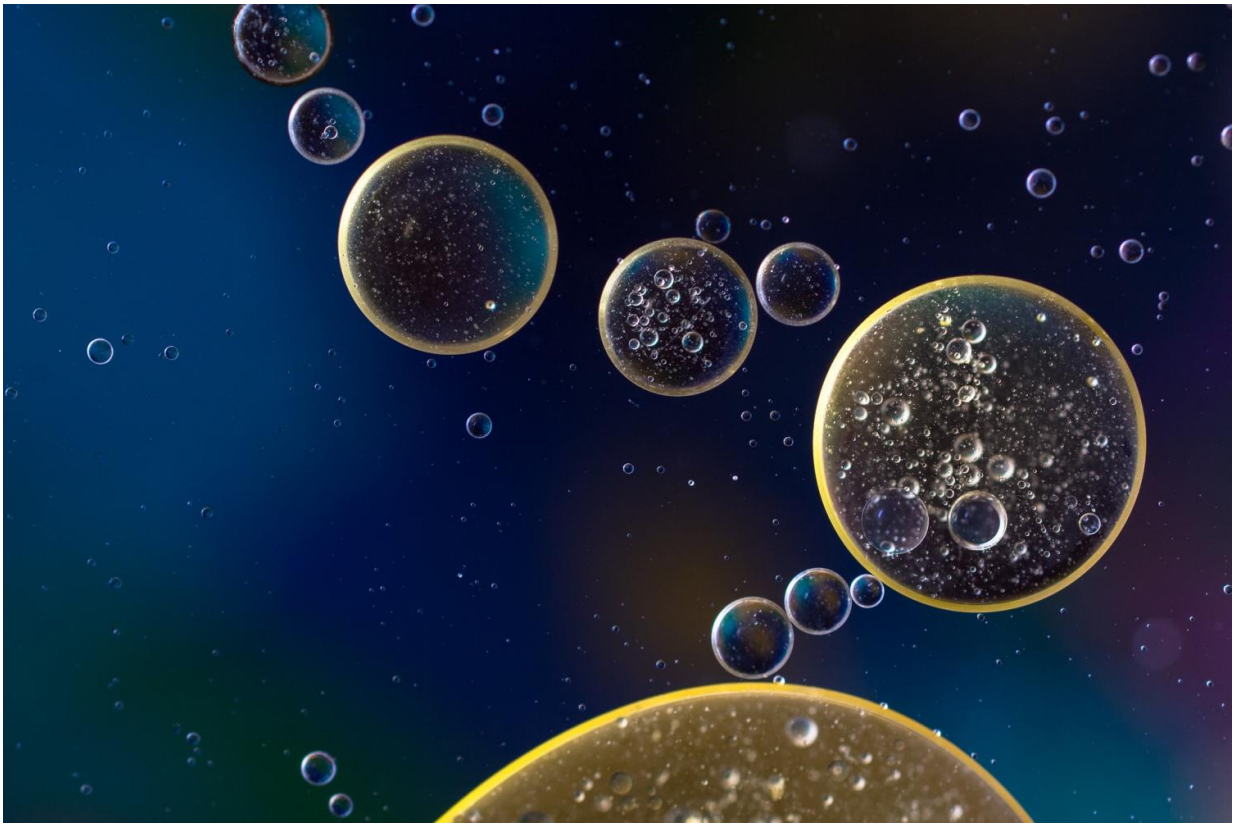

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Researchers at University of California San Diego School of Medicine and Moores Cancer Center at UC San Diego Health report successfully removing the nucleus out of a type of ubiquitous cell, known as

enucleation, then using the genetically engineered cell as a unique cargo-carrier to deliver therapeutics precisely to diseased tissues.

The findings published in the December 20, 2021 issue of *Nature Biomedical Engineering*.

Precisely targeting and delivering drugs or therapies to diseased cells and tissues significantly boosts therapeutic benefit while decreasing side effects. In the new study, a team led by senior author Richard Klemke, Ph.D., professor of pathology at UC San Diego School of Medicine, genetically modified mesenchymal stromal cells (MSCs) to boost their disease-seeking behavior, then removed their nuclei while retaining organelles that produce energy and proteins needed for therapeutic functions.

In mouse models of acute inflammation and of pancreatitis, researchers engineered the enucleated cells, dubbed "Cargocytes," with an anti-inflammatory cytokine—a signaling protein that spurs the immune response and can reduce inflammation and related disease and then systemically administered them into mice where they produced bioactive therapeutics at high levels in their targeted locations for several days, ameliorating the disease.

"These Cargocytes retain most of their cellular functionality, but now also possess greatly enhanced capacity to carry and deliver therapeutics specifically to targeted tissues in a safe manner," said Klemke. "That opens the possibility of treating diseases by delivering drugs precisely where they can do the most good, with less likelihood of unwanted side effects caused by those drugs going elsewhere."

The authors said the use of enucleated, modified MSCs has several advantages over approaches that employ intact cells as delivery vehicles.

First, it is difficult to get regulatory approval for clinical use of extensively engineered stem cells, which also possess the ability to proliferate and differentiate, due to safety concerns.

Second, primary cells collected from donors for therapeutic delivery purposes have limited bioengineering and therapeutic capacities.

Third, Cargocytes have a more defined and predictable fate after administration to the body because they cannot perform new gene transcription, eliminating the possibility that they may produce unwanted factors, differentiate into unwanted cell types or graft onto tissues in undesirable ways.

"What this means is that what we engineer ex vivo, in the lab, will correctly work in vivo, inside the body," said Klemke. "This makes the use of Cargocytes more precise and reliable for clinical applications."

Klemke said next steps involve optimizing the ability of Cargocytes to deliver multiple different therapeutics to diseased tissues in vivo, explore opportunities to engineer and enucleate other cell types, such as immune cells, and develop a similar approach to seek out and eradicate metastatic cancers that have spread throughout the body.

More information: Huawei Wang et al, Genetically engineered and enucleated human mesenchymal stromal cells for the targeted delivery of therapeutics to diseased tissue, *Nature Biomedical Engineering* (2021). DOI: 10.1038/s41551-021-00815-9

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