Genetically engineered nanoparticle delivers dexamethasone directly to inflamed lungs

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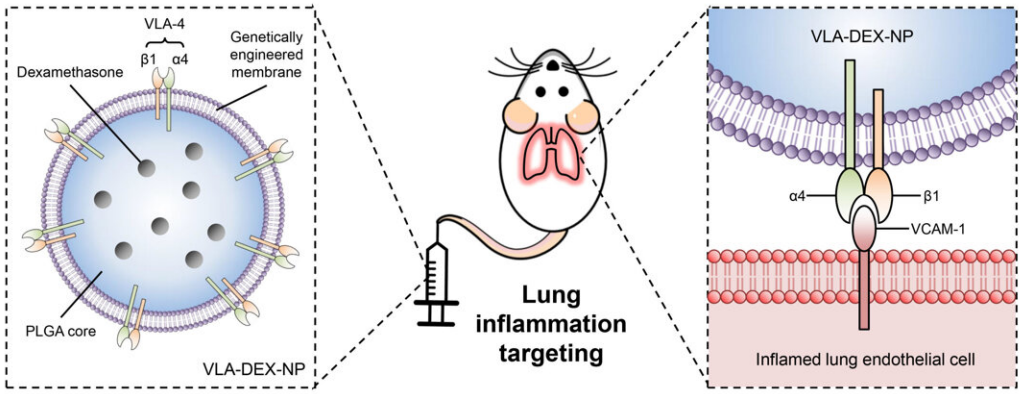

Schematic of genetically engineered cell membrane-coated nanoparticles for drug delivery to inflamed lungs. Credit: Zhang Lab

Nanoengineers at the University of California San Diego have developed immune cell-mimicking nanoparticles that target inflammation in the lungs and deliver drugs directly where they're needed. As a proof of concept, the researchers filled the nanoparticles with the drug dexamethasone and administered them to mice with inflamed lung tissue. Inflammation was completely treated in mice given the nanoparticles, at a drug concentration where standard delivery methods did not have any efficacy.

The researchers reported their findings in *Science Advances* on June 16.

What's special about these nanoparticles is that they are coated in a cell membrane that's been genetically engineered to look for and bind to inflamed lung cells. They are the latest in the line of so-called cell membrane-coated nanoparticles that have been developed by the lab of UC San Diego nanoengineering professor Liangfang Zhang. His lab has previously used cell membrane-coated nanoparticles to absorb toxins produced by MRSA; treat sepsis; and train the immune system to fight cancer. But while these previous cell membranes were naturally derived from the body's cells, the cell membranes used to coat this dexamethasone-filled nanoparticle were not.

"In this paper, we used a genetic engineering approach to edit the surface proteins on the cells before we collected the membranes. This significantly advanced our technology by allowing us to precisely overexpress certain functional proteins on the membranes or knockout some undesirable proteins," said Zhang, who is a senior author of the paper.

Joon Ho Park, a graduate student in Zhang's lab and first author of the paper, said the researchers noticed that when endothelial cells become inflamed, they overexpress a protein called VCAM1, whose purpose is to attract immune cells to the site of inflammation. In response, the immune cells express a protein called VLA4, which seeks out and binds to VCAM1.

"We engineered cell membranes to express the full version of VLA4 all the time," said Park. "These membranes constantly overexpress VLA4 in order to seek out VCAM1 and the site of inflammation. These engineered cell membranes allow the nanoparticle to find the inflamed sites, and then release the drug that's inside the nanoparticle to treat the specific area of inflammation."

While the nanoparticle won't directly enhance the efficacy of the

drug—dexamethasone in this case—concentrating it at the site of interest may mean a lower dosage is required. This study showed that the dexamethasone accumulated at the site of interest at higher levels, and faster, than standard drug delivery approaches.

"We're delivering the exact same drug used in the clinic, but the difference is we're concentrating the drugs to the point of interest," said Park. "By having these nanoparticles target the inflammation site, it means a larger portion of the medicine will wind up where it's needed, and not be cleared out by the body before it can accumulate and be effective."

The researchers note that this genetically engineered cell membrane approach is a platform technology that in theory can be used to target not only inflammation in other areas of the body— VCAM1 is a universal signal of inflammation—but much broader use cases as well.

"This is a versatile platform, not just for lung inflammation but any type of inflammation that upregulates VCAM1," said Park. "This technology can be generalized; this engineered cell membrane-coated nanoparticle doesn't have to overexpress VLA4, it could be swapped out to another protein that can target other areas of the body or accomplish other goals."

To engineer the cell membranes to overexpress the VLA4 protein, Park and the team start with packaging VLA4 genes into a viral vector. They then insert this reprogrammed viral vector into lab-grown host cells derived from mice. The cells incorporate the genes that the viral vector is carrying into their own genome and as a result, produce membranes that constantly overexpress VLA4.

The researchers' next step is to study the process using human cell membranes, instead of mice cell membranes, that are engineered to

express the human version of VLA4. There are still many steps needed before the technology could be tested in human clinical trials, but the researchers say that these early results from the platform technology are encouraging.

"By leveraging the established gene editing techniques, this study advances the cell membrane-coated nanoparticles to a new level and opens up new opportunities for targeted drug delivery and other medical applications", concluded by Zhang.

More information: "Genetically engineered cell membrane–coated nanoparticles for targeted delivery of dexamethasone to inflamed lungs" *Science Advances* (2021). advances.sciencemag.org/lookup … .1126/sciadv.abf7820

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