NEXT-GENERATION NANOPARTICLE DELIVERY

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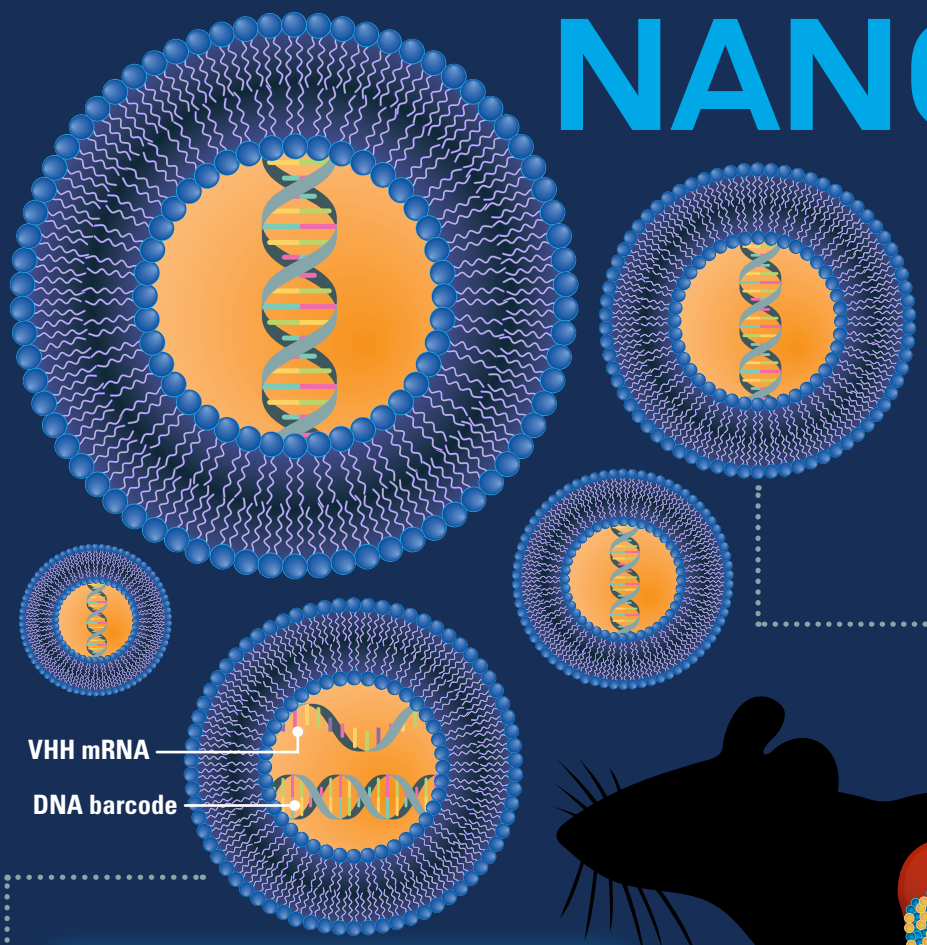
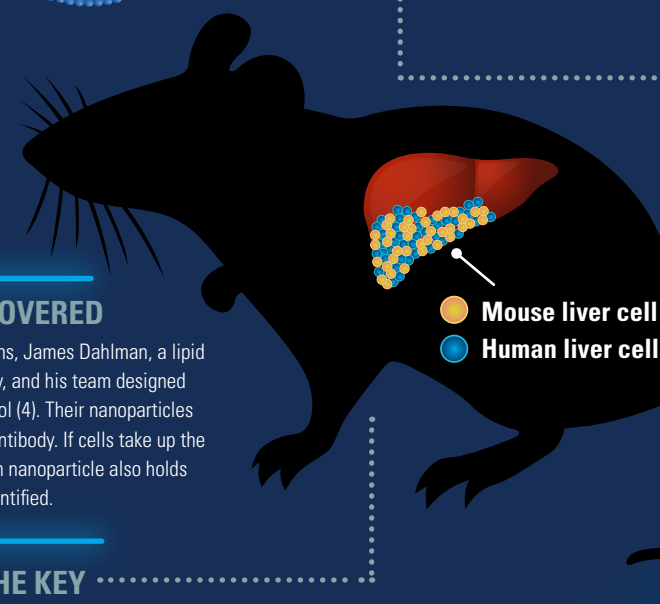


LIPID NANOPARTICLES DELIVER NUCLEOTIDE MESSAGES

With their starring role in the first COVID-19 vaccines, lipid nanoparticles have gained renown for their ability to shuttle genetic material into cells. These particles are tiny, on the order of 10 to 100 nm in size (1). They carry their nucleotide payload within a shell made of a single layer of lipids. Scientists can alter properties of the nanoparticle such as size, surface charge, lipid type, and the kinds of molecules that decorate its surface to help it enter specific cells. The FDA approved the first nanoparticle-based drug, patisiran, in 2018 (2), and since then, the gene therapy and RNA therapeutics fields have embraced the potential of nanoparticle-delivered therapies.

TRADITIONAL TESTING STARTS IN A MOUSE

The biggest challenge facing nanoparticle drugs is how to test them. Typically, scientists screen large libraries of nanoparticles simultaneously in mice (3), but a nanoparticle that works well in mice will not necessarily work the same way in humans. This is why the traditional drug discovery pipeline of testing nanoparticles in mice, then in non-human primates, and finally in humans often fails.



NANOPARTICLES READY TO BE DISCOVERED

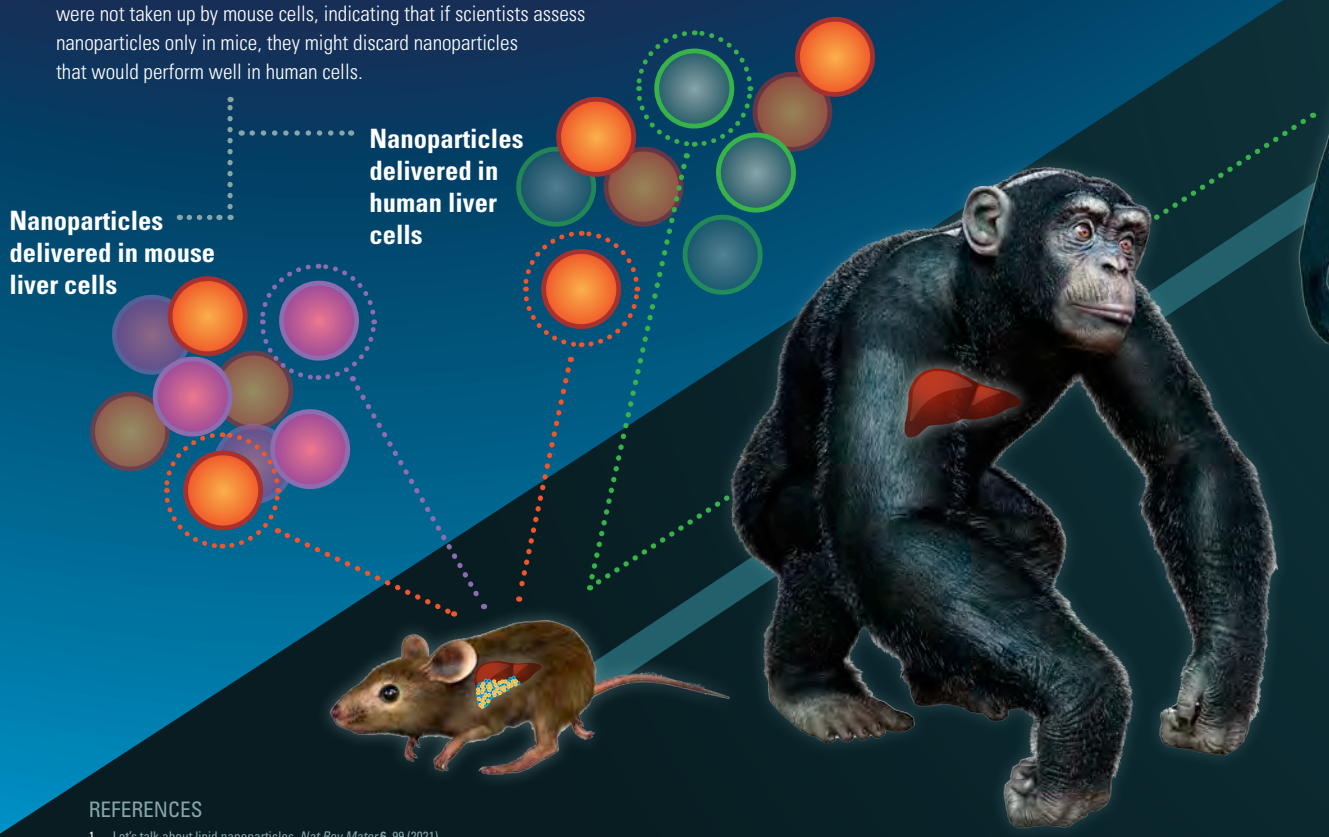
To improve the translation of nanoparticles from mice to humans, James Dahlman, a lipid nanoparticle bioengineer at the Georgia Institute of Technology, and his team designed a species-agnostic nanoparticle delivery screening (SANDS) tool (4). Their nanoparticles each contained an mRNA sequence encoding a camelid VHH antibody. If cells take up the nanoparticles, they express this antibody on their surface. Each nanoparticle also holds a DNA barcode so that the successful nanoparticles can be identified.

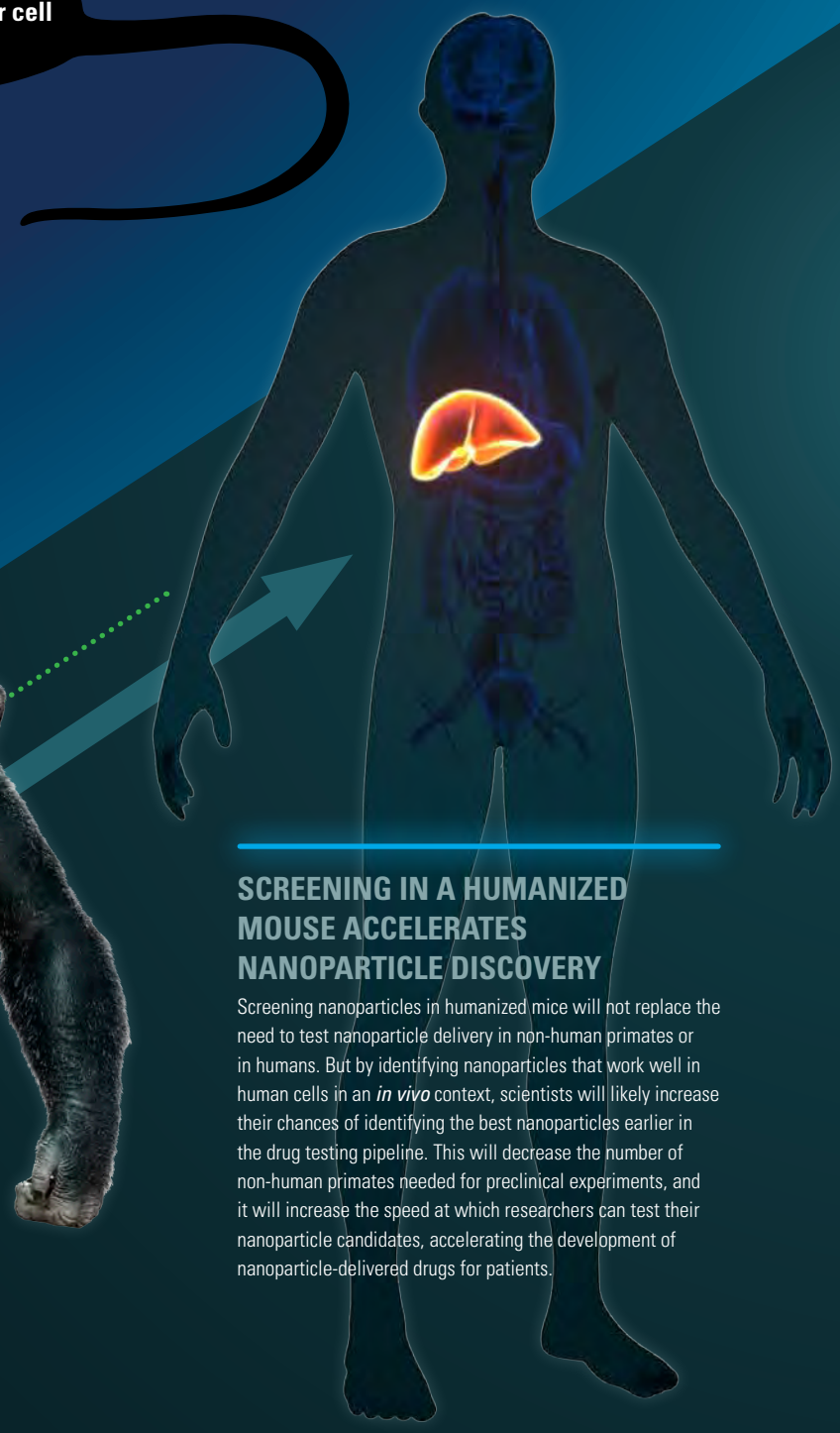
A HUMAN-MOUSE HYBRID HOLDS THE KEY

To find nanoparticles that have an improved chance of working in humans, Dahlman and his team created mice that contained human liver cells engrafted onto a mouse liver. By performing high-throughput screening in these humanized mice, the researchers determined which nanoparticles delivered their mRNA message to either the human or mouse liver cells within the same animal.

NANOPARTICLE DELIVERY TO HUMAN AND MOUSE CELLS IS NOT THE SAME

Some nanoparticles that successfully made their way into human cells were not taken up by mouse cells, indicating that if scientists assess nanoparticles only in mice, they might discard nanoparticles that would perform well in human cells.





SCREENING IN A HUMANIZED MOUSE ACCELERATES NANOPARTICLE DISCOVERY

Screening nanoparticles in humanized mice will not replace the need to test nanoparticle delivery in non-human primates or in humans. But by identifying nanoparticles that work well in human cells in an *in vivo* context, scientists will likely increase their chances of identifying the best nanoparticles earlier in the drug testing pipeline. This will decrease the number of non-human primates needed for preclinical experiments, and it will increase the speed at which researchers can test their nanoparticle candidates, accelerating the development of nanoparticle-delivered drugs for patients.

REFERENCES

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4. Hatit, M.Z.C., Lokugamage, M.P., Dobrowolski, C.N. *et al.* Species-dependent in vivo mRNA delivery and cellular responses to nanoparticles. *Nat. Nanotechnol* (2022).