Nanoparticles deliver small interfering RNA to slow multiple myeloma

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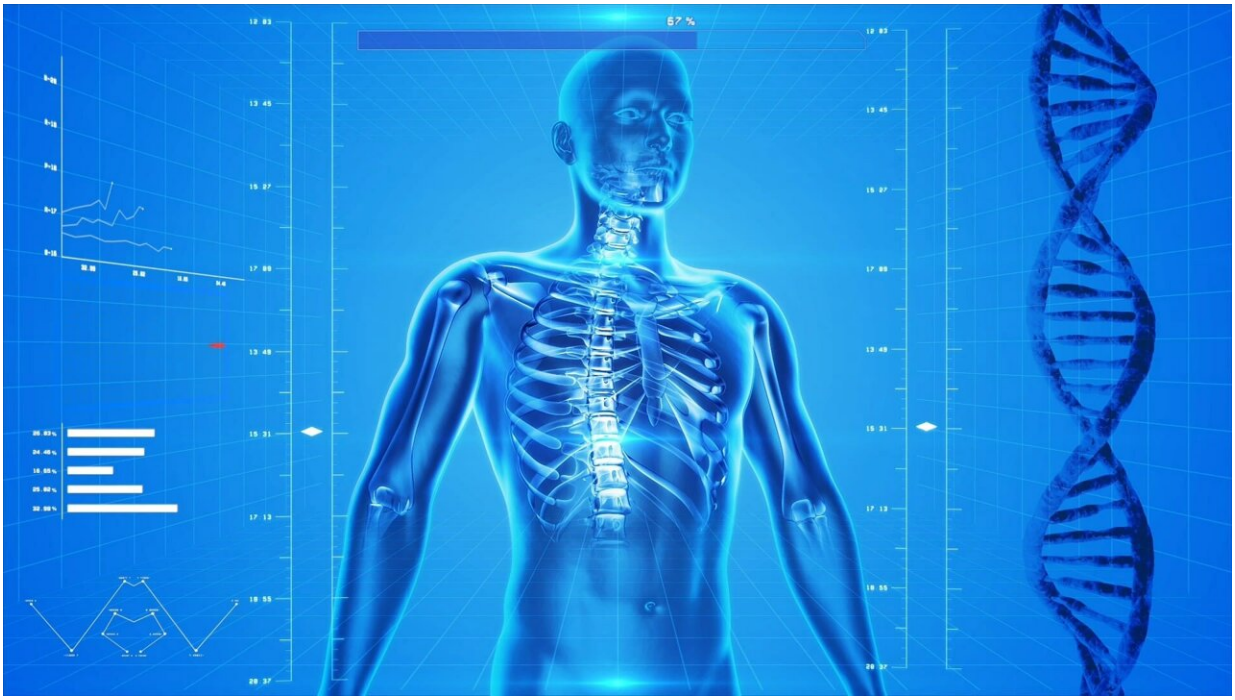

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Research led by the University of Pennsylvania, Philadelphia, has used siRNA-based silencing of protein cyclophilin A (CyPA) to reduce tumor burden and extend the lives of patients with multiple myeloma.

In the paper, "In vivo bone marrow microenvironment siRNA delivery using lipid–polymer nanoparticles for multiple myeloma therapy,"

published in *PNAS*, the researchers detail a targeted nanoparticle platform to deliver nucleic acid therapeutics to bone marrow endothelial cells with a therapeutic payload.

Multiple myeloma (MM) is a blood cancer that occurs in the bone marrow and can form tumors outside bone marrow in the body's organs (extramedullary disease). MM is currently treatable but incurable, with inevitable relapse after treatment and typically short survival rates of 3 to 6 months for those with relapse as they build resistance to the treatments.

Endothelial cells within the bone marrow microenvironment are thought to play a critical role. Specifically, cyclophilin A (CyPA), a protein secreted by bone marrow endothelial cells, is involved in progression, survival, and chemotherapeutic resistance.

Inhibiting CyPA could simultaneously inhibit MM progression and make MM more vulnerable to chemotherapeutics, but getting inhibiting molecules into the bone marrow endothelium is challenging.

Small interfering RNA (siRNA) therapeutics have broad potential to silence any targeted gene and are a great candidate for CyPA silencing but are limited by instability in the bloodstream and an inability to traverse cell membranes easily.

The researchers needed a way to get the potential therapy to the correct location and turned to a nanoparticle delivery system. The team developed nanoparticles comprised of a polymer-lipid hybrid material and a lipid-polyethylene glycol (PEG) to enable nucleic acid encapsulation.

The nanoparticles reduced the degradation of the RNA by enzymes in the blood and were able to deliver the payload siRNA to specific tissues

via functionalization of the nanoparticle surface chemistry,

The nanoparticle delivery platform and a CyPA silencing siRNA payload were deployed in a living mouse model, and it worked. The silencing of CyPA decreased multiple myeloma invasion across bone marrow endothelial cells and disrupted interactions. When combined with a therapeutic, bortezomib, CyPA silencing sensitized cancer cells to therapy, which reduced proliferation and angiogenesis, and ultimately extended mouse survival.

The authors suggest that this nanoparticle platform may provide a broadly enabling technology to deliver nucleic acid therapeutics to other malignancies.

More information: Pedro P. G. Guimarães et al, In vivo bone marrow microenvironment siRNA delivery using lipid–polymer nanoparticles for multiple myeloma therapy, *Proceedings of the National Academy of Sciences* (2023). DOI: 10.1073/pnas.2215711120