New adaptable nanoparticle platform enables enhanced delivery of gene therapies

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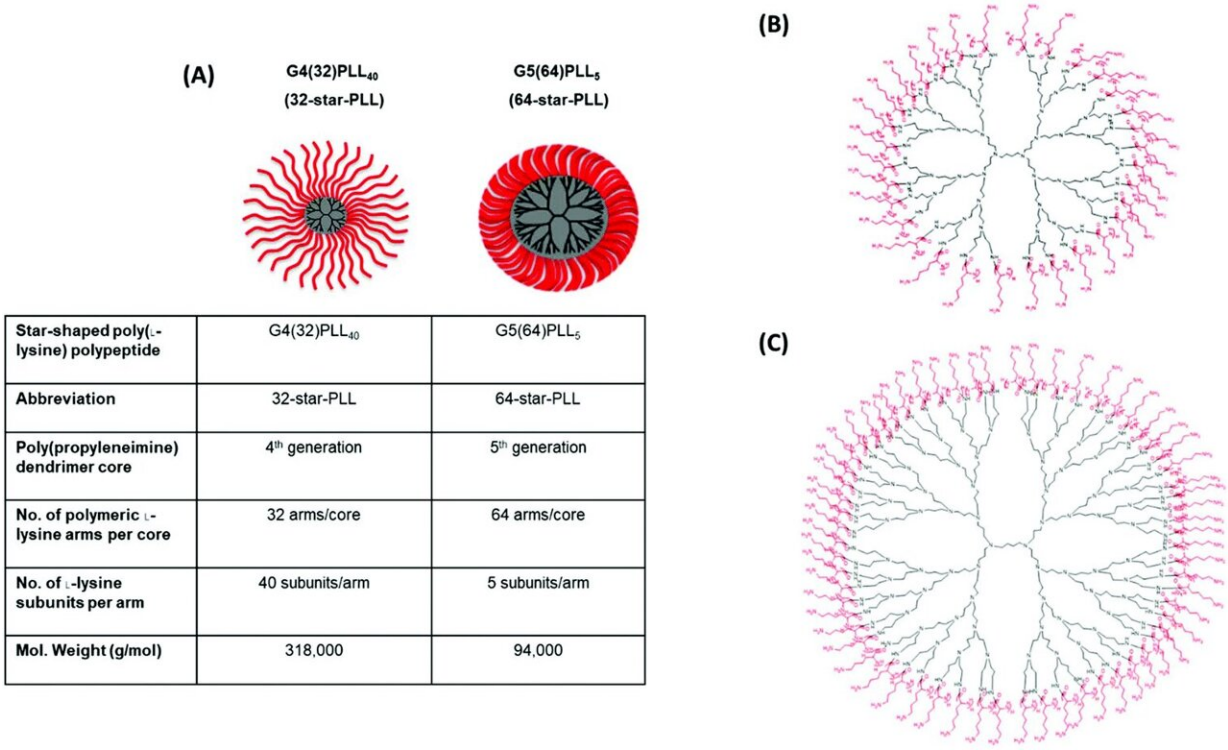

Star-shaped poly(L-lysine) polypeptide	G4(32)PLL$_{40}$	G5(64)PLL$_{5}$
Abbreviation	32-star-PLL	64-star-PLL
Poly(propyleneimine) dendrimer core	4th generation	5th generation
No. of polymeric L-lysine arms per core	32 arms/core	64 arms/core
No. of L-lysine subunits per arm	40 subunits/arm	5 subunits/arm
Mol. Weight (g/mol)	318,000	94,000

Fig. 1 Structural overview of star-PLLs. Illustrated above is (A) a structural outline of the two star-PLLs used in this study, namely G4(32)PLL40 (32-star-PLL) and G5(64)PLL5 (64-star-PLL), (B) chemical structure of 32-star-PLL and (C) chemical structure of 64-star-PLL. Reproduced from ref. 1 with permission from Elsevier, copyright 2018.

Scientists have developed polypeptide-based materials that act as

effective vectors for delivering gene therapies. The first-of-its-kind platform enables the vectors to be adapted to suit the specific gene therapy cargo.

The work, led by researchers from RCSI University of Medicine and Health Sciences and funded by Science Foundation Ireland, is published in *Biomaterials Science*.

A major challenge for gene therapies is preparing them in a way that can deliver the genetic information into the host cells. For the COVID-19 vaccines that use mRNA technology, the genetic information is delivered in a lipid nanoparticle to maintain its stability and deliver it into cells. The success of the COVID vaccines has established nanoparticles as key to the development of many advanced therapies.

The researchers developed a platform that produces bespoke star-shaped polypeptide nanoparticles, which effectively deliver a range of therapies, including gene therapies. Crucially, these polypeptides are more flexible and easier to handle than lipids. To demonstrate the potential of this material, the researchers used it to deliver a gene therapy that regenerated bone.

In preclinical work, the researchers loaded the material with DNA molecules that promote bones and blood vessels to regrow. They placed these nanomedicines in a scaffold that could be implanted into a defect site and deliver the genetic cargo into infiltrating host cells. The gene-loaded scaffold accelerated bone tissue regeneration, with a six-fold increase in new bone formation compared to a scaffold alone.

"With the success of the COVID-19 vaccines, the potential of gene therapies is becoming apparent, and advanced nanoparticle delivery systems are key to enabling their use clinically. We have shown that these nanoparticles have real potential to be a game changer in the

delivery of gene therapies," said Professor Sally-Ann Cryan, the study's senior author and Professor of Drug Delivery, RCSI.

"While more testing is needed before these therapies can be used clinically, our platform allows us to design our polypeptides to meet a variety of delivery scenarios and provide tailored solutions to gene delivery challenges," added Professor Andreas Heise, project collaborator and Professor of Polymer Chemistry, RCSI.

More information: David P. Walsh et al, Gene activated scaffolds incorporating star-shaped polypeptide-pDNA nanomedicines accelerate bone tissue regeneration in vivo, *Biomaterials Science* (2021). DOI: 10.1039/D1BM00094B

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