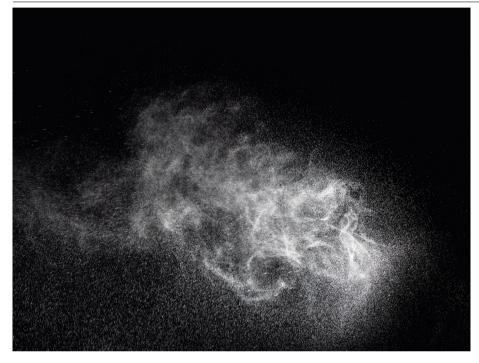
Research highlights

Drug delivery

https://doi.org/10.1038/s44222-022-00018-0

Inhalable polymer delivers RNA to the lungs



Nucleic acid therapeutics and preventives, for example, mRNA vaccines, require delivery by nanoparticles to protect nucleic acids and to allow their cellular update. For example, lipid nanoparticles have enabled the systemic administration of COVID-19 mRNA vaccines. However, the treatment of respiratory virus infections would greatly benefit from nucleic acid administration directly into the lungs by inhalation. Lung delivery of nucleic acids could further improve the treatment of other pulmonary pathogens and diseases, such as influenza and cystic fibrosis. Now, writing in Nature Materials, Philip J. Santangelo and team identified a polymeric nanoparticle, based on a poly-β-amino-thio-ester, that can be inhaled to deliver nucleic acids into the lungs of various animal species, regardless of cargo size and complexity.

Owing to their success in delivering mRNA for vaccination against COVID-19, lipid nanoparticles have also been explored for the delivery of nucleic acid therapeutics into specific organs, including the lung. Excitingly, inhaled lipid nanoparticles have already entered clinical trials, for example, for the treatment of cystic fibrosis; however, they have yet failed to produce sufficient protein to improve lung function in cystic fibrosis patients.

As an alternative to lipid nanoparticles, Santangelo and colleagues have explored polymeric nanoparticles for lung delivery. The team has previously demonstrated that poly-β-amino-esters (PBAEs) are particularly suited to inhalable delivery of nucleic acids. Building on this work, they now used a combinatorial synthesis strategy with a nebulizer-based particle screening system to assess 166 PBAEs and PBAE-containing formulations in mice. "We developed sensitive reporter mRNAs and a nose-only delivery system that allowed us to rapidly screen many polymer chemistries, because we could use very small amounts of mRNA and polymer for testing," explains Santangelo.

The team identified one specific formulation (P76) that is safe and well tolerated in mice, and that can be administered by a nebulizer. "We found that the addition of an ethane dithiol improves the polymer significantly in terms of delivery efficiency and resistance to shear forces in the nebulizer," says Santangelo. The incorporation of thiols in P76 further enables co-delivery of short *trans*-activating crispr RNA (crRNAs) with long mRNAs, making these polymer nanoparticles potentially suitable for CRISPR-based therapeutics.

The formulation also works safely across a range of species, including hamsters, ferrets, cows and rhesus macaques, which can be used as models for human viral infections, such as influenza and SARS-CoV-2. "Clearly, we cannot guarantee that these formulations will work in humans, but we think we have done a very good job de-risking the platform through successful delivery to multiple species, including non-human primates," states Santangelo.

Importantly, protein expression could be increased; in a SARS-CoV-2-challenged hamster model, a four times lower dose of P76-delivered Cas13a mRNA was sufficient to demonstrate similar efficacy as the gold standard of systemic neutralizing antibody treatment, as compared to other PBAE formulations.

"We developed sensitive reporter mRNAs and a nose-only delivery system that allowed us to rapidly screen many polymer chemistries"

Using this polymer, the researchers are now exploring a number of mRNA-based therapeutics for the lung. "We are moving towards good manufacturing practice (GMP) production, and are hopeful to move this into the clinic in the future," concludes Santangelo.

Christine-Maria Horejs

Original article: Rotolo, L. et al. Species-agnostic polymeric formulations for inhalable messenger RNA delivery to the lung. *Nat. Mater.* https://doi.org/10.1038/ s41563-022-01404-0 (2022)