Insights into better ways to package and deliver RNA into human cells.

A study to support the development of RNA based vaccines: BioNTech, a company that together with Pfizer developed one of the first COVID-19 vaccines, in collaboration with the University of Mainz and the European Molecular Biology Laboratory (EMBL) conducted synchrotron X-ray scattering experiments at DESY's PETRA III beamline P12 operated by EMBL. The obtained results will help the scientists to better package mRNA in nanoparticles for vaccines or individualized drugs.

CHALLENGE:

The vaccine candidates from BioNTech and Pfizer, as well as those from biotech company Moderna, belong to a new class of vaccines that use messenger RNA (mRNA): an instruction-carrying molecule that tells a cell to make a specific protein. In this new approach, mRNA molecules that contain instructions for making a key protein of a pathogen are introduced into the human body. Cells that take up the mRNA start to produce the pathogen's protein. This lasts only for a short time, because the mRNA is soon degraded. The mRNA and its resulting protein do not make a person ill, but are sufficient to train the immune system to recognise and destroy the pathogen. Interestingly, this method can be used to gain immunity not only to bacterial and viral infections, but also to certain types of cancer. However, delivering the mRNA into cells is challenging. If pure mRNA was injected into the body, it would be immediately degraded before it could even be taken up by cells. To protect the precious mRNA from damage, scientists develop ways to package it into tiny particles, known as nanoparticles, and deliver it into cells.

METHOD

Researchers used small-angle X-ray scattering (SAXS) at the EMBL beamline P12 at PETRA III to investigate the internal organisation of lipid nanoparticles and compared their effectiveness in different organs.

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INSIGHTS AND ANALYSIS

The team has succeeded for the first time in directly demonstrating changes in the structure of model membranes containing the ionisable lipid nanoparticles. The pH influences the internal structure of the nanoparticles. This knowledge can be used to develop optimised transport systems for transfecting specific types of cells, since the pH varies from one type of cell to another.
The efficiency of mRNA transfection can also be increased by using the right combination of different materials to make the nanoparticles (demonstrated in another research project). Hybrid nanoparticles, containing both lipids and polymers suitably combined, achieved a significantly better transfection than pure lipid or pure polymer nanoparticles. Structural analyses, in particular those at the EMBL's P12 beamline at PETRA III, show that the particles with the highest transfection efficiency are characterised by a heterogeneous internal structure in which well-ordered and less well-ordered areas alternate in a characteristic pattern.

References: DOI: 10.3390/cells9092034, DOI: 10.1021/acsanm.0c01834, DOI: 10.1021/acs.langmuir.0c02446

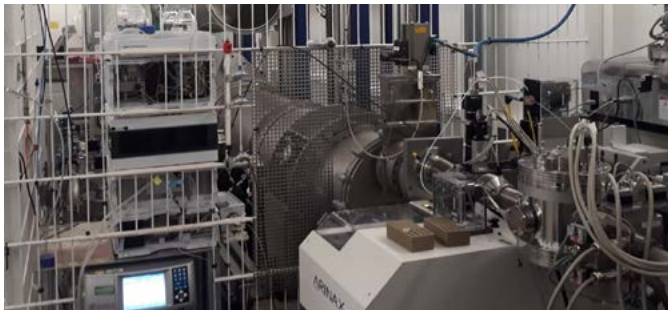

Figure 1 | The beamline P12 at EMBL Hamburg allows studying the structure of molecules in solution using small-angle X-ray scattering (SAXS) technique. (Svergun group/EMBL)

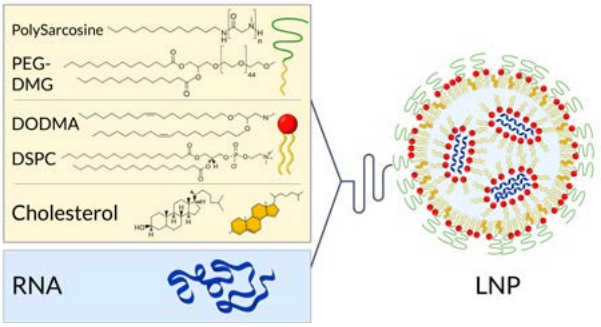

Figure 2 | Lipid nanoparticles (LNP) are tiny particles (less than 100n diameter) made of lipids, which are used in the biotechnology industry to deliver molecules, such as RNA, to cells. Polyethyleneglycol-Dimyristoyl glycerol (PEG-DMG), 1,2-Dioleyloxy-3-dimethylaminopropane (DODMA), 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC). (Cristina Sala/BioNTech)

BENEFITS

The analysis at DESY helped BioNTech together with the academic partners to study the structure, efficiency, and behaviour of nanoparticles made of lipids, or a combination of lipids and biopolymers, under different conditions. Although the mRNA-based technology is very new and its long-term efficacy still needs to be tested, it has great potential to enable rapid development of vaccines and treatments for various diseases in future. This work also shows the importance of collaboration between industry and research facilities such as those at EMBL, to drive progress and innovation in technology and medicine.

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