

# Big Molecules and Small Particles

## Lennart Lindfors

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Modified messenger RNA constitutes an interesting new approach for transient protein expression in different therapies, including the recently approved SARS-Cov-2 vaccines. However, the details of the intracellular delivery of such macromolecules using so-called lipid nanoparticles remains unknown. In this work we have prepared lipid nanoparticles (LNPs) of two different ionizable lipids (DLin-MC3-DMA and DLin-DMA), cholesterol, distearylphosphatidyl choline (DSPC) and a PEG lipid. We then dosed these two LNPs intravenously in mice measuring LNP uptake, mRNA delivery and the concurrent protein expression in liver cells, i.e. hepatocytes, liver sinusoidal endothelial cells (LSEC) and Kupffer cells (KC). The in vivo data clearly showed that although uptake of lipid and delivered mRNA is very similar for both types of LNPs, the protein expression in hepatocytes is order of magnitude different.

In order to rationalize these in vivo observations, mRNA LNPs were characterized by several techniques e.g. <sup>13</sup>C-NMR and small-angle x-ray scattering. Previously, we have shown that LNPs have a core-shell structure and here we focused our efforts into studying the core of LNPs, as bulk phases. By careful analysis of the inverse hexagonal phase structure of both ionizable lipids, we put forward a hypothesis on why DLin-MC3-DMA LNPs outperforms DLin-DMA LNPs in vivo.

### References

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### Presenter biography

Lennart Lindfors is currently a Senior Principal Scientist at Pharmaceutical Sciences at AstraZeneca with a PhD in Physical Chemistry at Chalmers University of Technology (1988). At AstraZeneca he has been working on oral vaccines, molecular simulations, nanoparticle systems of poorly soluble drugs and, recently, on lipid nanoparticles and exosomes incorporating messenger RNA.

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