Big Molecules and Small Particles

Lennart Lindfors
Pharmaceutical Sciences, BioPharmaceutical R&D, AstraZeneca Gothenburg, Sweden | Lennart.Lindfors@astrazeneca.com

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, distearylphophatidyl 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. 13C-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

[1] *Successful reprogramming of cellular protein production through mRNA delivered by functionalized lipid nanoparticles*, M. Yanez Arteta, T. Kjellman, S. Bartesaghi, S. Wallin, X. Wu, A. J. Kvistc, A. Dabkowska, N. Székely, A. Radulescu, J. Bergenholtz, L. Lindfors, *Proceedings of the National Academy of Sciences*, 2018, E3351.
[2] *Linkage between endosomal escape of LNP-mRNA and loading into EVs for transport to other cells*, M. Maugeri , M. Nawaz , A. Papadimitriou, A. Angerfors, A. Camponeschi, M. Na, M. Hölttä, P. Skantze, S. Johansson, M. Sundqvist, J. Lindquist, T. Kjellman, I.-L. Mårtensson, T. Jin, P. Sunnerhagen, S. Östman, L. Lindfors, H. Valadi, *Nature Communications*, 2019, 4333.
[3] *pH-dependent structural transitions in cationic ionizable lipid mesophases are critical for lipid nanoparticle function*, J. Philipp, A. Dabkowska, A. Reiser , K. Franka, R. Krzysztoń, C. Brummer, B. Nickel, C. E. Blanchet , A. Sudarsan, M. Ibrahim, S. Johansson, P.Skantze, U. Skantze, S. Östman, N. Henderson, K. Elvevold, B. Smedsrød, N. Schwierz, L. Lindfors, and J.O. Rädler *Proceedings of the National Academy of Sciences*, 120, e2310491120 (2023).
[4] *Lipid shape and packing are key for optimal design of pH-sensitive mRNA lipid nanoparticles*, G. Tesei, Y-W. Hsiao, A. Dabkowska, G. Grönberg, M. Yanez Arteta, D. Ulkoski, D. J. Bray, M. Trulsson, J. Ulander, M. Lund, L. Lindfors, *Proceedings of the National Academy of Sciences*, 121, e2311700120 (2024).

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.

Thursday, December 5, 2024

10:45 AM (UTC-05:00) Eastern Time (US & Canada) | Hybrid format, remote presentation

Attend in person (room K04B, NCNR) if you have access to the NIST campus, or remotely using the link below. NCNR access is not required.

https://nist.zoomgov.com/j/1619237673?pwd=D3eYG0IzM6bxB1jzrsD2YGHhqkNq8B.1

Meeting ID: 161 923 7673

Passcode: 995753

One tap mobile
+16692545252,,1619237673#,,,,*995753# US (San Jose)
+16469641167,,1619237673#,,,,*995753# US (US Spanish Line)

Dial by your location
• +1 669 254 5252 US (San Jose)
• +1 646 964 1167 US (US Spanish Line)
• +1 646 828 7666 US (New York)
• +1 415 449 4000 US (US Spanish Line)
• +1 551 285 1373 US (New Jersey)
• +1 669 216 1590 US (San Jose)
Meeting ID: 161 923 7673
Passcode: 995753

Find your local number:
https://nist.zoomgov.com/u/aHQRk0c7C

Join by SIP
• 1619237673@sip.zoomgov.com

Join by H.323
• 161.199.138.10 (US West)
• 161.199.136.10 (US East)
Meeting ID: 161 923 7673
Passcode: 995753