

# Lipid nanoparticles for RNA delivery: achievements and challenges

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RNA delivery represents one of the key tools for new therapeutic strategies. Messenger RNA (mRNA) can open new horizons in the treatment of diseases characterized by an altered protein expression. The two approved RNA-based vaccines clearly demonstrated the potentialities of mRNA for vaccination, which can be extended not only to the prevention of viral infections but also in the fight against cancer. On the other hand, from the discovery of RNA interference (RNAi) the knowledge on the pivotal role of non-coding RNA oligonucleotides, e.g. small interfering RNA (siRNA) and micro RNA (miRNA), in regulating cell process boosted research studies for using these synthetic RNA fragment as new potential drugs. However, the development of RNA-based therapies is hampered by poor biopharmaceutical profile. Nanomedicine represent a powerful tool to overcome the poor stability in biological fluid as well as the negligible entry into cells. Despite the development of different nanomedicine platform based on different biomaterials, lipid nanoparticles (LNPs) are considered the leading solution to develop RNA-based therapeutics, due to the approval of Onpattro® and following unquestionable success of the two RNA-based vaccines Comirnaty® and Spikevax®. LNP can be successfully used for the delivery of non-coding RNA, e.g. miRNA, for the treatment of different form of cancer. Targeted LNP encapsulating miRNAs have been also proposed [1]. LNP encapsulating miRNA have also been used to overcome chemoresistance occurring in the case of immunotherapy [2,3]. Recently, the ability to use LNP to deliver therapeutic miRNA in the CNS to treat brain metastasis has also been demonstrated [4]. Finally, LNP encapsulating miRNAs have also been proposed to reduce the brain damage following ischemia (submitted manuscript). Despite the success of lipid nanoparticles (LNP), some issues still need to be addressed, among them the poor physical stability of RNA-encapsulating LNP that requires low temperatures for storage and transport. Our research group developed a novel nanotechnology approach named lipid self-assembling nanoparticle (SANP) as alternative platform for RNA delivery. Lipid SANP formulations, previously developed by our group have shown remarkable biocompatibility, high RNA encapsulation efficiency, and enhanced intracellular release. Furthermore, SANP have been designed to be prepared at room temperature immediately before use by simple mixing of three components, namely, calcium/phosphate dispersion, RNA and cationic liposomes. By using this approach, the RNA can be stored and used in a lyophilized form, which ensures greater stability against degradation compared to freezing. This approach could also be used for personalized medicine, thus developing into the hospital personalized formulations encapsulating non-coding RNA selected for the specific patient. SANPs developed for the delivery miRNA [5] or siRNA [6] in the treatment of different tumors have been proposed. SANPs encapsulating mRNA for vaccination purpose are also under investigation. Further development includes the inclusion of “bioactive” components into the SANP able to prevent neuron damage following oxidative stress, thus making this technology of interest for the treatment of neurodegenerative diseases.

## References

- [1] Di Martino MT, et al. PLoS One, 9(2):e90005 (2014).
- [2] Fattore L. Oncogene. Jan;42(4):293-307 (2023).
- [3] Fattore L. Int J Mol Sci. 21(6):1930 (2020).
- [4] Dinami R. EMBO Mol Med. Jan 11;15(1):e16033 (2023).
- [5] Campani V. Int J Pharm. Oct 15;588:119693 (2020).
- [6] Delle Donne et al. Commun Biol. Aug 2;5(1):780 (2022).