Vol. 16, No. 2, 2025
ISSN 2233-4203/ e-ISSN 2093-8950
ARTICLE www.msletters.org | Mass Spectrometry Letters

Development of an Analytical Method for Ionizable Lipids in Lipid Nanoparticles Using LC-MS/MS

Mi Kyeong Ju[1,2*], Jin-Ju Byeon[1], Minkyu Park[1], Sujin Ahn[1], and Soo Jae Lee[2]

[1]Yuhan R&D Institute, Yuhan Corporation, 25, Tapsil-ro 35beon-gil, Giheung-gu, Yongin-si, Gyeonggi-do, Republic of Korea
[2]College of Pharmacy, Chungbuk National University, 194-21, Osongsaengmyeong 1-ro, Osong-eup, Heungdeok-gu, Cheongju-si, Chungcheongbuk-do, Republic of Korea

Received April 3, 2025, Revised June 11, 2025, Accepted June 12, 2025
First published on the web June 30, 2025; DOI: 10.5478/MSL.2025.16.2.58

Abstract : RNA therapeutics and mRNA vaccines have emerged as a promising class of medicines for the treatment of various diseases. The successful application of these modalities depends on the safe and effective delivery of mRNA into target cells. Lipid nanoparticle (LNP) is a novel carrier for delivery. Ionizable lipid is a key component of LNP and plays a crucial role in encapsulating and protecting mRNA molecules. Given the incorporation of novel carrier components, such as synthetic lipids, in LNPs, extensive preclinical biodistribution studies are essential to evaluate their in vivo exposure profiles. To assess the biodistribution of ionizable lipids, an analytical method using liquid chromatography-tandem mass spectrometry (LC-MS/MS) was developed for the quantitation of ionizable lipids such as SM-102 and ALC-0315, enabling their precise quantification in biological matrices. The method was successfully established, demonstrating good selectivity, linearity ($r^2 \geq 0.9950$ over the range of 1-2000 ng/mL), accuracy (ranging from 89.7% to 117.4% for SM-102, from 93.8% to 115.2% for ALC-0315), precision (≤ 19.7% for SM-102, ≤ 15.3% for ALC-0315), and a lower limit of quantification (1.0 ng/mL). This method is expected to contribute to the comprehensive evaluation of biodistribution for novel ionizable lipids in LNP formulations.

Keywords : ionizable lipid, SM-102, ALC-0315, biodistribution

Introduction

Recently, RNA-based therapeutics have emerged as a promising class of medicines for the treatment of various diseases. Among various delivery systems, lipid nanoparticles (LNPs) are the most widely used for nucleic acid-based therapies, particularly for mRNA-based vaccines and treatments.[1,2] LNPs serve as protective carriers that prevent enzymatic degradation of nucleic acids, enhance drug stability, and facilitate endosomal escape to enable efficient cytoplasmic delivery. In addition, LNPs exhibit high encapsulation efficiency and structural flexibility, allowing for the delivery of mRNA molecules of virtually any length. These distinctive properties distinguish LNPs from other gene delivery platforms and have played a pivotal role in the advancement of RNA-based therapeutics.[3,4]

A typical LNP formulation consists of four main components: cholesterol, a neutral phospholipid, a polyethyleneglycol (PEG)-lipid, and an ionizable cationic lipid.[5,6] While cholesterol and neutral phospholipids are natural lipids, the ionizable and PEGylated lipids are synthetic lipids to optimize delivery and stability. The ionizable lipid, which constitutes approximately half of the LNP composition, plays a crucial role in nucleic acid encapsulation and endosome membrane disruption to release the nucleic acid cargo into the cytosol.[7]

Regulatory agencies, such as the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA), provide guidance on the necessity of biodistribution studies for RNA therapeutics. EMA generally recommends conducting these studies unless the specific RNA therapeutic design justifies an exemption.[8] The FDA, on the other hand, advises biodistribution studies primarily for new vector classes or when significant modifications are made to vector backbones, formulations, administration routes, dosing levels, or schedules.[9] Additionally, novel carrier components, such as the lipids in LNPs, require individual preclinical studies. Biodistribution studies are generally not required for LNP formulations that include already approved lipids. However, such studies should be per-

*Reprint requests to Mi Kyeong Ju
https://orcid.org/0009-0000-0097-775X
E-mail: juju1980@yuhan.co.kr

formed for novel carrier components such as a new ionizable lipid in LNP.[10] Since ionizable lipids are often unique proprietary compounds in the development of RNA-based therapies, biodistribution studies in the preclinical stage are essential to assess their safety and efficacy. These regulatory considerations highlight the importance of comprehensive preclinical evaluation in the development of RNA-based therapies.

In this study, the method for the analysis of ionizable lipids such as SM-102 and ALC-0315 was developed in biological matrices using liquid chromatography-tandem mass spectrometry (LC-MS/MS). SM-102 is a synthetic lipid used in lipid nanoparticles (LNPs) for mRNA delivery and was a key component of Moderna's COVID-19 vaccine, aiding in the encapsulation and transport of mRNA into cells.[11,12] Similarly, ALC-0315 is a synthetic ionizable lipid used in LNP formulations and played a crucial role in Pfizer-BioNTech's COVID-19 vaccine by facilitating efficient mRNA delivery.[12] This analytical approach provides a robust and sensitive tool for assessing lipid biodistribution, supporting the preclinical evaluation of novel LNP formulations.

Experimental

Materials

SM-102 and ALC-0315 were purchased from BroadPharm (USA). Acetonitrile (ACN) and methanol (MeOH) were obtained from Burdick & Jackson (USA). Formic acid and ethanol (EtOH) were purchased from Sigma-Aldrich (USA). All materials were of LC-MS grade.

Standard Solution Preparation

Stock solutions of SM-102 and ALC-0315 were prepared by dissolving them in ethanol (EtOH) at a concentration of 20 mg/mL and stored at -80°C until use. Working solutions of SM-102 and ALC-0315 were prepared by serial dilution of the stock solutions with ethanol (EtOH) to generate calibration curves and quality control (QC) samples at concentrations of 20, 100, 200, 1000, 2000, 10000, 20000, and 40000 ng/mL for calibration standard and at concentration of 20, 60, 12000, and 32000 ng/mL for QC samples. Tolterodine, used as the internal standard (IS), was dissolved in DMSO at a concentration of 1 mg/mL. The extraction solvent was prepared by diluting the IS stock solution to 50 ng/mL with ACN:MeOH mixture (9:1, *v/v*).

Sample Preparation

Calibration standards were prepared by diluting the working solutions 1:20 with blank serum or blank homogenized liver, resulting in a concentration range of 1 to 2000 ng/mL. QC samples were similarly prepared at specific concentrations (1, 3, 600, and 1600 ng/mL). A 40 μL aliquot of calibration standards or QC samples was transferred into a 1.5 mL microtube. Then, 200 μL of extraction solvent containing the IS was added, and the mixture was thoroughly vortexed and placed inside the refrigerator at 4°C for 10 min to facilitate the protein precipitation process. Then, the mixtures were centrifuged at 18000 g for 10 min at 4°C, and 100 μL of the supernatant was transferred into glass vials for analysis.

Liver samples and distilled water (DW) were mixed at a ratio of 1:9 (*w/v*) in 15 mL Precellys tubes, including 2.8 mm ceramic beads (zirconium oxide), and homogenized using a Precellys tissue homogenizer (Precellys® Evolution Touch). 40 μL of serum or homogenized liver samples were prepared using the same extraction method for analysis.

Liquid Chromatography and Tandem Mass Spectrometry (LC-MS/MS) Conditions

Ionizable lipid analysis was performed using a Triple Quad™ 6500 System (AB SCIEX, USA) coupled with a Nexera X2 UPLC system (Shimadzu, Japan) with electrospray ionization (ESI) in positive ion mode. Chromatographic separation was achieved using a Kinetex Biphenyl 100 Å column (2.6 μm, 50 × 2.1 mm, Phenomenex) with a SecurityGuard™ UHPLC column (Biphenyl, 2.1 mm, Phenomenex). The mobile phase consisted of distilled water (DW) containing 0.1% (*v/v*) formic acid (Phase A) and methanol (MeOH) containing 0.1% (*v/v*) formic acid (Phase B). The flow rate was set to 0.6 mL/min, and the injection volume was 0.3 μL for SM-102 and 2.0 μL for ALC-0315. The mobile phase gradient was as follows: 0-0.3 min: 25% B, 0.3-0.7 min: 25% to 99% B, 0.7–2.0 min: 99% B, 2.0-2.05 min: 99% to 25% B, 2.05-3.0 min: 25% B. The autosampler and column oven temperatures were maintained at 10°C and 40°C, respectively. The mass spectrometer (MS) was operated with the following parameters: source temperature of 650°C, ion spray voltage of 5500 V, collision gas at 9 psig, curtain gas at 30 psig, and ion source gases at 50 psig. Multiple reaction monitoring (MRM) was used for selective and sensitive determination. LC-MS/MS data were processed using Analyst 1.7.2 software (AB SCIEX). The transition peak area ratios of ionizable lipids to the IS were used for quantification if the following conditions were met: retention times for all three transitions were consistent, the signal-to-noise ratio (S/N) for the transition peak was greater than 5.

In vivo biodistribution in mice

The animal experiments were conducted following the principles of animal care and use, and the study protocol was approved by the Institutional Animal Care and Usage Committee (IACUC) of Yuhan Corporation (Approval No.: 24095). Lipid nanoparticles (LNPs) were manufactured at the Yuhan Institute using SM-102 and ALC-0315, respectively. The LNP suspension was prepared in Dulbecco's Phosphate-Buffered Saline (DPBS) at 1 mg/15 mL. A total of 20 female Balb/c mice were randomly assigned to 2 groups. Each LNP suspension was intravenously adminis-

tered via the tail vein at a dose of 0.5 mg/7.5 mL/kg ($n = 10$/group). At 24 and 168 hours post-dose, 5 mice per group were anesthetized, and approximately 400 μL of whole blood was collected from the inferior vena cava. The liver was excised for further analysis. Blood samples were placed at room temperature for 30 min, and serum was obtained by centrifugation at 1200 g for 15 min. All samples were stored in a deep freezer at approximately -70°C until bioanalysis.

Results and Discussion

Liquid Chromatography and Multiple Reaction Monitoring

Ionizable lipids are amphiphilic molecules that contain three domains: a polar head group, a hydrophobic tail region, and a linker between the two domains.[13] SM-102 and ALC-0315 share some common structural features, including a tertiary amine with a hydroxyalkyl group, branched tails, and ester linkers.[14] SM-102 has only three, and one of them is along lipid, while ALC-0315 has four very short tails.[15] Ionizable lipids are neutral at physiological pH, but are protonated at low pH, making them positively charged.[16] The pKa values of SM-102 and ALC-0315 are 6.68 and 6.09, respectively (Figure 1). Therefore, the biphenyl column and a mobile phase with formic acid were used for the separation of SM-102 and ALC-0315. Multiple reaction monitoring (MRM) was used for selective and sensitive determination. For MRM analysis in positive ion

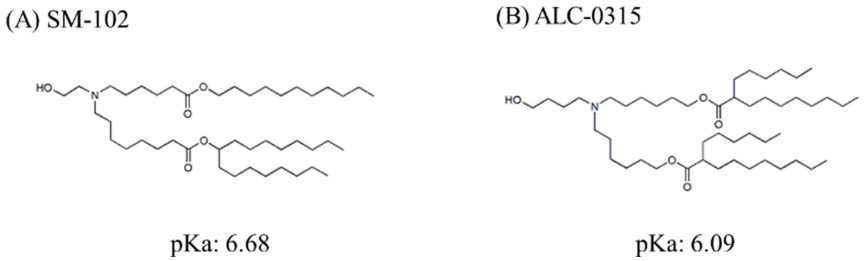

Figure 1. Structure and pKa value of SM-102 (A), and ALC-0315 (B).

Table 1. Analytical condition of SM-102, ALC-0315 and tolterodine (IS).

(A) Ultra-performance liquild chromatography (UPLC): Nexera X2 UPLC system (Shimadzu, Japan)

Column	Kinetex Biphenyl 100 Å column (2.6 μm, 50 × 2.1 mm, Phenomenex)		
Column temperature	40°C		
Flow rate	0.6 mL/min		
Mobile phase	A: Distilled water + 0.1% formic acid B: Methanol + 0.1% formic acid		
	Time (min)	A (%)	B (%)
	0.00	75	25
	0.30	1	99
	0.70	1	99
	2.00	1	99
	2.05	75	25
	3.00	75	25
Injection volume	SM-102	0.3 μL	
	ALC-0315	2.0 μL	

(B) Mass spectrometry (MS): Triple Quad™ 6500 System (AB SCIEX, USA)

Compound	Exact mass (amu)	Retention time (min)	MRM transitions				
			Precursor ion (*m/z*)	Product ion (*m/z*)	DP (V)	CE (V)	CXP (V)
SM-102	709.658	1.98	710.6	472.5	146	53	6
ALC-0315	765.721	1.96	766.5	510.4	146	73	6
Tolterodine (IS)	325.496	1.53	326.3	121.1	140	46	10

DP, declustering potential energy; CE, collision energy; CXP, cell exit potential

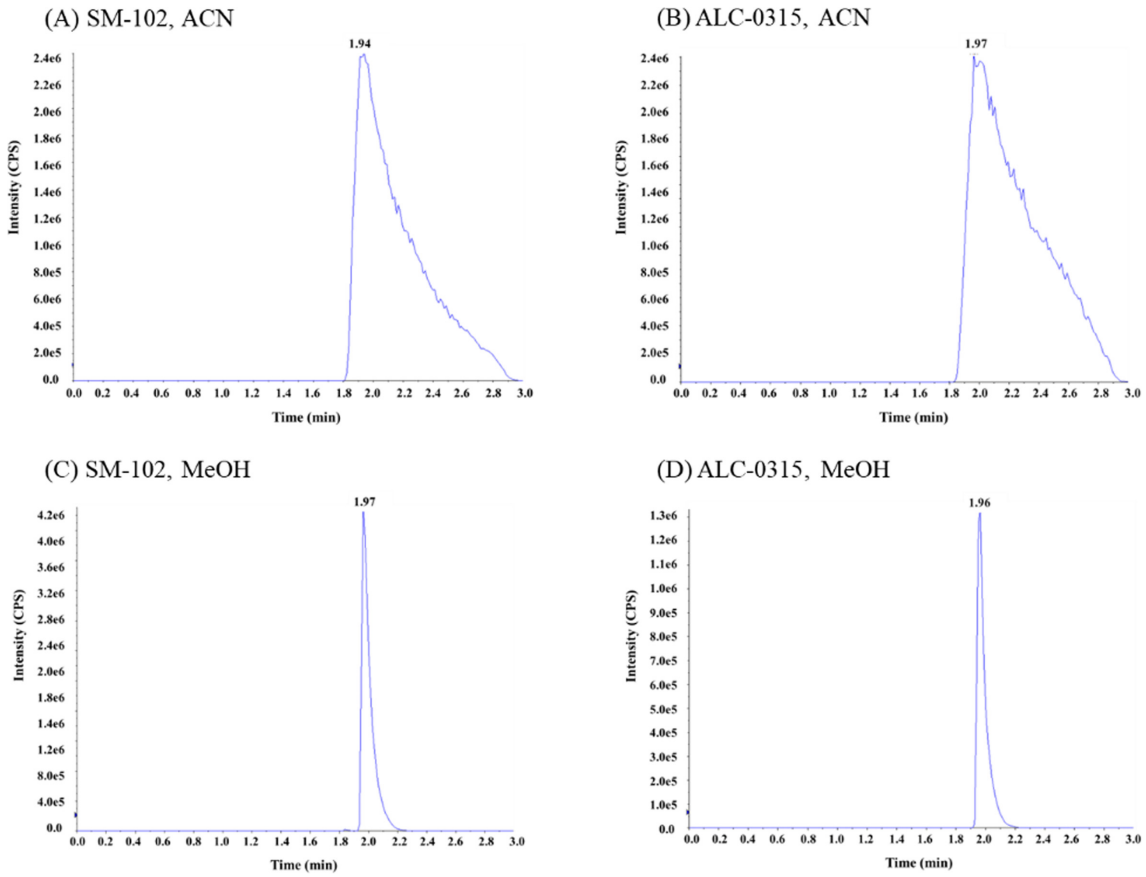

Figure 2. Chromatograms of SM-102 (A, C) and ALC-0315 (B, D) following the mobile phase B composition (A and B, ACN; C and D, MeOH)

mode, $[M+H]^+$ ions were selected as precursor ions (*m/z* 710.6, 766.5, and 326.3 for SM102, ALC-0315, and IS, respectively). Product ions of transitions were decided based on the results from product ion scans (PIS) of the precursor ions. The most intense fragment ion in each PIS spectrum was chosen (*m/z* 472.5, 510.4, and 121.1 for SM102, ALC-0315, and IS, respectively) (Table 1). When ACN was used as mobile phase B (Figure 2A and 2B), peak broadening was observed in both SM-102 and ALC-0315. In contrast, when MeOH was used, selectivity improved due to better resolution, and peak broadening was reduced (Figure 2C and 2D). Therefore, DW and MeOH were selected as mobile phase A and mobile phase B, respectively. Tolterodine was selected as the IS for its analytical convenience, demonstrating high stability and consistent performance under the established LC-MS/MS conditions.

Method validation and *in vivo* sample analysis

The method was validated by evaluating specificity, linearity, sensitivity (lower limit of quantification, LLOQ), accuracy, and precision. The results of these parameters were expected to have an accuracy of 80-120% and a precision (coefficient of variation, CV) of 20% or less at the LLOQ level, while an accuracy of 85–115% and a precision (CV of accuracy) of 15% or less were required at other levels.

Specificity was confirmed by comparing the chromatograms of blank mouse serum with spiked samples. The peaks corresponding to SM-102, ALC-0315, and IS were observed at approximately 1.98, 1.96, and 1.53 min, respectively. However, no significant interference was observed in the blank mouse serum chromatogram. Linearity of the method was verified across a selected concentration range (1, 5, 10, 50, 100, 500, 1000, and 2000 ng/mL) using three calibration curves. The back-calculated accuracy values of the calibrators ranged from 88.3% to 112.6% (CV values less than 9.5%) for SM-102 and ranged from 89.3% to 107.9% (CV values less than 10.7%) for ALC-031. Additionally, the mean correlation coefficient (R^2) values of the three calibration curves ranged from 0.9954 to 0.9965 for SM-102 and ranged from 0.9954 to 0.9977 for ALC-0315, respectively. Sensitivity was determined by evaluating the LLOQ, which had a signal-to-noise ratio of greater than 5, with accuracy within ±20% and precision (CV%) not exceeding 20% (Table 2).

Reproducibility of the method was verified by intra- and

Table 2. Back-calculated accuracy (%) and its coefficient of variation (CV, %) of calibrators for SM102 and ALC-0315 (*n* = *3*). SD stands for standard deviation.

	SM102			ALC-0315		
Nominal concentration (ng/mL)	Calculated concentration (Mean ± SD, ng/mL)	Accuracy (%)	CV (%)	Calculated concentration (Mean ± SD, ng/mL)	Accuracy (%)	CV (%)
1	0.98 ± 0.02	98.3	2.35	1.00 ± 0.03	99.7	2.53
5	5.22 ± 0.45	104.3	8.72	4.88 ± 0.52	97.6	10.63
10	10.80 ± 0.41	108.0	3.79	10.61 ± 0.57	106.1	5.38
50	52.48 ± 4.85	105.0	9.24	53.95 ± 2.53	107.9	4.69
100	112.64 ± 5.94	112.6	5.27	105.29 ± 3.07	105.3	2.92
500	484.09 ± 28.79	96.8	5.95	486.15 ± 31.02	97.2	6.38
1000	972.02 ± 52.36	97.2	5.39	969.23 ± 63.41	96.9	6.54
2000	1765.93 ± 30.52	88.3	1.73	1786.05 ± 48.31	89.3	2.71
R^2	0.9954 - 0.9965			0.9954 - 0.9977		

Table 3. Accuracy and precision (coefficient of variation of accuracy) assessed from quality control samples. SD stands for standard deviation.

			SM-102				ALC-0315			
Nominal concentration (ng/mL)			1	3	600	1600	1	3	600	1600
Intra day	Batch 1 (*n* = *5*)	Mean	0.98	2.83	580.76	1684.65	1.00	3.41	601.62	1500.15
		SD	0.10	0.23	29.97	80.53	0.12	0.42	30.29	55.80
		Accuracy (%)	98.4	94.3	96.8	105.3	100.2	113.7	100.3	93.8
		Precision (%)	9.9	8.0	5.2	4.8	12.0	12.4	5.0	3.7
	Batch 2 (*n* = *5*)	Mean	1.16	3.10	614.86	1737.30	1.15	3.30	645.75	1570.71
		SD	0.15	0.44	29.28	40.25	0.12	0.36	31.61	75.60
		Accuracy (%)	116.2	103.4	102.5	108.6	115.2	109.9	107.6	98.2
		Precision (%)	13.2	14.2	4.8	2.3	10.5	10.8	4.9	4.8
	Batch 3 (*n* = *5*)	Mean	1.17	2.74	538.22	1758.27	0.96	3.35	671.31	1557.57
		SD	0.23	0.25	55.68	55.79	0.15	0.35	33.26	71.65
		Accuracy (%)	117.4	91.3	89.7	109.9	96.0	111.7	111.9	97.3
		Precision (%)	19.7	9.0	10.3	3.2	15.3	10.4	5.0	4.6
Inter-day (*n* = *15*)		Mean	1.11	2.89	577.95	1726.74	1.04	3.35	639.56	1542.81
		SD	0.181	0.336	49.401	65.059	0.148	0.353	41.849	70.676
		Accuracy (%)	110.7	96.3	96.3	107.9	103.8	111.7	106.6	96.4
		Precision (%)	16.4	11.6	8.5	3.8	14.2	10.5	6.5	4.6

inter-day analyses. Five samples were prepared and measured over consecutive days for 1 (LLOQ), 3 (low quality control, LQC), 600 (medium quality control, MQC), and 1600 ng/mL (high quality control, HQC). For SM-102, the inter-day accuracy values at LLOQ, LQC, MQC and HQC levels were 98.4–117.4%, 91.3–103.4%, 89.7–102.5% and 100.9-108.6%, respectively. The precision values of both intra- and inter-day results did not exceed 19.7 and 16.4%, respectively. For ALC-0315, the inter-day accuracy values at LLOQ, LQC, MQC and HQC levels were 96.0–115.2%, 109.9–113.7%, 100.3–111.9% and 93.8-97.3%, respectively. The precision values of both intra- and inter-day results did not exceed 15.3 and 14.2 %, respectively (Table 3).

Table 4. Ionizable lipid concentrations in serum and liver at 24 h after a single intravenous administration of LNPs in mice (ng/mL, Mean ± SD, *n* = *5*). SD stands for standard deviation.

Matrix	Time (h)	Concentration (Mean ± SD, ng/mL)	
		SM-102	ALC-0315
Serum	24	4.26 ± 0.26	203.99 ± 23.84
	168	BLQ	25.17 ± 2.71
Liver	24	40267.60 ± 12604.63	111468.80 ± 11355.75
	168	1210.172 ± 305.05	60851.00 ± 7912.38

* BLQ: below the limit of quantification

Based on the validated method, the present method exhibited excellent analytical performance for the determination of SM-102 and ALC-0315 in mouse serum and liver (Table 4). The biodistribution data revealed that ALC-0315 exhibited higher concentrations than SM-102 in both serum and liver at 24 and 168 hours post-dose. While SM-102 was below the lower limit of quantification in serum at 168 hours, ALC-0315 remained detectable. In the liver, the concentrations of ALC-0315 were consistently higher than those of SM-102 at both 24 and 168 hours. These results indicate distinct differences in biodistribution and clearance profiles between the two ionizable lipids.

Conclusions

The analysis method of ionizable lipids in biological matrices was well developed, evaluating various parameters such as specificity, linearity, sensitivity, accuracy, and precision. Ionizable lipids such as SM-102 and ALC-0315 were successfully analyzed in serum and liver samples. This method is expected to contribute to the comprehensive evaluation of biodistribution for novel ionizable lipids in LNP formulations.

Acknowledgments

This study was financially supported by Yuhan Corporation.

References

1. Pardi, N.; Tuyishime, S.; Muramatsu, H.; Kariko, K.; Mui, B.L.; Tam, Y.K.; Madden, T.D.; Hope, M.J.; Weissman, D. *Journal of Controlled Release* **2015**, 217, 345. https://doi.org/https://doi.org/10.1016/j.jconrel.2015.08.007.
2. Wang, Y.; Miao, L.; Satterlee, A.; Huang, L. *Advanced Drug Delivery Reviews* **2015**, 87, 68. https://doi.org/https://doi.org/10.1016/j.addr.2015.02.007.
3. Buschmann, M.D.; Carrasco, M.J.; Alishetty, S.; Paige, M.; Alameh, M.G.; Weissman, D. *Vaccines* **2021**, 9, 65.
4. Hassett, K.J.; Benenato, K.E.; Jacquinet, E.; Lee, A.; Woods, A.; Yuzhakov, O.; Himansu, S.; Deterling, J.; Geilich, B.M.; Ketova, T.; Mihai, C.; Lynn, A.; McFadyen, I.; Moore, M.J.; Senn, J.J.; Stanton, M.G.; Almarsson, Ö.; Ciaramella, G.; Brito, L.A. *Molecular Therapy - Nucleic Acids* **2019**, 15, 1. https://doi.org/https://doi.org/10.1016/j.omtn.2019.01.013.
5. Schoenmaker, L.; Witzigmann, D.; Kulkarni, J.A.; Verbeke, R.; Kersten, G.; Jiskoot, W.; Crommelin, D.J.A. *International Journal of Pharmaceutics* **2021**, 601, 120586. https://doi.org/https://doi.org/10.1016/j.ijpharm.2021.120586.
6. Evers, M.J.W.; Kulkarni, J.A.; Van Der Meel, R.; Cullis, P.R.; Vader, P.; Schiffelers, R.M. *Small Methods* **2018**, 2, 1700375. https://doi.org/10.1002/smtd.201700375.
7. Hald Albertsen, C.; Kulkarni, J.A.; Witzigmann, D.; Lind, M.; Petersson, K.; Simonsen, J.B. *Advanced Drug Delivery Reviews* **2022**, 188, 114416. https://doi.org/https://doi.org/10.1016/j.addr.2022.114416.
8. European Commission, Commission Directive 2009/120/EC, **2009**.
9. U.S. Food and Drug Administration, Preclinical Assessment of Investigational Cellular and Gene Therapy Products, **2013**.
10. World Health Organization, WHO Technical Report Series, No. 927, Annex 1, **2005**.
11. Semple, S.C.; Akinc, A.; Chen, J.; Sandhu, A.P.; Mui, B.L.; Cho, C.K.; Sah, D.W.Y.; Stebbing, D.; Crosley, E.J.; Yaworski, E.; Hafez, I.M.; Dorkin, J.R.; Qin, J.; Lam, K.; Rajeev, K.G.; Wong, K.F.; Jeffs, L.B.; Nechev, L.; Eisenhardt, M.L.; Jayaraman, M.; Kazem, M.; Maier, M.A.; Srinivasulu, M.; Weinstein, M.J.; Chen, Q.; Alvarez, R.; Barros, S.A.; De, S.; Klimuk, S.K.; Borland, T.; Kosovrasti, V.; Cantley, W.L.; Tam, Y.K.; Manoharan, M.; Ciufolini, M.A.; Tracy, M.A.; de Fougerolles, A.; MacLachlan, I.; Cullis, P.R.; Madden, T.D.; Hope, M.J. *Nature Biotechnology* **2010**, 28, 172. https://doi.org/10.1038/nbt.1602.
12. Ye, T.; Zhong, Z.; García-Sastre, A.; Schotsaert, M.; De Geest, B.G. *Angewandte Chemie International Edition* **2020**, 59, 18885. https://doi.org/10.1002/anie.202008319.
13. Hou, X.; Zaks, T.; Langer, R.; Dong, Y. *Nature Reviews Materials* **2021**, 6, 1078. https://doi.org/10.1038/s41578-021-00358-0.
14. Sun, D.; Lu, Z.-R. *Pharmaceutical Research* **2023**, 40, 27. https://doi.org/10.1007/s11095-022-03460-2.
15. Paloncýová, M.; Čechová, P.; Šrejber, M.; Kührová, P.; Otyepka, M. *The Journal of Physical Chemistry Letters* **2021**, 12, 11199. https://doi.org/10.1021/acs.jpclett.1c03109.
16. Hajj, K.A.; Whitehead, K.A. *Nature Reviews Materials* **2017**, 2, 17056. https://doi.org/10.1038/natrevmats.2017.56.