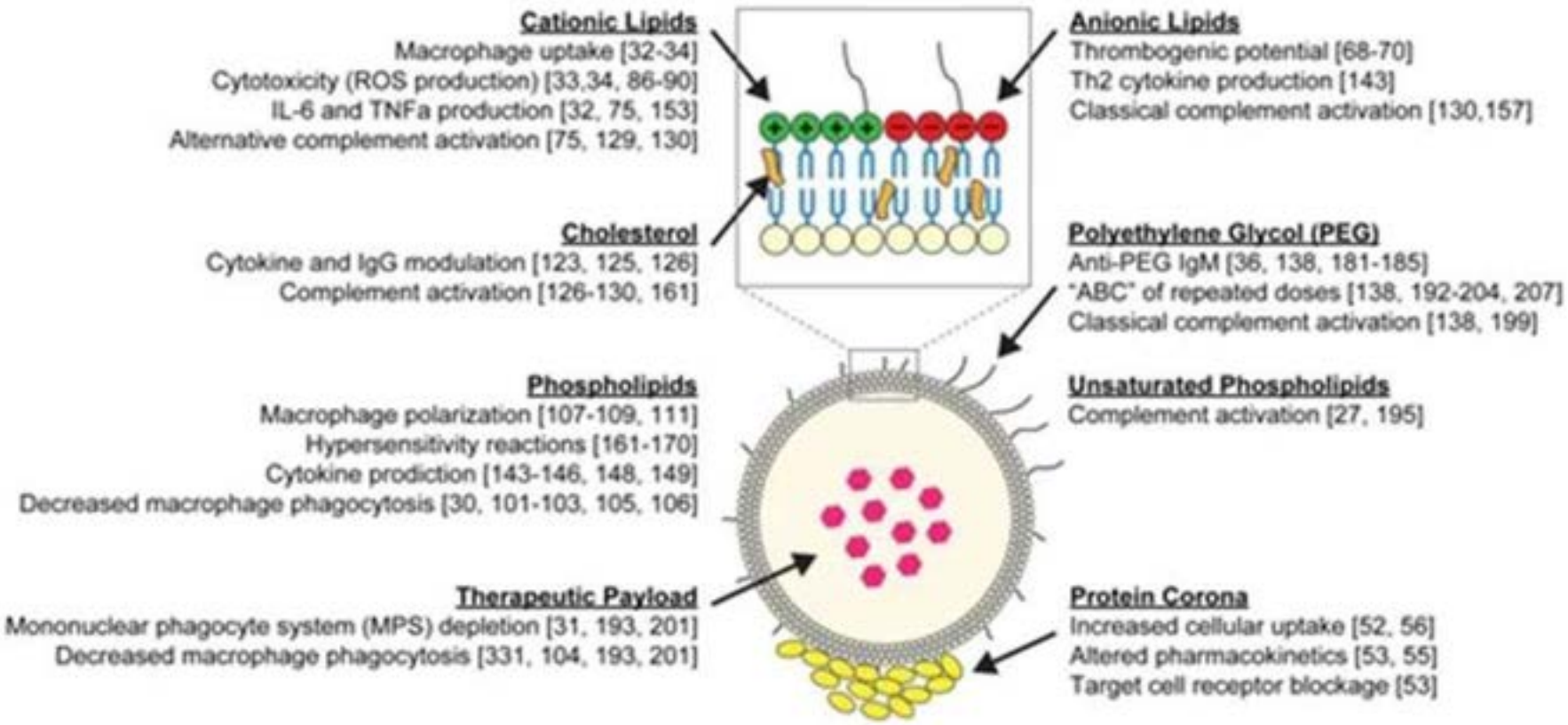
Was Pfizer wusste

Dr. Sabine Stebel

https://drbine.substack.com/p/erhebliche-risiken-durch-comirnaty
https://drbine.substack.com/p/was-pfizer-wusste-reloaded

Folgende in der wissenschaftlichen Literatur generell bekannte Problembereiche der Lipidnanotechnologie waren im Januar 2020 noch nicht gelöst:



https://www.mdpi.com/2079-4991/10/2/190

1.
Das kationische Lipid ALC-0315 ist toxisch

https://fragdenstaat.de/dokumente/236331-104a-pf00161-mtr-pfem-en-002/

SAFETY DATA SHEET

Revision date 14-Dec-2021 Version 2 Page 1 / 11

Section 1: IDENTIFICATION OF THE SUBSTANCE/MIXTURE AND OF THE COMPANY/UNDERTAKING

1.1. Product identifier

Product Name	Pfizer-BioNTech Covid-19 vaccine Tris-Sucrose
Product Code(s)	PF00161
Synonyms	PF-07302048 containing PF-07305885 (BNT162b2); Covid19 Ready to Use Formulation; Pfizer-BioNTech Covid-19 vaccine for ages 5 through 11: 5 to 11, Dilute to use Orange Cap; Pfizer-BioNTech Covid-19 vaccine for ages 12 and older: 12 years and older, Ready to use Grey Cap; PF-07302048 containing PF-07305885 (BNT162b2); CorVAC Containing PF-07305885 (BNT162b2) ; CoVVAC Containing PF-07305885 (BNT162b2); COVID Vaccine Containing PF-07305885 (BNT162b2); COVID-19 Vaccine Containing PF-07305885 (BNT162b2)
Trade Name:	Not applicable
Compound Number	PF-07302048
Item Code	H000024713; H000024714; H000024864; H000024865; H000025770; H000025768; H000025769; H000025892; H000026609; H000026610
Chemical Family:	Lipid Nanoparticles containing PF-07305885 (BNT162b2) and Lipids

ALC-0315

Pfizer Occupational Exposure Band (OEB): OEB 3 - Contact Hazards Unknown (control exposure to the range of 10ug/m³ to < 100ug/m³)

Tromethamine

Pfizer Occupational Exposure Band (OEB): OEB 1 (control exposure to the range of 1000ug/m³ to 3000ug/m³)

PF-07305885

Pfizer Occupational Exposure Band (OEB): V-OEB

PF-07302048

Pfizer Occupational Exposure Band (OEB): V-OEB

ALC-0159

Pfizer Occupational Exposure Band (OEB): OEB 3 - Contact Hazards Unknown (control exposure to the range of 10ug/m³ to < 100ug/m³)

8.2. Exposure controls

ALC-0315 keiner separaten Studie zur Toxizität unterzogen, obwohl es der Sicherheitsstufe OEB3 zugeordnet wurde.

Novel excipients

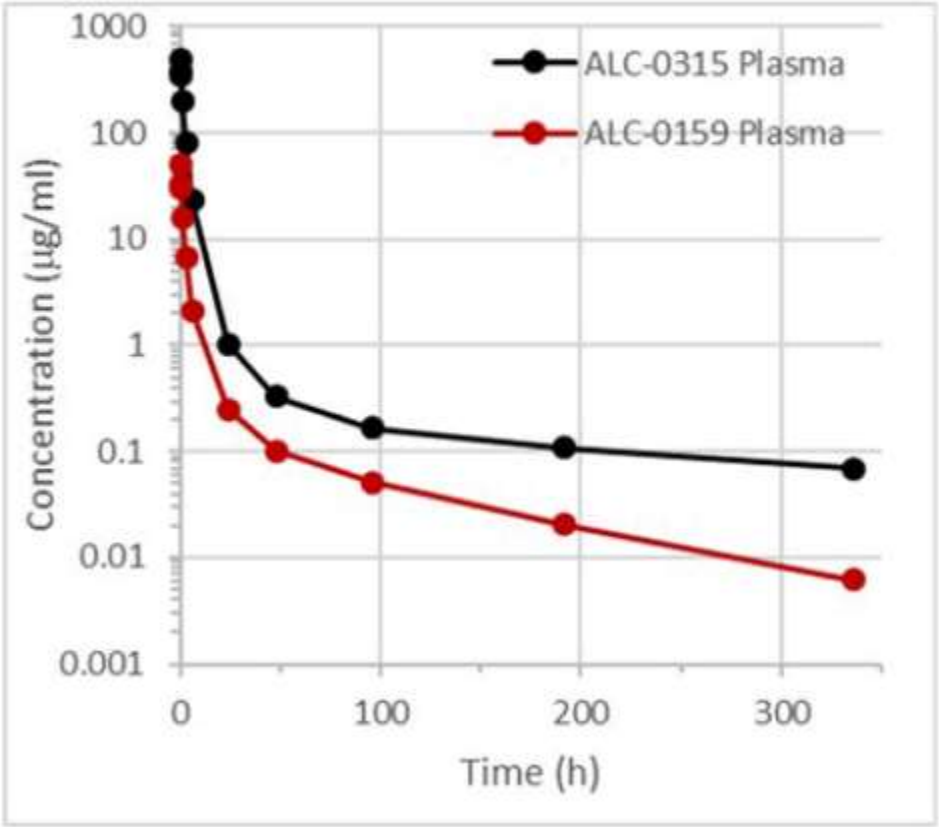
The toxicity of LNP formulation or the novel excipients alone was not specifically studied. In the repeat dose toxicity studies with the clinical candidate vaccine (BNT162b2 V9) and BNT162b2 V8,

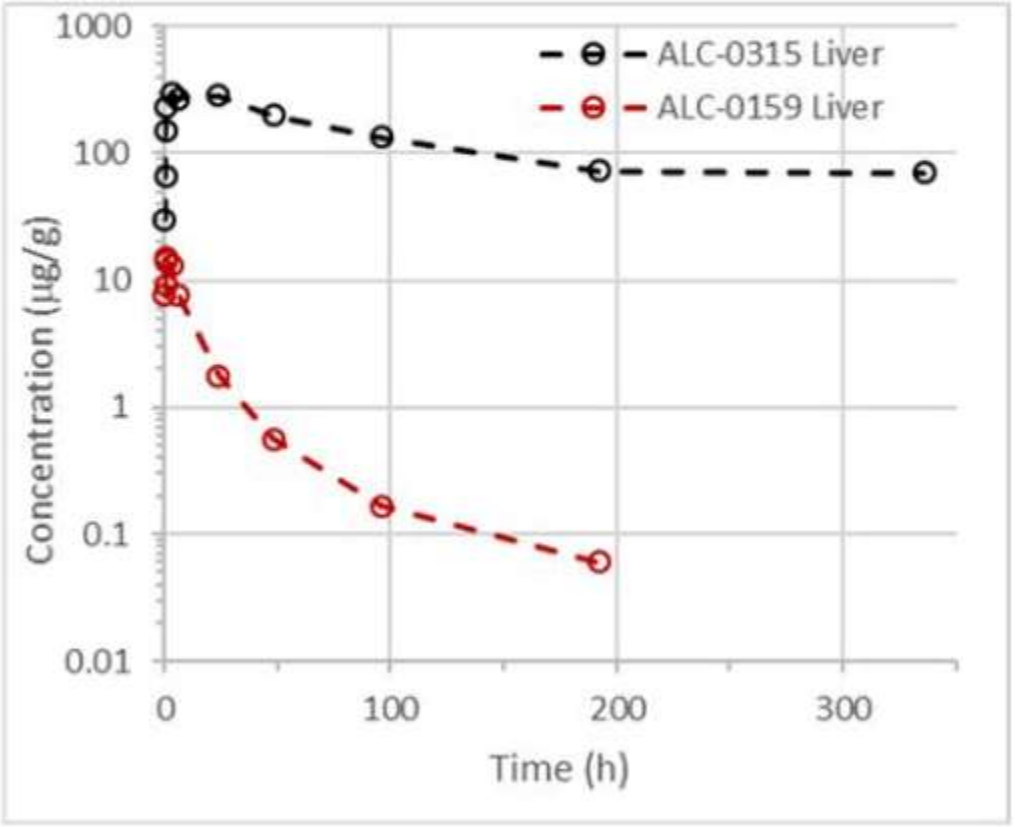
Safety of the novel excipients was not assessed in a second species. No further data would be submitted as stated by the Sponsor. In response to the TGA enquiry regarding the toxicity assessment of the novel excipients in the LNP formulation, the Sponsor referred to the evaluation of the siRNA product Onpattro™ (patisiran) [1,2] administered as a LNP formulation, which is approved in the US, Europe and Canada (not reviewed by TGA) for the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) by IV infusion every 3 weeks. The LNP in Onpattro™ is composed of DLin-MC3-DMA, PEG2000-C-DMG, DSPC, and cholesterol. No nonclinical safety concerns regarding excipients, impurities, or degradation products were identified in the FDA and EMA evaluations. The primary toxicity observed in both rats and monkeys was an elevation in liver enzymes, with hepatocyte vacuolation. Therefore, the Sponsor argued that ALC-0315 and ALC-0159 would have

similar toxicity profile to the lipids DLin-MC3-DMA and PEG2000-C DMG, respectively, as they were structurally and functionally similar (See Section 1.4). However, while the pegylated lipids (ALC-0159 and PEG2000-C DMG) are structurally similar, the structures of ALC-0315 and DLin-MC3-DMA are not similar. Nonetheless, given that both the novel excipients are amino or amino/PEG lipids and the potential lifetime exposure is expected to be low (see discussion below), the Sponsor's justification for not conducting repeat dose toxicity studies with the novel excipients in a second animal species is acceptable.

https://www.tga.gov.au/sites/default/files/foi-2389-06.pdf

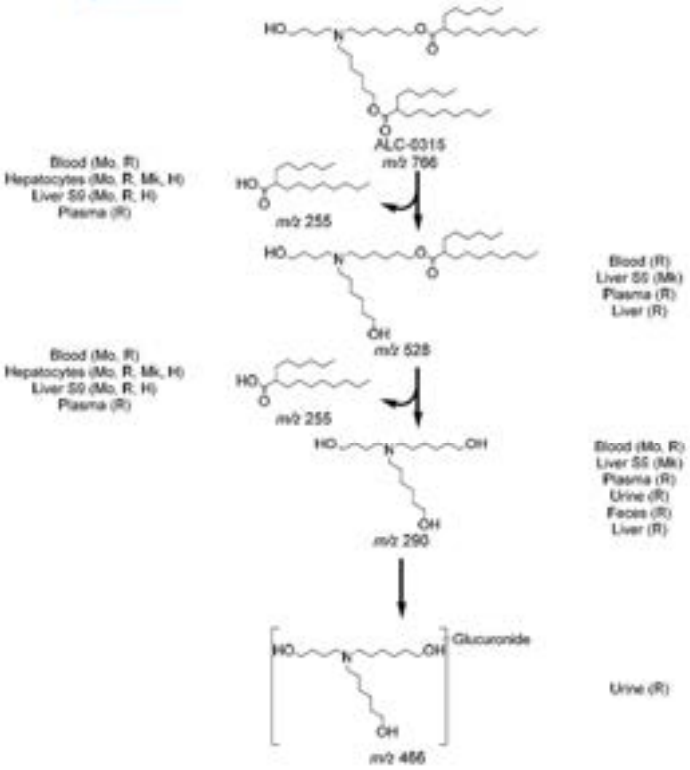
Figure 2.6.4-1. Plasma and Liver Concentrations of ALC-0315 and ALC-0159 in Wistar Han Rats After IV Administration of LNPs Containing Surrogate Luciferase RNA at 1 mg/kg





https://www.judicialwatch.org/wp-content/uploads/2022/03/JW-v-HHS-prod-3-02418.pdf S. 16

Figure 2.4.3-3. Proposed Biotransformation Pathway of ALC-0315 in Various Species



Metabolism of ALC-0315 occurs via two sequential ester hydrolysis reactions, first yielding the monoester metabolite (*m/z* 528) followed by the doubly deesterified metabolite (*m/z* 290). Subsequent metabolism of the doubly deesterified metabolite resulted in a glucuronide metabolite (*m/z* 466), which was only observed in urine from the rat PK study. Additionally, 6-hexyldecanoic acid (*m/z* 255), the acid product of both hydrolysis reactions of ALC-0315, was identified.

DLin-MC3-DMA (MC3), SM-102 und ALC-0315**, ionisierbare kationische Lipide, die von der US-amerikanischen Food and Drug Administration (FDA) für den RNA-Transport zugelassen sind, sind Monoaminolipide. […]* ***Keines dieser drei ionisierbaren kationischen Lipide ist jedoch biologisch abbaubar und ihre Anreicherung im Körper ist potenziell zytotoxisch.
https://pubmed.ncbi.nlm.nih.gov/39067162/

https://www.judicialwatch.org/wp-content/uploads/2022/03/JW-v-HHS-prod-3-02418.pdf S. 21

Der pks-Wert (Englisch pka), des kationischen Lipids ALC-0315 ist ungeeignet für eine intramuskuläre Injektion.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Assessment report
Comirnaty
Common name: COVID-19 mRNA vaccine (nucleoside-modified)
Procedure No. EMEA/H/C/005735/0000
19 February 2021
EMA/707383/2020 Corr.1
Committee for Medicinal Products for Human Use (CHMP)

Page 42/140

The potency of the RNA vaccine is further optimised by encapsulation of the RNA into lipid nano particles (LNPs), which protects the RNA from degradation by RNAses and enable transfection of host cells after intramuscular (i.m.) delivery. The functional and ionizable lipid, ALC-0315, is identified as the primary driver of delivery as it allows the LNPs to have a neutral charge in a physiological environment to facilitate internalization; the endosomal environment exhibits a positive charge and therefore triggers the translocation of RNA into the cytosol (Midoux & Pichon, 2015; Hassett et al. 2019; Patel et al. 2019); ALC-0159 is included in the formulation to provide a steric [illegible] to: 1) facilitate the control of particle size and homogeneity during manufacturing and pro[illegible], and 2) regulate the association of plasma and proteins with the LNP surface. The compo[illegible] of the LNPs may also affect the distribution of injected BNT162b2. In addition, it cannot be ex[illegible] the LNP composition contributes to the overall immunogenicity.

Figure 6. EMA Assessment Report on Comirnaty by Pfizer/ BioNTech, date 19 February 2021, page 42.

tween IM and IV performance could be that the optimal physical or chemical properties differ between the two routes. One strong determinant of immunogenicity was the lipid pKa, with a range of 6.6–6.9 being optimal for IM immunogenicity (Figure 2C). This differs from the optimal pKa range for [illegible] delivery of siRNAs and mRNAs, which has been reported as 6.2–6.6.[11,23] mRNA encapsulation efficiencies and LNP sizes ranged from 69% to 100% and from 50 to 142 nm, respectively. While there was no relationship between

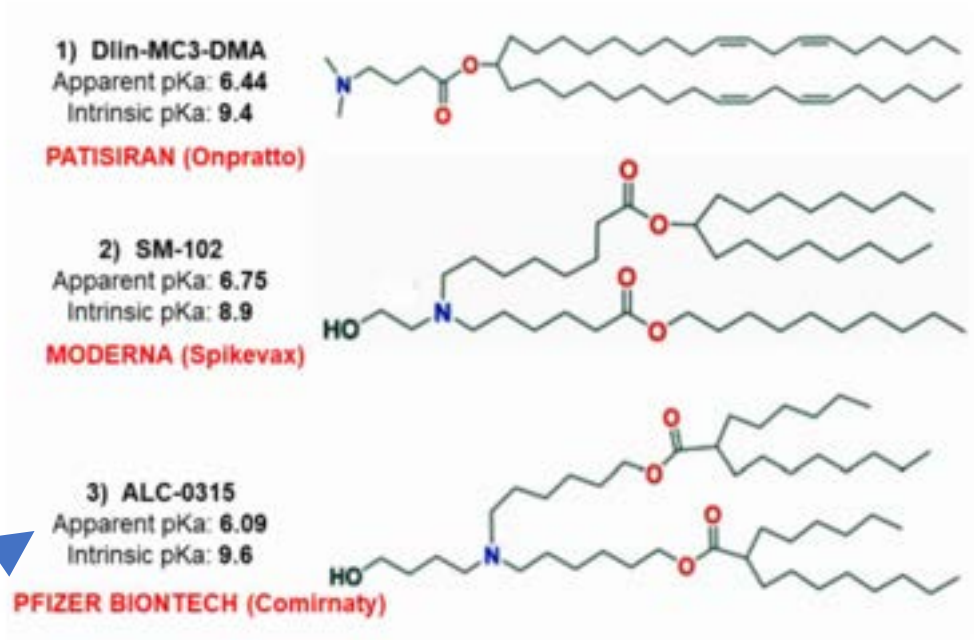


Figure 4. Structure and pKa values of amino-lipids: 1) DLin-MC3-DMA (*Onpratto/ Patisiran* by Alnylam): apparent pKa 6.44, intrinsic pKa 9.4 2), SM-102 (*Spikevax* by Moderna): apparent pKa 6.75, intrinsic pKa 8.9 3) Alc-0315 (*Comirnaty* by Pfizer BioNTech): apparent pKa 6.09, intrinsic pKa 9.6.

https://doi.org/10.56098/ijvtpr.v3i1.84
https://pubmed.ncbi.nlm.nih.gov/30785039/

Avanti Polar Lipids, Inc. 700 Industrial Park Drive, Alabaster, AL 35007,USA • (800) 227-0651 • (205) 663-2494 • Fax(800) 229-1004•(205) 663-0756 • E-mail Orders: orders@avantilipids.com • E-mail Inquiries: info@avantilipids.com • E-mail Technical Questions: technical@avantilipids.com • Visit www.avantilipids.com

ABSCHNITT 1: Bezeichnung des Stoffs beziehungsweise des Gemischs und des Unternehmens

1.1 Produktidentifikatoren

Produktname : ALC-0315

Produktnummer : 890900O
Marke : Avanti
REACH Nr. : Eine Registriernummer für diesen Stoff ist nicht vorhanden, da der Stoff oder seine Verwendung von der Registrierung ausgenommen sind, die jährliche Tonnage keine Registrierung erfordert oder die Registrierung für einen späteren Zeitpunkt vorgesehen ist.

1.2 Relevante identifizierte Verwendungen des Stoffs oder Gemischs und Verwendungen, von denen abgeraten wird

Identifizierte Verwendungen : Laborchemikalien, Herstellung von Stoffen

ABSCHNITT 11: Toxikologische Angaben

11.1 Angaben zu toxikologischen Wirkungen

Akute Toxizität
Oral: Keine Daten verfügbar
Einatmung: Keine Daten verfügbar
Haut: Keine Daten verfügbar

Ätz-/Reizwirkung auf die Haut
Keine Daten verfügbar

Schwere Augenschädigung/-reizung
Keine Daten verfügbar

Sensibilisierung der Atemwege/Haut
Keine Daten verfügbar

Keimzell-Mutagenität
Keine Daten verfügbar

Karzinogenität
Keine Daten verfügbar

Reproduktionstoxizität
Keine Daten verfügbar

Spezifische Zielorgan-Toxizität - einmalige Exposition
Keine Daten verfügbar

Spezifische Zielorgan-Toxizität - wiederholte Exposition
Keine Daten verfügbar

Aspirationsgefahr
Keine Daten verfügbar

ABSCHNITT 12: Umweltbezogene Angaben

12.1 Toxizität
Keine Daten verfügbar

12.2 Persistenz und Abbaubarkeit
Keine Daten verfügbar

12.3 Bioakkumulationspotenzial
Keine Daten verfügbar

12.4 Mobilität im Boden
Keine Daten verfügbar

12.5 Ergebnisse der PBT- und vPvB-Beurteilung
Dieser Stoff/diese Mischung enthält keine Komponenten in Konzentrationen von 0,1 % oder höher, die entweder als persistent, bioakkumulierbar und toxisch (PBT) oder sehr persistent und sehr bioakkumulierbar (vPvB) eingestuft sind.

12.6 Endokrinschädliche Eigenschaften
Produkt:

Bewertung	:	Der Stoff/dieses Gemisch enthält keine Bestandteile, die gemäß REACH Artikel 57(f) oder der delegierten Verordnung (EU) 2017/2100 der Kommission oder der delegierten Verordnung (EU) 2018/605 der Kommission in Mengen von 0,1 % oder mehr endokrinschädliche Eigenschaften aufweisen.

12.7 Andere schädliche Wirkungen
Keine Daten verfügbar

11.2 Zusätzliche Informationen

Endokrinschädliche Eigenschaften

Produkt:

Bewertung	Der Stoff/dieses Gemisch enthält keine Bestandteile, die gemäß REACH Artikel 57(f) oder der delegierten Verordnung (EU) 2017/2100 der Kommission oder der delegierten Verordnung (EU) 2018/605 der Kommission in Mengen von 0,1 % oder mehr endokrinschädliche Eigenschaften aufweisen.

Gemäss unseren Kenntnissen sind die chemischen, physikalischen und toxikologischen Eigenschaften nicht umfassend untersucht worden.
Gemäss unseren Kenntnissen sind die chemischen, physikalischen und toxikologischen Eigenschaften nicht umfassend untersucht worden.

https://www.sigmaaldrich.com/DE/de/sds/avanti/890900o?userType=anonymous

Table 3.2.P.1-1. Composition of BNT162b2 Drug Product, multi-dose vial (225 µg/vial)

Name of Ingredients	Reference to Standard	Function	Concentration (mg/mL)	Amount per vial	Amount per dose
BNT162b2 drug substance	In-house specification	Active ingredient	0.5	225 µg	30 µg
ALC-0315	In-house specification	Functional lipid	7.17	3.23 mg	0.43 mg
ALC-0159	In-house specification	Functional lipid	0.89	0.4 mg	0.05 mg
DSPC	In-house specification	Structural lipid	1.56	0.7 mg	0.09 mg
Cholesterol	Ph. Eur.	Structural lipid	3.1[a]	1.4 mg	0.2 mg
Sucrose	Ph. Eur.	Cryoprotectant	103[a]	46 mg	6 mg
Sodium chloride	Ph. Eur.	Buffer component	6	2.7 mg	0.36 mg
Potassium chloride	Ph. Eur.	Buffer component	0.15	0.07 mg	0.01 mg
Dibasic sodium phosphate, dihydrate[b]	Ph. Eur.	Buffer component	1.08	0.49 mg	0.07 mg
Monobasic potassium phosphate[c]	Ph. Eur.	Buffer component	0.15	0.07 mg	0.01 mg
Water for Injection	Ph. Eur.	Solvent/vehicle	q.s.	q.s.	q.s.
Processing Aids/Residues[d]					
Ethanol	Ph. Eur.	Processing aid	N/A		
Citric acid monohydrate	Ph. Eur.	Processing aid			
Sodium citrate	Ph. Eur.	Processing aid			
Sodium hydroxide	Ph. Eur.	Processing aid			
HEPES	In-house specification	Drug substance buffer component			
EDTA	Ph. Eur., USP-NF	Drug substance buffer component			

[a. Values are rounded to maintain the same level of precision as the label claim, with trailing zeros not shown

https://www.whatdotheyknow.com/request/naoh_and_hcl_excipients_in_pfize/response/2313527/attach/3/description%20and%20composition.pdf

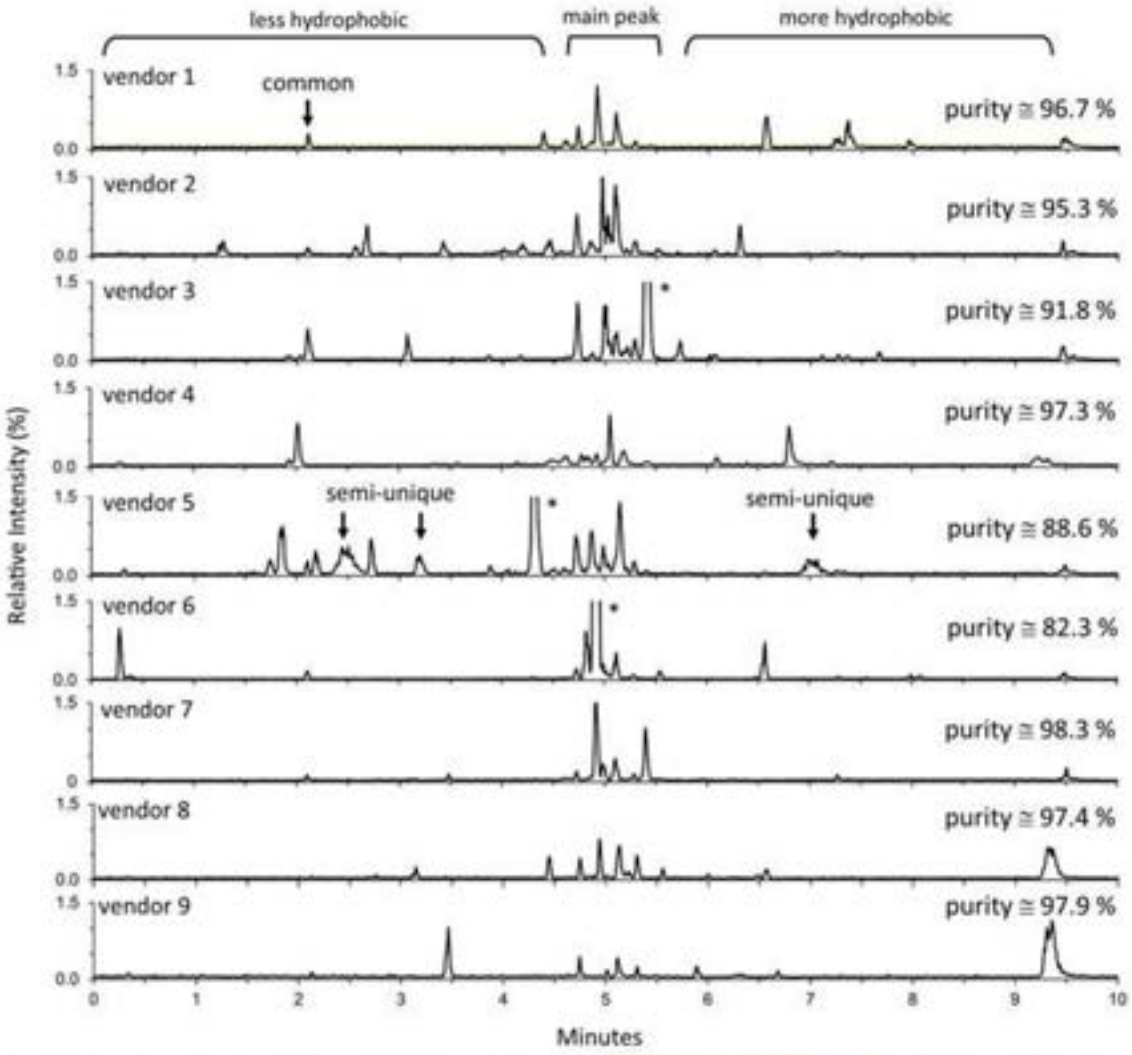


Fig. 3. Impurity profile comparison. Base peak ion chromatogram impurity profiles of ALC-0315 from 9 vendors with data acquisition performed using a single quadrupole MS. Chromatograms were normalized by intensity to the main ionizable peak at 766.8 *m/z* prior to subtraction. Purity was determined based on peak area of the ionizable lipid relative to total observed peak area.

https://www.sciencedirect.com/science/article/pii/S1570023224000138?via%3Dihub

2.
Das PEGylierte Lipid ALC-0159 ist toxisch

Received: 22 January 2023 | Accepted: 26 March 2023

DOI: 10.1111/eci.13998

RESEARCH LETTER

WILEY

Batch-dependent safety of the BNT162b2 mRNA COVID-19 vaccine

Die Hypothese

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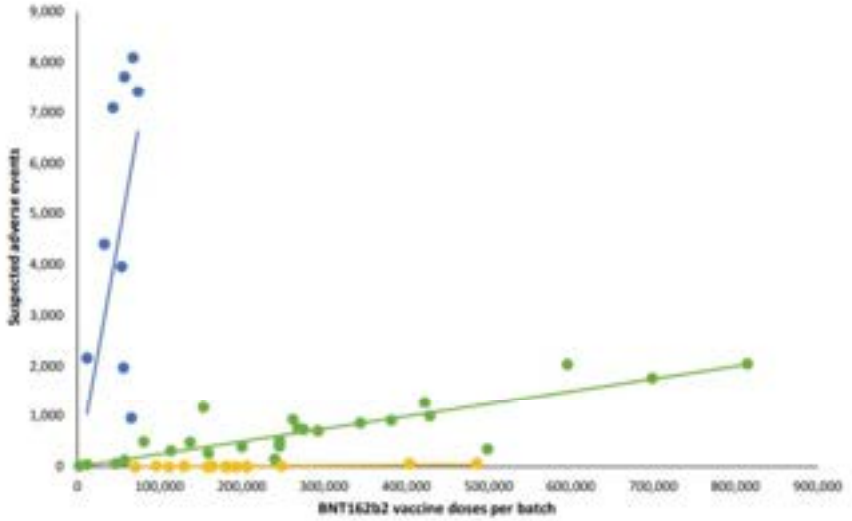

FIGURE 1 Numbers of suspected adverse events (SAEs) after BNT162b2 mRNA vaccination in Denmark (27 December 2020–11 January 2022) according to the number of doses per vaccine batch. Each dot represents a single vaccine batch. Trendlines are linear regression lines. Blue: $R^2 = 0.78$, $\beta = 0.0898$ (95% confidence interval [CI] 0.0514–0.1281), green: $R^2 = 0.89$, $\beta = 0.0025$ (95% CI 0.0021–0.0029), yellow: $R^2 = 0.68$, $\beta = 0.000087$ (95% CI 0.000056–0.000118). Vaccine batches representing the blue, green and yellow trendlines comprised 4.22%, 63.69% and 32.09% of all vaccine doses, respectively, with 70.78%, 27.49% and 47.15% (blue trendline), 28.84%, 71.50% and 51.99% (green trendline), and 0.38%, 1.01%, and 0.86% (yellow trendline) of all SAEs, serious SAEs, and SAE-related deaths, respectively.

https://onlinelibrary.wiley.com/doi/10.1111/eci.13998

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The Biomolecular Corona of Lipid Nanoparticles for Gene Therapy

Valentina Francia*, Raymond M. Schiffelers, Pieter R. Cullis, and Dominik Witzigmann*

Cite this: *Bioconjugate Chem.* 2020, 31, 9, 2046−2059
Publication Date: August 7, 2020
https://doi.org/10.1021/acs.bioconjchem.0c00366

Read Online | PDF (4 MB)

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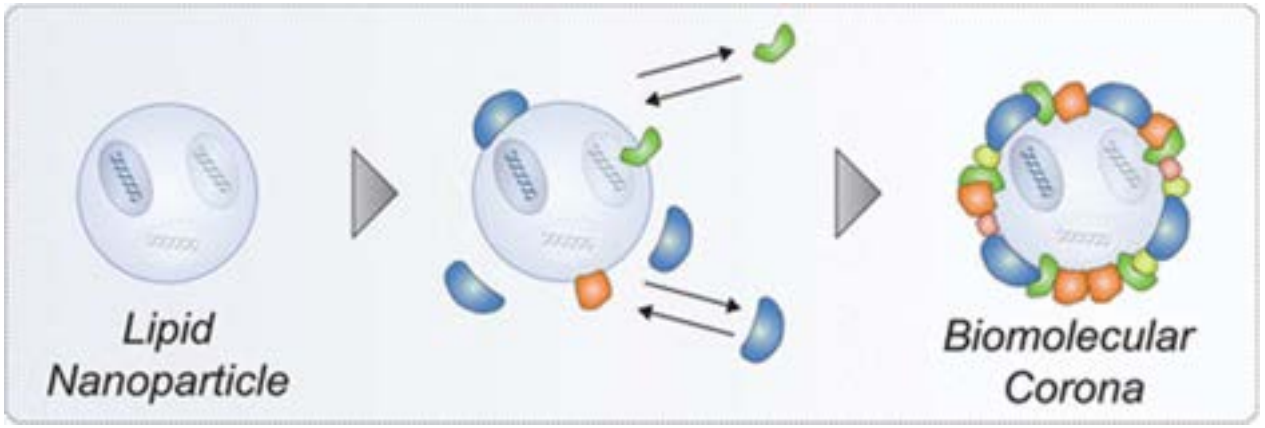
noparticles, Peptides and proteins, Targeting

Bioconjugate Chemistry

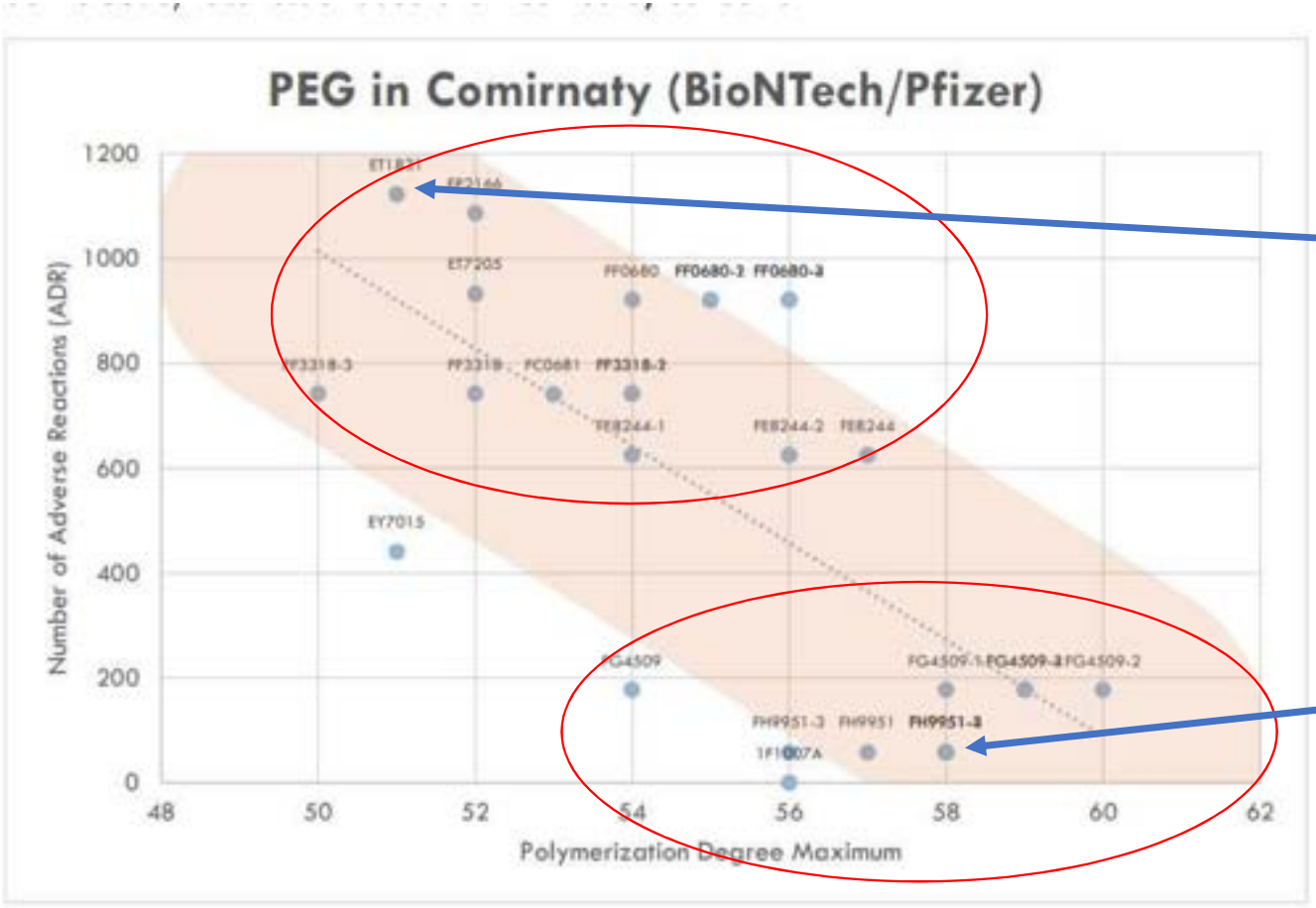
https://pubs.acs.org/doi/10.1021/acs.bioconjchem.0c00366

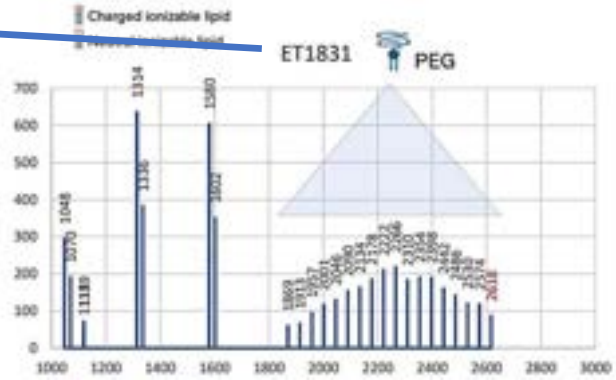
DE: ***Nicht nur das Vorhandensein von PEG, sondern auch seine Länge und Oberflächendichte sind für die Erreichung seiner (der Coronas) Funktion entscheidend***.
EN: **4 Not only the presence of PEG but also its length and surface density are essential to achieving its function.**

Corona = Grenzflächeneffekt / Boundary layer effect



Je länger der PEG- Schwanz, desto geringer die Nebenwirkung
The longer the PEG-Tail the less the SAE





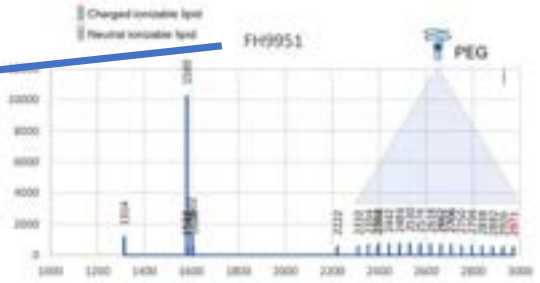


Figure 7: *From the mass spectra of samples from different batches of Comirnaty vaccine (BioNTech/Pfizer), the maximum chain lengths were compared with the number of reported vaccination complications. A clear correlation can be seen. The blue dots are associated with the BioNTech/Pfizer batch numbers analysed.*

(https://expertcouncil.one/wp-content/uploads/2023/03/AG-Impfstoffe-erste-Ergebnisse-Juli-2022_expertcouncil_one.pdf)

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Immunogenicity of Polyethylene Glycol Based Nanomedicines: Mechanisms, Clinical Implications and Systematic Approach

Nicola d'Avanzo, Christian Celia, Antonella Barone, Maria Carafa, Luisa Di Marzio, Hélder A. Santos, and Massimo Fresta**

peated administrations.[48,49] In particular, it was demonstrated that the second administration of PEGylated nanocarriers was rapidly cleared from the blood circulation, when administered at a specific time course after the injection of the first dose.[50,51] This unexpected pharmacokinetic modification, or accelerated blood clearance (ABC)[52,53] phenomenon, caused a large accumulation of PEGylated nanocarriers in the liver and it was widely studied by Dams et al. and Ishida and Kiwada using PEGylated liposomes.[54,55] This phenomenon is true for PEGylated nanocar-

tibody titer has significantly increased, and recently Yang et al. reported an incidence of anti-PEG antibodies of 72% on normal healthy patients that never interacted with PEGylated drugs. The meta-analysis of this data demonstrated that the distribution of anti-PEG antibodies in the selected cohort of healthy patients was: 18% responsiveness to IgG, 25% responsiveness to IgM, and 30% responsiveness to both anti-PEG antibodies.[22] In this study, Yang and co-workers highlighted that there was an increase in healthy patients that are positive of anti-PEG antibodies in

Je länger der PEG Schwanz – desto mehr Platz für anti-PEG Antikörper?
The longer the PEG-tail – the more space for antibodies to bind?

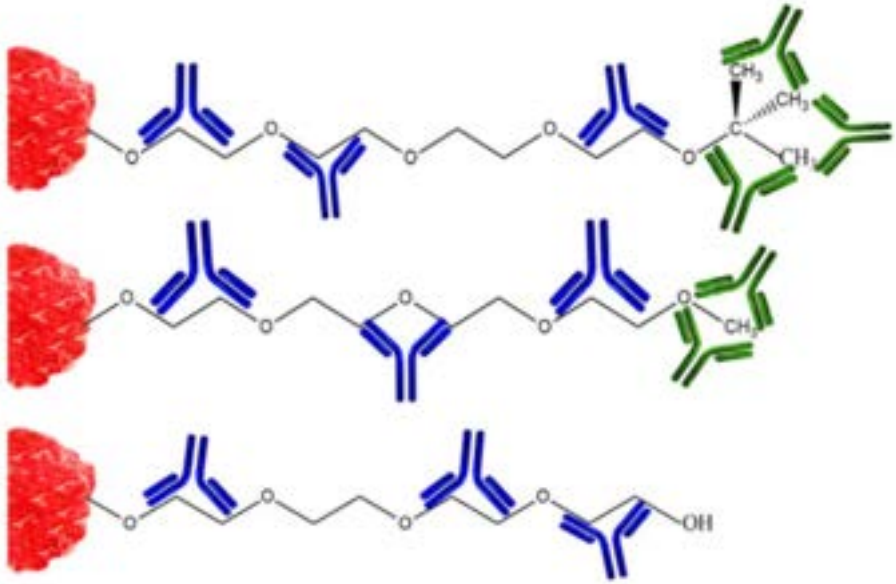
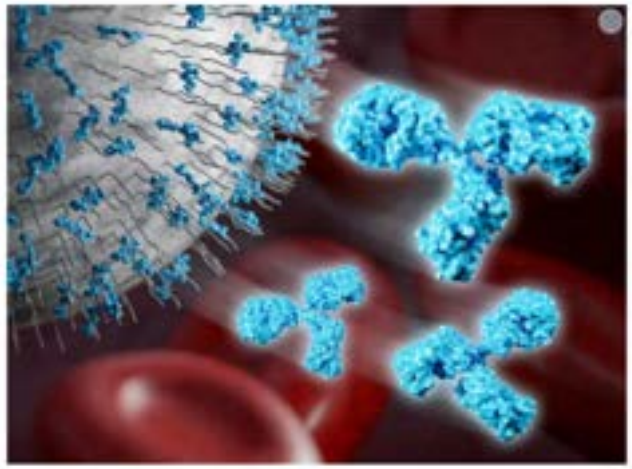


Figure 1. Schematic representation of different anti-PEG antibodies. The blue immunoglobulin is directed versus the backbone of the polymer, while the green antibodies are specific for the end-group. The picture shows that the immunogenicity of PEG is directly related to the hydrophobicity of the end-chain.

https://onlinelibrary.wiley.com/doi/abs/10.1002/adtp.201900170

Forschungsergebnisse

Molekulare Abwehrkräfte: Studie zeigt Antikörper gegen Polyethylenglykol bei 83 Prozent der deutschen Bevölkerung



Anti-PEG Antikörper zirkulieren im Blut vieler Menschen und binden an PEGylierte Nanoträger | Download

https://nachrichten.idw-online.de/2023/10/20/molekulare-abwehrkraefte-studie-zeigt-antikoerper-gegen-polyethylenglykol-bei-83-prozent-der-deutschen-bevoelkerung

Issue 10, 2023

Previous Article Next Article

From the journal:
Nanoscale Horizons

Anti-PEG antibodies enriched in the protein corona of PEGylated nanocarriers impact the cell uptake†

Check for updates

Mareike F. S. Deuker,[a] Volker Mailänder,[ba] Svenja Morsbach [*a] and Katharina Landfester [a]

Author affiliations

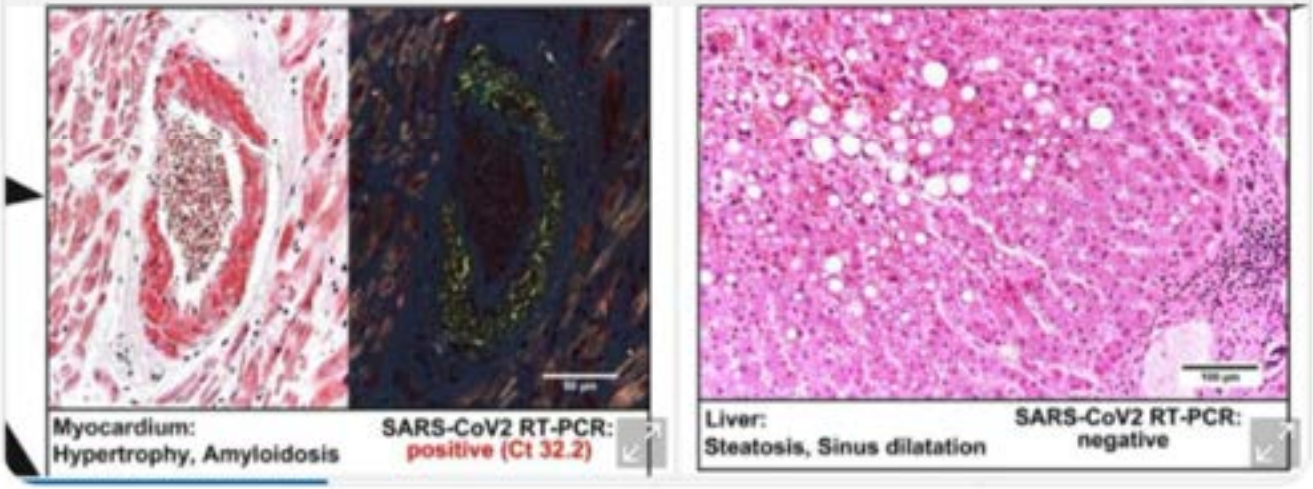
Deuker MFS, Mailänder V, Morsbach S, Landfester K. Anti-PEG antibodies enriched in the protein corona of PEGylated nanocarriers impact the cell uptake. Nanoscale Horiz. 2023 Sep 26;8(10):1377-1385. doi: 10.1039/d3nh00198a. PMID: 37591816. https://pubmed.ncbi.nlm.nih.gov/37591816/

https://twitter.com/53v3n0fn1n3/status/1713446963536965738

Seven of Nine, MD
@53v3n0fn1n3

Thats why its so interesting, that the first autopsy of a breakthrough case had exactly the predicted liver changes, but no positive PCR.
pubmed.ncbi.nlm.nih.gov/33872783/
Arne did find liver pathology but not always spike expression.
LIVER is major "immune" organ. Acute phase metabolism.
Post übersetzen

13. Juni 2021



8:49 vorm. · 15. Okt. 2023 · 67 Mal angezeigt

Seven of Nine, MD @53v3n0fn1n3 · 1 Std.
In 2021-2022 I have treated some liver tox myself. Skin not so much.

Even the care home death report in the corona comittee was full of major liver symptoms: dizziness up to coma, itchy skin up to yellowish colouring. Stomach pain only if organ swollen. Decolouring of poo.

1 · 1 · 26

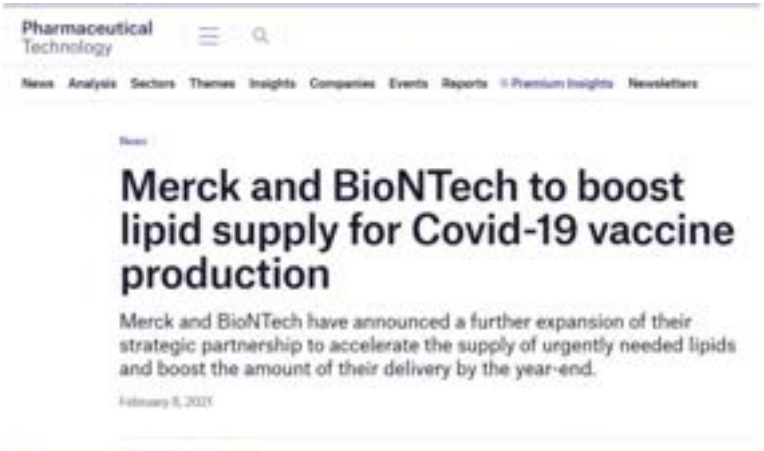
sn-glycero-3-phosphoethanolamine-Poly(ethylene glycol) (PEG-DSPE) with Tween 20 containing short (C11) PEG alkyl chain [155]. The authors found that the usage of the short PEG alkyl chain led to a significantly improved lymph node targeting after intramuscular administration in mice [155]. Few studies focused on actively targeting of lymphocytes. Ramishetti et al. functionalized the LNP surface by anti-CD4 monoclonal antibody to target CD4+ T cells [156]. Veiga et al. have used an ASSET (Anchored Secondary scFv Enabling

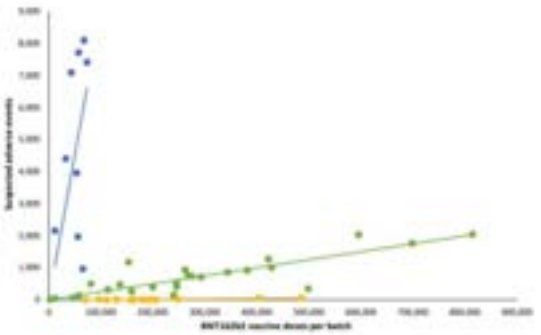
thus improving the effectivity of LNP-siRNA drug [80]. This study is in agreement with the previous study by Judge et al. where the authors found less formed anti-PEG antibodies and a substantial reduction of side effects upon repetitive dosing in mice when PEGylated liposomes containing a shorter alkyl chain (C14) PEG-lipid versus a longer alkyl chain C16 PEG-lipid were used [151]. Studies directly examining the effects of anti-PEG antibodies on the efficacy and safety of LNP-mRNA drugs containing PEG lipids are

Vlatkovic I. Non-Immunotherapy Application of LNP-mRNA: Maximizing Efficacy and Safety. Biomedicines. 2021 May 10;9(5):530. doi: 10.3390/biomedicines9050530. PMID: 34068715; PMCID: PMC8151051. https://pubmed.ncbi.nlm.nih.gov/34068715/

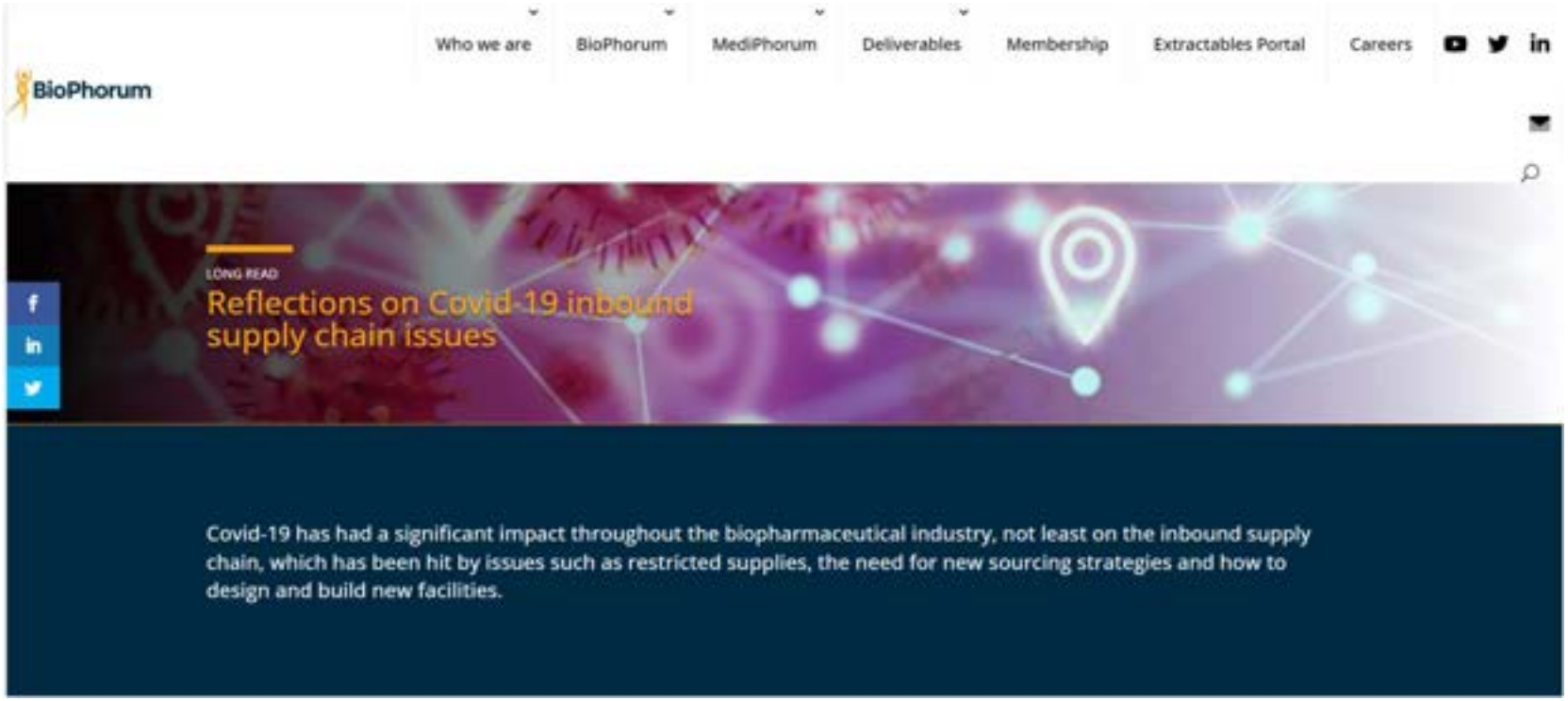
=== Zulieferer für Nanolipide ===

1. **Croda** = Avanti (haben Avanti aus “Project Lightspeed” 2020 gekauft)
2. **Merck** ab Februar 2021 zusätzlich ab 2022 mit seiner im Februar 2022 für 750-780 Millionen USD gekauften Firma Exelead
3. **Evonik** ab April 2021





https://drbine.substack.com/p/liste-der-biontech-zulieferer-work



Specific comments said that delays in supply change notifications are often too late to plan for, that **suppliers and biomanufacturers may have different standards in quality systems, and there is a need for proactive communication about changes. "Interactions are unlikely to ever be classed as optimal and so will be an ongoing need," said Bob Brooks, BioPhorum Supply Partner Leader. "But the survey shows the strength of feeling at the current time and that people understand that more work needs to be done in this space."**

https://www.biophorum.com/reflections-on-covid-19-inbound-supply-chain-issues/

Chromatographie?
Massenspektrometrie?
Warum nur? Da hätte man ja Verunreinigungen sehen können.

▪ ***Table·P.4-3.·Specification·for·ALC-0315[a].¶***

Quality Attribute	Analytical Procedure	Acceptance Criteria
Appearance	Visual examination	Colorless to pale yellow oil which contains no foreign matter
Identity	Infrared spectroscopy	IR spectrum of the sample corresponds to that of the reference spectrum
Microbial Contamination	Ph. Eur. 2.6.12	TAMC NMT 100 CFU/g or NMT 100 CFU/mL

a. In order to release a batch for use in the manufacture of LNP drug product, results from the supplier are also required for the following tests. For details regarding the specification and methods for these tests performed at the supplier, refer to Section 3.2.A.3.4 Control of Excipients [ALC-0315]. The drug product manufacturer intends to implement these tests as part of incoming materials testing following qualification of the methods.

1. Assay
2. Impurities
3. Residual solvents

Abbreviations: IR = infrared; NMT = not more than; LNP = lipid nanoparticle; TAMC = Total aerobic microbial count; Ph. Eur. = European Pharmacopeia

¶

ALC-0159·(2-[(polyethylene·glycol)-2000]-N,N-ditetradecylacetamide)·–·non-compendial,·novel·excipient¶

Rapporteur Rolling Review critical assessment report, Quality aspects, S. 159

4. The Participating Member State acknowledges that the Vaccine and materials related to the Vaccine, and their components and constituent materials are being rapidly developed due to the emergency circumstances of the COVID-19 pandemic and will continue to be studied after provision of the Vaccine to the Participating Member States under the PA. The Participating Member State further acknowledges that the long-term effects and efficacy of the Vaccine are not currently known and that there may be adverse effects of the Vaccine that are not currently known. Further, to the extent applicable, the Participating Member State acknowledges that the Vaccine shall not be serialized.

Wie konnte das passieren?

Das sind die Folgen, wenn man nicht serialisiert.

*„Der teilnehmende Mitgliedsstaat erkennt an, dass der Impfstoff und die mit dem Impfstoff zusammenhängenden Materialien sowie ihre Komponenten und Bestandteile aufgrund der Notsituation der COVID-19-Pandemie rasch entwickelt und nach der Bereitstellung des Impfstoffs an die teilnehmenden Mitgliedstaaten im Rahmen des APA weiter untersucht werden. Der teilnehmende Mitgliedsstaat erkennt ferner an, dass die langfristigen Auswirkungen und die Wirksamkeit des Impfstoffs derzeit nicht bekannt sind und dass der Impfstoff unerwünschte Wirkungen haben kann, die derzeit nicht bekannt sind. Weiterhin, soweit anwendbar, erkennt der Teilnehmerstaat an, dass **der Impfstoff nicht in Serie produziert werden wird.**"*

https://d7694293-ffb8-4ed0-a014-3581d49070e4.usrfiles.com/ugd/d76942_5af19ff7389d405585ae0c9db50eb306.pdf

3.
Das komplette Lipidnanopartikel BNT162B2 ist toxischer als seine Einzelkomponenten

Natriumchlorid, Technisch
Pfizer - Arbeitsplatzgrenzwert-bereich (OEB): OEB1 (Kontrollieren der Exposition im Bereich von 1000ug/m³ bis 3000ug/m ³)

ALC-0315
Pfizer - Arbeitsplatzgrenzwert-bereich (OEB): OEB 3 - Kontaktgefahren unbekannt (zu überwachender Expositionsbereich 10 ug/m³ bis < 100 ug/m³)

Kaliumchlorid
Pfizer - Arbeitsplatzgrenzwert-bereich (OEB): OEB1 (Kontrollieren der Exposition im Bereich von 1000ug/m³ bis 3000ug/m ³)

PF00092

Pharmaceutical Sciences
Worldwide Research & Development
Reference Standard Certificate

STANDARD INFORMATION	
Compound	PF-07302048
Reference Standard Lot	PF-07302048-DP-RM
Reevaluation / Expiration Date	05-AUG-2021
Occupational Exposure Band	OEB 5
Long Term Storage Condition	(b) (4) °C
Short Term Storage Condition	N/A
Primary Contact	(b) (6)
Authorized By	Rebekah Ward
Authorized On	01-Feb-2021

TESTS AND RESULTS	
Fluorescence assay	
RNA Content	mg/mL

FOOTNOTES
Parent drug product lot (b) (4)
°C for up to days if sampled aseptically

https://twitter.com/a_nineties/status/1729782228782117036
https://phmpt.org/wp-content/uploads/2023/11/125742_S11_M3_32r_pf-07302048-dp-rm-coa.pdf

Produktcode PF00092
Form Nanoform
Synonyme Comirnaty; PF-07302048 containing PF-07305885 (BNT162b2); CorVAC Containing PF-07305885 (BNT162b2) ; CoVVAC Containing PF-07305885 (BNT162b2); COVID Vaccine Containing PF-07305885 (BNT162b2); COVID-19 Vaccine Containing PF-07305885 (BNT162b2)
Handelsname: Nicht zutreffend
Verbindungszahl PF-07302048

SICHERHEITSDATENBLATT

Abschnitt 1: BEZEICHNUNG DES STOFFS BEZIEHUNGSWEISE DES GEMISCHS UND DES UNTERNEHMENS

1.1. Produktidentifikator

Produktbezeichnung	Pfizer-BioNTech COVID-19 Vaccine
Produktcode	PF03092
Form	Nanoform
Synonyme	Comirnaty; PF-07302048 containing PF-07305885 (BNT162b2); CorVAC Containing PF-07305885 (BNT162b2) ; CoVVAC Containing PF-07305885 (BNT162b2); COVID Vaccine Containing PF-07305885 (BNT162b2); COVID-19 Vaccine Containing PF-07305885 (BNT162b2)
Handelsname:	Nicht zutreffend
Verbindungszahl	PF-07302048
Produktcode	H000022941; H000023057;H000024547; H000024742
Chemische Familie:	Lipid Nanoparticles containing PF-07305885 (BNT162b2) and Lipids

1.2. Relevante identifizierte Verwendungen des Stoffs oder Gemischs und Verwendungen, von denen abgeraten wird

Abschnitt 6: MASSNAHMEN BEI UNBEABSICHTIGTER FREISETZUNG

6.1. Personenbezogene Vorsichtsmaßnahmen, Schutzausrüstungen und in Notfällen anzuwendende Verfahren

Personenbezogene Vorsichtsmaßnahmen Einsatzkräfte	Reinigungspersonal muss geeignete Personenschutzausrüstung tragen (siehe Abschnitt 8). Exposition minimieren. In Abschnitt 8 empfohlene persönliche Schutzausrüstung verwenden.

6.2. Umweltschutzmaßnahmen

Umweltschutzmaßnahmen	Abfälle zur Entsorgung in einen ordnungsgemäß beschrifteten, versiegelten Behälter füllen. Es ist darauf zu achten, dass der Stoff nicht freigesetzt wird.

6.3. Methoden und Material für Rückhaltung und Reinigung

Methoden für Rückhaltung Verfahren zur Reinigung	Weitere Leckagen oder Verschütten vermeiden, wenn gefahrlos möglich. Verschüttungsquelle eindämmen, sofern dies ohne Gefährdung möglich ist. Verschütten Stoff mit Absorptionsmittel aufnehmen. Verschüttungsbereich gründlich reinigen.
Vermeidung sekundärer Gefahren	Verschmutzte Gegenstände und Flächen unter Beachtung der Umweltvorschriften gründlich reinigen.

6.4. Verweis auf andere Abschnitte

Verweis auf andere Abschnitte	Weitere Informationen finden Sie in Abschnitt 8. Weitere Informationen finden Sie in Abschnitt 13.

Abschnitt 4: ERSTE-HILFE-MASSNAHMEN

4.1 Beschreibung der Erste-Hilfe-Maßnahmen

Einatmen	An die frische Luft bringen. Sofort ärztliche Hilfe hinzuziehen.
Augenkontakt	Mit reichlich Wasser mindestens 15 Minuten lang gründlich spülen, dabei das obere und untere Augenlid anheben. Ärztliche Hilfe hinzuziehen.
Hautkontakt	Kontaminierte Kleidung entfernen. Bereich mit großen Mengen Wasser spülen. Seife verwenden. Medizinische Versorgung veranlassen.
Verschlucken	Niemals etwas über den Mund verabreichen, wenn die Person nicht bei Bewusstsein ist. Mund mit Wasser auswaschen. Keinesfalls Erbrechen herbeiführen, außer unter Anleitung von medizinischem Personal. Sofort medizinische Versorgung veranlassen.

4.2. Wichtigste akute und verzögert auftretende Symptome und Wirkungen

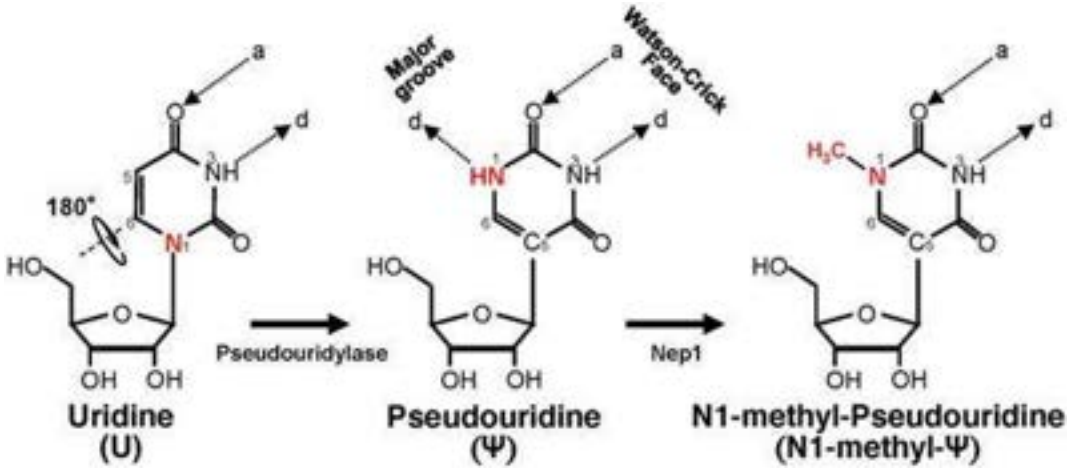
Wichtigste Symptome und Wirkungen	Zu Informationen über potentielle Anzeichen und Symptome der Exposition siehe Abschnitt 2 - Gefahrenfeststellung und/oder Abschnitt 11 - Toxikologische Information.

8.2. Begrenzung und Überwachung der Exposition

Technische Steuerungseinrichtungen	Für alle Tätigkeiten, bei denen dieses Material verwendet wird, müssen Maßnahmen zur Verhinderung von Freisetzungen und zum Schutz vor Exposition festgelegt werden. Diese Maßnahmen werden durch eine Risikobewertung ermittelt, die mit geeigneten Instrumenten zur Risikobewertung in der Arbeitshygiene durchgeführt wird. Die für die Tätigkeit erforderliche Containment-Stufe sollte auf den Ergebnissen der Risikobewertung beruhen. Bei Bedarf sollten technische Kontrollen, wie z. B. Biosicherheitskabinen, als primäres Mittel zur Expositionskontrolle eingesetzt werden.
Begrenzung und Überwachung der Umweltexposition	Es liegen keine Informationen vor.
Persönliche Schutzausrüstung	Wenden Sie sich bei der Auswahl der richtigen Schutzbekleidung / Ausrüstung, die auf einer Bewertung der Arbeitsbedingungen, anderer am Arbeitsplatz und am Arbeitsplatz vorhandener Chemikalien sowie spezifischer Betriebsabläufe beruht, mit Ihrem Sicherheitsfachmann oder Sicherheitsausrüster in Verbindung. Die Auswahl und Verwendung von persönlicher Schutzausrüstung (PPE) hat sich nach den maßgeblichen nationalen Standards und Vorschriften zu richten.
Augen-/Gesichtsschutz	Tragen Sie Schutzbrille als Mindestschutzbrille (Schutzbrille empfohlen). (Der Augenschutz muss den Normen gemäß EN166, ANSI Z87.1 oder internationalem Äquivalent entsprechen).
Handschutz	Tragen Sie undurchlässige Handschuhe (z. B. Nitril usw.), um Hautkontakt zu vermeiden. (Schutzhandschuhe müssen die Normen gemäß EN374, ASTM F1001 oder internationales Äquivalent erfüllen).
Haut- und Körperschutz	Undurchlässige wegwerfbare Schutzkleidung beim Umgang mit dieser Verbindung tragen. Vollständiger Körperschutz empfohlen (je nach Ausmaß). (Schutzkleidung muss die Anforderungen nach EN 13982, ANSI 103 oder internationales Äquivalent erfüllen).
Atemschutz	Wenn die Betriebs- und Handhabungsbedingungen zu einer Freisetzung in die Luft führen, ist ein geeignetes Atemschutzgerät mit einem Schutzfaktor zu tragen, der ausreicht, um die Exposition zu kontrollieren (z. B. Partikelpatrone mit Vollgesichtsmaske, P3-Filter). (Atemschutzgeräte müssen die Normen gemäß EN136, EN143, ASTM F2704-10 oder internationalem Äquivalent erfüllen.).

4. Der Inhalt des Lipidnanopartikels (therapeutic payload) ist toxisch

4.1 Die modRNA selbst ist durch die Verwendung von N1-Metyhlpseudouridine toxischcher als seine Einzelkomponenten



"RNA wird durch zelluläre RNasen abgebaut und dem Nukleinsäurestoffwechsel unterworfen. Der Nukleotidstoffwechsel findet in der Zelle kontinuierlich statt, wobei das Nukleosid zu Abfallprodukten abgebaut und ausgeschieden ***oder für die Nukleotidsynthese wiederverwendet wird. Daher werden keine Studien zum RNA- oder Proteinstoffwechsel oder zur Ausscheidung durchgeführt."***

https://pubmed.ncbi.nlm.nih.gov/34805188/

The protein encoded by the RNA in BNT162b2 is expected to be proteolytically degraded like other endogenous proteins. RNA is degraded by cellular RNases and subjected to nucleic acid metabolism. Nucleotide metabolism occurs continuously within the cell, with the nucleoside being degraded to waste products and excreted or recycled for nucleotide synthesis. Therefore, no RNA or protein metabolism or excretion studies will be conducted.

https://phmpt.org/wp-content/uploads/2022/03/125742_S1_M2_26_pharmkin-written-summary.pdf#page=9

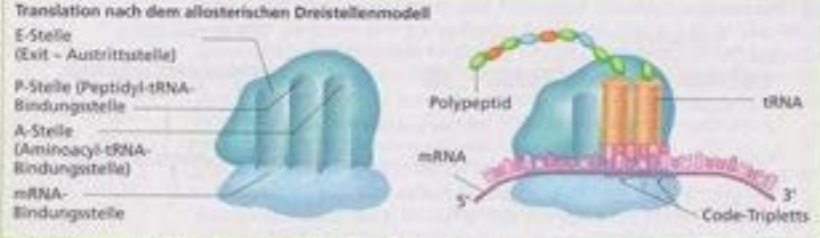
Ein N1-modifiziertes Ψ-Derivat handelt ist N1-Methyl-Ψ, eine natürlich vorkommende Modifikation in der 18S rRNA (N1-modified Ψ-derivative is N1-methyl-Ψ, a naturally occurring modification found in 18S rRNA)
https://pubmed.ncbi.nlm.nih.gov/34805188/

„diese Änderungen werden typischerweise in einer posttranskriptionellen Posttranskriptionsreaktion eingeführt, wobei nur wenige Beispiele für cotranskriptionellen Modifikation bekannt sind." https://pubmed.ncbi.nlm.nih.gov/21823225/

„Mit der Gleichen schlechten Qualität von 28S/18S oder 23S/16S Werten als unter dem Standard evaluiert."
https://www.fortunejournals.com/articles/huaier-effects-on-functional-compensation-with-destructive-ribosomal-rna-structure-after-antisarscov2-mrna-vaccination.html

	Eukaryot	rRNA	Prokaryot	rRNA	Mitochondrium	rRNA
Ribosom	80S		70S		55S	
Kleine Untereinheit	40S	**18S**	30S	16S	28S	12S
Große Untereinheit	60S	28S 5,8S 5S	50S	30S 5S	29S	16S

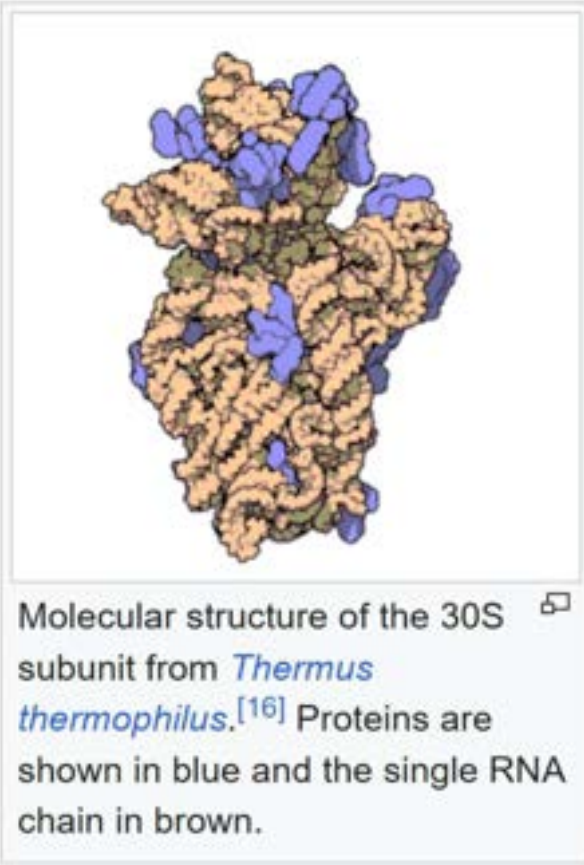
Translation nach dem allosterischen Dreistellenmodell



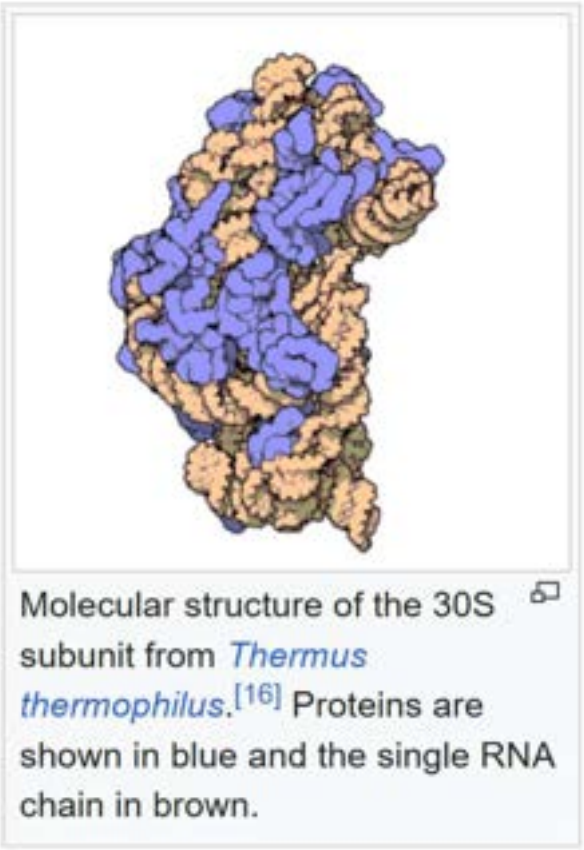
Initiation	Bildung des Initiationskomplexes durch Vereinigung von der ersten tRNA (Met), mRNA, kleiner ribosomaler Untereinheit und abschließend der großen Untereinheit. Die Met-tRNA ist dabei in der P-Stelle lokalisiert.
Elongation	In der Kettenwachstumsphase kommt es zur zyklischen Wiederholung von drei Reaktionsschritten. 1. Aminoacyl-tRNA-Bindung in der A-Stelle durch Codon-Anticodon-Paarung zwischen mRNA und Aminoacyl-tRNA. 2. Peptidyltransfer, d. h., unter Aufbau einer Peptidbindung wird die Aminosäure bzw. bei folgenden Zyklen der Peptidyl-Rest auf den Aminosäurerest in der A-Stelle übertragen. 3. Translokation, die Peptidyl-tRNA rückt mit der mRNA um ein Triplett in die P-Stelle weiter. Die entladene tRNA rückt in die E-Stelle und wird dort abgegeben. Die frei gewordene A-Stelle kann erneut besetzt werden und ein weiterer Elongationszyklus beginnt.
Termination	Wenn nach erfolgter Translokation eines der drei Terminationscodone (UAA, UAG, UGA) in der A-Stelle auftritt, wird die Proteinsynthese abgebrochen. Nach Freisetzung des Polypeptids kommt es auch zur Dissoziation des Translationskomplexes (Ribosoms).

An einem mRNA-Molekül werden gleichzeitig mehrere Polypeptide synthetisiert, da nach Verlassen der Initiationsregion sofort weitere Ribosomen binden. Die Ribosomengruppen werden als **Polysomen** bezeichnet. Schon vor Beendigung der Peptidsynthese beginnen sich die Ketten zur Sekundär- und Tertiärstruktur zu falten. So entstehen Proteinmoleküle mit spezifischer biologischer Funktion.

	Eukaryot	rRNA	Prokaryot	rRNA	Mitochondrium	rRNA
Ribosom	80S		70S		55S	
Kleine Untereinheit	40S	**18S**	30S	16S	28S	12S
Große Untereinheit	60S	28S 5,8S 5S	50S	30S 5S	29S	16S



Molecular structure of the 30S subunit from *Thermus thermophilus*.[16] Proteins are shown in blue and the single RNA chain in brown.



Molecular structure of the 30S subunit from *Thermus thermophilus*.[16] Proteins are shown in blue and the single RNA chain in brown.

https://en.wikipedia.org/wiki/Ribosome

4.2 das durch die modRNA kodierte Spike-Protein ist toxisch

Was wusste das PEI?

Messen, was verbindet – Gewebeschäden durch Zellfusion in COVID-19 und die Rolle des Spikeproteins

03 / 2021

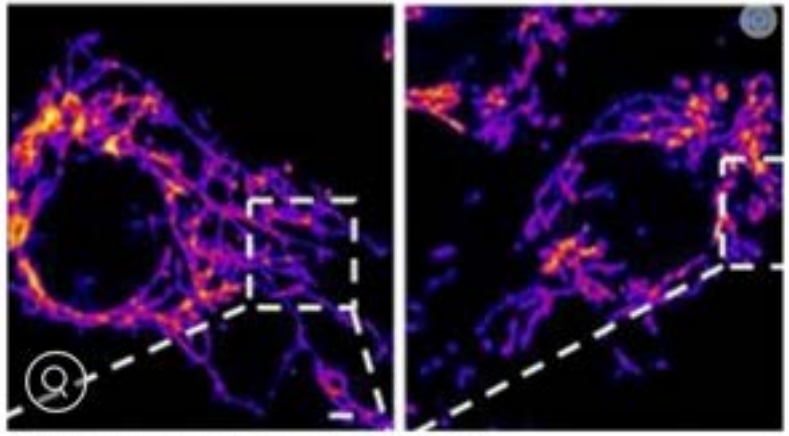
Das Coronavirus SARS-CoV-2 gelangt durch Membranfusion nach Kontakt seines Spikeproteins mit dem ACE2-Rezeptor in menschliche Zellen. Neue Studien belegen eine zweite Rolle des Proteins in COVID-19: das Verschmelzen von Körperzellen. Ein Forschungsteam des Paul-Ehrlich-Instituts hat vielversprechende Assays entwickelt, mit denen sich diese Membranfusionen messen lassen. Schon geringste Mengen des Spikeproteins reichen in Zellkultur aus, infizierte und nicht infizierte Zellen verschmelzen und absterben zu lassen. Viruspartikel mit Spikeprotein auf ihrer Oberfläche können sogar nur durch Kontakt Zellen veranlassen, mit ihren Nachbarn zu fusionieren. Über die Ergebnisse berichtet iScience in seiner Onlineausgabe vom 09.02.2021.

Positionen
PEI-Zweijahresberichte
Pflichtberichte
Social Media
Veranstaltungen
Veröffentlichungen zu Arzneimitteln
Videos, Audios und Infografiken
WHO-CC-Jahresberichte
Zentrale Zulassungen
Coronavirus und COVID-19
Brexit
HIV-Selbsttests
Mitteilungen für medizinische und pharmazeutische Fachkreise
Bundesgesundheitsblatt

https://www.pei.de/DE/newsroom/pm/jahr/2021/03-gewebeschaeden-zellfusion-covid-19-rolle-spikeprotein.html

ntv RESSORTS SPORT BÖRSE WETTER VIDEO AUDIO TV PROG

Forscher: Covid-19 ist eine Gefäßerkrankung



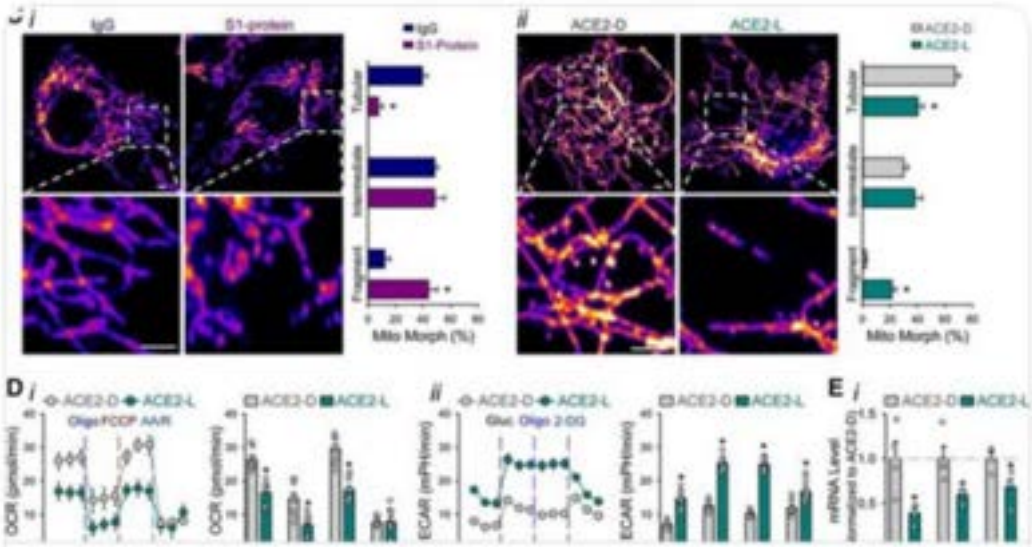
Dass das Spike-Protein des Coronavirus etwas Besonderes ist, weiß man schon länger. Offenbar ist es jedoch schon für sich betrachtet äußerst verhängnisvoll. Das zeigen Forscher an einem "Pseudovirus".

Bisher wird das Spike-Protein des Coronavirus vor allem mit der besonderen Ansteckungsgefahr von Sars-Cov-2 in Verbindung gebracht. Eine Studie zeigt nun, dass die Proteine auch bei der durch das Virus ausgelösten Covid-19-Erkrankung eine Schlüsselrolle spielen.

https://www.n-tv.de/wissen/Forscher-Covid-19-ist-eine-Gefaesserkrankung-article22529342.html

Karl Lauterbach
@Karl_Lauterbach

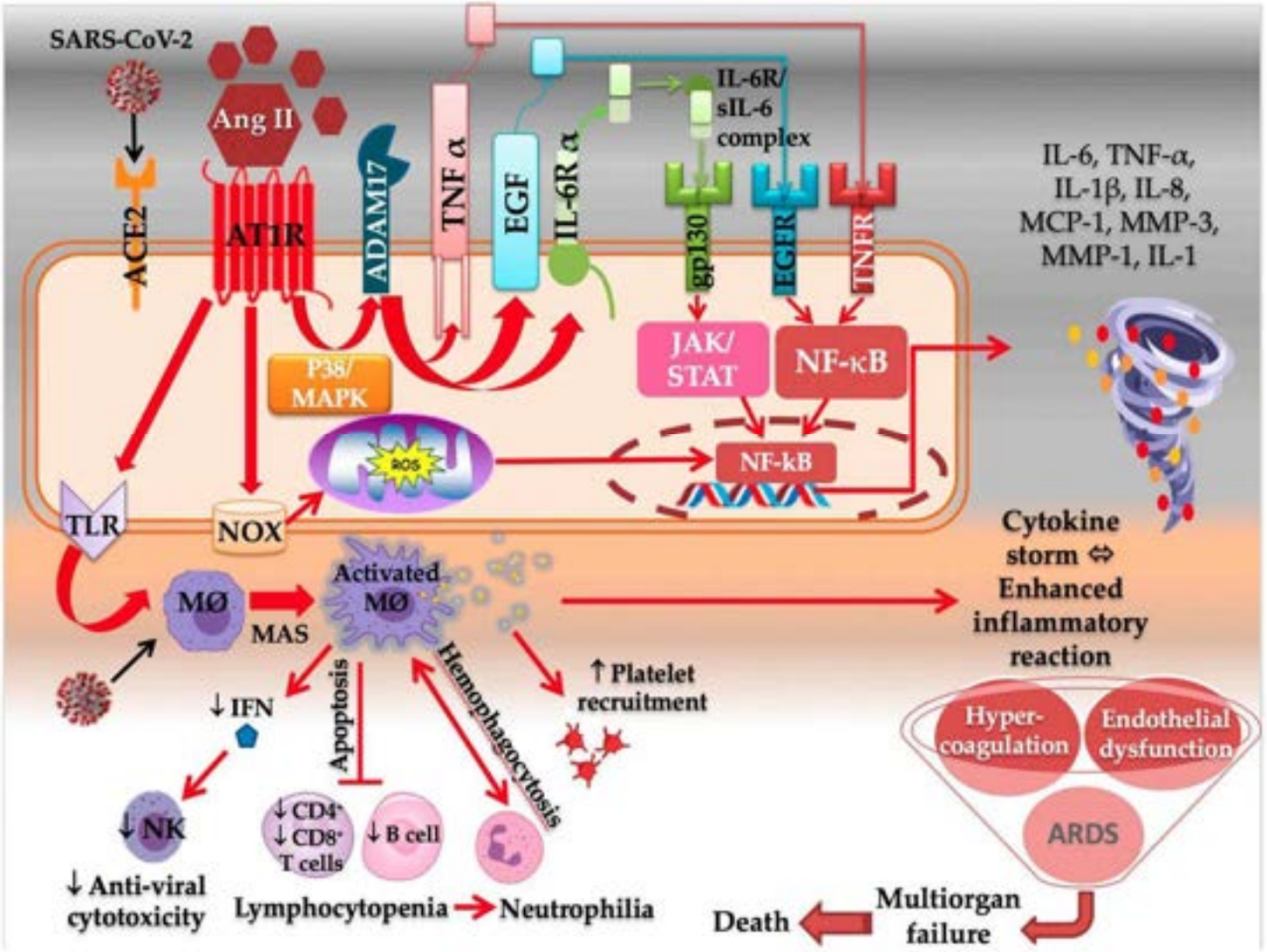
(1) Diese wichtige Studie aus Kalifornien belegt, was lange vermutet wurde. Covid ist viel mehr eine Gefässkrankheit als eine Lungenkrankheit. Das erklärt auch die Schäden an Nieren, Gehirn und Herz. Das Spike Protein selbst beschädigt die Gefässe.

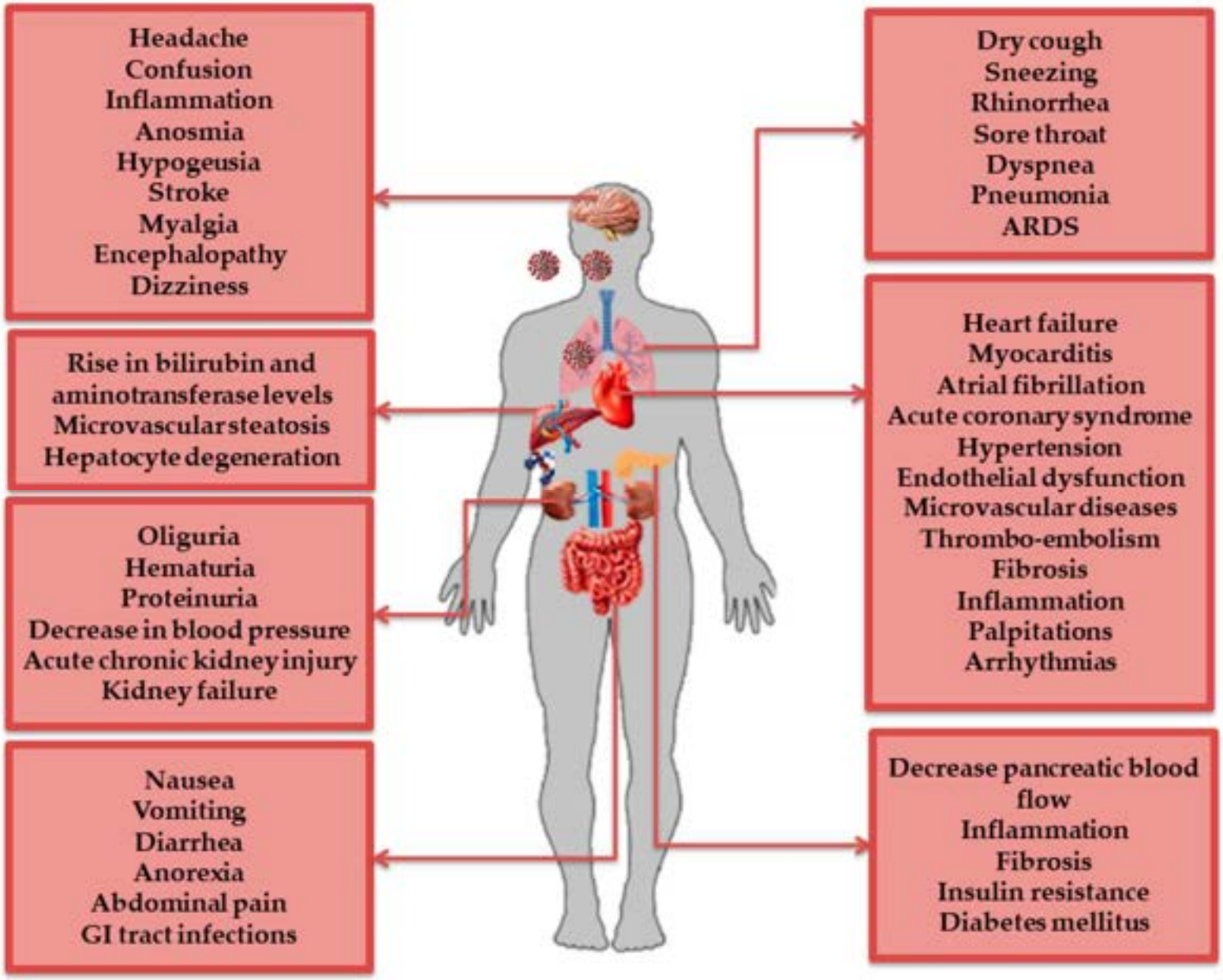


ahajournals.org
SARS-CoV-2 Spike Protein Impairs Endothelial Function via Downregulation of ACE 2

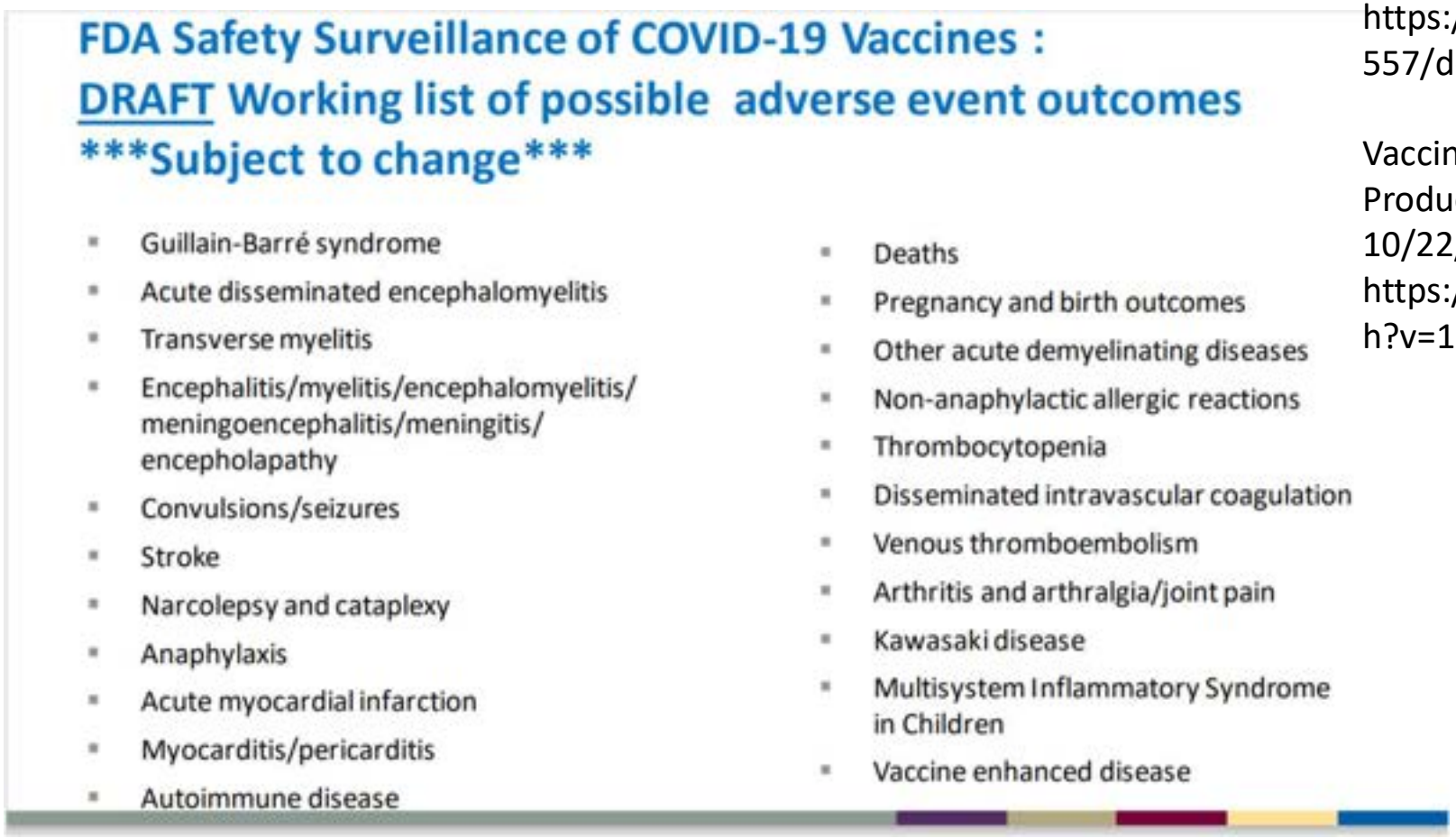
https://twitter.com/Karl_Lauterbach/status/1392477044135579652

https://pubmed.ncbi.nlm.nih.gov/35408447/




Headache
Confusion
Inflammation
Anosmia
Hypogeusia
Stroke
Myalgia
Encephalopathy
Dizziness
Rise in bilirubin and aminotransferase levels
Microvascular steatosis
Hepatocyte degeneration
Oliguria
Hematuria
Proteinuria
Decrease in blood pressure
Acute chronic kidney injury
Kidney failure
Nausea
Vomiting
Diarrhea
Anorexia
Abdominal pain
GI tract infections
Dry cough
Sneezing
Rhinorrhea
Sore throat
Dyspnea
Pneumonia
ARDS
Heart failure
Myocarditis
Atrial fibrillation
Acute coronary syndrome
Hypertension
Endothelial dysfunction
Microvascular diseases
Thrombo-embolism
Fibrosis
Inflammation
Palpitations
Arrhythmias
Decrease pancreatic blood flow
Inflammation
Fibrosis
Insulin resistance
Diabetes mellitus

Die berühmte Folie 17 der FDA vom 22.10.2020



https://www.fda.gov/media/143557/download

Vaccines and Related Biological Products Advisory Committee - 10/22/2020
https://www.youtube.com/watch?v=1XTiL9rUpkg&t=9220s

SARS-CoV2 spike protein pathogenicity research collection:
https://zenodo.org/records/14269255

Consensus: AI-powered Academic Search Engine
https://react19.org/1250-covid-vaccine-reports/

Studienbibliothek zur COVID-19-Pandemie - Gesundheit für Österreich
https://www.gesundheit-oesterreich.at/studienbibliothek/

Scientific Studies on Vaccine Injuries - KC's COVID Facts
https://ladycasey.substack.com/p/scientific-studies-on-vaccine-injuries

5. DNA Verunreinigungen

COMMENT 1

Provide additional data and/or information characterizing the size distribution of residual DNA fragments and residual intact circular plasmid by Dec 1, 2023.

RESPONSE

In support of the commitment, the following response provides additional information of Comirnaty (BNT162b2) Omicron XBB.1.5 variant Linear DNA template starting material [redacted] and the corresponding residual DNA within the Drug Substance.

The starting material in BNT162b2 DS manufacture includes [redacted] No DNA material is used or introduced in the manufacturing process other than the initial use of the DNA plasmid. DS and DP quality, safety and efficacy have been demonstrated for more than 1 billion doses administered to individuals worldwide over the last 3 years. no study!

Currently, information [redacted] presented in the dossier focuses solely on [redacted]

However, the above-mentioned plasmid DNA starting material also contains [redacted] SV40 Promoter? [redacted] Data on the origin/source, location and hypothetical function of those elements are provided in Table 3.2.S.2.3-2 in the 3.2.S.2.3 Control of Materials – Source, History and Generation of Plasmids [Omicron (XBB.1.5) Variant] leaflet included in this submission.

Pfizer: Im Herstellungsprozess wird kein anderes DNA-Material verwendet oder eingeführt als das anfängliche DNA-Plasmid. Die Qualität, Sicherheit und Wirksamkeit von DS und DP wurden in den letzten drei Jahren bei mehr als einer Milliarde verabreichter Dosen an Personen weltweit nachgewiesen.

Ein entscheidendes Ausgangsmaterial für die Herstellung von mRNA ist die DNA-Vorlage, die das Antigen kodiert. Bei Pfizer haben wir auf die Expertise des Pfizer-Gentherapieprogramms im Bereich der Herstellung von Plasmid-DNA (pDNA) zurückgegriffen

https://drbine.substack.com/p/pfizer-gibt-dna-verunreinigungen
https://pubmed.ncbi.nlm.nih.gov/36162187/

Pfizer:

„Bei der Risikobewertung wurden mehrere Schlüsselaspekte berücksichtigt, und es besteht Einigkeit darüber, dass die Wahrscheinlichkeit, dass Rest-DNA in das menschliche Genom integriert wird, ***als vernachlässigbar angesehen wird.****"*

"Die von SV40 abgeleiteten Sequenzen machen nur einen kleinen Teil der gesamten Rest-DNA von Comirnaty aus."

"Der aktuelle wissenschaftliche Die aktuellen wissenschaftlichen Erkenntnisse, die in der Risikobewertung geprüft wurden, bestätigen, dass keines dieser Elemente die chromosomale Integration erleichtert und auch nicht zur Persistenz oder Replikation des Plasmids im menschlichen Körper beiträgt. Keine SV40-Proteine sind im Impfstoff kodiert oder vorhanden. Außerdem sind die SV40-Sequenzelemente keine Onkogene und lösen keinen Krebs aus."

„Daher besteht allgemein Einigkeit darüber, dass das Vorhandensein von DNA-Resten in Comirnaty, die unterhalb der zugelassenen Grenzwerte liegen, und ***das mögliche Vorhandensein der nicht verwendeten SV40-Sequenzelemente*** *in den DNA-Resten das allgemeine Sicherheitsprofil des Impfstoffs nicht verändern und kein Risiko für die Impflinge darstellen."*

https://drbine.substack.com/p/pfizer-gibt-den-sv40-promotor-in

Sieht Moderna anders als BioNTech/Pfizer

Zum Beispiel kann sich die eingeführte DNA mit einer gewissen Häufigkeit in die genomische DNA der Wirtszelle integrieren, was zu Veränderungen und/oder Schäden an der genomischen DNA der Wirtszelle führt. Alternativ kann die in eine Zelle eingeführte heterologe Desoxyribonukleinsäure (DNA) von Tochterzellen (unabhängig davon, ob die heterologe DNA in das Chromosom integriert wurde oder nicht) oder von Nachkommen vererbt werden.
https://patents.google.com/patent/US20130259924A1/en

Die im mRNA-Herstellungsprozess verwendete DNA-Vorlage muss entfernt werden, um die Wirksamkeit der Therapeutika und die Sicherheit zu gewährleisten, da DNA-Reste in Arzneimitteln die Aktivierung der angeborenen Immunantwort auslösen können und das Potenzial haben, in Patientengruppen onkogen zu wirken.
*https://patents.google.com/patent/*US20210230578A1*/en*

Hier ein paar Paper zum SV40 Problem:

1997: Import of plasmid DNA into the nucleus is sequence specific - PubMed
1999: Cell-specific nuclear import of plasmid DNA - PubMed
2007: Enhancement of DNA vaccine-induced immune responses by a 72-bp element from SV40 enhancer - PubMed
2015: Nuclear entry of nonviral vectors - PMC
2016: p53 elevation in human cells halt SV40 infection by inhibiting T-ag expression - PubMed
2024: The SV40 virus enhancer functions as a somatic hypermutation-targeting element with potential tumorigenic activity – PubMed

RESEARCH ARTICLE

BioNTech RNA-Based COVID-19 Injections Contain Large Amounts Of Residual DNA Including An SV40 Promoter/Enhancer Sequence

ULRIKE KÄMMERER VERENA SCHULZ KLAUS STEGER *

PEER REVIEWED, CLINICAL RESEARCH 12/03/2024 v5.2019-2024

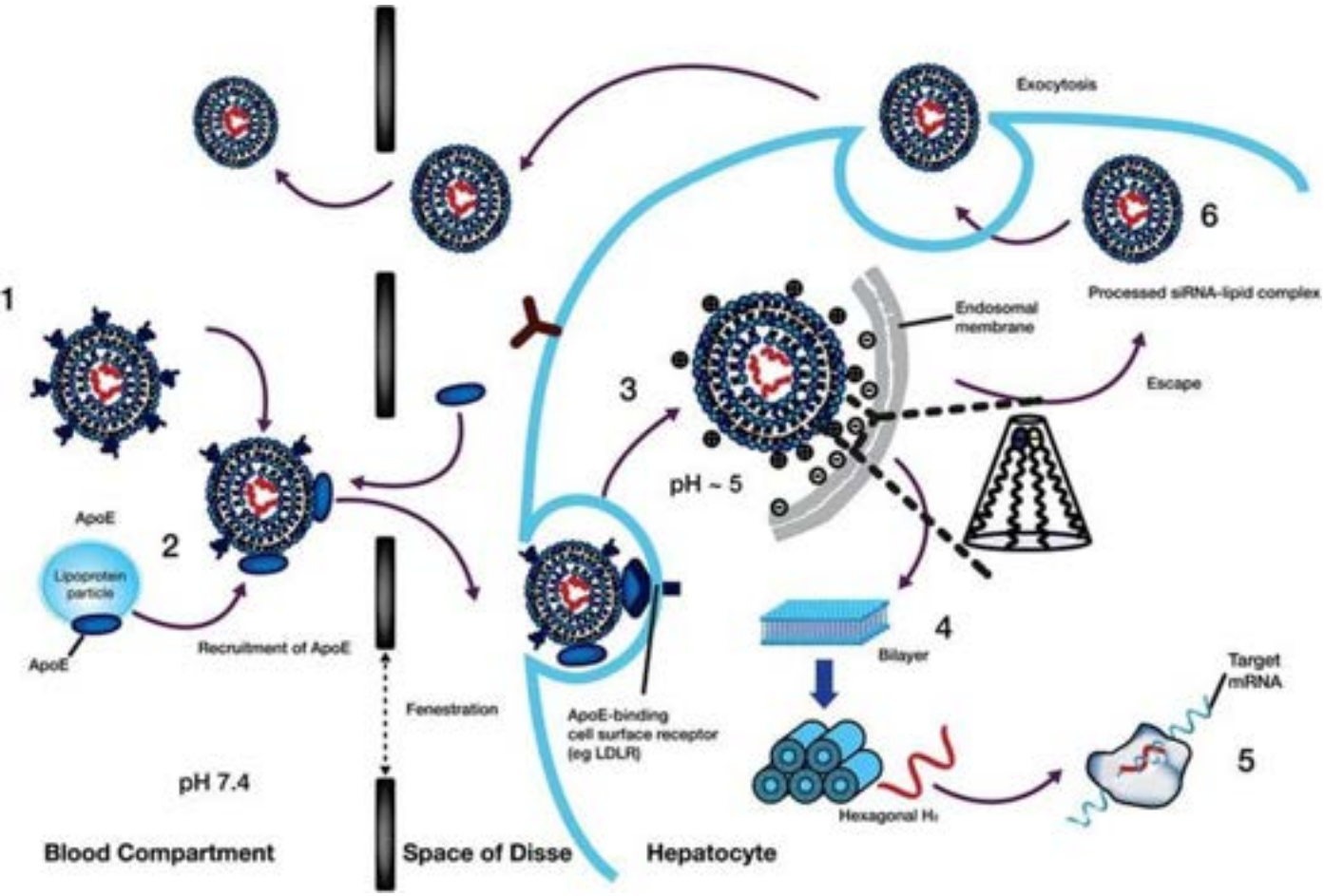
https://publichealthpolicyjournal.com/biontech-rna-based-covid-19-injections-contain-large-amounts-of-residual-dna-including-an-sv40-promoter-enhancer-sequence/

Ergebnisse: *Wir konnten eine erfolgreiche Transfektion von nukleosidmodifizierter mRNA (modRNA) in HEK293-Zellen nachweisen und zeigen robuste Konzentrationen von Spike-Proteinen über mehrere Tage der Zellkultur.* ***Die Sekretion in den Zellüberstand erfolgte überwiegend über extrazelluläre Vesikel, die mit Exosomenmarkern angereichert sind.*** *Wir haben den RNA- und DNA-Gehalt dieser Fläschchen weiter analysiert und n****ach dem RNase-A-Verdau in allen Chargen große DNA-Mengen mit Konzentrationen zwischen 32,7 ng und 43,4 ng pro klinischer Dosis festgestellt. Dies übersteigt bei weitem die maximal zulässige Konzentration von 10 ng pro klinischer Dosis,*** *die von internationalen Aufsichtsbehörden festgelegt wurde.* ***Genanalysen mit ausgewählten PCR-Primerpaaren zeigten, dass die Rest-DNA nicht nur Fragmente der DNA-Matrizen darstellt, die für das Spike-Gen kodieren, sondern von allen Genen des Plasmids, einschließlich des SV40-Promotors/Enhancers und des Antibiotikaresistenz-Gens.***
Schlussfolgerung: Unsere Ergebnisse geben Anlass zu ernsten Bedenken hinsichtlich der Sicherheit des BNT162b2-Impfstoffs und fordern einen sofortigen Stopp aller RNA-Biologika, solange diese Bedenken nicht ausgeräumt werden können.

Shedding

ModRNA kann
a) Exosomen mit modRNA über die Leber shedden
b) Exosomen mit Spike aus dem Golgi-Apparat shedden

ModRNA kann
a) Exosomen mit modRNA über die Leber shedden



(6) Ein Teil der internalisierten LNPs wird durch Exozytose aus den späten Endosomen/Lysosomen wieder in den Blutkreislauf abgegeben.

Die Onpattro (Patisiran) Exosomen haben eine Halbwertszeit von 60-80 Tagen (https://pubmed.ncbi.nlm.nih.gov/31777097/).

Vorgeschlagener Mechanismus der Leberaufnahme von Onpattro/Patisiran LNP und der Freisetzung aus der Leber nach intravenöser Verabreichung.

(https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7187331/)


J Clin Pharmacol. 2020 May; 60(5): 573–585. PMCID: PMC7187331
Published online 2019 Nov 27. doi: 10.1002/jcph.1553 PMID: 31777097

Pharmacokinetics of Patisiran, the First Approved RNA Interference Therapy in Patients With Hereditary Transthyretin-Mediated Amyloidosis

Xiaoping Zhang, MD, PhD,[*,1] Varun Goel, PhD,[1] and Gabriel J. Robbie, PhD[1]

• Author information • Article notes • Copyright and License information PMC Disclaimer

2.1	**Material:** 1x Heparin- oder Citratblut (8ml) oder Serum (mind. 4ml)	**Nachweis von Impf-mRNA (Pfizer, Moderna) in Exosomen**	☐	**174,30**

(https://www.mmd-labor.de/.cm4all/uproc.php/0/Auftrgasformulare/Auftragsformular%20X%20Post%20Covid%20Post%20Vac_1.pdf?cdp=a&_=18cb53d2708)

Exosomen beladen mit modRNA, die über die Leber shedden haben im Blut eine Halbertszeit von 60-80 Tagen

ModRNA kann
b) Exosomen mit Spike aus dem Golgi-Apparat shedden

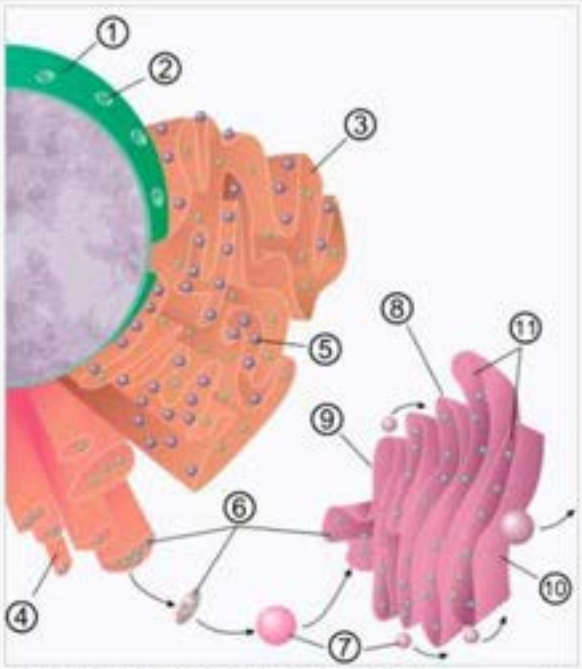
8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.
- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental exposure during pregnancy:
  - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by inhalation or skin contact.
  - A male family member or healthcare provider who has been exposed to the study intervention by inhalation or skin contact then exposes his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted

https://cdn.prod.www.manager-magazin.de/media/4cc0d9db-b895-4b7f-ba07-42ef335634d8/BiontechPfizer_Clinical_Protocol.pdf

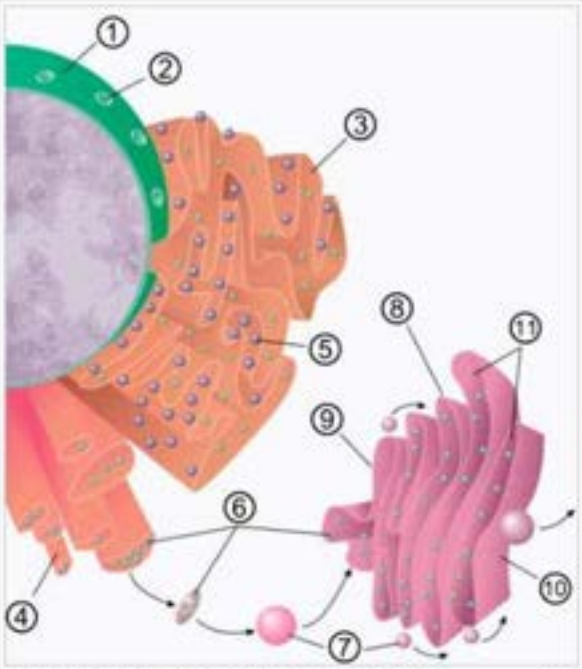


Schematische Darstellung von Zellkern, Endoplasmatischem Retikulum (ER) und Golgi-Apparat.
(1) Kernmembran,
(2) Kernpore,
(3) Raues ER,
(4) Glattes ER,
(5) Ribosom auf dem rauen ER,
(6) Transportvesikel mit Proteinen,
(7) Transport-Vesikel,
(8) Golgi-Apparat,
(9) *cis*-Golgi-Netzwerk,
(10) *trans*-Golgi-Netzwerk,
(11) *Zisternen* des Golgi-Apparates.

Postmetapher [Bearbeiten | Quelltext bearbeiten]

Der Golgi-Apparat funktioniert im Grunde wie die Post. Er empfängt Proteinpäckchen aus dem Endoplasmatischen Retikulum. Innerhalb des Golgi werden diese Proteine modifiziert, indem Zuckermonomere entfernt oder ersetzt werden. Zusätzlich werden die Proteine sortiert, indem Identifikationssymbole wie Phosphatgruppen (ähnlich einer Postleitzahl) angehängt werden. Diese „Postleitzahl" nennt den Zielort. Schließlich werden die Proteine in Transportvesikeln versendet.[4]

https://de.wikipedia.org/wiki/Golgi-Apparat



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Document 6

Nonclinical Evaluation of BNT162b2 [mRNA] COVID-19 vaccine (COMIRNATY) — Submission No. PM-2020-05461-1-2

The expressed S protein co-localised with an endoplasmic reticulum (ER) marker, suggesting the S protein is synthesised and processed within the ER for surface expression or secretion. The expressed P2 S had high binding affinity to human ACE2 peptidase domain and an anti-RBD human neutralising antibody (K_D ~1.2 nM) and also bound to antibodies from COVID-19 convalescent patients. CryoEM analysis of the purified S2 protein expressed from DNA confirmed the prefusion conformation of the P2 S similar to previously reported structures of P2 S (Cai et al. 2020; Henderson et al. 2020, Wrapp et al. 2020).

Immunofluorescence staining of HEK-293 cells transfected with BNT162b2-RNA (DS) was used to investigate whether the construct was processed within the endoplasmic reticulum (ER).

Major findings

- Co-localisation of the S-protein antigen with an ER marker was detected, suggesting the S protein is processed within the ER (Figure 2-19).
- The non-transfected cells did not express the S1 protein.

https://www.tga.gov.au/sites/default/files/foi-2389-06.pdf

https://de.wikipedia.org/wiki/Golgi-Apparat

In vivo expression and co-localization of the antigens with an endoplasmic reticulum marker was shown using immunofluorescence in HEK293T cells expressing BNT162b1 (modRNA encoding V5) and BNT162c2 (saRNA encoding V9), respectively (Figure 7). These results show that both antigens are processed within the endoplasmic reticulum for secretion and/or surface expression, which is a prerequisite for increased bioavailability and improved induction of an immune response.

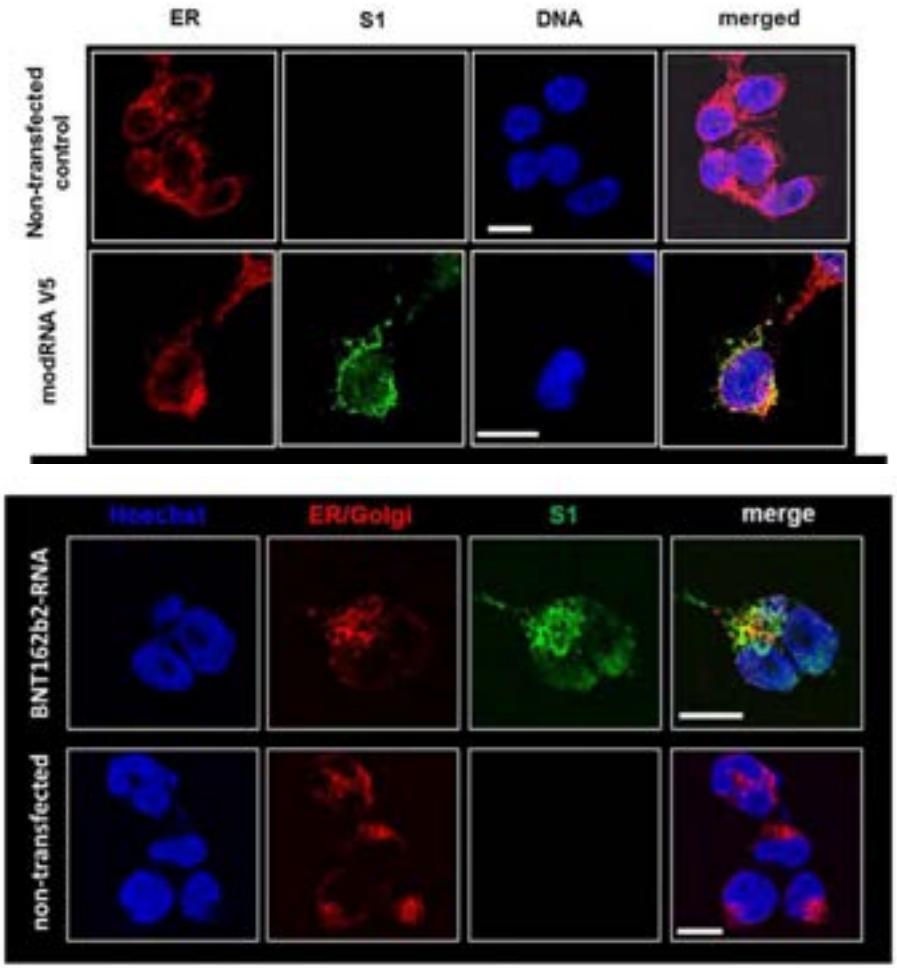

Figure 2-19. Immunofluorescence staining of transfected cells

https://www.tga.gov.au/sites/default/files/foi-2389-03-1.pdf

https://www.tga.gov.au/sites/default/files/foi-2389-06.pdf

1.2	**Material:** 1x Heparin- oder Citratblut (8ml) oder Serum (mind. 4ml)	**Quantitative Bestimmung des SARS-CoV-2 Spikeproteins in Exosomen**	☐	**110,75**

(https://www.mmd-labor.de/.cm4all/uproc.php/0/Auftrgasformulare/Auftragsformular%20X%20Post%20Covid%20Post%20Vac_1.pdf?cdp=a&_=18cb53d2708)

Volume 207, Issue 10
15 November 2021

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Article Contents

RESEARCH ARTICLE | NOVEMBER 15 2021

Cutting Edge: Circulating Exosomes with COVID Spike Protein Are Induced by BNT162b2 (Pfizer–BioNTech) Vaccination prior to Development of Antibodies: A Novel Mechanism for Immune Activation by mRNA Vaccines FREE

Sandhya Bansal; Sudhir Perincheri; Timothy Fleming; Christin Poulson; Brian Tiffany; Ross M. Bremner; Thalachallour Mohanakumar

+ Author & Article Information

J Immunol (2021) 207 (10): 2405–2410.

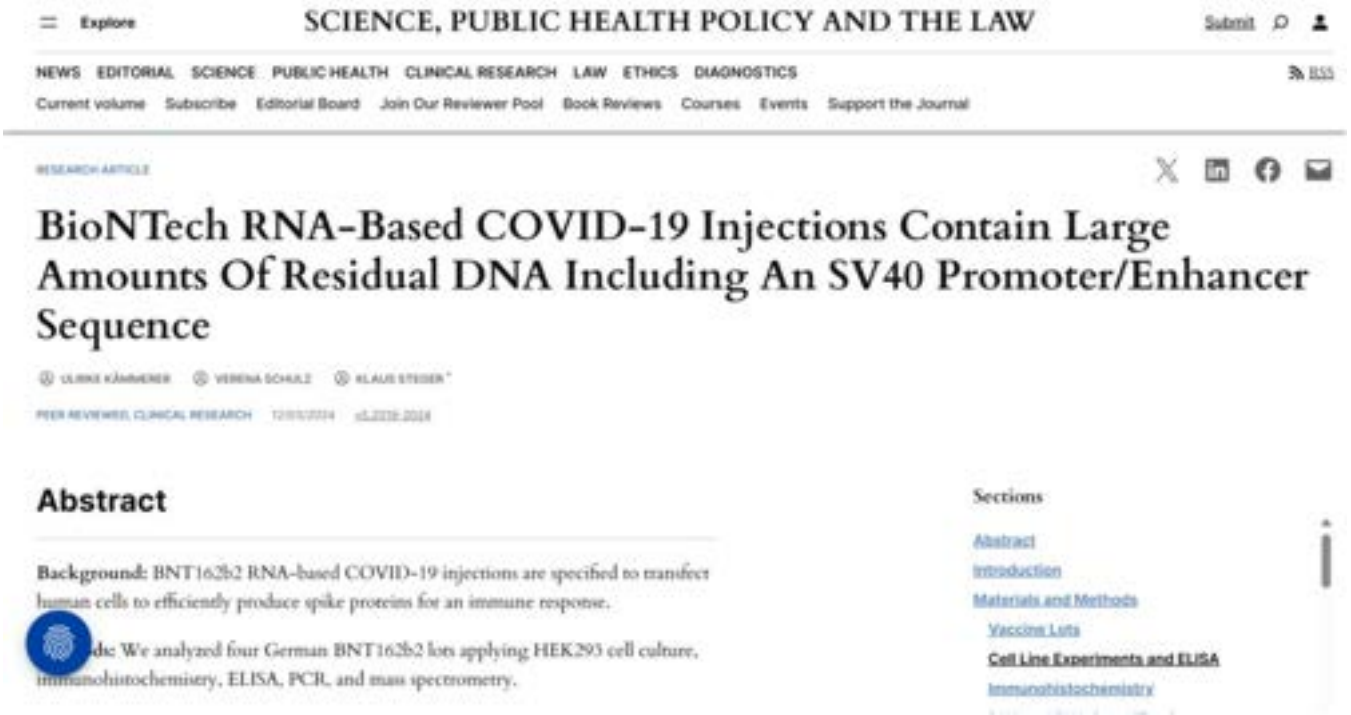
https://doi.org/10.4049/jimmunol.2100637 **Article history**

Connected Content

A reference has been published: Comment on "Cutting Edge: Circulating Exosomes with COVID Spike Protein Are Induced by BNT162b2 (Pfizer-BioNTech) Vaccination prior to Development of Antibodies: A Novel Mechanism for Immune Activation by mRNA Vaccines"

A reference has been published: Response to Comment on "Cutting Edge: Circulating Exosomes with COVID Spike Protein Are Induced by BNT162b2 (Pfizer-BioNTech) Vaccination prior to Development of Antibodies: A Novel Mechanism for Immune Activation by mRNA Vaccines"

https://journals.aai.org/jimmunol/article/207/10/2405/234284/Cutting-Edge-Circulating-Exosomes-with-COVID-Spike



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RESEARCH ARTICLE

BioNTech RNA-Based COVID-19 Injections Contain Large Amounts Of Residual DNA Including An SV40 Promoter/Enhancer Sequence

ULRIKE KÄMMERER VERENA SCHULZ KLAUS STEGER*

PEER REVIEWED, CLINICAL RESEARCH

Abstract

Background: BNT162b2 RNA-based COVID-19 injections are specified to transfect human cells to efficiently produce spike proteins for an immune response.

Methods: We analyzed four German BNT162b2 lots applying HEK293 cell culture, immunohistochemistry, ELISA, PCR, and mass spectrometry.

Sections

Abstract
Introduction
Materials and Methods
Vaccine Lots
Cell Line Experiments and ELISA
Immunohistochemistry

Conclusion

We demonstrated that transfection of the human cell line HEK293 with four different BNT162b2 lots results in the production of spike proteins over several days, which are released into the cell supernatant via exosomes. We detected residual plasmid-DNA in all vials at concentrations far exceeding the allowed EMA limit of 0.33 ng dsDNA per 1 mg RNA. We identified all plasmid genes as well as the two copies of the SV40 promoter/enhancer element. The DNA was shown to enter and persist in the cells.

https://publichealthpolicyjournal.com/biontech-rna-based-covid-19-injections-contain-large-amounts-of-residual-dna-including-an-sv40-promoter-enhancer-sequence/

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Article | Open access | Published: 15 October 2020

Isolation, characterisation and detection of breath-derived extracellular vesicles

Garima Dobhal, Amrita Datta, Deanna Ayupova, Paul Teesdale-Spittle & Renee V. Goreham ✉

Scientific Reports 10, Article number: 17381 (2020) | Cite this article

7992 Accesses | 13 Citations | 307 Altmetric | Metrics

JACI The Journal of Allergy and Clinical Immunology

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LETTER TO THE EDITOR · Volume 132, Issue 1, P219-222.E3, July 2013

Exosome-enclosed microRNAs in exhaled breath hold potential for biomarker discovery in patients with pulmonary diseases

Anirban Sinha, MSc [a] · Amit Kumar Yadav, MSc [a] · Samarpana Chakraborty, MSc [a, ...] · Debasis Dash, PhD [a] · Balaram Ghosh, PhD [a] · Anurag Agrawal, MD, PhD [a] ✉ ... Show more

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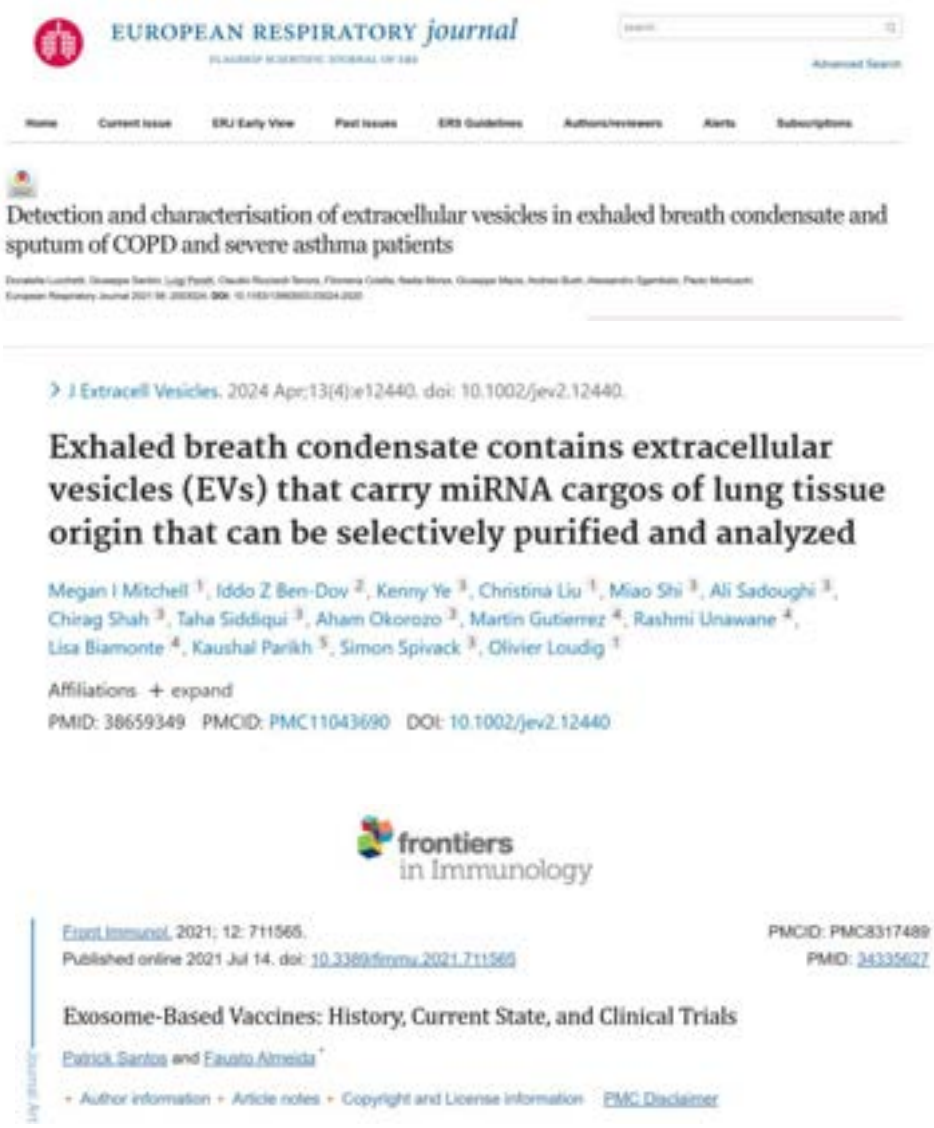

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Detection and characterisation of extracellular vesicles in exhaled breath condensate and sputum of COPD and severe asthma patients

European Respiratory Journal 2021; 58: 2003024; DOI: 10.1183/13993003.03024-2020

› J Extracell Vesicles. 2024 Apr;13(4):e12440. doi: 10.1002/jev2.12440.

Exhaled breath condensate contains extracellular vesicles (EVs) that carry miRNA cargos of lung tissue origin that can be selectively purified and analyzed

Megan I Mitchell [1], Iddo Z Ben-Dov [2], Kenny Ye [3], Christina Liu [1], Miao Shi [3], Ali Sadoughi [3], Chirag Shah [3], Taha Siddiqui [3], Aham Okorozo [3], Martin Gutierrez [4], Rashmi Unawane [4], Lisa Biamonte [4], Kaushal Parikh [5], Simon Spivack [3], Olivier Loudig [1]

Affiliations + expand

PMID: 38659349 PMCID: PMC11043690 DOI: 10.1002/jev2.12440

frontiers in Immunology

Front Immunol. 2021; 12: 711565. PMCID: PMC8317489
Published online 2021 Jul 14. doi: 10.3389/fimmu.2021.711565 PMID: 34335627

Exosome-Based Vaccines: History, Current State, and Clinical Trials

Patrick Santos and Fausto Almeida*

Author information · Article notes · Copyright and License information PMC Disclaimer

Review > Int J Mol Sci. 2022 Sep 24;23(19):11247. doi: 10.3390/ijms231911247.

Update on Extracellular Vesicle-Based Vaccines and Therapeutics to Combat COVID-19

Tamanna Mustajab [1 2], Moriasi Sheba Kwamboka [1 2], Da Ae Choi [1 2], Dae Wook Kang [1 2], Junho Kim [1 2], Kyu Ri Han [1 2], Yujin Han [1 2], Sorim Lee [1 2], Dajung Song [1 2], Yong-Joon Chwae [1 2]

Affiliations + expand

PMID: 36232549 PMCID: PMC9569487 DOI: 10.3390/ijms231911247

Vaccine candidate						
	Exosomes purified from lung spheroid cells (Lung-Exo) and loaded with spike protein mRNA	Ultrafiltration	Adaptive immunity	In vitro/ In vivo	Inhalable	[29]
	Exosomes purified from lung spheroid cells (Lung-Exo) and conjugated with the RBD of spike protein	Ultrafiltration	Adaptive immunity	In vitro/ In vivo	Inhalable	[30]
	Bacterial OMV conjugated with RBD of spike protein	Ultracentrifugation	Adaptive immunity	In vitro/ In vivo	Inhalable	[31]

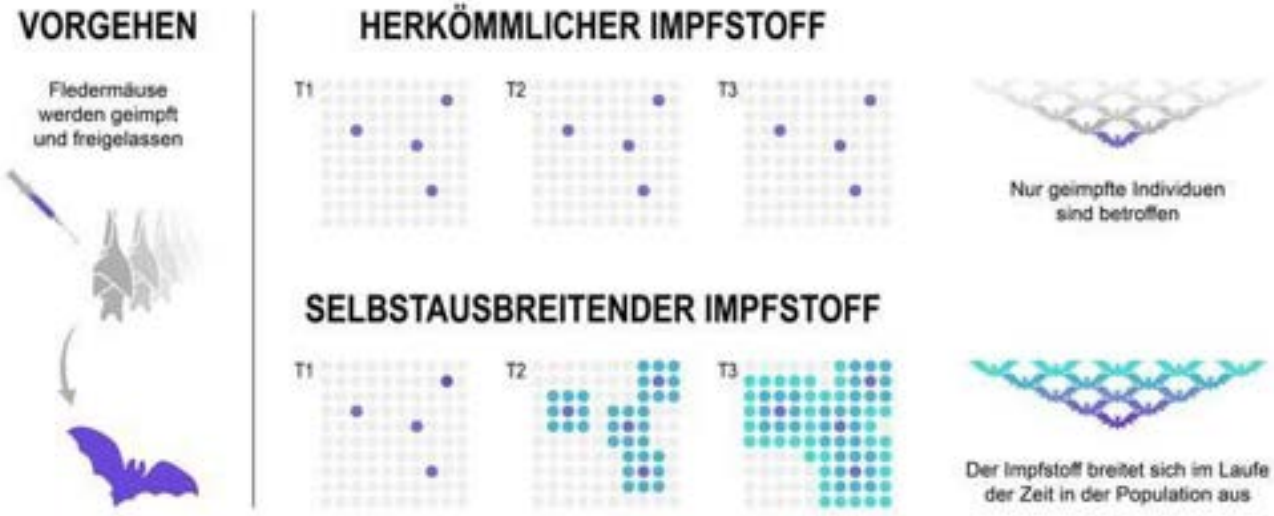
https://pubmed.ncbi.nlm.nih.gov/36232549/

https://www.nationalgeographic.de/wissenschaft/2022/01/impfungen-die-sich-wie-ein-virus-uebertragen-gefaehrlich-oder-die-zukunft

Selbstausbreitende Impfstoffe: das Regelwerk fehlt

Reeves betont, dass es bislang schwierig einzuschätzen sei, wie sich solche Impfstoffe in freier Wildbahn verhalten. „Es bedarf mehr Planung", sagt er. „Diese Arten von Impfstoffen sind dafür gemacht, sich zu verteilen – sie erkennen keine Landesgrenzen an." Außerdem könne man nicht einschätzen, wie sich der Impfstoff über eine längere Zeit innerhalb einer Population entwickeln würde. Hier sei es wichtig, internationale Gespräche über Gesetze und Regeln zu führen, bevor ein selbstausbreitender Impfstoff genutzt würde.

„Insgesamt würden wir uns wünschen, dass die Forschenden genauer erklären, wie genau die Impfstoffe ihren vollen Nutzen entfalten können. Wie genau können wir diese Impfstoffe berechenbar machen?", sagt Reeves.



ModRNA kann
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b) Exosomen mit Spike aus dem Golgi-Apparat shedden

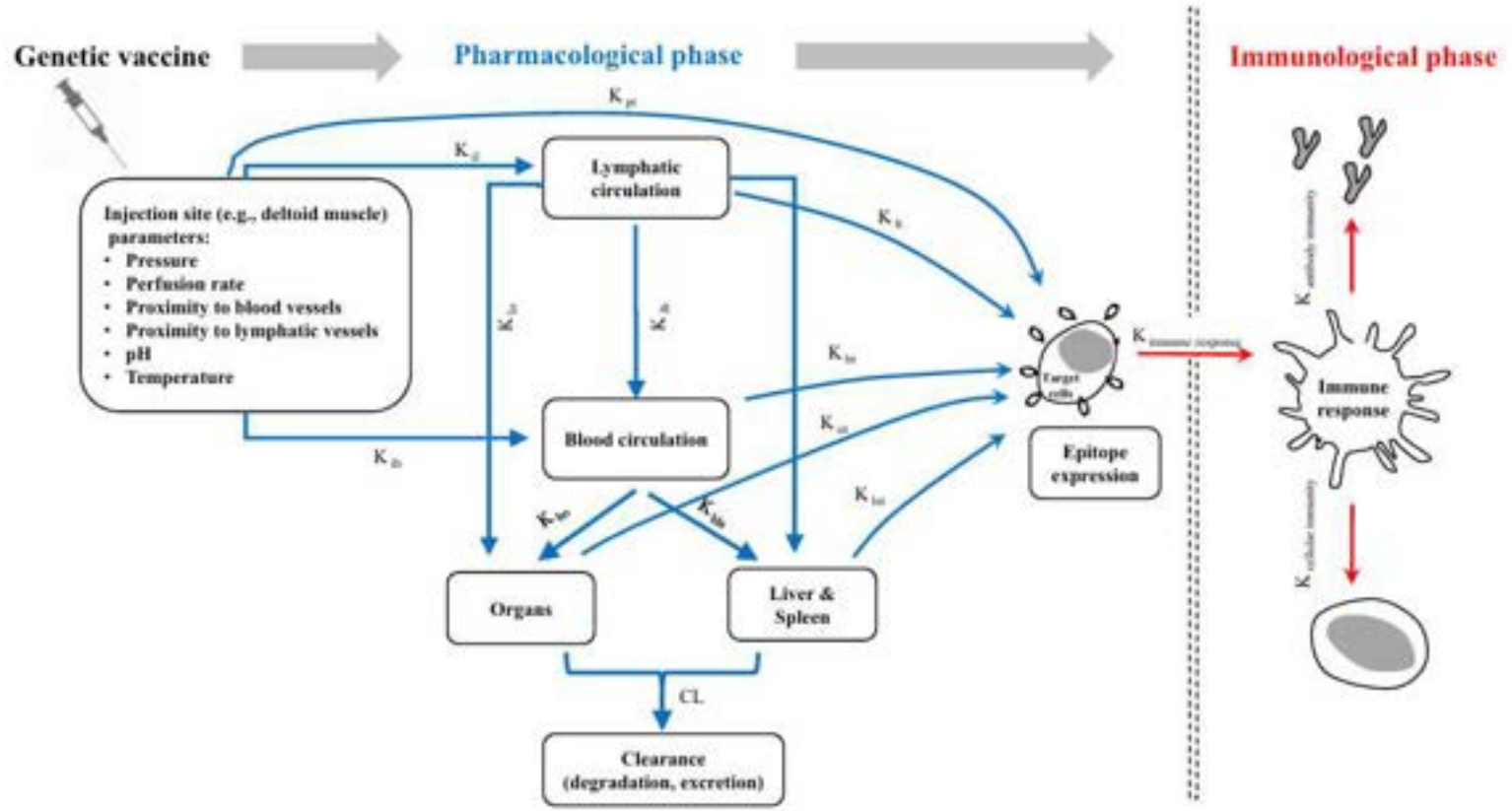

Fig. 1 A generic PBPK model describing the two major response phases, their components, and pertinent kinetic coefficients

https://link.springer.com/article/10.1007/s40262-022-01149-8

Review > Nat Rev Drug Discov. 2024 Apr;23(4):281-300. doi: 10.1038/s41573-023-00859-3.
Epub 2024 Jan 23.

Strategies to reduce the risks of mRNA drug and vaccine toxicity

Dimitrios Bitounis [1 2], Eric Jacquinet [2], Maximillian A Rogers [2 3], Mansoor M Amiji [4]

Affiliations – collapse

Affiliations

1 Department of Pharmaceutical Sciences, Northeastern University, Boston, MA, USA.
2 Moderna, Inc., Cambridge, MA, USA.
3 Intellia Therapeutics, Cambridge, MA, USA.
4 Departments of Pharmaceutical Sciences and Chemical Engineering, Northeastern University, Boston, MA, USA. m.amiji@northeastern.edu.

PMID: 38263456 DOI: 10.1038/s41573-023-00859-3

Toxicodynamics of extracellular LNP–mRNA

In vitro, only 1–2% of lipid nanoparticle (LNP)-mediated nucleic acid delivery leads to successful cell transfection[2,9]. However, the pathogenic potential of the remaining 98% is understudied. On

„In vitro führen nur 1-2 % der durch Lipidnanopartikel (LNP) vermittelten Nukleinsäureübertragung zu einer erfolgreichen Zelltransfektion. Das pathogene Potenzial der restlichen 98 % ist jedoch noch nicht ausreichend erforscht.“ (https://pubmed.ncbi.nlm.nih.gov/38263456/).

LNPs können
CARPA Reaktionen auslösen

CARPA Reaktionen

Table 4
Features of C activation by liposomes and factors that influence it.

All types of liposomes can activate C in human serum or plasma
Sensitivity for C activation by different liposomes shows substantial individual variation
Individual sensitivity for C activation is liposome specific
Activation may proceed via both the CP and AP
Activation can be triggered by the binding of: IgG, IgM, C3, CRP and C1q
C activation by liposomes is enhanced by:
• Positive or negative surface charge
• Increasing the size of liposomes
• Inhomogeneity
• Endotoxin contamination
• Presence of aggregates
• Presence of doxorubicin or similar drugs in the extraliposome medium
• High percentage (>50%) of cholesterol in the membrane
• PEGylation of liposomes via negatively charged phospholipid anchors (e.g., DSPE)
• Polyamino-coating

Findings and conclusion based on previous studies and several reviews of the literature (Szebeni, 1998; Szebeni et al., 2003, 2006, 2007a, 2011; Szebeni and Barenholz, 2012).

CARPA Reaktionen sind Komplement aktivierte Pseudoallergien, die nicht vorhersagbar, nicht testbar, schnell oder langsam eintreten können und mitunter tödlich enden. 5% bis 45% der Menschen reagieren mit einer CARPA Reaktion auf Nanolipide im Gegensatz zu weniger als 2% auf Penicillin.

https://linkinghub.elsevier.com/retrieve/pii/S0161589014001692

CARPA Reaktionen

https://linkinghub.elsevier.com/retrieve/pii/S0161589014001692

Table 1
Drugs causing pseudoallergy.

Liposomal drugs	Micelle-solubilized drugs	Antibodies	PEGylated proteins	Contrast media	Enzymes/proteins/peptides	Miscellaneous
Abelcet	**Cyclosporine**	Avastin	Adagen	Diatrizoate	Abbokinase	ACE inhibitors
AmBisome	Elitec	Campath	Neulasta	Iodipamide	ACH	AR blockers
Amphotec/Amphocyl	Etoposide	Erbitux	Oncaspar, Pegaspargas	Iodixanol	Actimmune	Aspirin
DaunoXome	Fasturec	Herceptin		Iohexol	Activase	Cancidas
Doxil, Caelyx	**Taxol**	**Infliximab**		Iopamidol	Aldurazyme	Copaxone
Myocet	**Taxotere**	Muronomab		Iopromide	Avonex	Corticosteroids
Visudyne	Vumon	Mylotarg		Iothalamate	Fasturtec	Cyclofloxacin
		Remicade		Ioversol	Neulasta	Eloxatin
		Rituxan		Ioxaglate	Neupogen	Intralipid
		Vectibix		Ioxilan	Plenaxis	Opiates
		Xolair		Magnevist	protamine	Orencia
				Metrizamide	Urokinase	Salicilates
				SonoVue	Zevalin	Vancomycin

The manufacturers, exact composition, indication areas, incidence of HSRs and reported symptoms of HSRs of the drugs in columns 1–4 were specified in a previous review (Szebeni, 2012).

Table 2
Symptoms of pseudoallergy.

Cardiovascular	Broncho-pulmonary	Hematological	Mucocutaneous	Gastro-intestinal	Neuro-psycho-somatic	Systemic
Angioedema	Apnea	Granulopenia	Cyanosis	Bloating	Back pain	Chills
Arrhythmia	Bronchospasm	Leukopenia	Erythema	Cramping	Chest pain	Diaphoresis
Cardiogenic shock	Coughing	Lymphopenia	Flushing	Diarrhea	Chest tightness	Feeling of warmth
Edema	Dyspnea	Rebound leukocytosis	Nasal congestion	Metallic taste	Confusion	Fever
Hypertension	Hoarseness	Rebound granulocytosis	Rash	Nausea	Dizziness	Loss of consciousness
Hypotension	Hyperventilation	Thrombocytopenia	Rhinitis	Vomiting	Feeling of imminent death	Rigors
Hypoxia	Laryngospasm		Swelling		Fright	Sweating
Myocardial infarction	Respiratory distress		Tearing		Headache	Wheezing
Tachycardia	Shortness of breath		Urticaria		Panic	
Ventricular fibrillation	Sneezing					
Syncope	Stridor					

The most frequent symptoms are shaded with gray, and those that are the most dangerous on life, are bolded.

https://dam.biontech.de/assets/OgwPLzvEr44WWr0ffNXefA/PMI44ltsU54Hp3VWP5DBoA/Original%20file/BNT_COM_GI_COMIRNATY_30%C2%B5g_12Jahre_Fertigl%C3%B6sung_230831.pdf

- Schlaflosigkeit
- Jucken an der Injektionsstelle
- allergische Reaktionen wie Ausschlag oder Juckreiz
- Schwächegefühl oder Energiemangel/Schläfrigkeit
- verminderter Appetit
- Schwindelgefühl
- starkes Schwitzen
- nächtliche Schweißausbrüche

Seltene Nebenwirkungen: kann bis zu 1 von 1 000 Behandelten betreffen
- vorübergehendes, einseitiges Herabhängen des Gesichtes
- allergische Reaktionen wie Nesselsucht oder Schwellung des Gesichts

Sehr seltene Nebenwirkungen: kann bis zu 1 von 10 000 Behandelten betreffen
- Entzündung des Herzmuskels (Myokarditis) oder Entzündung des Herzbeutels (Perikarditis), die zu Atemnot, Herzklopfen oder Thoraxschmerzen führen können

Nicht bekannt (Häufigkeit auf Grundlage der verfügbaren Daten nicht abschätzbar)
- schwere allergische Reaktionen
- ausgedehnte Schwellung der geimpften Gliedmaße
- Anschwellen des Gesichts (ein geschwollenes Gesicht kann bei Patienten auftreten, denen in der Vergangenheit dermatologische Filler im Gesichtsbereich injiziert wurden)
- eine Hautreaktion, die rote Flecken oder Stellen auf der Haut verursacht, die wie ein Ziel oder eine Zielscheibenmitte mit einer dunkelroten Mitte aussehen können, das von hellroten Ringen umgeben ist (Erythema multiforme)
- ungewöhnliches Gefühl in der Haut, wie Prickeln oder Kribbeln (Parästhesie)
- vermindertes Gefühl oder verminderte Empfindlichkeit, insbesondere der Haut (Hypoästhesie)
- starke Menstruationsblutungen (die meisten Fälle schienen nicht schwerwiegend und vorübergehend zu sein)

4. Welche Nebenwirkungen sind möglich?

Wie alle Impfstoffe kann auch Comirnaty Nebenwirkungen haben, die aber nicht bei jedem auftreten müssen.

Sehr häufige Nebenwirkungen: kann mehr als 1 von 10 Behandelten betreffen
- an der Injektionsstelle: Schmerzen, Schwellung
- Ermüdung
- Kopfschmerzen
- Muskelschmerzen
- Schüttelfrost
- Gelenkschmerzen
- Durchfall
- Fieber

Einige dieser Nebenwirkungen traten bei Jugendlichen zwischen 12 und 15 Jahren etwas häufiger auf als bei Erwachsenen.

Häufige Nebenwirkungen: kann bis zu 1 von 10 Behandelten betreffen
- Rötung an der Injektionsstelle
- Übelkeit
- Erbrechen
- vergrößerte Lymphknoten (häufiger beobachtet nach einer Auffrischungsdosis)

Gelegentliche Nebenwirkungen: kann bis zu 1 von 100 Behandelten betreffen
- Unwohlsein
- Armschmerzen

Table 2
Symptoms of pseudoallergy. (https://doi.org/10.1016/j.molimm.2014.06.038)

Cardiovascular	Broncho-pulmonary	Hematological	Mucocutaneous	Gastro-intestinal	Neuro-psycho-somatic	Systemic
Angioedema	Apnea	Granulopenia	Cyanosis	Bloating	Back pain	Chills
Arrhythmia	Bronchospasm	Leukopenia	Erythema	Cramping	Chest pain	Diaphoresis
Cardiogenic shock	Coughing	Lymphopenia	Flushing	Diarrhea	Chest tightness	Feeling of warmth
Edema	Dyspnea	Rebound leukocytosis	Nasal congestion	Metallic taste	Confusion	Fever
Hypertension	Hoarseness	Rebound granulocytosis	Rash	Nausea	Dizziness	Loss of consciousness
Hypotension	Hyperventilation	Thrombocytopenia	Rhinitis	Vomiting	Feeling of imminent death	Rigors
Hypoxia	Laryngospasm		Swelling		Fright	Sweating
Myocardial infarction	Respiratory distress		Tearing		Headache	Wheezing
Tachycardia	Shortness of breath		Urticaria		Panic	
Ventricular fibrillation	Sneezing					
Syncope	Stridor					

The most frequent symptoms are shaded with gray, and those that are the most dangerous on life, are bolded.

LNPs Technologie und Schwangerschaftsrisiken

REVIEW ARTICLE

Lipid Nanoparticles: A Novel Approach for Brain Targeting

Ravi Shankar[1], Monika Joshi[2] and Kamla Pathak[3,*]

[1]*Department of Pharmaceutics, Kashi Institute of Pharmacy, Varanasi, UP, India;* [2]*Department of Pharmaceutics, Ashoka institute of Tech & Management, Varanasi, UP, India;* [3]*Department of Pharmaceutics, Pharmacy College Saifai, Uttar Pradesh University of Medical Sciences, Saifai, Etawah, Uttar Pradesh 206130, India*

ARTICLE HISTORY

Received: November 07, 2017
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DOI:
10.2174/2211738506666180611100416

Abstract: ***Background***: Brain is a delicate organ, separated from general circulation and is characterized by the presence of relatively impermeable Blood Brain Barrier (BBB). The BBB maintains homeostasis in the brain thus restricting the entrance of foreign bodies and several molecules from reaching the brain. As a result several promising molecules do not reach the target site and fail to produce *in vivo* response. Nevertheless, lipid nanoparticles are taken up readily by the brain because of their lipophilic nature. The bioacceptable and biodegradable nature of lipid nanoparticles makes them less toxic and suited for brain targeting.

Objective: In the present review the BBB, mechanism of transport across the BBB, strategies to bypass the blood-brain barrier have been presented. The aptness of lipid nanoparticles for brain targeting has been highlighted. The proposed mechanism of uptake of the lipid nanoparticles, methods of prolonging the plasma retention and various methods of preparation for formulation of effective delivery systems for brain targeting have been included and dealt in this review. **Conclusion:** Lipid based formulations can be designated as the current and future generation of drug delivery systems as these possess tremendous potential to bypass BBB and reach the target site due to their small size and ability to dodge the reticular endothelial system. However, these nanostructures need to be investigated intensively to successfully reach the clinical trials stage.

Keywords: Blood brain barrier, CNS delivery, NLCs, PLNs, solid lipid nanoparticles.

Shankar R, Joshi M, Pathak K. Lipid Nanoparticles: A Novel Approach for Brain Targeting. Pharm Nanotechnol. 2018;6(2):81-93. doi: 10.2174/2211738506666180611100416. PMID: 29886842. https://pubmed.ncbi.nlm.nih.gov/29886842/

THE NOBEL PRIZE

Nobel Prizes & laureates About Stories Educational Events & museums

Drew Weissman
Facts

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Photo: Clément Morin

Drew Weissman
The Nobel Prize in Physiology or Medicine 2023

Born: 7 September 1959, Lexington, MA, USA

Affiliation at the time of the award: Penn Institute for RNA Innovations, University of Pennsylvania, Philadelphia, PA, USA

Prize motivation: "for their discoveries concerning nucleoside base modifications that enabled the development of effective mRNA vaccines against COVID-19"

Prize share: 1/2

Work

A vaccine prevents diseases by stimulating the body's immune system to develop a defense against the infectious agent. One type of vaccine uses mRNA, which transfers genetic information from DNA to stimulate protein production. In 2005, Drew Weissman and Katalin Karikó discovered that certain modifications of the building blocks of RNA prevented unwanted inflammatory reactions and increased the production of desired proteins. The discovery laid the foundation for effective mRNA vaccines against COVID-19 during the pandemic that began in early 2020.

https://www.nobelprize.org/prizes/medicine/2023/weissman/facts/

SCIENCE ADVANCES | RESEARCH ARTICLE

HEALTH AND MEDICINE

Ionizable lipid nanoparticles for in utero mRNA delivery

Rachel S. Riley[1]*, Meghana V. Kashyap[2]*, Margaret M. Billingsley[1]*, Brandon White[2], Mohamad-Gabriel Alameh[3], Sourav K. Bose[2], Philip W. Zoltick[2], Hiaying Li[2], Rui Zhang[1], Andrew Y. Cheng[2], Drew Weissman[3], William H. Peranteau[2†], Michael J. Mitchell[1,4,5,6,7†]

Clinical advances enable the prenatal diagnosis of genetic diseases that are candidates for gene and enzyme therapies such as messenger RNA (mRNA)–mediated protein replacement. Prenatal mRNA therapies can treat disease before the onset of irreversible pathology with high therapeutic efficacy and safety due to the small fetal size, immature immune system, and abundance of progenitor cells. However, the development of nonviral platforms for prenatal delivery is nascent. We developed a library of ionizable lipid nanoparticles (LNPs) for in utero mRNA delivery to mouse fetuses. We screened LNPs for luciferase mRNA delivery and identified formulations that accumulate within fetal livers, lungs, and intestines with higher efficiency and safety compared to benchmark delivery systems, DLin-MC3-DMA and jetPEI. We demonstrate that LNPs can deliver mRNAs to induce hepatic production of therapeutic secreted proteins. These LNPs may provide a platform for in utero mRNA delivery for protein replacement and gene editing.

Riley RS, Kashyap MV, Billingsley MM, White B, Alameh MG, Bose SK, Zoltick PW, Li H, Zhang R, Cheng AY, Weissman D, Peranteau WH, Mitchell MJ. Ionizable lipid nanoparticles for in utero mRNA delivery. Sci Adv. 2021 Jan 13;7(3):eaba1028. doi: 10.1126/sciadv.aba1028. PMID: 33523869; PMCID: PMC7806221. https://pubmed.ncbi.nlm.nih.gov/33523869/

J Am Chem Soc. 2023 Mar 1;145(8):4691-4706. doi: 10.1021/jacs.2c12893. Epub 2023 Feb 15.

Ionizable Lipid Nanoparticles for *In Vivo* mRNA Delivery to the Placenta during Pregnancy

Kelsey L Swingle [1], Hannah C Safford [1], Hannah C Geisler [1], Alex G Hamilton [1], Ajay S Thatte [1], Margaret M Billingsley [1], Ryann A Joseph [1], Kaitlin Mrksich [1], Marshall S Padilla [1], Aditi A Ghalsasi [1], Mohamad-Gabriel Alameh [2 3], Drew Weissman [2 3], Michael J Mitchell [1 4 5 6 7 3]

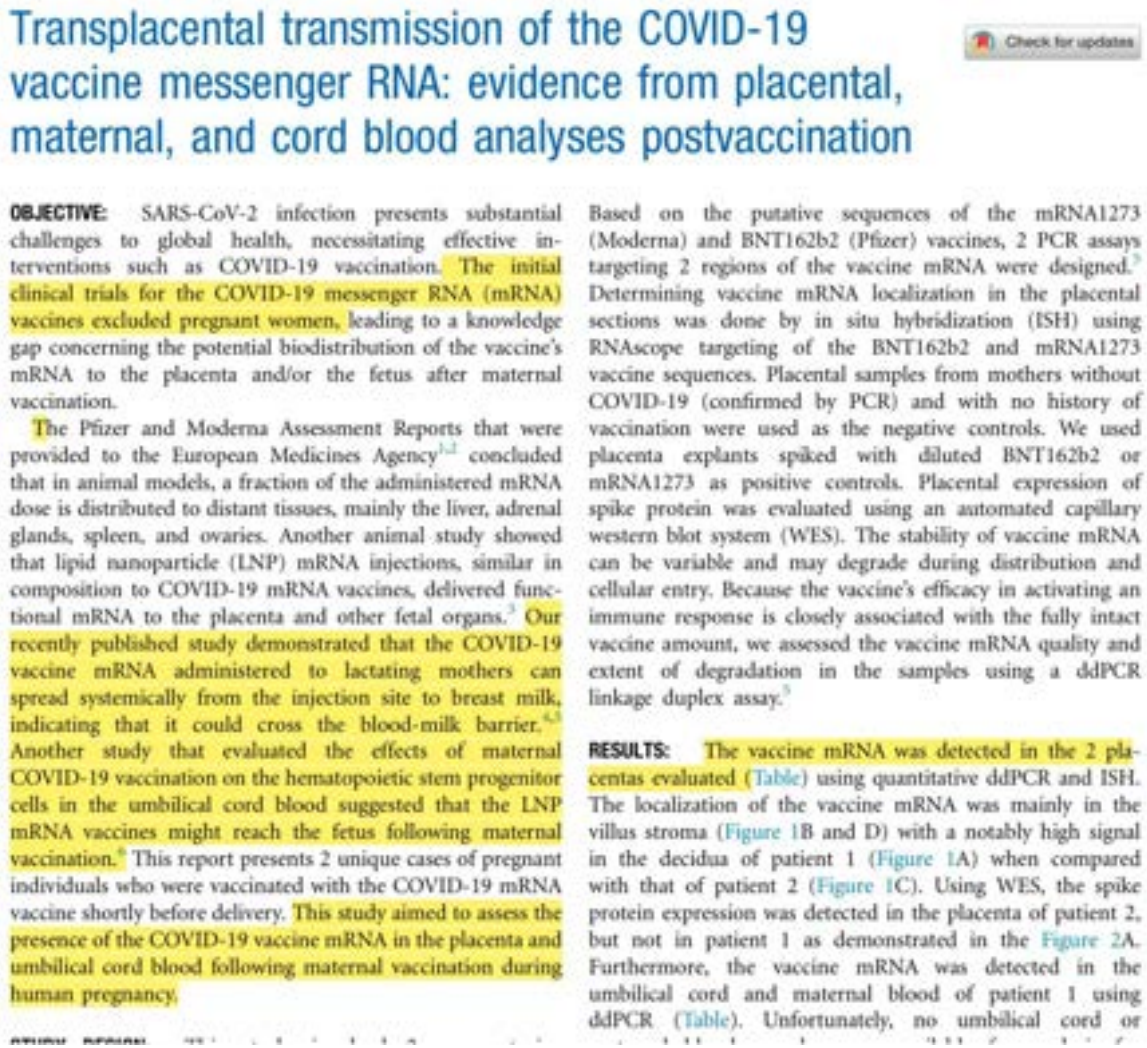
Affiliations

PMID: 36789893 PMCID: PMC9992266 DOI: 10.1021/jacs.2c12893

Abstract

Ionizable lipid nanoparticles (LNPs) are the most clinically advanced nonviral platform for mRNA delivery. While they have been explored for applications including vaccines and gene editing, LNPs have not been investigated for placental insufficiency during pregnancy. Placental insufficiency is caused by inadequate blood flow in the placenta, which results in increased maternal blood pressure and restricted fetal growth. Therefore, improving vasodilation in the placenta can benefit both maternal and fetal health. Here, we engineered ionizable LNPs for mRNA delivery to the placenta with applications in mediating placental vasodilation. We designed a library of ionizable lipids to formulate LNPs for mRNA delivery to placental cells and identified a lead LNP that enables *in vivo* mRNA delivery to trophoblasts, endothelial cells, and immune cells in the placenta. Delivery of this top LNP formulation encapsulated with VEGF-A mRNA engendered placental vasodilation, demonstrating the potential of mRNA LNPs for protein replacement therapy during pregnancy to treat placental disorders.

Swingle KL, Safford HC, Geisler HC, Hamilton AG, Thatte AS, Billingsley MM, Joseph RA, Mrksich K, Padilla MS, Ghalsasi AA, Alameh MG, Weissman D, Mitchell MJ. Ionizable Lipid Nanoparticles for *In Vivo* mRNA Delivery to the Placenta during Pregnancy. J Am Chem Soc. 2023 Mar 1;145(8):4691-4706. doi: 10.1021/jacs.2c12893. Epub 2023 Feb 15. PMID: 36789893; PMCID: PMC9992266.
https://pubmed.ncbi.nlm.nih.gov/36789893/



Transplacental transmission of the COVID-19 vaccine messenger RNA: evidence from placental, maternal, and cord blood analyses postvaccination

Check for updates

OBJECTIVE: SARS-CoV-2 infection presents substantial challenges to global health, necessitating effective interventions such as COVID-19 vaccination. The initial clinical trials for the COVID-19 messenger RNA (mRNA) vaccines excluded pregnant women, leading to a knowledge gap concerning the potential biodistribution of the vaccine's mRNA to the placenta and/or the fetus after maternal vaccination.

The Pfizer and Moderna Assessment Reports that were provided to the European Medicines Agency[1,2] concluded that in animal models, a fraction of the administered mRNA dose is distributed to distant tissues, mainly the liver, adrenal glands, spleen, and ovaries. Another animal study showed that lipid nanoparticle (LNP) mRNA injections, similar in composition to COVID-19 mRNA vaccines, delivered functional mRNA to the placenta and other fetal organs.[3] Our recently published study demonstrated that the COVID-19 vaccine mRNA administered to lactating mothers can spread systemically from the injection site to breast milk, indicating that it could cross the blood-milk barrier.[4,5] Another study that evaluated the effects of maternal COVID-19 vaccination on the hematopoietic stem progenitor cells in the umbilical cord blood suggested that the LNP mRNA vaccines might reach the fetus following maternal vaccination.[6] This report presents 2 unique cases of pregnant individuals who were vaccinated with the COVID-19 mRNA vaccine shortly before delivery. This study aimed to assess the presence of the COVID-19 vaccine mRNA in the placenta and umbilical cord blood following maternal vaccination during human pregnancy.

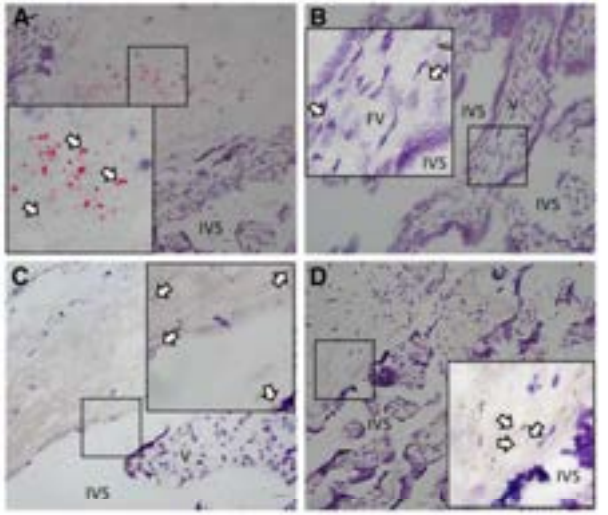
Based on the putative sequences of the mRNA1273 (Moderna) and BNT162b2 (Pfizer) vaccines, 2 PCR assays targeting 2 regions of the vaccine mRNA were designed.[7] Determining vaccine mRNA localization in the placental sections was done by in situ hybridization (ISH) using RNAscope targeting of the BNT162b2 and mRNA1273 vaccine sequences. Placental samples from mothers without COVID-19 (confirmed by PCR) and with no history of vaccination were used as the negative controls. We used placenta explants spiked with diluted BNT162b2 or mRNA1273 as positive controls. Placental expression of spike protein was evaluated using an automated capillary western blot system (WES). The stability of vaccine mRNA can be variable and may degrade during distribution and cellular entry. Because the vaccine's efficacy in activating an immune response is closely associated with the fully intact vaccine amount, we assessed the vaccine mRNA quality and extent of degradation in the samples using a ddPCR linkage duplex assay.[5]

RESULTS: The vaccine mRNA was detected in the 2 placentas evaluated (Table) using quantitative ddPCR and ISH. The localization of the vaccine mRNA was mainly in the villus stroma (Figure 1B and D) with a notably high signal in the decidua of patient 1 (Figure 1A) when compared with that of patient 2 (Figure 1C). Using WES, the spike protein expression was detected in the placenta of patient 2, but not in patient 1 as demonstrated in the Figure 2A. Furthermore, the vaccine mRNA was detected in the umbilical cord and maternal blood of patient 1 using ddPCR (Table). Unfortunately, no umbilical cord or

Lin X, Botros B, Hanna M, Gurzenda E, De Mejia CM, Chavez M, Hanna N. Transplacental transmission of the COVID-19 vaccine messenger RNA: evidence from placental, maternal, and cord blood analyses postvaccination. Am J Obstet Gynecol. 2024 Jun;230(6):e113-e116. doi: 10.1016/j.ajog.2024.01.022. Epub 2024 Feb 1. PMID: 38307473.
https://pubmed.ncbi.nlm.nih.gov/38307473/

FIGURE 1

COVID-19 vaccine mRNA detection in the placenta by in-situ hybridization



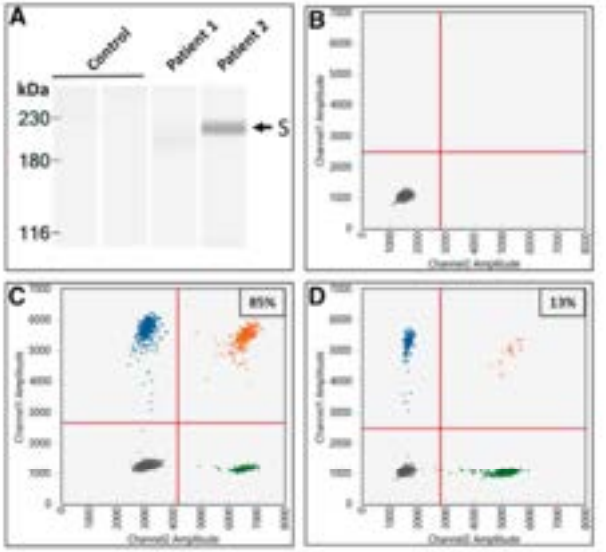
The panel demonstrates COVID-19 vaccine mRNA detected in paraffin embedded placental tissue using in situ hybridization (RNAscope). Panel A and B represent samples from patient 1 and demonstrate positive signals in the decidua (A) and the villi (B) using RNAscope Probe- S-encoding-mRNA-1273-C1. Panel C and D represent samples from patient 2 and demonstrate positive signals in the decidua (C) and the villi (D) using RNAscope Probe- S-encoding-BNT-162b2-C1.

Lin. Transplacental transmission of the COVID-19 vaccine messenger RNA. Am J Obstet Gynecol 2024.

with pregnant rats, LNPs successfully delivered various mRNAs, including one potentially useful for treating fetal anemia.[3] Although introducing mRNA to the fetus may potentially pose plausible risks, it may also have biologically plausible benefits. The potential of mRNA-based interventions to address maternal and fetal health issues is profound. Such insights could substantially advance the crafting of safer and more effective mRNA-based therapies during pregnancy. ■

FIGURE 2

The expression of S protein in the placenta and the integrity of vaccine mRNA in cord and maternal blood



A. Expression of S protein in tissue lysate of placental biopsies from patients 1 and 2, analyzed by automated capillary western blot system (WES). The control was a pre-pandemic placenta sample. C and D. Circulating vaccine mRNA integrity was assayed in a duplex ddPCR assay in samples from patient 1 maternal blood (C, relative linkage 85%) and cord blood (D, relative linkage 13%). B. represents a blood sample of an unvaccinated subject showing no positive signal. Droplets emitting 2-dimensional signals were separated into 4 groups, namely gray indicating double negative for mRNA1273-1 and mRNA1273-2; blue indicating positive for mRNA1273-1 but negative for mRNA1273-2; green indicating positive for mRNA1273-2 and negative for mRNA1273-1; and orange indicating double positive for both mRNA1273-1 and mRNA1273-2. The number of droplets in each single or double positive group was calculated using QX Manager Software, and the percentage linkage of each sample was expressed as a percentage of linked molecules in relation to the total molecules detected and normalized to the original vaccine stock solution.

Lin. Transplacental transmission of the COVID-19 vaccine messenger RNA. Am J Obstet Gynecol 2024.

Article

Skewed fate and hematopoiesis of CD34$^+$ HSPCs in umbilical cord blood amid the COVID-19 pandemic

Benjamin K. Estep,[1] Charles J. Kuhlmann,[1] Satoru Osuka,[4] Gajendra W. Suryavanshi,[5] Yoshiko Nagaoka-Kamata,[2] Ciearria N. Samuel,[1] Madison T. Blucas,[1] Chloe E. Jepson,[1] Paul A. Goepfert,[3] and Masakazu Kamata[1,6,*]

SUMMARY

Umbilical cord blood (UCB) is an irreplaceable source for hematopoietic stem progenitor cells (HSPCs). However, the effects of SARS-CoV-2 infection and COVID-19 vaccination on UCB phenotype, specifically the HSPCs therein, are currently unknown. We thus evaluated any effects of SARS-CoV-2 infection and/or COVID-19 vaccination from the mother on the fate and functionalities of HSPCs in the UCB. The numbers and frequencies of HSPCs in the UCB decreased significantly in donors with previous SARS-CoV-2 infection and more so with COVID-19 vaccination via the induction of apoptosis, likely mediated by IFN-γ-dependent pathways. Two independent hematopoiesis assays, a colony forming unit assay and a mouse humanization assay, revealed skewed hematopoiesis of HSPCs obtained from donors delivered from mothers with SARS-CoV-2 infection history. These results indicate that SARS-CoV-2 infection and COVID-19 vaccination impair the functionalities and survivability of HSPCs in the UCB, which would make unprecedented concerns on the future of HSPC-based therapies.

Estep BK, Kuhlmann CJ, Osuka S, Suryavanshi GW, Nagaoka-Kamata Y, Samuel CN, Blucas MT, Jepson CE, Goepfert PA, Kamata M. Skewed fate and hematopoiesis of CD34$^+$ HSPCs in umbilical cord blood amid the COVID-19 pandemic. iScience. 2022 Dec 22;25(12):105544. doi: 10.1016/j.isci.2022.105544. Epub 2022 Nov 11. PMID: 36406860; PMCID: PMC9650991. https://pubmed.ncbi.nlm.nih.gov/36406860/

PERIODIC SAFETY UPDATE REPORT #3
for
ACTIVE SUBSTANCE: COVID 19 mRNA vaccine (nucleoside modified) (BNT162b2)[1]

ATC CODE: J07BX03[2]

AUTHORISATION PROCEDURE in the EU: Centralised

INTERNATIONAL BIRTH DATE (IBD)[3]: 19 DECEMBER 2020

EUROPEAN UNION REFERENCE DATE (EURD): 19 DECEMBER 2020

INTERVAL COVERED BY THIS REPORT:

19 DECEMBER 2021 through 18 JUNE 2022

DATE OF THIS REPORT: 18 AUGUST 2022

SIGNATURE: [redacted] **Date: 18 August 2022**

- Three hundred twenty-two (322) baby/foetal cases, 283 serious and 39 non-serious. Cases are classified according to pregnancy outcome.
  - Pregnancy outcome: Live birth with congenital anomaly: Thirty-nine (39) of these cases reported 72 congenital anomalies that were coded to the PTs Foetal malformation (4), Atrial septal defect, Congenital anomaly, Ventricular septal defect (3 each), Congenital cystic lung, Congenital hydronephrosis, Congenital skin dimples, Exomphalos, Foetal cardiac disorder, Foetal chromosome abnormality, Foetal growth restriction, Kidney malformation, Pulmonary valve stenosis congenital (2 each), Anal atresia, Ankyloglossia congenital, Arnold-Chiari malformation, Cleft lip, Cleft palate, Cloacal exstrophy, Congenital amputation, Congenital foot malformation, Congenital haematological disorder, Congenital hand malformation, Congenital heart valve disorder, Congenital musculoskeletal disorder, Congenital musculoskeletal disorder of limbs, Congenital musculoskeletal disorder of spine, Congenital oral malformation, Cryptorchism, Double outlet right ventricle, Dysmorphism, Enlarged foetal cisterna magna, Fallot's tetralogy, Foetal arrhythmia, Foetal growth abnormality, Growth retardation, Heart disease congenital, Heart valve incompetence, Hepatic cytolysis,

https://tkp.at/wp-content/uploads/2023/03/3.PSUR-1.pdf S. 336

Study Identification

Unique Protocol ID	C4591015
Brief Title	To Evaluate the Safety, Tolerability, and Immunogenicity of BNT162b2 Against COVID-19 in Healthy Pregnant Women 18 Years of Age and Older
Official Title	A PHASE 2/3, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF A SARS-COV-2 RNA VACCINE CANDIDATE (BNT162b2) AGAINST COVID-19 IN HEALTHY PREGNANT WOMEN 18 YEARS OF AGE AND OLDER
Secondary IDs	2020-005444-35

19. Percentage of Infant Participants Reporting Adverse Event of Special Interest (AESI) From Birth Through 6 Months of Age
Type: Secondary | Time Frame: From birth through 6 months of age

Description	Percentage of infant participants who reported AESI including major congenital anomalies and developmental delay from birth through 6 months of age were reported in this outcome measure. Exact 2-sided 95% CI was based on the Clopper and Pearson method.	
Time Frame	From birth through 6 months of age	
Analysis Population Description	Safety population for infant participants included all infant participants born to maternal participants who received at least 1 dose of the study intervention. Here, "Overall Number of Participants Analyzed" signifies participants evaluable for this outcome measure. HIV positive participants were excluded from analysis as pre-specified in the SAP.	
Arm/Group Title	Infant Participants: BNT162b2 30 mcg	Infant Participants: Placebo
Arm/Group Description	Infant participants who were born to maternal participants vaccinated with BNT162b2 30 mcg during pregnancy were included. Infant participants were followed up to 6 months of age.	Infant participants who were born to maternal participants vaccinated with placebo during pregnancy were included. Infant participants were followed up to 6 months of age.
Overall Number of Participants Analyzed	156	159
Measure Type: Number (95% Confidence Interval) | Unit of Measure: Percentage of participants	5.1 (2.2 to 9.9)	1.3 (0.2 to 4.5)

```
> fisher.test(matrix(c(148,8,157,2),nrow=2))

        Fisher's Exact Test for Count Data

data:  matrix(c(148, 8, 157, 2), nrow = 2)
p-value = 0.0593
alternative hypothesis: true odds ratio is not equal to 1
95 percent confidence interval:
 0.0240889 1.2122944
sample estimates:
odds ratio
 0.2366524
```

```
> fisher.test(matrix(c(147,9,157,2),nrow=2))

        Fisher's Exact Test for Count Data

data:  matrix(c(147, 9, 157, 2), nrow = 2)
p-value = 0.03396
alternative hypothesis: true odds ratio is not equal to 1
95 percent confidence interval:
 0.02162883 1.03320613
sample estimates:
odds ratio
  0.208987
```

*Die Studie wurde genau an dem Punkt abgebrochen, an dem dieses Ergebnis *signifikant* werden sollte (bei p<0,05). Ein weiterer Fall in der geimpften Gruppe hätte ausgereicht, um in die Schlagzeilen zu geraten. Also wurde die Studie abgebrochen.*

https://clinicaltrials.gov/study/NCT04754594?tab=history&a=26

„Die Aufnahme in die Studie wurde mit unvollständigen Zahlen gestoppt, weil die Rekrutierung langsam war und es unvernünftig/unangemessen wurde, schwangere Frauen nach dem Zufallsprinzip auf Placebo zu setzen, angesichts der Menge an Beobachtungsdaten, die belegen, dass der Impfstoff sicher und wirksam ist, und angesichts der zunehmenden Zahl von Fachausschüssen, die die Immunisierung schwangerer Frauen unterstützen“, schrieb Jelena Vojicic, medizinische Leiterin für Impfstoffe bei Pfizer Canada, in der E-Mail von 2022

https://www.theepochtimes.com/health/pfizer-says-it-ended-covid-19-vaccine-pregnancy-trial-early_5088375.html?utm_source=partner&utm_campaign=ZeroHedge&src_src=partner&src_cmp=ZeroHedge

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https://www.arznei-telegramm.de/html/2006_07/0607068_02.html

◁ vorheriger Artikel a-t 2006; 37: 68

Nebenwirkungen

FEHLBILDUNGEN DURCH ACE-HEMMER IM ERSTEN SCHWANGERSCHAFTSDRITTEL?

Dass die Einnahme von ACE-Hemmern wie Enalapril (XANEF u.a.) im 2. und 3. Schwangerschaftsdrittel ein fetales Syndrom mit vermindertem Fruchtwasser, intrauteriner Wachstumsverzögerung, schwerer Hypoplasie des Schädelknochens und Nierenversagen bis hin zum Tod des Neugeborenen hervorrufen kann, ist seit vielen Jahren bekannt (a-t 1992;

3. RESULTS

Of the 673 case reports identified in the search, 458 involved BNT162b2 exposure during pregnancy (mother/fetus) and 215 involved exposure during breast-feeding.

- In 210 out of the 458 cases, maternal exposure (PTs Maternal exposure timing unspecified, Maternal exposure during pregnancy, Maternal exposure before pregnancy,

- There were 53 reports of spontaneous abortion (51)/ abortion (1)/ abortion missed (1) following BNT162b2 vaccination. Of these reports, 4 cases were COVID-19 positive (including suspected), and 13 cases had relevant medical history of endometriosis (1), abortion spontaneous (10), polycystic ovaries (1), menstruation irregular (1). These cases were therefore excluded from the review. One patient had a medical history of COVID-19 (unknown if ongoing) and was excluded from the review. The remaining 39 cases are summarized in Table 1.

Exposure during pregnancy) was reported either with no associated AEs or with AE off-label use/product use issue for either the mother or the baby.

- Among the remaining 248 cases, the most commonly reported AEs were product use issue (83), off-label use (81), pain (including but not limited to vaccination site pain/pain/pain in extremity)(101), headache (57), abortion spontaneous (51), fatigue (43), pyrexia (26), chills (24), myalgia (23), nausea (22), arthralgia (16), dizziness (15), malaise (12), lymphadenopathy (11) and asthenia (11).

- There were 6 cases reporting AE(s) related to premature deliveries.

  - AER 2021166927 Baby report of fetal tachycardia noted 1 week after the neonate's mother received the second dose of the vaccine. The baby was delivered at 35 weeks and 3 days of gestation due to non-reassuring status during monitoring post vaccination. The baby was hospitalized for 5 days. The clinical outcome of fetal tachycardia was unknown.

  - AER 2021015910 Maternal report of a 29-year old female who was pregnant when receiving BNT162B2. She had spontaneous rupture of membranes at 36 weeks of gestation, one day after her 2nd dose of vaccine. Unspecified therapeutic measures were taken as a result of premature rupture of membranes and the mother was recovering.

  - AER 2021191405 Baby case of a fetus of unspecified gender who received BNT162B2 transplacentally. The patient's mother received vaccination during the second trimester (13-28 weeks) and experienced premature labor. A live infant was delivered but passed away a day later. Cause of death was cited as extreme prematurity with severe respiratory distress and pneumothorax.

  - AER 2021182609 Maternal report (AER 2021193635 associated Baby report) of a 32-year-old female patient received BNT162B2 during the second-trimester (13-28 weeks) and experienced preterm premature rupture of membranes, premature baby/Premature delivery. Outcome of preterm premature rupture of membranes and premature delivery was recovered with sequelae. Concomitant medications included acetylsalicylic acid and dalteparin sodium.

  - AER 2021155967 Baby report: A neonate patient's mother (mother was reported as 37-year-old) received BNT162B2 during 13-28 weeks of gestation and experienced foetal exposure during pregnancy, premature baby less than 26 weeks, respiratory distress and pneumothorax. Cause of death for the neonate was premature baby less than 26 weeks and severe respiratory distress and pneumothorax.

  - AER 2021203938 Baby report: Patient's 33-year old mother had preterm delivery at 24 weeks and 2 days via emergency caesarean section. The fetus experienced maternal exposure during pregnancy via transplacental route on an unspecified date.

Table 1. Summary of Patients with Outcome of Pregnancy – Abortion spontaneous

Age	Medical History	Outcome of Pregnancy
40 years	Not provided	The patient was unaware of her pregnancy at the time of vaccination. Suspected abortion occurred at 6 weeks of pregnancy.
37 years	Not provided	Patient received vaccine during first trimester (1-12 weeks) on 19 Jan 2021 and suffered spontaneous abortion on 3 Feb 2021.
33 years	Not provided	Patient received first dose of vaccine during first trimester (1-12 weeks). Abortion occurred at 3 weeks of pregnancy.
32 years	Not provided	Patient was vaccinated during first trimester (1-12 weeks) on 23 Dec 2020 and suffered a spontaneous abortion on 06 Jan 2021.
39 years	Asthma / Eosinophilic oesophagitis	Patient received vaccination at gestation of 6 weeks and spontaneous abortion occurred 11 days post vaccination.
31 years	Not provided	Patient experienced spontaneous abortion 8 days after receiving 2nd vaccine at 6 weeks pregnant.
35 years	Asthma / Gastrooesophageal reflux disease	Patient experienced missed abortion in the 7th week of pregnancy on an unspecified date with outcome of unknown.
33 years	Pregnancy	The patient was unaware of her pregnancy at the time of vaccination, which occurred at gestational age of approximately 3 weeks. Spontaneous abortion occurred at gestational age of 6 weeks.
34 years	Pregnancy	Patient was 3 weeks pregnant at the time of the first vaccination, without knowing she was pregnant. She found out she was pregnant one week after the vaccination. She then had a spontaneous abortion in week 6 of pregnancy.
Unknown	Not provided	Patient received vaccine at an unspecified time during pregnancy Spontaneous abortion, gestational age unknown.
34 years	Continuous positive airway pressure / Overweight / Sleep apnoea syndrome	Patient reported that she was unknowingly pregnant upon receiving COVID-19 vaccine dose 1. Spontaneous abortion occurred at 4 weeks of pregnancy.
Unknown	Not provided	Patient received vaccine during first trimester of pregnancy. Spontaneous abortion occurred at 5 weeks of gestation.
37 years	Not provided	Patient received vaccine during first trimester of pregnancy. Spontaneous abortion occurred at 6 weeks of pregnancy.
31 years	Not provided	Patient received vaccine during first trimester of pregnancy. Spontaneous abortion occurred at 5 weeks of gestation.
32 years	Not provided	Patient received her first vaccine dose at 3 weeks of pregnancy and experienced spontaneous abortion about 5-6 days before her second dose.

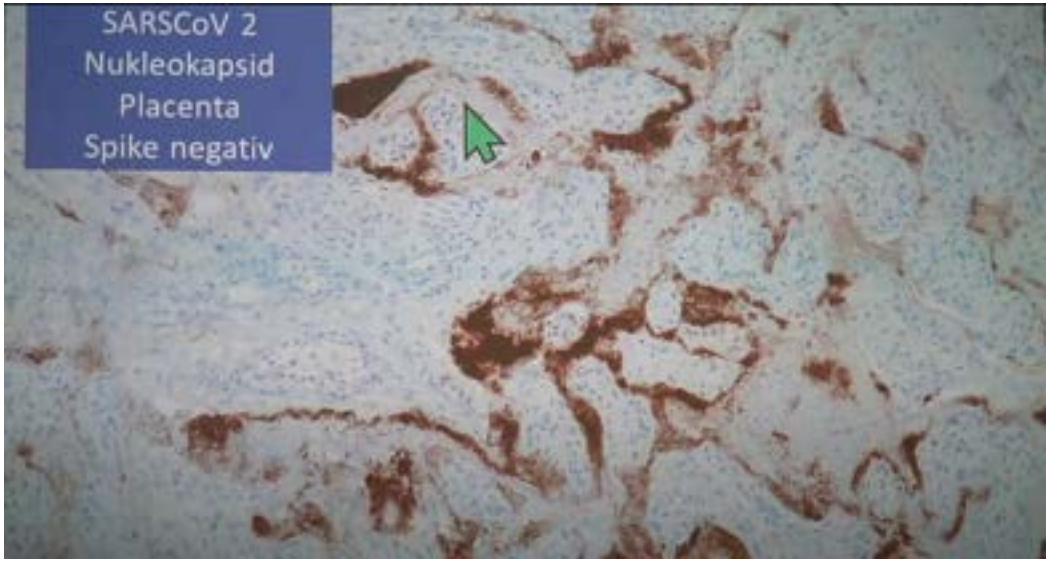
- The remaining 215 cases reported exposure via lactation. In 174 of the 215 reports, there was no AE reported other than 'Exposure via breast milk/maternal exposure during breast feeding'. In the remaining 41 cases, AEs were reported in the infants following BNT162b2 exposure via lactation (see Table 2).

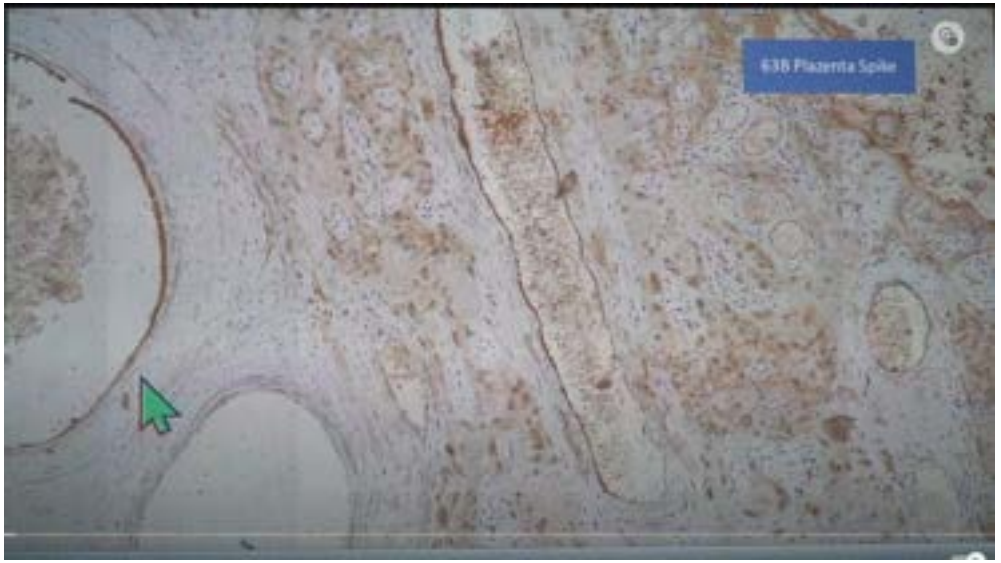
Table 2. Number of Adverse Events Reported in Infants with 'Exposure via Lactation'

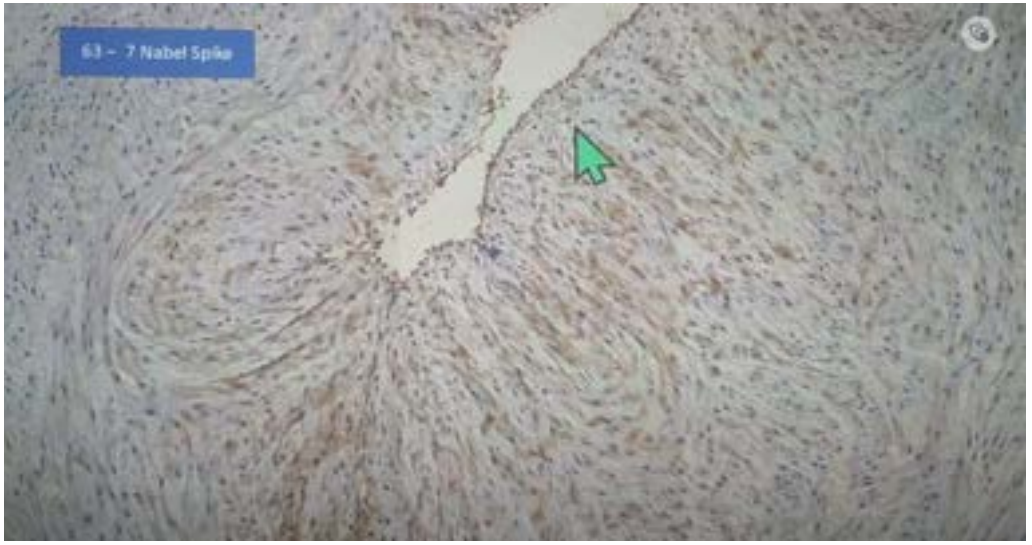
Preferred Term	Number of Events
Pyrexia	9
Off label use	8
Product use issue	7
Infant irritability	5
Headache	5
Rash	5
Diarrhoea	3
Illness	3
Insomnia	3
Suppressed lactation	3
Breast milk discoloration	2
Infantile vomiting	2
Lethargy	2
Pain	2
Peripheral coldness	2
Urticaria	2
Vomiting	2
Abdominal discomfort	1
Agitation	1
Allergy to vaccine	1
Angioedema	1
Anxiety	1
Axillary pain	1
Breast pain	1
Breast swelling	1
Chills	1
Cough	1
Crying	1
Dysgeusia	1
Dysphonia	1
Eructation	1
Epistaxis	1
Eyelid ptosis	1
Facial paralysis	1
Fatigue	1
Increased appetite	1
Lymphadenopathy	1
Myalgia	1
Nausea	1
Paresis	1
Poor feeding infant	1
Poor quality sleep	1
Pruritis	1
Restlessness	1

Drei Fälle, die uns aktuell vorliegen

Potentielles Risiko in der Schwangerschaft?







https://www.youtube.com/watch?v=2vrzH37ng2U

Gibt es irgendwelche Grenzwerte?

Die WHO hat Moderna, BioNTech und CureVac vorgeladen, um Grenzwerte zu erstellen. Die Firmen haben sich geweigert Grenzwerte festzulegen, da

„die Art der Verunreinigungen von Charge zu Charge stark variieren, insbesondere wenn sie in unterschiedlichen Größenordnungen und nach unterschiedlichen Verfahren hergestellt werden.“
https://pubmed.ncbi.nlm.nih.gov/36351479/

*Es gibt **keine veröffentlichten behördlichen Leitlinien** zu den potenziellen Auswirkungen einer geringen Anzahl von VPs auf die Patientensicherheit. Daher ist die Sicherheitsbewertung von VPs in DPs eine Praxis der **Selbstregulierung und -bewertung in der pharmazeutischen Industrie**.*
https://pubmed.ncbi.nlm.nih.gov/38975062/

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European Pharmacopoeia updates testing for particulate contamination in pharmaceutical preparations

20/02/2020

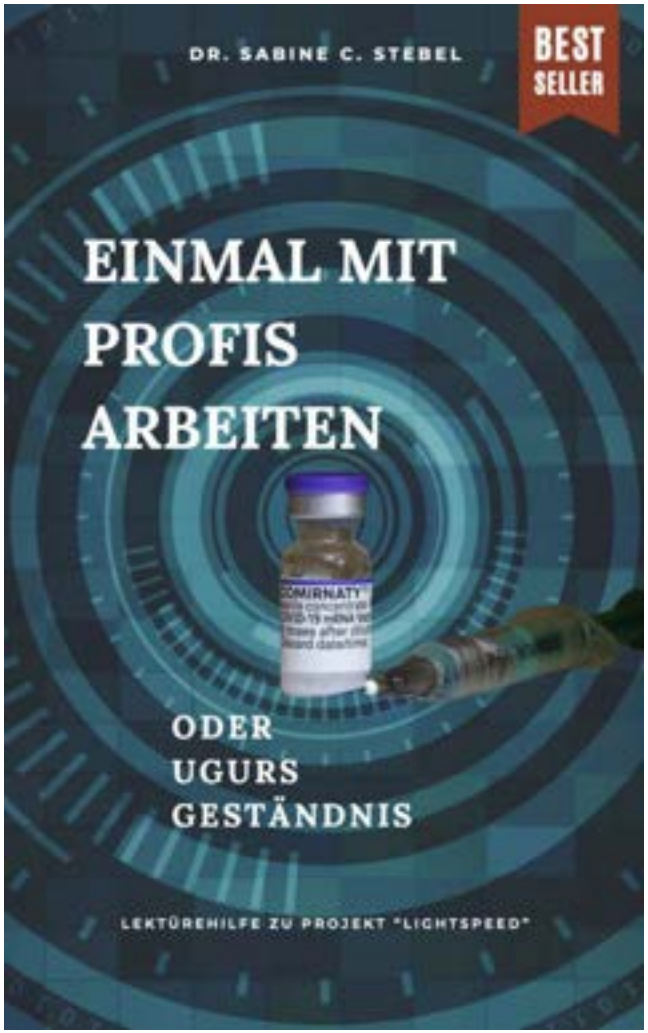
Strasbourg, France

At its 165th session in November 2019, the European Pharmacopoeia Commission adopted two general chapters related to testing for particulate contamination in pharmaceutical preparations.

The revisions to **general chapter *2.9.19. Particulate contamination: sub-visible particles*** supplement the Pharmacopoeial Discussion Group (PDG) harmonised text with alternative local requirements applicable to biological parenteral preparations. Such preparations are provided in low volumes and the local requirements – marked in the text with white diamonds – allow testing of these and other preparations to be performed using volumes smaller than 5 mL where suitable instrumentation is available. The PDG remains committed to further revising the chapter in order to integrate these changes into the harmonised text.

The new, non-mandatory **general chapter *5.17.2. Recommendations on testing of particulate contamination: visible particles*** provides information on visual inspection and control of visible particles in liquid preparations for which testing according to the general chapter *2.9.20. Particulate contamination: visible particles* applies. The text highlights the different sources of foreign particle contamination of liquid preparations and the fact that every effort should be made to avoid their presence. Consideration is given to the different inspection stages during

https://www.edqm.eu/en/w/european-pharmacopoeia-updates-testing-for-particulate-contamination-in-pharmaceutical-preparations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