Corona Investigative Committee

Current state of knowledge on the pharmacokinetics of mRNA vaccines

Corona Investigative Committee, February 17, 2023

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here my publications and authenticated peer-review
https://www.webofscience.com/wos/author/record/2107575

Excuse my very bad English (I stopped academic research in 1986 and do not practice oral English)

Pharmacokinetics

Definition

Pharmacokinetics: action of the organism on a drug, i.e. the fate of the drug, from its entry to its exit from the organism, the evolution according to time of its absorption, its bioavailability, its distribution, its metabolism and its excretion

Regulation of gene therapy trials

RNA vaccines should in principle be assimilated to GTP

- For conventional vaccines, there is no need for pharmacokinetic studies
- mRNA vaccines correspond to the definition of gene therapy products of the regulatory agencies (FDA, NIH, EMA, WHO): They are products that exert their action by translation of genetic material.
- There are no specific regulations for mRNA vaccines
- It is difficult to justify that mRNA vaccines are not considered in the same way as gene therapies with regard to these regulations, since the only difference is that they are supposed to protect against a disease and not cure it : According to the EMA, the same mRNA is a GTP if it cures and a vaccine if it protects against an infectious disease
- According to GTP regulations, mRNA vaccines should have undergone biodistribution and excretion studies by all of the following routes: feces; secretions (urine, saliva, nasopharyngeal fluids, semen, etc.), or through the skin (healthy or with pustules, lesions, wounds).

Vaccine shedding

Classically refers to the possible excretion of a virus by a person freshly vaccinated against this virus

- This is only valid for live attenuated virus vaccines (MMR, varicella, rotavirus, flu nasal spray)
- No risk with Covid vaccines (do not use these formulas): a vaccinated person cannot transmit vaccine virus.
- However, it has been widely published that freshly vaccinated people are more likely to be infected with the COVID-19 virus and thus to infect others with this virus.
- COVID-19 mRNA vaccines = first to be used in humans worldwide and no studies have been conducted regarding the possible shedding of the vaccine itself (lipid nanoparticles containing the mRNA) or the vaccine mRNA or the vaccine product, that is the spike protein translated by the cells of the vaccinee.
- Vaccine mRNA = "prodrug" or « pro-vaccine », that is a pharmacologically inactive substance (mRNA) that is converted in the body into a pharmacologically active substance (spike protein).

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The hypothesis is shedding of the vaccine and transmission to non-vaccinated

Anti-Covid vaccine are mRNA translated by the body into spike protein

- Why are we interested in this hypothesis?

- There are testimonies from patients and doctors but without scientific value
- They are Non-vaccinated people who have been in close contact with vaccinated people and have experienced adverse events identical to those related to the Covid mRNA vaccine
- Reminder: The vaccines are all based on the spike protein which has since been recognized as the main responsible for the pathogenicity of the SARS-CoV-2 virus. Therefore, in the event that the vaccine or its product (spike) is passed from vaccinated to unvaccinated, the adverse effects of the vaccine could be found in some unvaccinated individuals in contact with vaccinated individuals.
- If this remains an unexplored hypothesis, it leads to an unhealthy climate of suspicion and division in the population.

Infectious Diseases Research

Infectious Diseases Research | 2022, Vol. 3 | Issue (4): No.22 DOI:10.53388/IDR20221125022

Being questioned **Current state of knowledge on the excretion of mRNA and spike produced by anti-COVID-19 mRNA vaccines; possibility of contamination of the entourage of those vaccinated by these products**

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Cite this article:
Banoun H. Current state of knowledge on the excretion of mRNA and spike produced by anti-COVID-19 mRNA vaccines; possibility of contamination of the entourage of those vaccinated by these products. *Infect Dis Res.* 2022;3(4):22. doi:10.53388/IDR20221125022

Current state of knowledge on the excretion of mRNA and spike produced by anti-Covid-19 mRNA vaccines; possible contamination of the entourage of persons vaccinated with these products

Infection Diseases Research November 2022

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What is known about the biodistribution and excretion of LNPs from mRNA vaccines (Pfizer trial)

Biodistribution of the vaccine and its products

What is known about the biodistribution and excretion of LNPs from mRNA vaccines (Pfizer trial)

- Pfizer documents obtained by FOIA: only 2 components of LNPs (ALC-0315 and ALC-0159) were studied in rats injected by IM
- Biodistribution: blood, liver, spleen, adrenal glands, ovaries mainly but found in all organs
- Excretion was studied only in urine and feces

Biodistribution of vaccine & its products

What is known about the biodistribution and excretion of LNPs from mRNA vaccines (Pfizer trial)

- Pfizer's Phase I/II/III trial protocol mentions the possibility of passage of the study product through inhalation or skin contact, passage through the semen of a man exposed through inhalation or skin contact, and passage through breast milk; the possibility of an adverse reaction to the vaccine following these exposures is also mentioned.
- Exposure during breastfeeding was also to be reported immediately during the trial: presumably the investigator was concerned that a breastfeeding mother could transmit the experimental mRNA to her baby if she received the vaccine directly or if she is "exposed to the study intervention through inhalation or skin contact."

Biodistribution of LNPs & mRNA

What do we know from the manufacturer's independent studies

- IM injected mRNA carrier LNPs pass into lymphatic and blood circulation, accumulate mainly in liver and spleen
- mRNA present in blood from day 1 of injection, persists at least 2 weeks, encapsulated in LNPs, in plasma (not cells), capable of being translated into spike
- mRNA persists in lymph nodes at least 60 days, in deltoid muscle at least 1 month

Passage of mRNA in milk

Manufacturer independent studies

- mRNA was found in the milk of 4 women out of 40 studied (concentration 2ng/l) in the week after injection
- Other study: mRNA was found free and encapsulated in EVs (extracellular vesicles) within 48h after injection; with a priority presence in EVs
- Vaccine mRNA is encapsulated in artificial lipid nanoparticles (LNPs) that have the same structure as the natural exosomes (or extracellular vesicles EVs) that they seek to mimic
- Natural EVs are generated by all cells = they are natural carriers of many molecules and are involved in inter-cellular communication: LNPs and EVs fuse with cell membranes and release their contents into the cell.
- Natural EVs are more efficient than artificial LNPs to transport and deliver molecules to cells
- The cargo of EVs is protected from gastric juices: not destroyed in the digestive tract.

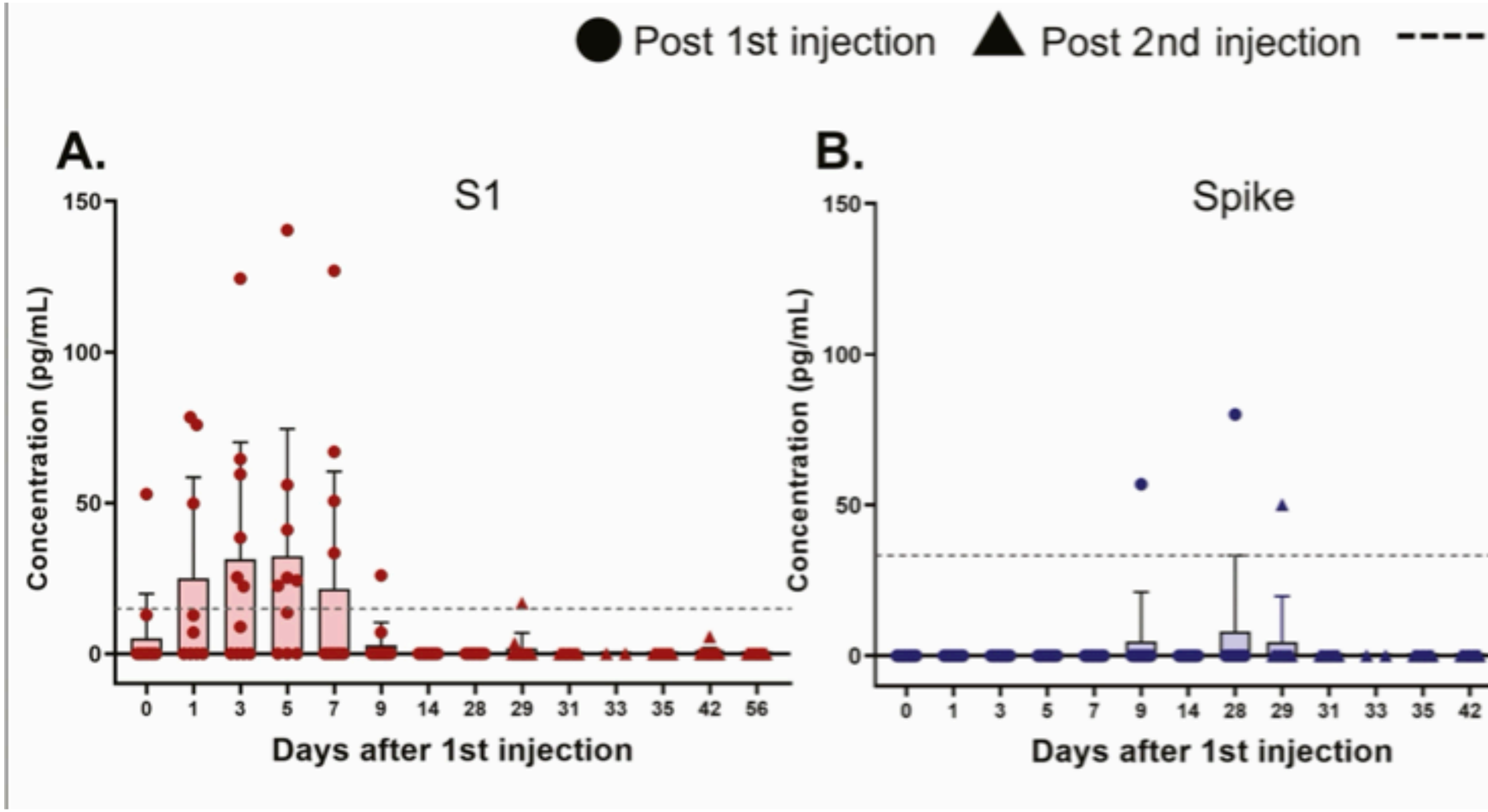
Expression & biodistribution of spike protein

What do we know from manufacturer's independent studies

- In mice: production of spike at the injection site lasts 6 to 10 days (in the muscle)
- in humans: after vaccination, spike circulates in the blood as early as day 1 (according to a study in 96% of vaccinees), and for at least 15 days (Röltgen et al.)
- the S1 subunit is detected months after the vaccine in circulating monocytes in patients suffering from Covid-long due to the Covid vaccine (Patterson et al.)
- Spike rate is highly variable among vaccinated individuals (Ogata et al.)
- Spike is spontaneously enveloped in circulating EVs up to 4 months (in humans)
- Spike is found in injured keratinocytes (skin cells) 3 months after vaccination
- After autopsy spike was found in heart, muscles, brain; germinal center, capillaries, 3 weeks after injection
- In a patient who died of myocarditis: spike was found in the myocardium 21 days after injection

Highly variable spike rates obtained in vaccinees

Alana F Ogata, Chi-An Cheng, Michaël Desjardins, Yasmeen Senussi, Amy C Sherman, Megan Powell, Lewis Novack, Salena Von, Xiaofang Li, Lindsey R Baden, David R Walt, Circulating Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Vaccine Antigen Detected in the Plasma of mRNA-1273 Vaccine Recipients, *Clinical Infectious Diseases*, Volume 74, Issue 4, 15 February 2022, Pages 715–718, https://doi.org/10.1093/cid/ciab465



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What do we know in general about the pharmacokinetics of LNPs and mRNA (this has not been studied specifically for mRNA vaccines)

As I told you, the nanoparticles that carry the mRNA of the vaccines are very close to the natural extracellular vesicles that they try to imitate

Vaccine Spike and mRNA are naturally embedded in EVs by the cells

- EVs (exosomes or natural extracellular vesicles) measure 20 to 4,000 nanometers, carry proteins and RNA, fuse with cell membranes and deliver content. The size of vaccine LNPs is 60 to 100 nanometers

- Vaccine mRNA and vaccine spike can be naturally embedded in EVs and transported throughout the body (EVs capable of delivering content to distal organs).

- There is a bi-directional traffic of natural EVs during pregnancy (cross placenta in both directions), capable of delivering drug to the fetus.

Fate of EVs and LNPs in the body

Concerns natural EVs & LNPs similar to those of mRNA vaccines

- EVs circulating in the blood are naturally excreted in sweat (some RNAs are enriched in sweat EVs)
- Keratinocytes excrete EVs (capable of transporting RNA from cell to skin cell)
- EVs are naturally present in sputum
- EVs with RNA cargo are able to cross the placental barrier
- No evidence of EVs passing into sperm has been shown (but no studies on this subject!) but the toxicity of nanoparticles on male reproductive function is established

Ability of EVs and LNPs to penetrate through different pathways

This has not been studied for LNPs of mRNA vaccines

- Exposure of the human body to nanoparticles can occur accidentally by inhalation, skin contact or ingestion
- Small mRNAs (20-200 bp) are found in sweat EVs, they are functional (can be translated), RNAs are protected from skin nucleases in EVs
- Nanoparticles are used therapeutically by inhalation, transdermal, in utero and conjunctival routes.
- Intranasal, oral, intraocular and subconjunctival administration of drug-carrying EVs has been successfully tested

Vaccination trials & respiratory gene therapy with nanoparticles

(LNPs containing nucleic acids)

- The formulation of LNPs is optimized to allow pulmonary penetration: mRNA is translated after inhalation following nebulization in mice.
- Nasal route is used for cystic fibrosis gene therapy with mRNA encapsulated in LNPs in mice and humans.
- Inhaled influenza mRNA vaccine (including PEG polyethylene glycol-containing LNPs) has been successfully tested
- LNPs with mRNA used in utero: the protein of interest is translated in liver, lungs, fetal intestine

Trial of transdermal vaccination with LNPs

Healthy skin (through hair follicles) and injured skin is permeable to LNPs

- LNPs with plasmid containing HBsAg genetic code, administered transfollically results in antibody response
- In transdermal clinical trials HIV vaccine: plasmid DNA codes for virus antigens in LNPs and allows successful immunization in humans.
- In the DEFUSE project (EHA for DARPA) it was about transcutaneous administration of vaccines in animals using nanoparticles

Therapeutic and vaccine trials COVID-19

Plantar or inhalation route

- 60 clinical trials are underway with MSCs (mesenchymal stem cells) in the treatment of COVID: efficacy is demonstrated by nebulization of EVs containing MSCs.
- In COVID-19: trials are underway for immunization with natural EVs by plantar route (mouse foot pad) or by inhalation; natural EVs are more efficient than LNPs to transport mRNA

Conclusion

Excretion and penetration of EVs and LNPs is biologically plausible

- All these studies show that EVs carrying mRNA and spike could therefore be excreted by different body fluids and could enter by transcutaneous or inhalation route in unvaccinated individuals (as well as by breast milk in infants and by transplacental passage in fetuses and why not by semen). Naked mRNA could also be excreted and enter.

- The mRNA vaccines (and adenovirus) correspond exactly to the definition of gene therapy given by the health agencies (FDA, NIH and EMA).

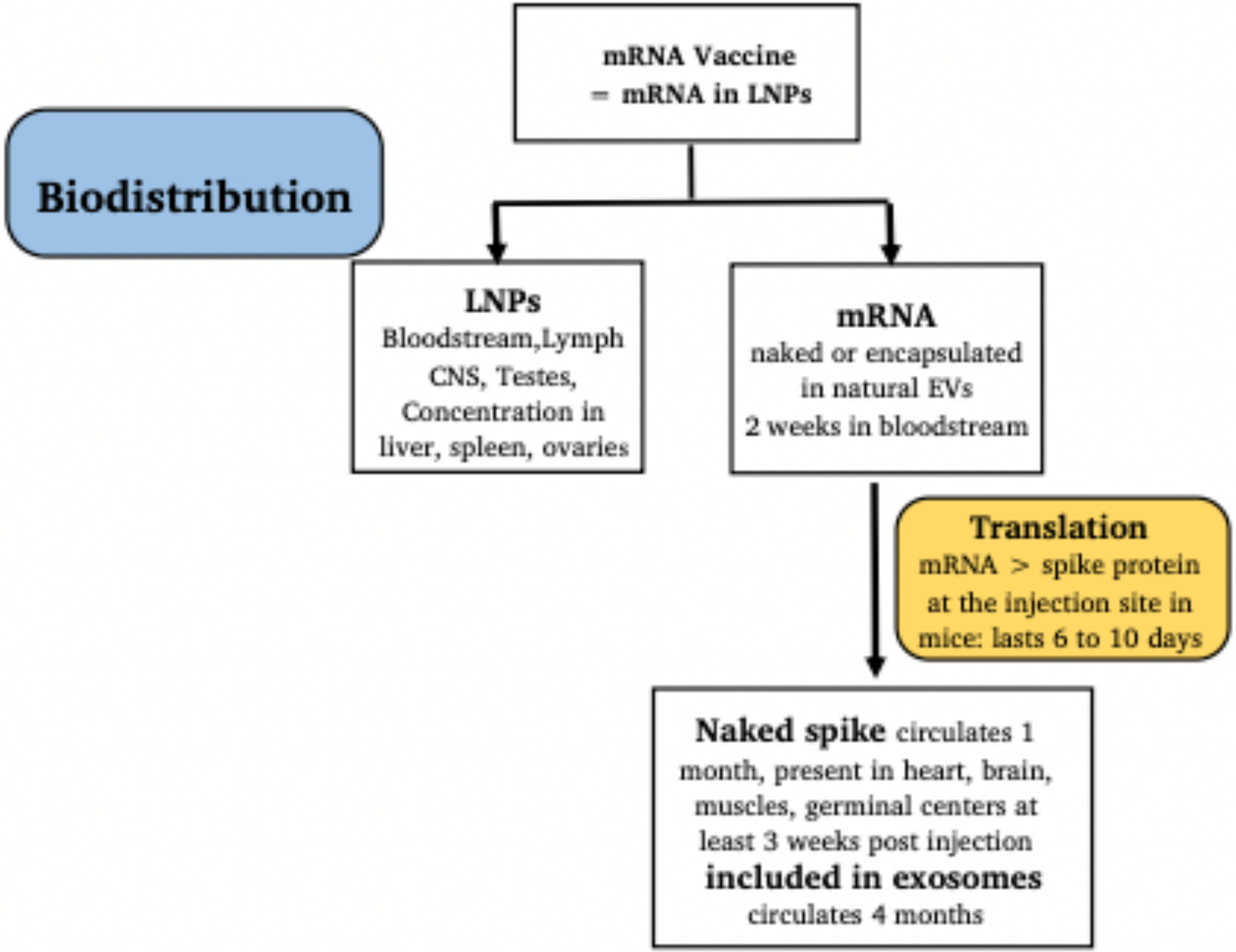
- According to the regulations of these agencies, these products should be subject to additional pharmacokinetic studies (in particular excretion studies)

Généralisation des vaccins ARNm?

Moderna pipeline = mRNA « vaccines » against:
Covid, influenza, Human metapneumovirus, parainfluenzae, RSV, HCoV, CMV, EBV, varicella, Herpes, HIV, Zika, Nipah

- Moderna's mRNA flu vaccine is in Phase 3
- **Do not panic or reject the vaccinated.**
- **To take into account the notion of duration of excretion: it may be possible only over a short period of time after vaccination (example breast milk: 1 week).**
- **The notion of quantity: it is necessary to differentiate possible excretion of spike (in EVs) from that of RNA (naked or in EVs): mRNA is theoretically more dangerous because it would be translated into an unknown quantity of spike; the spike transmitted directly would be once and for all.**
- **It is also possible that only people who have produced a lot of spike and then suffered more or less serious adverse reactions are able to transmit the vaccine or spike**

State of knowledge on biodistribution of mRNA vaccines



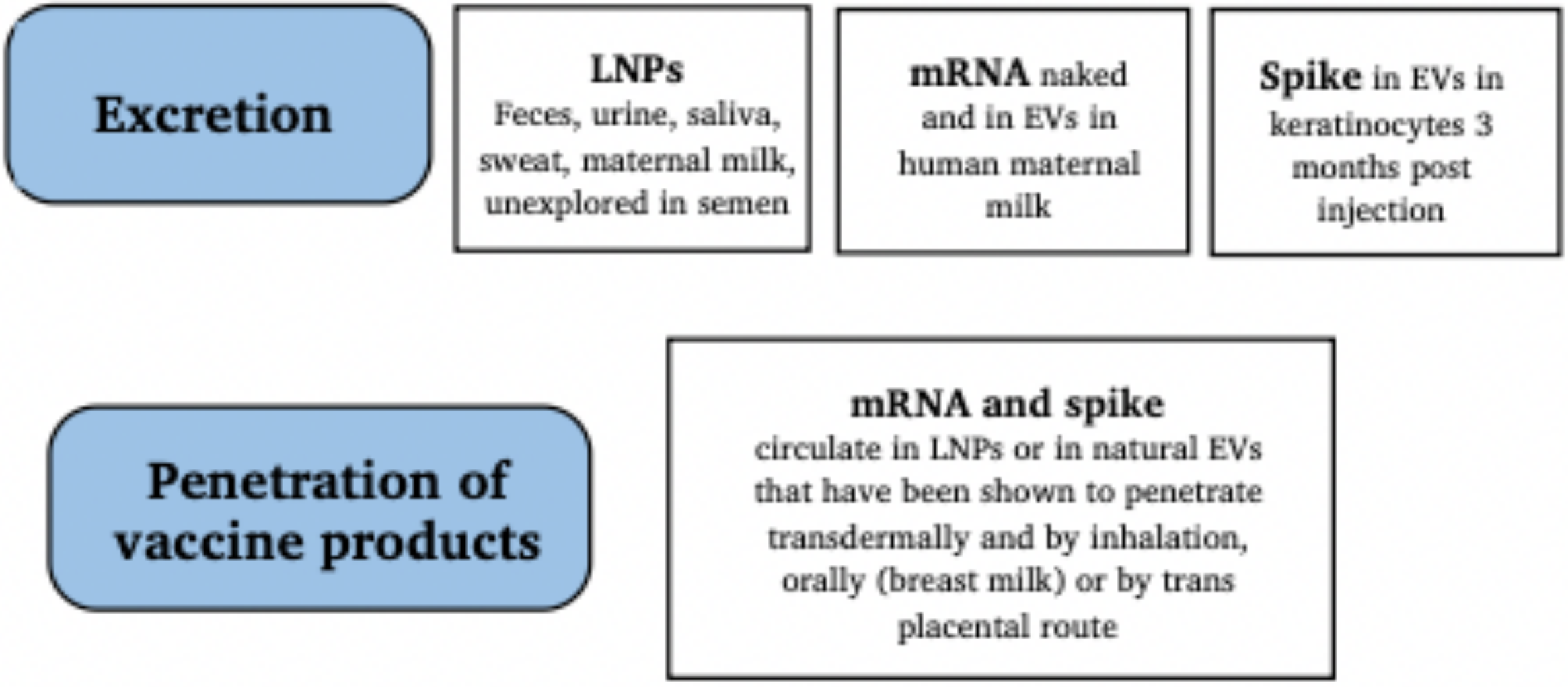


Figure 1 State of knowledge on excretion of mRNA vaccines