Review and Commentary: "Strategies to reduce the risks of mRNA drug and vaccine toxicity"

Useful confirmation of what has been known to many, but a limited hangout rather than the "whole truth and nothing but the truth"

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Review article Check for updates

Strategies to reduce the risks of mRNA drug and vaccine toxicity

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"Lipid nanoparticle structural components, production methods, route of administration and proteins produced from complexed mRNAs all present toxicity concerns."

Bitounis, D. et al. Strategies to reduce the risks of mRNA drug and vaccine toxicity. Nat Rev Drug Discov. 23 January 2024. https://doi.org/10.1038/s41573-023-00859-3; PMID: 38263456

Nature Reviews (Drug Discovery), one of the prestigious "Nature" family of academic journals, has published a review paper written by four pharmacologists addressing mRNA lipid nanoparticle drug toxicity. All authors have non-clinical toxicology expertise (although none appear to be boarded toxicologists). Three have close ties to Moderna, and the corresponding author is an academic whose potential links to Moderna are neither discussed nor disclosed. I have received multiple requests for independent review and comment on the publication. I was not asked nor did I participate in the pre-publication review process.

Authors and Conflicts of Interest (COI)

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Competing interests

Eric Jacquinet is employed by Moderna, Inc. Dimitrios
post-doctoral fellow with a Moderna, Inc.-sponsored fe
affiliated with Intellia Therapeutics, but completed thi

It should be noted that the Journal itself is owned by S
by World Economic Foundation (WEF) partner Holtzbr
information and detail concerning the pervasive role o
both the academic and lay press information sphere as
"The World Economic Forum, 'The Lancet', and COVID-19 Knowledge Gatekeeping",
International Journal of Arts and Social Science ISSN: 2581-7922 Volume 5 Issue 12, December 2022.

The UN's Under-Secretary-General for Global Communications, Melissa Fleming, in a discussion with the World Economic Forum during October 2022:

"We partnered with Google, for example, if you Google 'climate change,' you will, at the top of your search, you will get all kinds of UN resources. We started this partnership when we were shocked to see that when we Googled 'climate change,' we were getting incredibly distorted information right at the top. We're becoming much more proactive. ***We own the science,*** *and we think that the world should know it, and the platforms themselves also do,"*

Key Definitions: Limited Hangout, Modified Limited Hangout

A limited hangout is **a propaganda technique of displaying a subset of the available information**. It involves deliberately revealing some information to try to confuse and/or prevent discovery of other information.

It misdirects an incautious audience, because information needs a context for correct interpretation. Subtly omitting information changes the interpretation of the surrounding information.

A modified limited hangout goes further by slightly changing the information disclosed. Commercially-controlled media is often a form of limited hangout, although it often also modifies information and so can represent a modified limited hangout.

For those interested in complementary editorial analysis, please see

Bombshell? Ex-Moderna Preclinical Scientists Acknowledge Serious Safety Concern with Current mRNA Technology

Trial Site News

Trial Site News' Chief Editor was the person who originally brought this article to my attention.

Content and Purpose of the Article

In this recent review article (23 January, 2024), Bitounis et al. provide a partial disclosure and examination of known risks and toxicities associated with the modified messenger ribonucleic acid/lipid nanoparticle pharmaceutical delivery platform. In general, what makes this publication particularly remarkable is that (collectively) the authors have significant employment or other ties to Moderna therapeutics, a pharmaceutical company whose very name (MODified RNA) indicates its corporate dependency on the feasibility of this technology. As a veteran of prior biopharmaceutical corporations, it is inconceivable to me that these authors do not have pre-existing restrictive non-disclosure agreements with Moderna, and therefore it is highly likely that Moderna pre-approved this publication.

Therefore, my most generous interpretation of the overall intent of the article is that this article summarizes and represents information concerning risks and toxicities of this platform technology which Moderna wishes to have disclosed in a manner which puts the firm, its activities and the underlying platform technology in the best possible light. A less generous interpretation of intent is that this article represents a subtle form of propaganda strategy commonly referred to as a limited hangout.

The essay includes extensive speculation concerning how emerging new technologies such as artificial intelligence and organoids (simplified tissue culture structures mimicking an organ, that are derived from stem cells), as well as well established 'high tech" approaches such as single cell sequencing can be used to minimize animal model use (a specific NIH objective). They are intended to facilitate more efficient pharmaceutical development and toxicologic analysis of modified-mRNA drug and vaccine development technologies.

Through the jaded eyes of this highly experienced proposal reviewer, this mostly reads like a forward looking justification for increased investment in a variety of expensive new pharmaco-toxicology infrastructure advances which would be in the financial and professional interest of the authors, while avoiding and overlooking time tested approaches to characterizing the profound and wide ranging toxicities of these pharmaceutical preparations.

In other words, this reads as an extended justification for spending a lot of money on new goodies for pharmacologists and toxicologists while avoiding the obvious and less sexy basics that still have yet to be performed and reported.

Abstract

(***RWM comments added in italics***)

> mRNA formulated with lipid nanoparticles is a transformative technology that has enabled the rapid development and administration of billions of coronavirus disease 2019 (COVID-19) vaccine doses worldwide.

<RWM- I disagree. Teams of Cuban, Russian and Indian researchers produced SARS-CoV-2/COVID vaccines on a similar timeline using conventional technology. A case can even be made that the Cuban vaccine was more effective than the mod-mRNA products. What enabled the rapid development of the mod-mRNA products was bypassing time-tested, previously established non-clinical toxicology and clinical trial international norms. That is what compressed the timeline/GANTT chart for these products. This statement is propaganda.>

> However, avoiding unacceptable toxicity with mRNA drugs and vaccines presents challenges.

<RWM- That seems self-evident at this point.>

> Lipid nanoparticle structural components, production methods, route of administration and proteins produced from complexed mRNAs all present toxicity concerns.

<RWM- This is actually a small subset of the actual toxicity concerns. For example; shedding, secretion, biodistribution, pharmacokinetics and general pharmacotoxicology; reproductive toxicology and genotoxicity/insertional mutagenesis; toxicities, metabolism and clearance of each active pharmaceutical ingredient; off and on-target impact on immune system function are a few of the many additional concerns. Once again, due to the lack of rigor and completeness in disclosure, the appearance here is that we are dealing with what is essentially a limited hangout.>

> Here, we discuss these concerns, specifically how cell tropism and tissue distribution of mRNA and lipid nanoparticles can lead to toxicity, and their possible reactogenicity.

*<RWM- "their possible reactogenicity" is ambiguous and misleading. Are the authors referring to the modified mRNA or the formulated lipid nanoparticles or both? **Reactogenicity** represents the physical manifestation of the inflammatory response to vaccination, and can include injection-site pain, redness, swelling or induration at the injection site, as well as systemic symptoms, such as fever, myalgia, or headache. These formulations are unequivocally reactogenic. The implication of "Possible reactogenicity" is another falsehood.>*

> We focus on adverse events from mRNA applications for protein replacement and gene editing therapies as well as vaccines, tracing common biochemical and cellular pathways. The

> potential and limitations of existing models and tools used to screen for on-target efficacy and de-risk off-target toxicity, including in vivo and next-generation in vitro models, are also discussed.

*<RWM- Adverse toxicologic effects are categorized as chemical-based, **on-target**, or **off-target** effects. On-target refers to exaggerated and adverse pharmacologic effects at the target of interest in the test system. Off-target refers to adverse effects as a result of modulation of other targets; these may be related biologically or totally unrelated to the target of interest.>*

General Impression

<RWM> Overall, reading through this review, what I find is a typical academic overview of a wide variety of early stage technologies (such as hollow, coated, or dissolvable microneedle delivery). This review highlights combinatorial chemistry approaches which have been around for decades and never fulfilled their marketing hype. This "blue sky" approach is coupled with acknowledgement of known toxicologic responses, optimistic speculation concerning future development opportunities, the usual futuristic toxicology wish lists (induced pluripotent stem cell (iPSC) organoids, spheroids and microfluidics) and a complete failure to address the most concerning risks, which include:

- Genotoxicity, integration and the effects of the overlooked DNA fragment byproduct of the mod-mRNA manufacturing process.
- Coagulopathy - pathologic micro- and macro-vascular blood clots
- Widely distributed and unregulated expression of foreign proteins throughout the bodies of recipients- with associated innate, humoral and cellular immune responses to those cells.
- Frameshifting, inherent in the use of pseudouridine, resulting in production of unintended and uncharacterized proteins in the bodies of recipients.
- Prolonged, poorly characterized production of foreign transgene-encoded proteins.
- Fundamental bioethical considerations regarding widespread administration of foreign genetic material.

Examining the two "blue sky" items highlighted above:

I have written microneedle grant and contract proposals for multiple vaccine companies over at least twenty years, and they never go anywhere. There are unsolvable problems associated with the wide variety of patch-based cutaneous vaccine delivery platforms that have been investigated, and at least a billion dollars of public and private investment has lead to a string of failures.

In the case of "combinatorial chemistry", likewise there are decades of experience with this approach, most of which has also come to naught. Basically, resorting to producing random arrays of new chemical compounds is a complete waste of time, and invoking this old saw mostly serves to underscore that the pharmaceutical chemistry involved is so poorly understood and

rational drug design approaches are so inefficient that the pharmaceutical chemists might as well (functionally) just roll the dice in seeking to develop new compounds.

In other words, acknowledgment of the obvious problems, a lot of speculation and repurposed futurism which has historically been most useful in generating NIH grant funding and hoodwinking investors, combined with avoidance of the most pressing and obvious current issues including DNA fragment contamination, immunotoxicity, and ADME (absorption, distribution, metabolism and excretion) of both the synthetic lipids and the formulated self-assembling lipidic complexes.

Or more bluntly put, a limited hangout wrapped in speculative academic and biotech jargon, targeted at justifying public and private investment in toys for pharmaco-toxicologists. Most of which I have seen many times before over the preceding decades.

For heavens sake, although breathlessly discussed as a new emerging opportunity in this review, I even disclosed the use of circular RNA for drug and vaccine purposes in a patent disclosure written in 1989 and in 1990, I set up a collaboration with Tom Czech (Nobel Prize, catalytic RNA) at the time to that end (lariat form intermediate). Specific justification being avoidance of 3' to 5' RNA exonuclease activity, the predominant pathway for mRNA degradation. This disclosure was not understood by my boss, who never filed a patent application for the concept. This is just one of many examples of the "repurposed" decades-old ideas being repackaged in this review.

Acknowledged Toxicities (Covered in Review)

- Intravenous administration including hepatotoxicity
- Challenges with repeat intravenous administration.
- General Liver and spleen toxicity
- Immune responses to the RNA component, the PEG, and the overall formulation
- Toll like receptor and release of pro-inflammatory cytokines
- Inflammasome activation.
- Complement activation and hypersensitivity reactions.
- Toxicology of lipids and their metabolites

Outlook (concluding statements)

> "The rapid design of safe and efficient vaccines against COVID-19 was an inflexion point in biotherapeutics. Although mRNA therapeutics had been decades in the making, the **successful COVID-19 vaccines** from BioNTech–Pfizer and Moderna illustrated the **efficiency of the platform**. As a result, today, the once-waning nanomedicine field is reinvigorated. In academia, this is evident from an ever-increasing number of publications and heightened academic interest in RNA biology. In parallel, the pharmaceutical industry is allocating more resources towards the development of mRNA modalities for the treatment of rare diseases, many forms of cancer and infections. Arguably, the successful establishment of this new technology in the drug development space is largely dependent on its safety. A lethal case of

> systemic inflammation after the intravenous administration of an adenovirus vector during a phase I trial was a tragic event and halted progress in the entire gene therapy field for more than a decade. **It serves as a reminder of how serious concerns about the safety of any given mRNA-based drug could affect the entire platform**."

> "Preclinical screening of compositionally complex mRNA drugs and vaccines should transcend what is applied in small-molecule drug development. Primarily, there is a need for de-risking models that better recapitulate human physiology and pathology. Ideally, artificial intelligence-informed pharmacodynamic models and toxicogenomic networks should also be consulted for better data interpretation. A special note has to be made for single-cell techniques, which have massively expanded the volume of information that can be collected on the heterogeneity of single-cell responses to drugs in vitro and ex vivo. Towards safe and effective LNP–mRNA development, a combination of next-generation sequencing, DNA barcoding and single-cell RNA-seq was demonstrated to identify which lipid-specific LNP–mRNA compositions would preferentially target specific liver cell subtypes in vivo. As different LNP–mRNA modalities may share the same components (for example, ionizable lipids), single-cell techniques offer an opportunity to promote LNP–mRNA formulations with the desired pharmacodynamic profile and identify whether adverse effects are tissue- or immune system-specific. Early corrective engineering could be implemented, and animal use would be spared."

<RWM> I am at a bit of a loss as to where to begin in commenting on the conclusions section of the paper.

These Moderna and Bio-n-Tech/Pfizer products have certainly been successful from a commercial standpoint. So in that sense I agree with the authors. I personally remain convinced that my original assessment of the coronavirus vaccine literature circa early 2020 remains accurate - there has never been development of a successful human coronavirus vaccine which prevents infection or spread of this rapidly mutating and highly successful group of human molecular parasites.

And that our best hope circa 2020 (and even now) for treatment of those vulnerable to this laboratory engineered sarbeco-coronavirus variant remains in treating disease symptoms with available drugs.

As I noted very early on after deployment of these mod-mRNA "vaccine" products into humans was launched, the data demonstrate that this formulation and delivery platform, which incorporates major formulation advances most appropriately credited to Dr. Pieter Cullis and his team at the University of British Columbia (and various for-profit corporate spin outs) is the most potent non-viral delivery system ever invented to date. While efficiency is a subjective term, and the in-vivo transfection efficiency obtained remains extremely low as a fraction of total cells, the combination of advances in use of ionizable (typically tertiary rather than quaternary amine) cationic lipids, together with a PEG shell anchored by short acyl side chains which acts to reduce aggregation of these formulations, represents a major technological advance in non-viral gene delivery. So I also generally agree with the "efficiency" claim, recognizing that efficiency is

relative to what came before- particularly relative to the “naked” delivery and quaternary amine-based lipidic formulations and discoveries of my youth. Probably no where near as efficient as the systems I pioneered decades ago involving pulsed electrical fields, but that is another story.

I was personally deeply involved in whistle blowing concerning the Jesse Gelsinger death at the hands of U Penn Dr. James Wilson alluded to by the statement “adenovirus vector during a phase I trial was a tragic event”, and it destroyed that phase of my academic career. I applaud the cautionary note struck by the authors concerning the need for rigorous and complete characterization of both non-clinical and clinical toxicology of the mRNA platform technology.

What a shame that, while employed at Moderna, the authors failed to insist on and achieve the necessary level of characterization of non-clinical and clinical toxicology which would have mitigated the risk of widespread global damages associated with the premature deployment of these products. Although both Nature and the authors appear to be in denial about this, “**serious concerns about the safety of any given mRNA-based drug could affect the entire platform**” is a risk which has already manifested. The potential which I once envisioned and disclosed as a 28 year old graduate student, while admittedly naive, may never be realized because of the irresponsible rush to deploy an immature technology before its time.

As to the second paragraph cited above, from my perspective as someone who has both authored and reviewed far too many business plans, NIH and DoD funding proposals, this reads like a laundry list of speculative, high-risk developmental projects. I have seen both large pharma (ergo the Novartis investments in gene therapy and vaccines), non-governmental (Gates foundation “gatelet” non-profits), and biotech startups fall victim to this type of spending driven by internal champions. I guess I have just seen too much.

There is plenty left to do to characterize and comprehend the pharmaco-toxicologic profile of this platform and its variants. If I were overseeing this domain from within FDA, I would be insisting that these companies stop further advanced development until they had answered the many remaining simple questions, many of which are conveniently overlooked in this “peer reviewed” article. And if I were asked to serve as chairperson for a study section evaluating proposals for public funding of such activities, I would reject any proposal seeking funding for these high-risk speculative approaches rather than proposing to do the old school pick and shovel stuff that still remains to be performed.

In sum, I remain convinced that my initial impression of this paper remains correct. A limited hangout written by Moderna insiders and published by an organization which has become captured by the corporatist monstrosity known as the World Economic Forum. Academic obfuscation combined with a pitch for funding new toys and retread concepts which have repeatedly failed in the marketplace of technology and ideas. Absolutely not a balanced and objective review of the current state of the art.

Where have all the flowers gone, long time passing. Where have all the flowers gone, long time ago.

When will they ever learn.

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The most altruistic thing a person can do in life is teach someone the truth, If a person goes through life, and is successful but goes to the grave without sharing and teaching their knowledge to others, they are like a genetically modified piece of fruit that has its seeds genetically taken from it. Without those seeds that normally would continue the growth of new fruit the life of the plant is over. That's why teaching all of us is so important. That's why censorship is so dangerous. You are planting the seeds of knowledge into all of us and we do our best to spread the knowledge to others, thank you Dr. Malone. J.Goodrich

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