Why the COVID-19 vaccines are not gene therapy

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Blog post published November 9, 2021 in *Chris von Csefalvay*
https://doi.org/10.59350/a4wx8-0sm75

Abstract

There might be valid concerns about the mRNA vaccines. Then there are the clearly insane ones, such as the claims that it involves the injection of a microchip. The argument that mRNA vaccines are a form of 'gene therapy' are somewhere in the middle, and that makes responding to it somewhat difficult.

Keywords

Epidemiology (Subfield), Immune responses and vaccinations (Topic), Immunology (Subfield), Public Health, Vaccines

Recommended citation

von Csefalvay, C. (2021, November 9). Why the COVID-19 vaccines are not gene therapy. *Chris Von Csefalvay*. https://doi.org/10.59350/a4wx8-0sm75

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There might be valid concerns about the mRNA vaccines. Then there are the clearly insane ones, such as the claims that it involves the injection of a microchip. The argument that mRNA vaccines are a form of 'gene therapy' are somewhere in the middle, and that makes responding to it somewhat difficult.

The origin of this claim is pretty self-evident: since the 'payload' of the mRNA vaccine is, well, as the name suggests, mRNA,[1] it involves pushing genetic material into the recipient. That sounds rather gene therapy-y, does it not?

[1] Sort of. Strictly speaking, this is not entirely true: mRNA vaccines actually have three mRNA bases — C, G and A — and a fourth base, m1Ψ. This is a molecule called N1-methylpseudouridine, and it replaces U in the mRNA. It is 'read' and interpreted as U, but is vastly less immunogenic.

These folks certainly think so:

Except the devil's in the details. And the details are pretty unambiguous: mRNA vaccines are nowhere near a 'gene therapy'.

How gene therapies work

Let's start by looking at a typical gene therapy: Zolgensma aka onasemnogene abeparvovec (say that three times quickly). This is an in vivo gene therapy, meaning that all the action takes place in the patient. It is given to very young children (under the age of 24 months) who have a certain mutation in the SMN1 gene, which leads to Type I spinal muscular atrophy. Onasemnogene abeparvovec is a modified adeno-associated virus 9 (AAV-9) that infects cells and gets them to produce 'correct' SMN1. This, then, alleviates their symptoms.

The key part to note is that a viral platform is used for a reason: viruses know how to enter nuclei and get them to produce to their instructions. They do so by providing what is called a nuclear localisation signal (NLS), a sequence that allows proteins to be shuttled inside the nucleus, across the nuclear membrane, typically by way of a protein called importin, one of the karyopherins. The vast majority of gene therapies leverage viral NLSs, because they're pretty much free gifts from viral evolution. They work, and they're widely used.

Gene therapy admittedly has some kinks that still need to be ironed out. Some things only seem to work well when using an ex vivo approach. An example for the latter are the CAR-T treatments, where the patient's blood is drawn, T cells are isolated and then transfected with a viral vector. Currently, this approach works much better outside the patient (hence ex vivo) than inside them, largely because T cells make up such a small part of all cells in the body.

How mRNA vaccines work

mRNA vaccines work in a much simpler way. It is, in many ways, a shortcut to the entire nuclear entry problem. If all you want is to make some proteins, you can skip the part about entering the nucleus and just, well, pretend to be the nucleus. Here's how that roughly works.

DNA is the stable, long-term 'hard' storage of cells. It's slow and unwieldy, but relatively resilient. RNA is the volatile storage medium: small, quick and of a limited lifespan. During a process called translation, DNA is translated, eventually, into mRNA.[2] mRNA then heads for the ribosomes like a sort of work order, which the ribosomes fulfil by making the protein it describes. This is a quick and dirty description of the central dogma of molecular biology, of course.

[2] More specifically: it is translated into pre-mRNA, which is then spliced to get mRNA.

Because mRNA vaccines only need to make relatively simple proteins (compared to having to make a whole virus), they can simply go directly to the ribosomes: no need to get involved in that whole mess about nuclear entry. The tradeoff, of course, is that mRNA is quite rapidly degraded. For applications like Zolgensma, where we want cells to keep producing SMN1 for a prolonged period, the extra effort to effect nuclear entry makes sense. For mRNA vaccines, on the other hand, all we really need is a 'spill' of proteins that approximate some of the shapes of the Spike protein from SARS-CoV-2. That's enough to elicit an immune reaction, create antibodies and memory lymphocytes and with that, the whole infrastructure of humoral and cellular immunity.

Or, by way of analogy: you receive other vaccines as a one-time shot, rather than as a lifelong intravenous infusion, right? Immunity doesn't need sustained exposure — the immune system is pretty quick at catching on. For the very same reason, there's no need to permanently express the Spike-like protein the way there is a need to keep expressing SMN1 in the Zolgensma example.

Why mRNA vaccines are not gene therapy

This is hardly a differentiation without distinction. Gene therapy is, well, serious business. Almost 22 years ago, a young man named Jesse Gelsinger died from what we would today call a Multisystem Inflammatory Syndrome (MIS) following an adenovirus-vectored treatment for X-linked ornithine transcarbamylase deficiency, an inborn defect of metabolism. Modern gene therapies are still in many ways in their infancy, requiring close supervision and, often, extensive pre-treatment. They might be ready for prime time, but they certainly aren't at the 'all audiences' stage just yet. And that's ok — the first antibiotics were equally quite iffy from today's perspective, and I am absolutely sure that within 25 years, the most frequent genetic disorders that gene therapy can fix — such as certain muscular dystrophies, cystic fibrosis or sickle cell anaemia — will be considered treatable with gene therapies. For now, however, gene therapies are complex treatments that demand experienced medical teams.

Fortunately, that is not the case for the COVID-19 mRNA vaccines. These vaccines are not only remarkably safe (I have written about their neurological safety, safety vs autoimmune disorders, overall safety and safety vs anaphylactic events, and there's a summary of these findings here) but also operate in a way entirely distinct from gene therapies. They do not enter the nucleus, they do not effect lasting changes (in fact, that's one of the reasons why mRNA approaches for the gene therapy of chronic diseases have so far been less than successful) and they do just what it says on the tin: produce Spike-like proteins to elicit an immune response.

Citation

BibTeX citation:

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@misc{csefalvay2021,
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  date = {2021-11-09},
  url = {https://chrisvoncsefalvay.com/posts/mrna-gene-therapy},
  doi = {10.59350/s2xc9-mwp25},
  langid = {en-GB}
}
```

For attribution, please cite this work as:

Chris von Csefalvay. 2021. "Why the COVID-19 Vaccines Are Not Gene Therapy." https://doi.org/10.59350/s2xc9-mwp25.