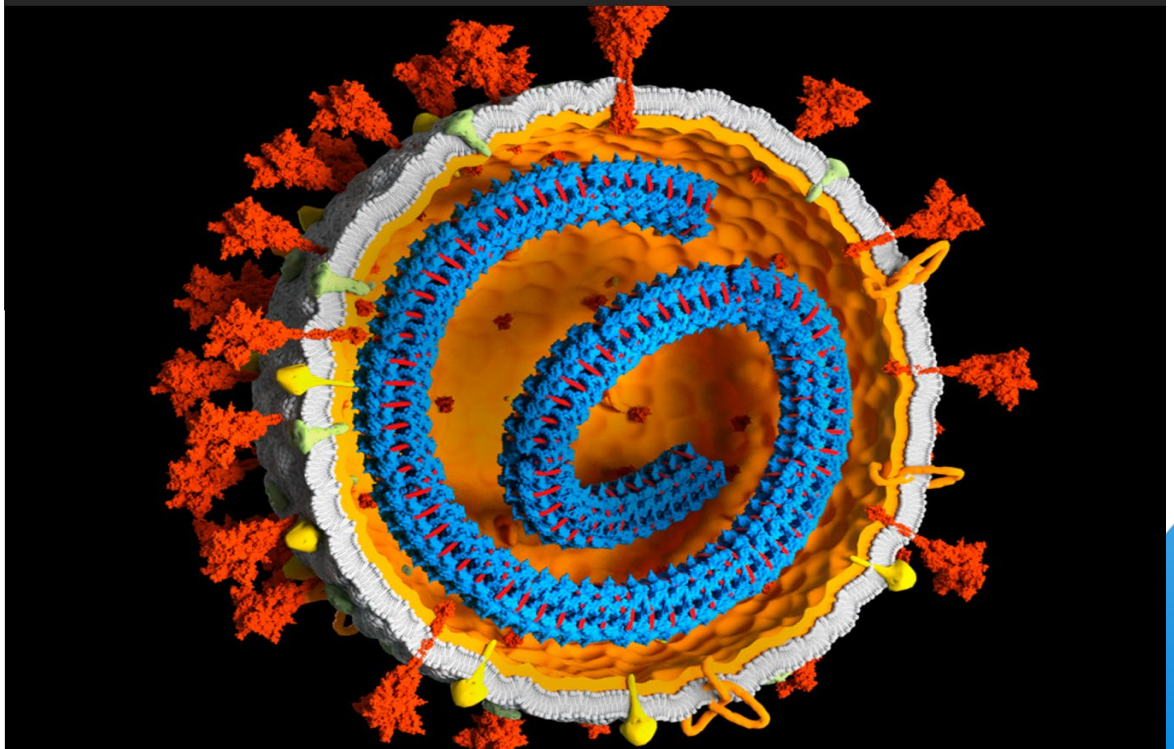
Team Re-RNA Presents:

Safeguards against **mRNA integration**

Further evidence supports controversial claim that SARS-CoV-2 genes can integrate with human DNA

After being challenged, research team provides more data to back its controversial hypothesis but the relevance to human health is unclear

6 MAY 2021 • BY JON COHEN



Cohen, J. (2021, May 6). Further evidence supports controversial claim that sars-cov-2 genes can integrate with human dna. *Science*. Retrieved December 2, 2024, from https://www.science.org/content/article/further-evidence-offered-claim-genes-pandemic-coronavirus-can-integrate-human-dna?adobe_mc=MCMID%3D34177018467205323402286326925583989068%7CMCORGID%3D242B6472541199F70A4C98A6%2540AdobeO

The Issue

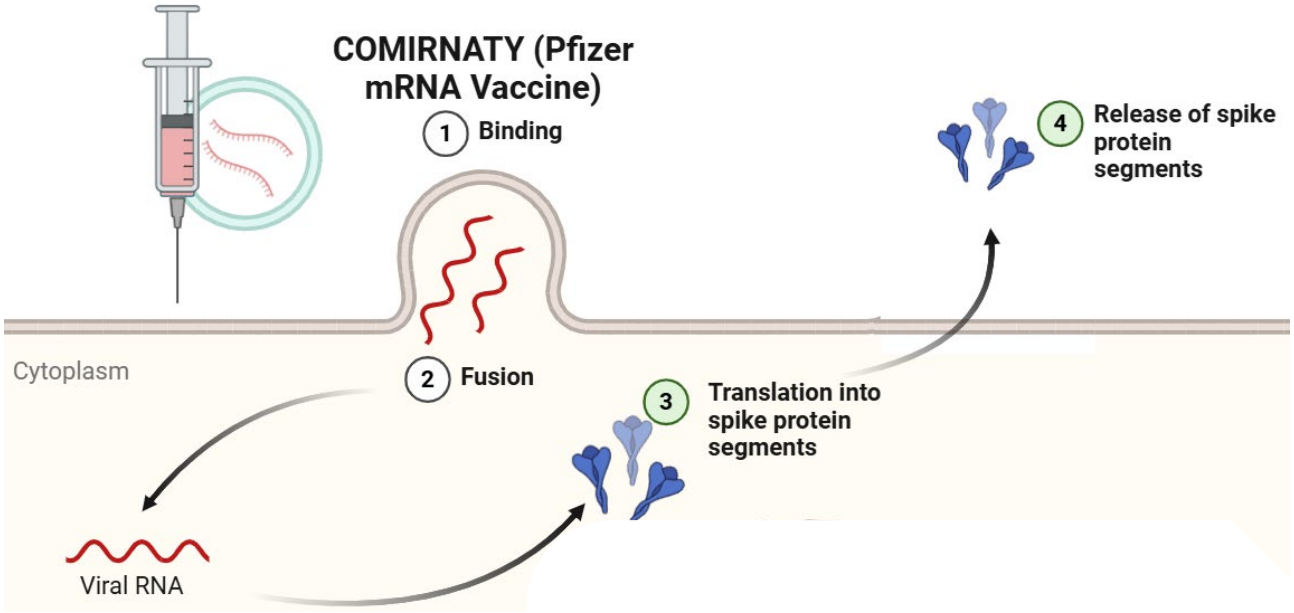
mRNA from the mRNA vaccines has the potential to integrate into immunocompromised patients who have heightened retrotransposon and theta polymerase activity.

FDA Focus Areas

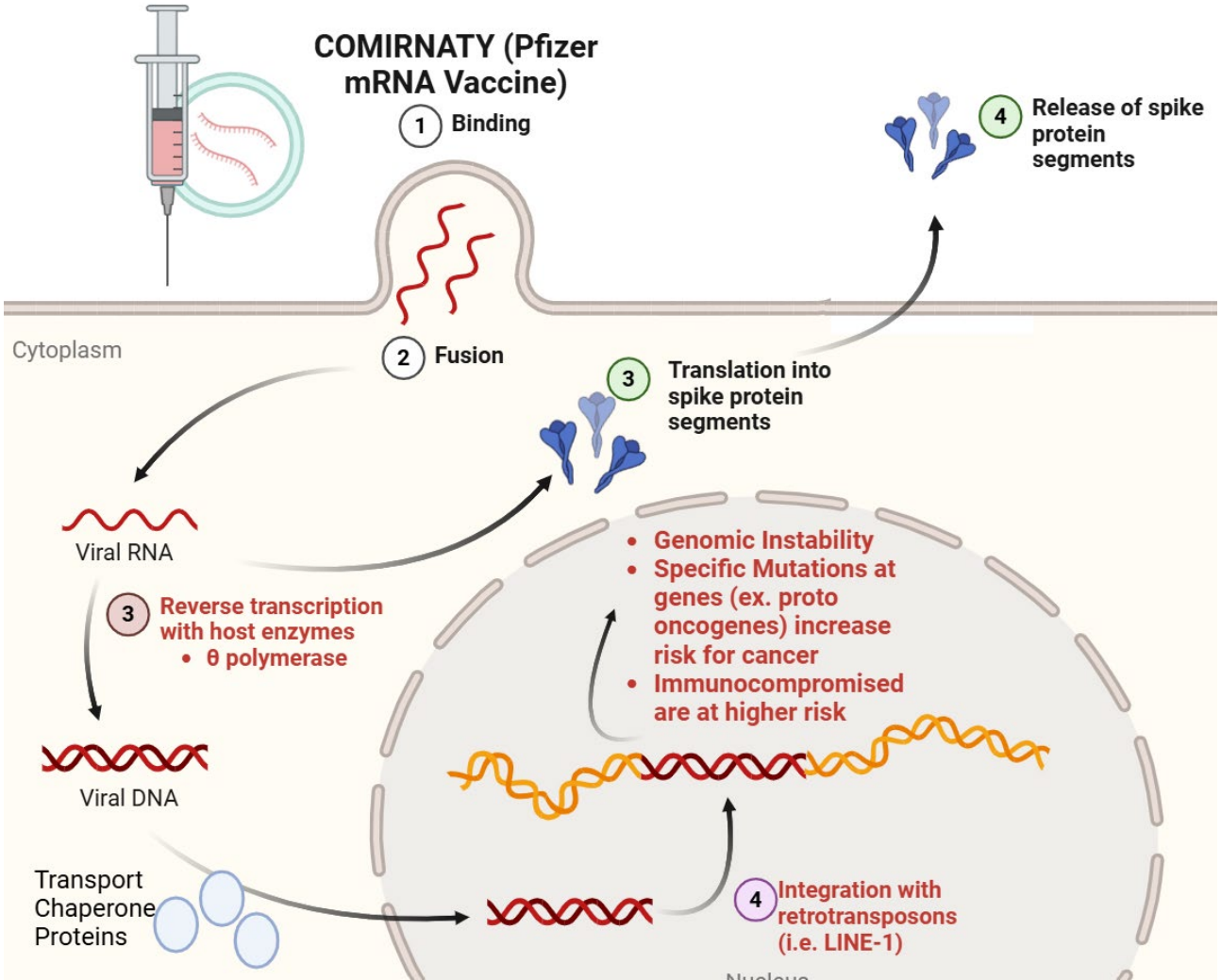
1. Medical countermeasures preparedness for emerging infectious diseases.[1]
2. Model-informed product development.[1]

1. U.S. Food and Drug Administration. (2022, September 6). 2022 Advancing Regulatory Science at FDA: FOCUS AREAS OF REGULATORY SCIENCE (FARS).

The Science



Zhang, L., Bisht, P., Flamier, A., Barrasa, M. I., Friesen, M., Richards, A., Hughes, S. H., & Jaenisch, R. (2023). LINE1-Mediated Reverse Transcription and Genomic Integration of SARS-CoV-2 mRNA Detected in Virus-Infected but Not in Viral mRNA-Transfected Cells. Viruses, 15(3), 629. https://doi.org/10.3390/v15030629



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Research

- Recent study focused on genomic integration of mRNA from Vaccinations
  - Viral RNA integration has been observed
- Multiple mechanisms:
  - Retrotransposons (in humans)
  - θ Polymerase (in humans)
- Need additional testing for immunocompromised patients

Integration Effects

- Genomic Instability
- Specific Mutations (ex. proto oncogenes)
- Immunocompromised are at higher risk

Acevedo-Whitehouse, K., & Bruno, R. (2023). Potential health risks of mRNA-based vaccine therapy: A hypothesis. *Medical hypotheses*, *171*, 111015. https://doi.org/10.1016/j.mehy.2023.111015

Regulation

Regulation Overview

- mRNA vaccines have been under development for decades, but only recently got approved for use during the pandemic
- Heightened potential to integrate has been shown in immunocompromised patients
- Current vaccine testing areas:
    - **CMC Safety evaluation**
        - Antigen detection
        - Affinity detection
        - Efficacy evaluation

Gurushankar Chandramouly *et al.*, Polθ reverse transcribes RNA and promotes RNA-templated DNA repair. *Sci. Adv.* 7, eabf1771 (2021). DOI: 10.1126/sciadv.abf1771

Chemistry Manufacturing and Controls (CMC)

- CMC: Manufacturing stage of pharmaceutical companies
- The FDA's Role:
  - Decide and disseminate CMC Guidances-rules that drug companies must follow while developing drugs
- Focus on safety on mRNA vaccines throughout vaccine regulation
- This is the most important stage to address RNA genomic integration

Workflow for Vaccines R & D. (n.d.). Acrobiosystems. Retrieved from https://www.acrobiosystems.com/A1167-Solutions-for-COVID-19-vaccine-safety-and-immunogenicity-evaluation.html?gad_source=1&gclid=CjwKCAiA3ZC6BhBaEiwAeqfvyot-_1z0CiRZAygdiLqtVdmdLG1TzTYh-kWbL058mlFcDm7u5xzsxxoCc50QAvD_BwE#p3.

Regulatory Solution

Safety tests for integration into genome:

- Nanopore DNA sequencing
  - Checks for entry into genome and genomic sequencing[1,3]
  - Inexpensive: ~$2,000 to buy the sequencer[3]
- Illumina
  - Faster than DNA sequencing[1,2]
  - More expensive [$3,350 for 150 cycles of high output sequencing][2]

1) Cohen, J. (2021, May 6). Further evidence supports controversial claim that sars-cov-2 genes can integrate with human dna. *Science*. Retrieved December 2, 2024, from https://www.science.
dna?adobe_mc=MCMID%3D34177018467205323402286326925583989068%7CMCORGID%3D242B6472541199F70A4C98A6%2540AdobeOrg%7CTS%3D1732569232.
2) Illumina NextSeq sequencing " Microarray and Sequencing Resource: Boston University. Microarray and Sequencing Resource RSS. (n.d.). https://www.bumc.bu.edu/microarray/pricing/illumina-pricing/
3) Minion Portable Nanopore sequencing device. Oxford Nanopore Technologies. (n.d.-b). https://nanoporetech.com/products/sequence/minion

Implementation

Steps FDA can take: Update CMC guidances for mRNA vaccine testing to include integration testing for companies to follow

Cohen, J. (2021, May 6). Further evidence supports controversial claim that sars-cov-2 genes can integrate with human dna. *Science*. Retrieved December 2, 2024, from https://www.science.org/content/article/further-evidence-offered-claim-genes-pandemic-coronavirus-can-integrate-human-dna?adobe_mc=MCMID%3D34177018467205323402286326925583989068%7CMCORGID%3D242B6472541199F70A4C98A6%2540AdobeOrg%7CTS%3D1732569232.

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Thank You!