COVID-19 mRNA vaccine (BNT162)

Mechanism of Action for BNT162B2

WHAT IS THE MECHANISM OF ACTION OF THE BNT162B2 VACCINE?

This letter includes information of an off-label nature. The candidate COVID-19 mRNA vaccine (BNT162b2) is an investigational product and currently not approved by regulatory agencies for use outside of the clinical trial setting.

Summary of the Mechanism of Action

Pfizer and BioNTech's COVID-19 vaccine candidate, BNT162b2, is comprised of a nucleoside-modified messenger RNA (modRNA) encoding an optimized viral full-length spike (S) glycoprotein of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The S glycoprotein is the target of virus neutralizing antibodies. The messenger RNA (mRNA) is encapsulated in lipid nanoparticles (LNPs) which enables entry into host cells by protecting the naked mRNA from RNases after injection and enhancing its uptake into cells surrounding the injection site by endocytosis. Thus, formulation in LNPs enables expression of the S protein, and elicitation of both antibody and cellular immune responses.[1,2,3]

mRNA is the connecting step between the protein-encoding deoxyribonucleic acid (DNA) and protein - or antigen - production in the cellular cytoplasm by ribosomes.[4,9] Once the mRNA used in a vaccine is inside the body's cells, the cells use their genetic machinery to translate the genetic information and produce the antigens encoded by the mRNA vaccine. The antigens are then displayed on the cell surface, where they are recognized by the immune system which generates a response, including the production of antibodies against the antigen.[4] Figure 1 provides an illustration of the proposed mechanism of action of LNP mRNA vaccines.

Figure 1. Schematic Illustration of the Mechanism of Action of LNP mRNA Vaccines[3]

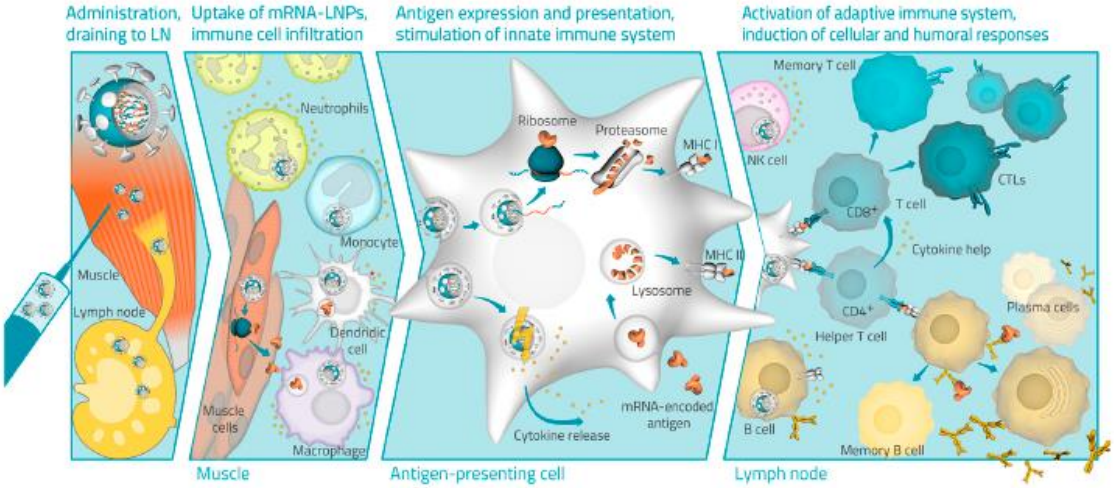


Image from Armbruster et al, 2019[3]

LITERATURE SEARCH

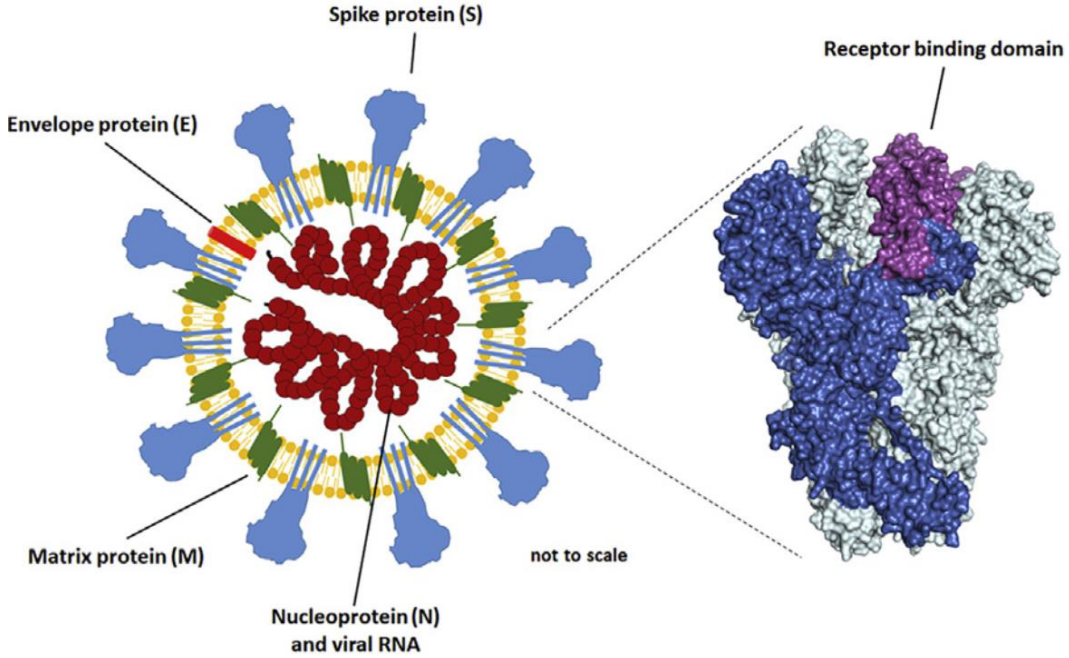
As of September 29, 2020, a search of the published medical literature identified some information regarding the mechanism of action for BNT162b2, including publications that discuss general information regarding the spike protein targets, the general structure of mRNA vaccines and a proposed mechanism of action of mRNA vaccines from an animal model of a rabies mRNA vaccine. A summary of this information follows.

DETAILED MECHANISM OF ACTION

Betacoronaviruses Group Viral Proteins

SARS-CoV-2 is a positive-strand RNA virus from the Betacoronavirus group which has 4 major structural proteins; the spike (S) protein, nucleocapsid (N) protein, membrane or matrix (M) protein, and the envelope (E) protein (Figure 2). The S protein is a densely glycosylated spike protein exposed at the viral surface which allows it to be directly recognized by the host's immune system. The S protein binds to the host cell angiotensin converting enzyme 2 (ACE2) receptor and mediates the virus entry into the target cell, which is essential in the pathogenicity process.[5,6,7,8]

Figure 2. Structure of a Coronavirus Particle and Spike Protein[7]



* The spike structure shown is based on the trimeric SARS-CoV-1 spike
Image from Amanat et al, 2020[7]

The SARS-CoV-2 S protein is a trimeric class 1 fusion protein which exists in a metastable prefusion conformation that must undergo rearrangement in order to engage with the host cell membrane. The receptor-binding-domain (RBD) of the S1 subunit undergoes hinge-like movements which expose or hide the determinants of the RBD, thus resulting in 2 different conformation states; “down” and “up”, corresponding to a receptor-inaccessible state and a receptor-accessible state, respectively. Since the correct function of the S protein is required for SARS-CoV-2 engagement with host cells, it is a suitable target for antibody-mediated neutralization.[5,8]

mRNA and Vaccine Mechanism of Action

mRNA is the connecting step between the translation of protein-encoding DNA and protein - or antigen - production in the cellular cytoplasm by ribosomes. BNT162b2 vaccine is comprised of a modRNA encoding an optimized viral full-length spike glycoprotein of SARS-CoV-2.[1,2,4,9] The spike protein RNA is modified by the introduction of 2 proline mutations which has been shown to stabilize the S protein in the prefusion conformation.[8,10,11]

Figure 3 depicts the structure of conventional mRNA-based vaccines. The open reading frame (ORF) encodes the protein of interest (S protein in the case of BNT162b2 vaccine), flanked by 5’ and 3’ untranslated regions (UTRs), a 5’ cap and a poly(A) tail. The mRNA is engineered to

resemble mature, fully processed mRNA molecules as naturally found in the cytoplasm of eukaryotic cells.[9] The BNT162b2 vaccine mRNA is encapsulated in LNPs which protect the mRNA from degradation by RNases and enable entry into host cells and expression of the S protein.[1,2,3]

Figure 3. Structure of Conventional mRNA Vaccine[12]

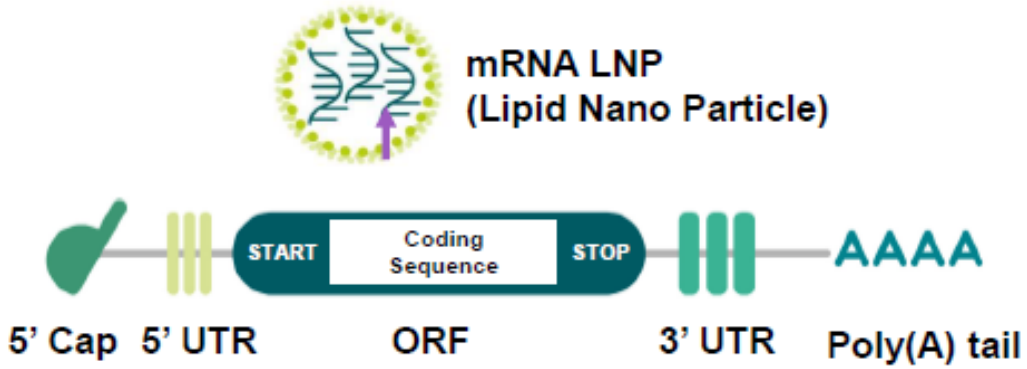


Image adapted from Jackson et al, 2020[12]

Based on preclinical studies in mice and non-human primates of an investigational mRNA rabies vaccine (CV7201; a vaccine candidate under investigation by CureVac AG) the following potential mechanism of action for LNP mRNA vaccines has been postulated: After its release in the cytoplasm of temporarily transfected cells, such as, induced neutrophils, nonleukocytic cells and resident professional antigen-presenting cells (APCs), the mRNA is expressed into the target antigen. These antigenic peptides are subsequently presented on major histocompatibility (MHC) class I and MHC class II molecules of immunologically relevant cells. The expression of the antigens on APCs surfaces leads to recognition by CD4+ and CD8+ cells resulting in immune response expansion. Additionally, intramuscular injection of the vaccine is expected to activate the innate immune system with transient local increases in proinflammatory cytokines, mainly IL-6 and tumor necrosis factor (TNF), which results in the formation of an immunostimulatory environment at the injection site and in draining lymph nodes. The detection of circulating antibodies in the blood of vaccinated animals showed that induction of high levels of antibody-producing B cells was associated with humoral responses.[3]

Please refer to Figure 1 above for an illustration of the mechanism of action of LNP mRNA vaccines.

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