COVID-19 mRNA Vaccines

Mechanism of Action for:
- Moderna COVID-19 Vaccine (mRNA-1273)
- Pfizer BioNTech COVID-19 Vaccine (BNT-162b2)

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Slides WITH Text
DNA versus RNA

• To understand mRNA vaccines it is important to understand fundamental differences between DNA and RNA
• DNA has two backbone strands whereas RNA usually has only one strand
• DNA functions to encode, store, and replicate genetic information
• RNA converts the genetic code information contained in the DNA to proteins
• RNA contains the uracil base pair in place of the thymidine base pair used in DNA

Image credit: Cognition Studio, Inc.
Basic Flow of Genetic Information for Protein Formation in Humans

- In human cells, the flow of genetic information to protein formation is DNA to RNA to protein
- DNA replication is the process whereby identical copies of the original DNA are made and this occurs in the nucleus of the cell
- Transcription occurs in the nucleus and it is the first step in protein synthesis: an RNA copy is made from DNA and the RNA then moves into the host cytoplasm
- Translation is the process by which mRNA is decoded in the process of protein synthesis and this occurs in the cell cytoplasm
Ribosome Structure and Function

- The ribosome is made up of about 2/3 rRNA and 1/3 proteins.
- Each ribosome has a large and small subunit.
- The ribosome provides template slots for the sequential addition of the amino acids in the formation of the polypeptide protein precursor.
- The ribosome also functions as an enzyme that catalyzes the reaction needed to link amino acids together.
Types of RNA

• The three most common types of ribonucleic acid (RNA) are:
  - messenger RNA (mRNA)
  - transfer RNA (tRNA)
  - ribosomal RNA (rRNA)

• The RNAs play an essential role in protein production

• mRNA carries the genetic information from the nucleus to make proteins in the cytoplasm

• tRNA connects mRNA with the amino acids encoded by the mRNA codon

• rRNA is the main structural functional component of the ribosome and it serves to catalyze reactions
SARS-CoV-2 Virus Structure

- SARS-CoV-2 is a single-stranded RNA enveloped virus
- The spike protein is the major surface protein on SARS-CoV-2 and it plays a key role in binding to the host cell receptors
- The spike protein is the primary target of the host immune response to SARS-CoV-2 infection
- Spike protein is an optimal immunologic target to use for COVID-19 vaccines
COVID-19 mRNA Vaccines

- COVID-19 mRNA vaccines consist of mRNA surrounded by a lipid nanoparticle (LNP)
- The LNP has two main functions:
  1. Protect the mRNA from being degraded and destroyed
  2. Facilitate cellular uptake of the mRNA
- The coding region (orange) is a genetically engineered sequence of nucleoside modified mRNA that encodes for the prefusion-stabilized SARS-CoV-2 spike protein
- The Cap 5’ and 3’ UTR elements enhance the stability and translation of the mRNA

Image credit: Cognition Studio, Inc.
COVID-19 mRNA Vaccines

- This is a simplified view of the lipid nanoparticle (LNP) that surrounds the mRNA
- The LNP has two main functions:
  1. Protect the mRNA from being degraded and destroyed
  2. Facilitate cellular uptake of the mRNA
- The coding region (orange) is a genetically engineered sequence of nucleoside modified mRNA that encodes for the prefusion-stabilized SARS-CoV-2 spike protein
- The Cap 5’ and 3’ UTR elements enhance the stability and translation of the mRNA

Image credit: Cognition Studio, Inc.
COVID-19 mRNA Vaccine Delivery

- The mRNA vaccines—Moderna COVID-19 Vaccine (mRNA-1273) and Pfizer-BioNTech COVID-19 (BNT-162b2)—are administered as intramuscular injections.

- Both of the mRNA vaccines require 2 doses.

  Moderna COVID-19 Vaccine
  - Give 2 doses (each 0.5 mL)
  - Give 1 month (28 days) apart
  - Each dose contains 100 µg mRNA

  Pfizer-BioNTech COVID-19 Vaccine
  - Give 2 doses (each dose 0.3 mL)
  - Give 3 weeks (21 days) apart
  - Each dose contains 30 µg mRNA

- The vaccines should not be interchanged.
Modernah COVID-19 Vaccine (mRNA-1273): Mechanism of Action

- The mRNA-1273 enters the cell cytoplasm and does not enter the nucleus
- The mRNA is non-replicating and is present transiently within the cell
- The mRNA is translated by the ribosomes to form prefusion-stabilized SARS-CoV-2 spike proteins
- The spike proteins are shuttled to the surface of the cell and are presented to the immune system
- The spike proteins are also processed into small peptides that also are presented to the immune system
Pfizer-BioNTech COVID-19 Vaccine (BNT-162b2): Mechanism of Action

- The BNT-162b2 mRNA enters the cell cytoplasm and does not enter the nucleus.
- The mRNA is non-replicating and is present transiently within the cell.
- The mRNA is translated by the ribosomes to form prefusion-stabilized SARS-CoV-2 spike proteins.
- The spike proteins are shuttled to the surface of the cell and are presented to the immune system.
- The spike proteins are also processed into small peptides that also are presented to the immune system.
Immune Response to COVID-19 mRNA Vaccines

- The immune system responds to the antigens on the surface of the cell produced by the COVID-19 mRNA vaccines.
- The vaccines generate cellular immune responses (T-cell) and and humoral responses (B-cell).
- The immune response includes:
  1. Activation of cytotoxic CD8⁺ T cells that can destroy cells infected with SARS-CoV-2
  2. Activation of CD4⁺ T cells that augment both CD8⁺ T-cell and B-cell responses
  3. Generation of memory T and B cells that can quickly respond to future SARS-CoV-2 infection
  4. Activation of B cells to produce antibodies against SARS-CoV-2

Image credit: Cognition Studio, Inc.
Moderna COVID-19 Vaccine (mRNA-1273)

• **Indication**
  - Investigational (Not approved by U.S. FDA)
  - Authorized for use under an Emergency Use Authorization (EUA) for active immunization to prevent coronavirus disease 2019 (COVID-19) in individuals 18 years of age and older

• **Dosing and Schedule**
  - Administer intramuscularly as a series of two doses (0.5 mL each) 1 month apart

• **Vaccine Storage (See EAU Fact Sheet* for Details)**
  - Multiple-dose vials are stored frozen between -25° to -15°C (-13° to 5°F)
  - Do not store on dry ice or at temperatures below -40°C (-40°F)
  - Vials can be stored refrigerated between 2° to 8°C (36° to 46°F) for up to 30 days prior to first use
  - Store in original carton to protect from light
  - Unpunctured vials may be stored between 8° to 25°C (46° to 77°F) for up to 12 hours
  - After first dose withdrawn, keep vial between 2° to 25°C (36° to 77°F) and discard vial after 6 hours and do not refreeze

*Moderna COVID-19 Vaccine Fact Sheet (https://www.fda.gov/media/144637/download)
Pfizer-BioNTech COVID-19 Vaccine (BNT-162b2)

• **Indication**
  - Investigational (Not approved by U.S. FDA)
  - Authorized for use under an Emergency Use Authorization (EUA) for active immunization to prevent coronavirus disease 2019 (COVID-19) in individuals 16 years of age and older.

• **Dosing and Schedule**
  - Administer intramuscularly as a series of two doses (0.3 mL each) 3 weeks apart

• **Vaccine Storage (See EAU Fact Sheet* for Details)**
  - Cartons arrive in thermal containers on dry ice
  - Thermal container maintains a temperature range of -90°C to -60°C (-130°F to -76°F)
  - Vials require storage in ultra-low temperature freezer at -80°C to -60°C (-112°F to -76°F)
  - Vials require protection from light until ready to use
  - Thaw and store undiluted vials in refrigerator at 2°C to 8°C (35°F to 46°F) for up to 5 days (120 hours)
  - For immediate use, thaw undiluted vials at room temperature [up to 25°C (77°F)] for 30 minutes
  - After dilution, store vials between 2°C to 25°C (35°F to 77°F) and use ≤6 hours from time of dilution; do not refreeze

*Pfizer-BioNTech COVID-19 Vaccine Fact Sheet (https://www.fda.gov/media/144413/download)
DNA versus RNA

Deoxyribonucleic acid (DNA)
- Adenine
- Guanine
- Cytosine
- Thymine

Ribonucleic acid (RNA)
- Adenine
- Guanine
- Cytosine
- Uracil

Image credit: Cognition Studio, Inc.
Basic Flow of Genetic Information for Protein Formation in Humans

DNA → Replication → RNA → Transcription → Translation → Protein

Image credit: Cognition Studio, Inc.
Ribosome Structure and Function

Ribosome

rRNA

Polypeptide

mRNA

Large Subunit

Small Subunit

Image credit: Cognition Studio, Inc.
Types of RNA

- mRNA
- tRNA
- Amino acid
- Ribosome
- rRNA

Image credit: Cognition Studio, Inc.
SARS-CoV-2 Virus Structure

- Spike protein (closed)
- Envelope (E) protein
- Membrane (M) protein
- Nucleocapsid protein
- Viral RNA
- Spike protein (open)
  - Receptor binding domain (RBD)

Image credit: Cognition Studio, Inc.
COVID-19 mRNA Vaccines

Image credit: Cognition Studio, Inc.
COVID-19 mRNA Vaccines

Lipid nanoparticle (LNP)

Cap 5' UTR  Coding region (ORF)  3' UTR  Poly (A) tail

5' mRNA

Phospholipid layer

Polyethylene glycol (PEG)

Image credit: Cognition Studio, Inc.
COVID-19 mRNA Vaccine Delivery

- mRNA vaccine
- Deltoid muscle
- Lymph node

Image credit: Cognition Studio, Inc.
Moderna COVID-19 Vaccine (mRNA-1273): Mechanism of Action

Extracellular space

mRNA-1273 mRNA in lipid nanoparticle

mRNA release

Ribosome

Polypeptide

Endoplasmic reticulum

Cytosol

SARS-CoV-2 peptide processing

Nucleus

Golgi

SARS-CoV-2 Spike protein membrane insertion

T-cell activation

MHC II

B-cell activation

BCR

Image credit: Cognition Studio, Inc.
Pfizer-BioNTech COVID-19 Vaccine (BNT162b2): Mechanism of Action

Extracellular space

BNT162b2 mRNA in lipid nanoparticle

mRNA release

Cytosol

Ribosome

Polypeptide

Endoplasmic reticulum

Nucleus

T-cell activation

SARS-CoV-2 peptide processing

SARS-CoV-2 Spike protein membrane insertion

MHC II

MHC I

BCR

B-cell activation

Image credit: Cognition Studio, Inc.
Immune Response to COVID-19 mRNA Vaccines

mRNA in LNP

LNP enters and releases mRNA

Antigen presenting cell

Spike protein/peptide presentation on surface

Translation

CD8+ cytotoxic T-cell activation

CD4+ helper T-cell activation

B-cell activation

Elimination of SARS-CoV-2-infected cells

Memory T and B cells

Immune response

SARS-CoV-2 neutralizing antibodies

Image credit: Cognition Studio, Inc.
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• **Dosing and Schedule**
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  – Multiple-dose vials are stored frozen between -25° to -15°C (-13° to 5°F)
  – Do not store on dry ice or at temperatures below -40°C
  – Vials can be stored refrigerated between 2° to 8°C (36° to 46°F) for up to 30 days prior to first use
  – Unpunctured vials may be stored between 8° to 25°C (46° to 77°F) for up to 12 hours
  – After first dose withdrawn, keep vial between 2° to 25°C (36° to 77°F) and discard vial after 6 hours

*Source: Moderna COVID-19 Vaccine Fact Sheet for Health Care Providers (https://www.fda.gov/media/144637/download)*
Pfizer-BioNTech COVID-19 Vaccine (BNT162b2)

• **Indication**
  - Investigational (Not approved by U.S. FDA)
  - Authorized for use under an Emergency Use Authorization (EUA) for active immunization to prevent coronavirus disease 2019 (COVID-19) in individuals 16 years of age and older.

• **Dosing and Schedule**
  - Administer intramuscularly as a series of two doses (0.3 mL each) 3 weeks apart

• **Vaccine Storage (See EUA Fact Sheet* for Details)**
  - Cartons arrive in thermal containers on dry ice
  - Thermal container maintains a temperature range of -90°C to -60°C (-130°F to -76°F).
  - Vials require storage in ultra-low temperature freezer at -80°C to -60°C (-112°F to -76°F)
  - Thaw and store undiluted vials in refrigerator [2°C to 8°C (35°F to 46°F)] for up to 5 days (120 hours)
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*Source: Pfizer-BioNTech COVID-19 Vaccine Fact Sheet (https://www.fda.gov/media/144413/download)