Module 3: Applications for mRNA Medicine
Summary

Prophylactic mRNA vaccines Part 1

- Prophylactic vaccines are used to prevent disease
- Vaccines work by exposing our immune system to a new infectious agent:
  - Antigen presenting cells (APCs) display antigens, or foreign proteins, on their surface
  - When the antigen is recognized by immune cells:
    - B cells mature and secrete antibodies specific to the pathogen
    - Cytotoxic T cells seek out the infection to eliminate it
  - mRNA vaccines use the LNP to provide APCs with the instructions to make the antigenic protein themselves
- Because a majority of the material required to create a complete pathogen is not present in mRNA vaccines, there is no way they can cause an active infection

Prophylactic mRNA vaccines Part 2

- mRNA vaccines can be multiplexed which means:
  - Combination vaccines can provide mRNA sequences for multiple infectious agents in one medicine
  - A vaccine can be produced even if the antigen is a multiprotein complex
- mRNA vaccines are limited by the maximum tolerated dose, or the largest amount of LNP that can be dosed without causing severe side effects:
  - Each mRNA sequence has its own potency
  - Therefore, multiplexed vaccines are limited by the total amount of mRNA needed to elicit an appropriate immune response, not the number of different mRNA sequences
- Advantages of mRNA vaccine development:
  - Can be made using equipment the size of a large refrigerator
  - Can be produced very quickly, helping to avoid genetic drift and, thus, increasing their efficacy
  - The component materials for both mRNAs and LNPs are the same, regardless of mRNA sequence
- Disadvantages of mRNA vaccines:
  - mRNA is relatively fragile
  - Must be kept at low temperatures to slow degradation
- Formulation modifications (e.g., lyophilization, microneedle patches) may help preserve vaccine potency

mRNA therapeutics that stimulate the immune system

- Individualized neoantigen therapies (INTs; aka personalized cancer vaccines):
  - Train the immune system to recognize an individual's unique cancer by activating the body's immune response to recognize neoantigens
  - Are created by sequencing patient tissue samples for neoantigen mutations and designing mRNAs that encode the neoantigen
  - Must be administered multiple times for optimal immune response, similar to prophylactic vaccines

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- INTs and prophylactic vaccines form a class called immunogenic mRNA medicines

Non-immunogenic mRNA therapeutics

- Non-immunogenic mRNA medicines supply the body with instructions for a protein to produce a therapeutic effect
- Potential uses include:
  - Treatment of metabolic diseases (intracellular protein replacement):
    - Most metabolic enzymes are intracellular and many are primarily produced in the liver
    - mRNA medicines targeting liver enzymes:
      - Require larger doses
      - Must be delivered systemically (e.g., intravenously)
      - Require chronic repeat dosing
    - Show promise in early-stage clinical trials
  - Transmembrane protein replacement:
    - E.g., CFTR protein replacement via inhalable mRNA therapy to treat cystic fibrosis
  - Regenerative medicine:
    - mRNAs encoding different signaling proteins can trigger immediate-early signaling events to cause stem cells to divide and differentiate
    - Examples being explored include stimulation of blood vessel growth and urinary sphincter muscle repair
  - Secreted protein therapy:
    - E.g., directing the body to make functional monoclonal antibodies to treat established infections