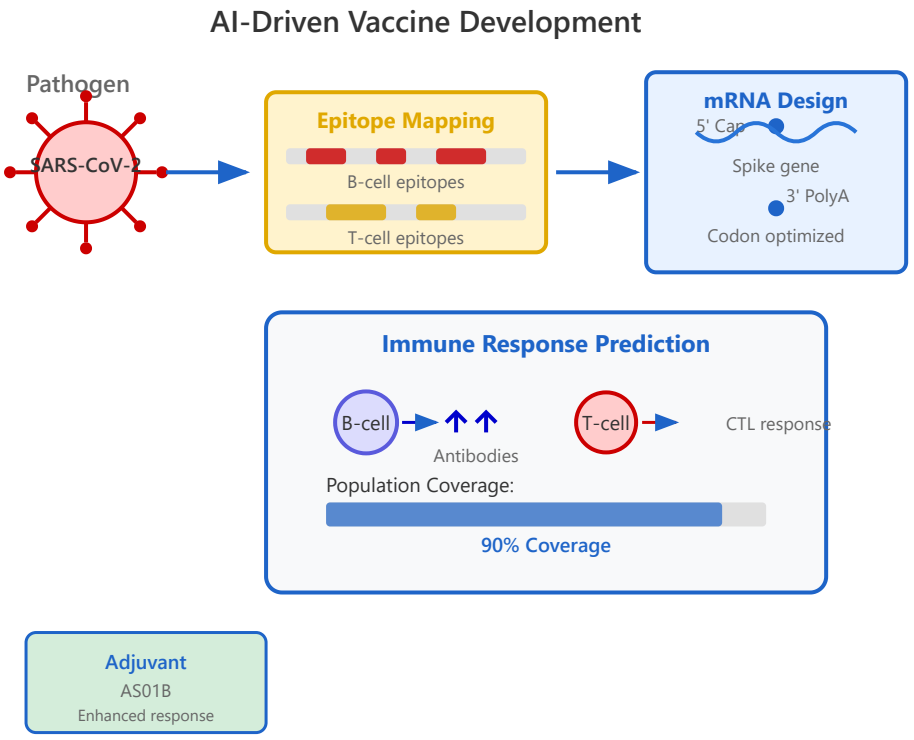
Vaccine Design



Epitope prediction
B-cell & T-cell epitopes

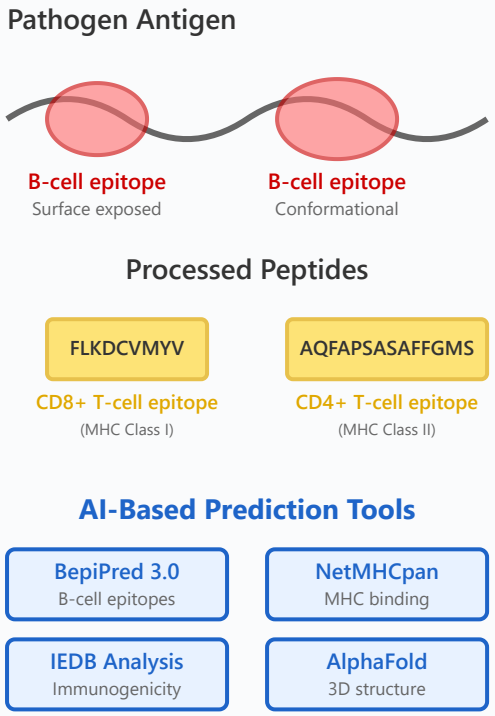
Immunogenicity
Immune response modeling

Coverage optimization
Population HLA diversity

Adjuvant selection
Enhance immune response

mRNA design
Codon optimization & stability

1. Epitope Prediction



Overview

Epitope prediction identifies specific regions on pathogen proteins that are recognized by the immune system. These epitopes serve as the primary targets for vaccine-induced immunity.

B-Cell Epitopes

B-cell epitopes are recognized by antibodies and can be:

- **Linear epitopes:** Continuous amino acid sequences (5-15 residues)
- **Conformational epitopes:** Discontinuous sequences brought together by protein folding
- **Surface accessibility:** Must be exposed on the pathogen surface

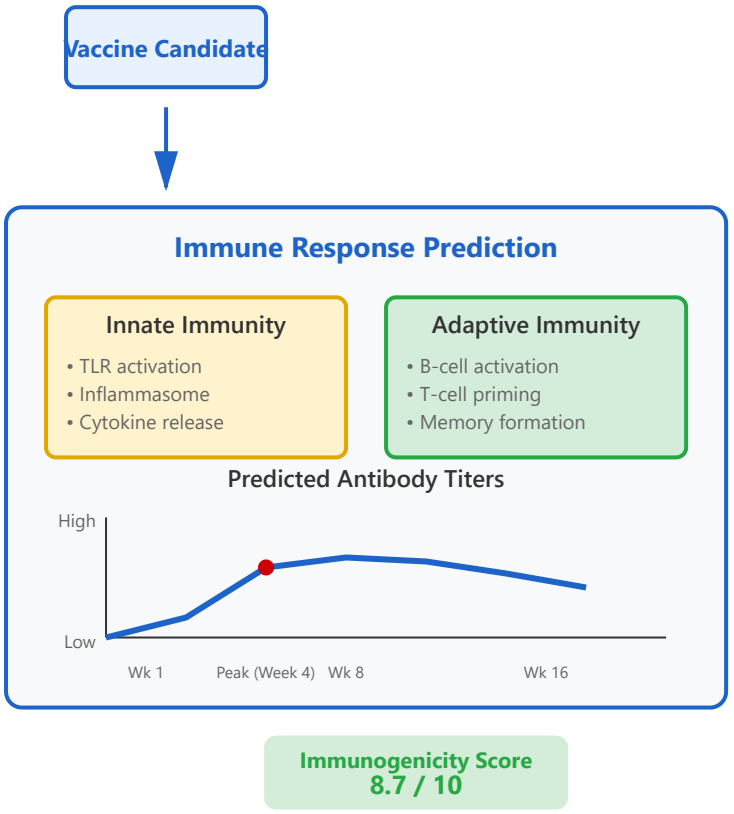
T-Cell Epitopes

T-cell epitopes are short peptide sequences presented by MHC molecules:

- **MHC Class I (8-11 amino acids):** Activates CD8+ cytotoxic T-cells
- **MHC Class II (13-25 amino acids):** Activates CD4+ helper T-cells
- **Processing requirements:** Must be cleaved and loaded properly

> **Key Tools:** Modern epitope prediction uses machine learning algorithms like BepiPred 3.0, NetMHCpan 4.1, and IEDB tools, achieving >85% accuracy in identifying immunogenic epitopes.

2. Immunogenicity Prediction



Overview

Immunogenicity prediction assesses how strongly a vaccine candidate will stimulate the immune system. This involves modeling both innate and adaptive immune responses.

Key Factors

- **Antigen dose:** Optimal concentration for immune activation without tolerance
- **Route of administration:** Intramuscular, subcutaneous, or intradermal delivery
- **Adjuvant effects:** Enhancement of immune recognition and response
- **Epitope density:** Number and spacing of immunogenic sites

Response Modeling

AI models predict multiple immune parameters:

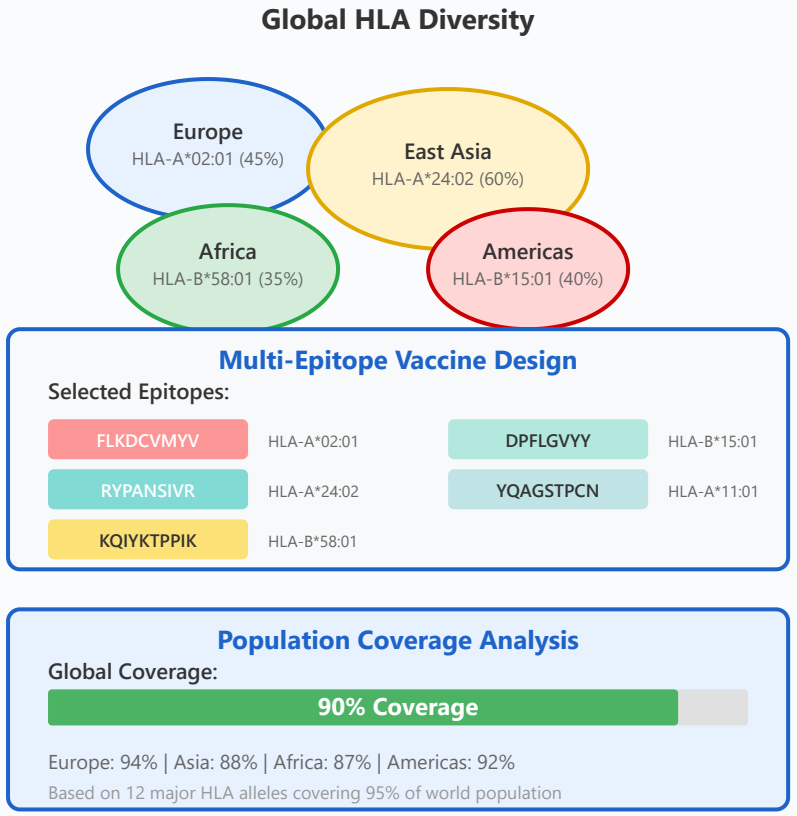
- **Antibody titers:** Concentration and kinetics over time
- **T-cell response:** CD4+ and CD8+ activation levels
- **Cytokine profiles:** Type and magnitude of inflammatory response
- **Memory formation:** Long-term protection durability

Clinical Validation: Immunogenicity predictions are validated against clinical trial data, with modern algorithms achieving >75% accuracy in predicting successful vaccine candidates.

Safety Considerations

Models also evaluate potential adverse reactions including autoimmunity risk, excessive inflammation, and allergic responses to ensure a favorable benefit-risk profile.

3. Population Coverage Optimization



Overview

Population coverage optimization ensures that a vaccine will be effective across diverse human populations, accounting for genetic variation in immune response genes (HLA alleles).

HLA Diversity Challenge

Human Leukocyte Antigen (HLA) genes are the most polymorphic in the human genome:

- **Thousands of alleles:** Over 28,000 HLA alleles identified globally
- **Geographic variation:** Different populations have distinct HLA frequency distributions
- **Peptide binding specificity:** Each HLA allele binds different peptide sequences

Optimization Strategy

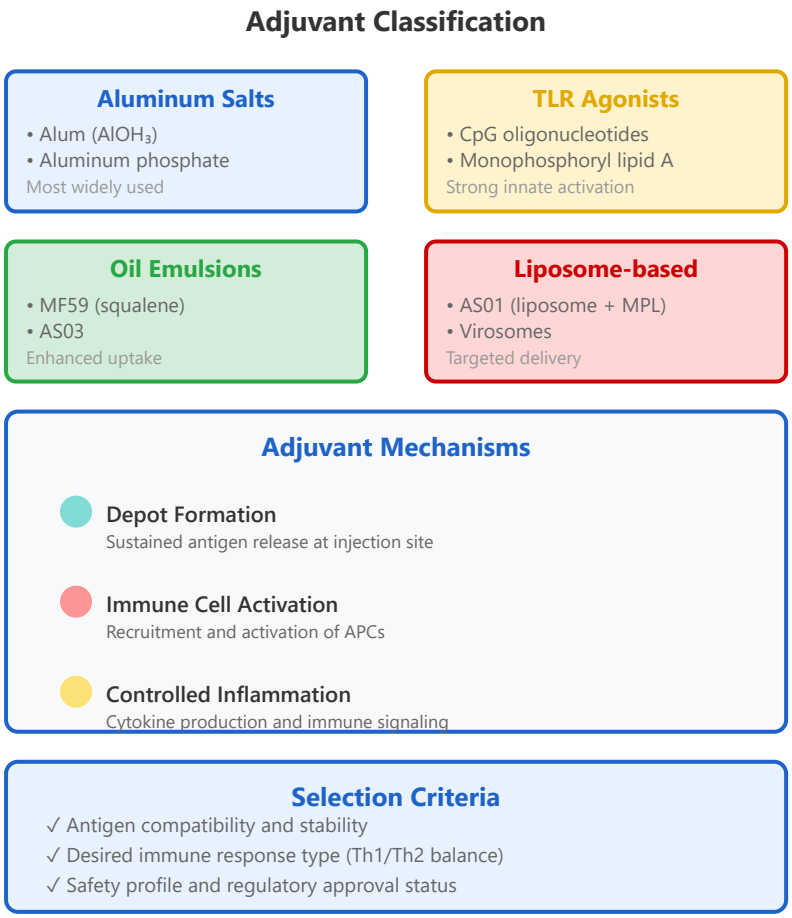
- **Multi-epitope approach:** Include 8-15 epitopes targeting multiple HLA alleles
- **Frequency weighting:** Prioritize alleles that are common across populations
- **Conserved regions:** Select epitopes from pathogen regions with low mutation rates
- **Redundancy:** Multiple epitopes per HLA allele for robust coverage

> **Coverage Targets:** Modern vaccines aim for ≥90% population coverage globally. The COVID-19 mRNA vaccines achieve ~95% coverage by targeting highly conserved spike protein epitopes.

Computational Tools

Tools like IEDB Population Coverage, OptiVax, and Vaxign use algorithms to select optimal epitope combinations that maximize coverage while minimizing the number of epitopes needed.

4. Adjuvant Selection



Overview

Adjuvants are substances added to vaccines to enhance and direct the immune response. Proper adjuvant selection is critical for vaccine efficacy and safety.

Functions of Adjuvants

- **Immunopotentiation:** Increase magnitude of immune response
- **Dose-sparing:** Achieve protection with less antigen
- **Response shaping:** Direct toward Th1 or Th2 response
- **Duration enhancement:** Prolong immune memory

Major Adjuvant Classes

Aluminum-based adjuvants: Most commonly used, promote Th2 responses and antibody production. Safe track record with over 70 years of use.

TLR agonists: Activate pattern recognition receptors, inducing strong innate immunity and Th1 responses. Examples include CpG-ODN (TLR9) and MPL (TLR4).

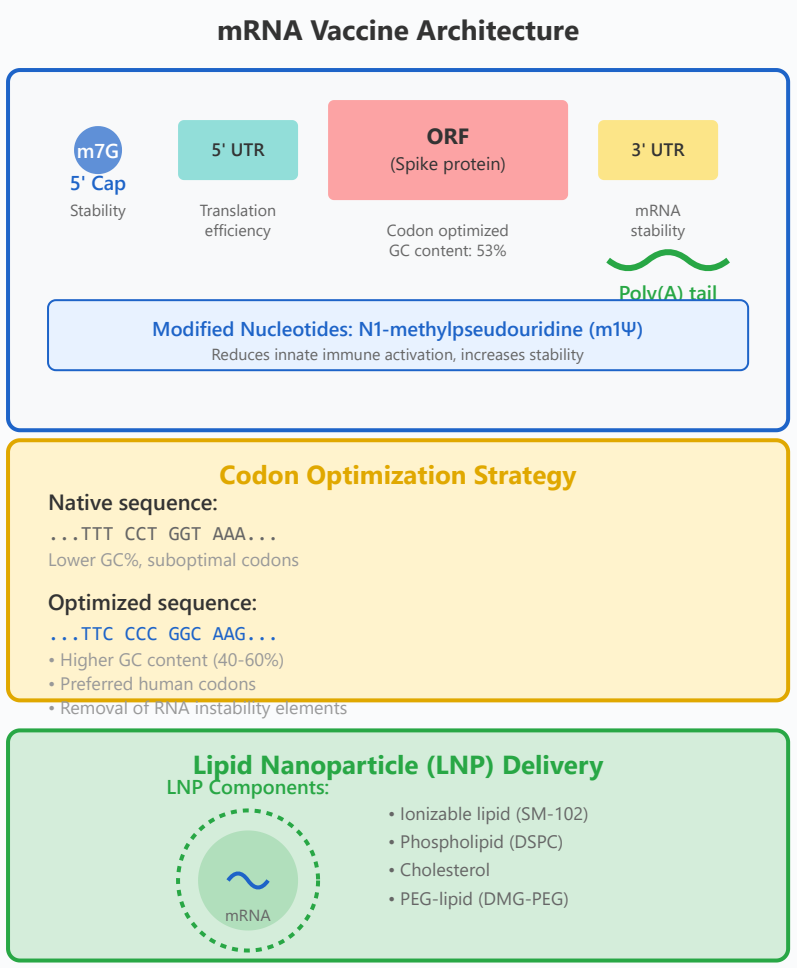
Emulsion-based: Oil-in-water emulsions like MF59 and AS03 enhance antigen uptake and presentation, particularly effective for influenza vaccines.

> **Case Study:** The AS01B adjuvant used in the Shingrix vaccine combines liposomes with MPL and QS-21 saponin, achieving >90% efficacy in elderly populations by strongly activating both innate and adaptive immunity.

Selection Strategy

Adjuvant choice depends on target pathogen, patient population (age, immune status), desired response type, and regulatory considerations. AI models can predict optimal adjuvant-antigen combinations based on immunological data.

5. mRNA Vaccine Design



Overview

mRNA vaccines represent a revolutionary platform that instructs cells to produce antigens directly. Successful design requires optimization of multiple molecular features for stability, translation efficiency, and immunogenicity.

Key Structural Elements

5' Cap structure: Modified guanosine cap (m7G or cap1) protects against degradation and enables ribosome binding for translation initiation.

Untranslated Regions (UTRs): The 5' UTR contains regulatory elements for translation efficiency, while the 3' UTR provides stability signals and poly(A) binding sites.

Open Reading Frame (ORF): Encodes the target antigen with extensive codon optimization to maximize expression while maintaining protein structure.

Codon Optimization

- **GC content balance:** Target 50-60% for optimal stability and translation
- **Codon usage:** Replace rare codons with frequently used human codons
- **Secondary structure:** Minimize hairpins and self-complementary regions
- **Immune evasion:** Remove CpG dinucleotides and uridine-rich motifs

Modified Nucleotides: COVID-19 mRNA vaccines use N1-methylpseudouridine instead of uridine. This modification reduces innate immune detection (TLR activation), increases translation efficiency by 10-fold, and improves mRNA stability.

Delivery System

Lipid nanoparticles (LNPs) encapsulate mRNA for protection and cellular delivery. The ionizable lipid component enables endosomal escape, releasing mRNA into the cytoplasm where translation occurs.

Quality Control

Critical parameters include mRNA integrity (>80%), encapsulation efficiency (>90%), particle size (80-100 nm), and endotoxin levels. AI models predict optimal sequences and formulations before synthesis.