Vaccines and Vaccination

- Chapter 21
- Components of a vaccine
- Selection of antigens to be used in a vaccine
- Immune effector mechanisms activated by vaccines
- Practical consideration for vaccine development and use
- Examples of successful vaccines
- Factors that prevent development of vaccines against certain microorganisms

Successful Human Vaccines

- Must choose protective antigen and appropriate delivery

- Current vaccines in human use:
  - Purified and protein-conjugated capsular polysaccharides of bacteria
  - Inactivated toxins (toxoids)
  - Recombinant protein antigens (hep B)
  - Inactivated bacterial cells and viral particles (Killed)
  - Attenuated bacterial cells and viral particles (Live)
  - Immune serum (rabies)

Successful Human Vaccines

- Patron Saint of Killed Vaccines:

  - Jonas Salk

  - Made killed flu vaccine with Thomas Francis Jr.

  - Proved polio vaccine worked in massive 1954 field trial

Inactivated Vaccines

- Licensed and Routine
  - Salk Polio vaccine
  - Influenza vaccine

- Special Risk Groups
  - Hepatitis A vaccine
  - Rabies
  - Japanese Encephalitis
Inactivated Vaccines

Inactivated Vaccines Pros and Cons

- Sufficient humoral immunity if boosters given
- No mutation or reversion
- Can be used with immunodeficient persons
- Can induce CD4 responses
- Poor at inducing CD8 responses
- Need to be given multiple times
- Safety concerns

Attenuated Vaccines

- Licensed and Routine
  - MMR
  - Varicella
  - Rotavirus
  - (Sabin Polio vaccine)
  - (Smallpox)

- Special Risk Groups Only
  - Adenovirus
  - Yellow Fever
**Attenuated Vaccine Pros and Cons**

- Local immunity is possible
- No boosters are necessary
- Immunity is rapid
- May lead to elimination of wild type virus in the field
- Can induce T and B cell responses
- Safety concerns
  - Shedding
  - Reversion
  - Induction of atypical infections

**Successful Human Vaccines?**

- Must choose protective antigen and appropriate delivery
- Experimental vaccines:
  - Tried only in animals or in early studies in humans
  - Anti-idiotypne (Figure 8.7)
  - Peptide-based
  - DNA-based
  - Antigen presentation from infected or transfected APCs
  - Live recombinant attenuated viruses
  - Recombinant bacterial cells expressing vaccine antigens for other organisms
  - Inclusion of adjuvants
  - Inclusion of purified cytokines or cytokine genes
Anti-idiotype Vaccines

- Idiotypic network theory
- The variable region of an antibody molecule represents a completely novel molecular epitope
- Host animal cannot have encountered previously
- Cannot be tolerant or immune
- The antibody will elicit an anti-idiotype antibody
- Specific for the first antibody’s antigen binding site
- It should mimic the three dimensional shape of the original antigen

Peptide-based Vaccines

- Synthetic or recombinant peptides mimicking known protective B or T cell epitopes on pathogens could be delivered safely
- Poor immunogenicity without adjuvants
- Can couple peptide to immunogenic support, to immunostimulating complexes (Iscoms), or to a carrier
- Must first identify the peptide epitopes
- Universally immunogenic peptides to T cells
- Usually not good for B cell epitopes and Ab production is low
Peptide-based Vaccines

- Peptide-based Vaccines Pros and Cons
  - Can induce antibody responses
  - Can be taken up, degraded, and presented by MHC Class II if coupled to a carrier
  - Overloading with peptide can force presentation by MHC class I (cross priming)
  - Expensive to make
  - Escape is common
  - Responses often weak and short lived

DNA-based Vaccines

- The DNA is a recombinant bacterial plasmid with the gene for the microbial antigen is expressed by a strong promoter
- DNA is injected and taken up into cells
- Transcription and translation occurs
- Cells present these intracellular recombinant microbial antigens on MHC class I

DNA-based Vaccines

DNA-based Vaccines

DNA-based Vaccines Pros and Cons

- Inexpensive and do not need refrigeration
- Can incorporate multiple genes in one plasmid
- Made de novo in cell
- Have been successful in animal models for HIV, Ebola, CMV
- Low dose seems to induce long lived immunity
- Do not necessarily need adjuvants

- Antigen has to be protein in nature
- Insertional mutagenesis a possible concern - recombination into genome
- Anti-DNA antibodies
- Immune tolerance

Adjuvants

- substances that when co-introduced with antigen enhance the immunogenicity of that antigen

<table>
<thead>
<tr>
<th>Table 21.6</th>
<th>Mechanisms of action of some adjuvantsa</th>
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<tbody>
<tr>
<td>Component of antigen</td>
<td>Examples of adjuvants</td>
</tr>
<tr>
<td>Facilitation of antigen uptake, transport, and presentation by APCs</td>
<td>ISCOMs, Quil A, Al(OH)₃, liposomes, cochleates, poly(lactic/glycolic acid)</td>
</tr>
<tr>
<td>Depot effect</td>
<td>Oil emulsions, Al(OH)₃, gels, polymer microspheres, nonionic block-copolymers</td>
</tr>
<tr>
<td>Alert/activate initial responding cells</td>
<td>Complement, CpG-rich motifs, LPS (monophosphoryl lipid A), mycobacteria (muramyl dipeptide), yeast extracts, cholera toxin, ISCOMs?</td>
</tr>
<tr>
<td>Danger signal</td>
<td>Oil-emulsion surface-active agents, Al(OH)₃, IFNs, heat shock proteins, hyperoxia, etc.</td>
</tr>
<tr>
<td>Recombinant signal 2</td>
<td>Cytokines, costimulatory molecules</td>
</tr>
</tbody>
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PRR, pattern-recognition receptors; HSPs, heat shock proteins.
Adjuvant Mechanisms of Action

Adjuvants

Table R.1 Type of adjuvants currently used or under investigation

<table>
<thead>
<tr>
<th>Adjuvant</th>
<th>Mode of action</th>
<th>Relative toxicity</th>
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<tbody>
<tr>
<td>Complete Freund's adjuvant</td>
<td>Activates TH1 cells through TLR2 and TLR4</td>
<td>Very high</td>
</tr>
<tr>
<td>Alum</td>
<td>Activates TH1 cells</td>
<td>Very low</td>
</tr>
<tr>
<td>Immunostimulating complexes</td>
<td>Activate CD4+ cells</td>
<td>Low</td>
</tr>
<tr>
<td>Modulate MHC, class II</td>
<td>Induce interferon-gamma</td>
<td>Low</td>
</tr>
<tr>
<td>Non-ionic block polymers</td>
<td>Increase antibody responses</td>
<td>Low</td>
</tr>
<tr>
<td>Monophosphoryl lipid A</td>
<td>Induces interferon-gamma and TNF</td>
<td>Moderate</td>
</tr>
<tr>
<td>Muramyl dipeptides</td>
<td>Induce humoral responses and augment</td>
<td>Moderate</td>
</tr>
<tr>
<td>Cytokines</td>
<td>Activity based on biologic specificity</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

Pathways of Adjuvant Activation

Antigen Production in Infected or Transfected Mammalian Cells

- Expression of protective antigen in mammalian APCs
- APCs will present protective antigen
- Donor collected APCs can be transfected and then reintroduced into original donor
- Or expose APCs to microbial antigens, ingest, process, and present on MHC, then reintroduce into original donor
- Also testing for use with tumor antigen presentation
Antigen Production in Infected or Transfected Mammalian Cells

Live Recombinant Attenuated Viruses
- Creation of attenuated strains of bacteria or virus that can be used to deliver antigens from another pathogen
- Pathogenic antigen expression from recombinant DNA inserted into attenuated bacterial or viral genome
- Attenuated strains are usually genetically modified so that the virulence genes are removed while the genes necessary for replication and packaging are intact
- Therefore, it can infect, replicate, package and reinfect new cells, but not cause disease.
Live Recombinant Attenuated Viruses
Pros and Cons
• Can be made from viral vectors that can infect but cannot replicate in human cells
• Can achieve high titers
• Can deliver via mucosal routes
• Host usually immunized against viral vector along with antigen
• Cannot be used in immunocompromised hosts
• Immunity often weak

Reverse Vaccinology
• Computer prediction of surface antigens capable of eliciting an immune response by using the genome sequence of the pathogen
• Use recombinant DNA of these identified genes to make a vaccine through DNA vaccines, transfected cells, or live, recomb vaccine
• Large number of recombinant proteins can be made quickly and easily
• Expressed and evaluated as vaccine candidate by using in vitro serology or CMI experiments as for live, recomb Vaccines

Reverse Vaccinology
Candidate Testing
Routes of Vaccination

- Must be introduced to a site where vaccine antigens will encounter immune effector cells
- Usually intramuscular
- Can form precipitates that persist and are very slowly dissolved and reabsorbed
- Increases the time of immune effector cell encounter
- Muscle tissue is filled with DCs - great APCs
- Routinely survey muscle tissue for antigens and transport those to the lymph nodes to activate T cells
- Readily accessible - large muscles like deltoid, quadracept, and gluteous maximus