Vaccines

Jenner’s Idea

- Cowpox virus (vaccinia) causes only mild infections in humans

Pasteur’s Idea

In 1879 Louis Pasteur showed that chicken cholera weakened by growing it in the laboratory could protect against infection with more virulent strains

Early History of Vaccination

- The tradition of vaccination may have originated in India in AD 1000
- Pioneered India and China in the 17th
- Powdered scabs from people infected with smallpox was used to protect against the disease (China around 1695)
- Smallpox was responsible for 8 to 20% of all deaths in several European countries in the 18th century
- In 1721 Lady Mary Wortley Montagu brought the knowledge of these techniques from Constantinople (now Istanbul) to England
- One percent of the smallpox vaccinees, however, died from the variolation itself
- Benjamin Jesty and, later, Edward Jenner could show that vaccination with the less dangerous cowpox could protect against infection with smallpox
- The word vaccination, which is derived from vacca, the Latin word for cow.

Figure 14.1 The Immune System, Bio[1] Garland Science 2006

Figure 14.2 The Immune System, Bio[1] Garland Science 2006

Figure 14.3 The Immune System, Bio[1] Garland Science 2006

Figure 14.4 The Immune System, Bio[1] Garland Science 2006

Figure 14.5 The Immune System, Bio[1] Garland Science 2006
How do ISCOMs work?

Dutch Vaccine Programme

Available vaccines for infectious diseases in humans

<table>
<thead>
<tr>
<th>Bacterial diseases</th>
<th>Types of vaccine</th>
<th>Viral diseases</th>
<th>Types of vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naphthosine</td>
<td>Toxoid</td>
<td>Yellow fever</td>
<td>Attenuated virus</td>
</tr>
<tr>
<td>Tetanus</td>
<td>Toxoid</td>
<td>Measles</td>
<td>Attenuated virus</td>
</tr>
<tr>
<td>Pertussis (whooping cough)</td>
<td>Killed bacteria, subunit vaccine composed of pertussis toxin and other bacterial antigens</td>
<td>Whooping cough</td>
<td>Attenuated virus</td>
</tr>
<tr>
<td>Paratyphoid Bineres (paratyphoid)</td>
<td>Killed bacteria</td>
<td>Robbins</td>
<td>Attenuated virus</td>
</tr>
<tr>
<td>Syphilis</td>
<td>Killed bacteria</td>
<td>Pule</td>
<td>Attenuated virus</td>
</tr>
<tr>
<td>Cholera (Vibrio cholerae)</td>
<td>Killed bacteria or cell extract</td>
<td>Veroce</td>
<td>Attenuated virus</td>
</tr>
<tr>
<td>Plague (Yersinia pestis)</td>
<td>Killed bacteria or cell extract</td>
<td>Pule</td>
<td>Attenuated virus</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Attenuated strain of bacillus Calmette–Guérin (BCG, bacille Calmette–Guérin)</td>
<td>Tuberculosis</td>
<td>Attenuated strain</td>
</tr>
<tr>
<td>Typhoid fever (Salmonella typhi)</td>
<td>Typhoid vaccine, killed vaccine.</td>
<td>Typhoid fever</td>
<td>Attenuated vaccine</td>
</tr>
<tr>
<td>Meningococcal (Neisseria meningitidis)</td>
<td>Meningococcal vaccine</td>
<td>Meningococcal</td>
<td>Attenuated vaccine</td>
</tr>
<tr>
<td>Meningococcal (Neisseria meningitidis)</td>
<td>Meningococcal vaccine</td>
<td>Meningococcal</td>
<td>Attenuated vaccine</td>
</tr>
<tr>
<td>Vaccinal pneumonia (Vaccinia virus)</td>
<td>Vaccinal pneumonia</td>
<td>Vaccinal pneumonia</td>
<td>Subcutaneous vaccine</td>
</tr>
<tr>
<td>Poliovirus</td>
<td>Inactivated virus</td>
<td>Poliovirus</td>
<td>Inactivated virus</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>Inactivated polysaccharide conjugate vaccine</td>
<td>Haemophilus influenzae</td>
<td>Inactivated vaccine</td>
</tr>
</tbody>
</table>

Figure 14.6 The Immune System, 4th ed. (Gallant Science 2008)

Figure 14.7 The Immune System, 4th ed. (Gallant Science 2008)
Routes of administration

- Deep subcutaneous or intramuscular route (most vaccines)
- Oral route (sabine vaccine, oral BCG vaccine)
- Intradermal route (BCG vaccine)
- Scarification (small pox vaccine)
- Intranasal route (live attenuated influenza vaccine)

A success story

- Polio vaccine – introduced in the 1950s
- Incredibly successful vaccine
- Two different versions of the polio vaccine
  - Salk inactivated ("killed" virus) injected – introduced first
  - Sabin attenuated (weakened virus) given orally

So, why the introduction of the second Sabin vaccine?

- Salk vaccine was certainly incredibly successful
- Sabin vaccine – given orally, vaccine virus is deposited on intestinal mucosal surfaces
- Wild-type polio virus most often infects intestinal mucosal surface, enters the body (via the intestinal epithelial cells) – can cause serious damage inside the body (lungs, nerves)
- Sabin establishes a mucosal immunity right at the location where the wild-type polio virus first attempts to infect the body
  - **STOP it there** before it even can attach to the epithelial cells
  - **SIgA** may be very important in preventing virus attachment to endothelial cells

Flumist: an inhaled, attenuated influenza vaccine

[Image of a graph showing reported cases of polio per 100,000 population from 1940 to 1990, with a peak in the 1950s and a decline after the introduction of the vaccine]

[Image of diagrams showing the exposure to influenza virus and the outcome for adults with and without anti-influenza virus antibodies]
Vaccine safety: Reversion of attenuated poliovirus to a neurovirulent strain

<table>
<thead>
<tr>
<th>Strain</th>
<th>Number of mutations</th>
<th>No. of amino acid changes</th>
<th>Mutations required for reversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sabin 1</td>
<td>57</td>
<td>23</td>
<td>&gt;10</td>
</tr>
<tr>
<td>Sabin 2</td>
<td>23</td>
<td>5</td>
<td>5-6</td>
</tr>
<tr>
<td>Sabin 3</td>
<td>6</td>
<td>3</td>
<td>1-2</td>
</tr>
</tbody>
</table>

Using recombinant DNA techniques

Epitope based vaccines (Polytopes)

- Advantages (Ishiioka et al. [1999]):
  - Can be more potent
  - Can be controlled better
  - Can induce subdominant epitopes (e.g. against tumor antigens where there is tolerance against dominant epitopes)
  - Can target multiple conserved epitopes in rapidly mutating pathogens like HIV and Hepatitis C virus (HCV)
  - Can be designed to break tolerance
  - Can overcome safety concerns associated with entire organisms or proteins

- Epitope-based vaccines have been shown to confer protection in animal models ([Snyder et al., 2004], Rodriguez et al. [1998] and Sette and Sidney [1999])

Prediction of antigens

- Protective antigens
  - Functional definition (phenotype)
  - Which antigens will be protective (genotype)?
  - They must be recognized by the immune system
  - Predict epitopes (include processing)
    - CTL (MHC class I)
      - [http://www.cbs.dtu.dk/services/NetCTL/](http://www.cbs.dtu.dk/services/NetCTL/)
    - Helper (MHC class II)
      - [http://mail1.imtech.res.in/raghava/hlapred/index.html](http://mail1.imtech.res.in/raghava/hlapred/index.html)
    - Antibody
      - [http://www.cbs.dtu.dk/services/BepiPred/](http://www.cbs.dtu.dk/services/BepiPred/)
Function and conservation

- Some of the epitopes must exist in the wild type
- Conservation
- Function
  - When is it expressed?
  - Where is it trafficked to?
    - SecretomeP
      - Non-classical and leaderless secretion of eukaryotic proteins.
    - SignalP
      - Signal peptide and cleavage sites in gram+, gram-
        and eukaryotic amino acid sequences.
    - TargetP
      - Subcellular location of proteins: mitochondrial,
        chloroplastic, secretory pathway, or other.
- Expression level?

Example: HIV A2 polytope

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Protein</th>
<th>Position</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>VLAEMSQV</td>
<td>Gag</td>
<td>362</td>
<td>Gag0</td>
</tr>
<tr>
<td>NTVATLYCV</td>
<td>Gag</td>
<td>80</td>
<td>Gag1</td>
</tr>
<tr>
<td>GLADQLHL</td>
<td>Vif</td>
<td>101</td>
<td>Vif2</td>
</tr>
<tr>
<td>ILKEPVHG</td>
<td>Pol</td>
<td>476</td>
<td>Pol3</td>
</tr>
<tr>
<td>SLYNTVAL</td>
<td>Gag</td>
<td>77</td>
<td>Gag4</td>
</tr>
</tbody>
</table>

Polytope optimization

- Successful immunization can be obtained only if the epitopes encoded by the polytope are correctly processed and presented.
- Cleavage by the proteasome in the cytosol, translocation into the ER by the TAP complex, as well as binding to MHC class I should be taken into account in an integrative manner.
- The design of a polytope can be done in an effective way by modifying the sequential order of the different epitopes, and by inserting specific amino acids that will favor optimal cleavage and transport by the TAP complex, as linkers between the epitopes.

Polytope optimization Algorithm

- Optimization of four measures:
  1. The number of poor C-terminal cleavage sites of epitopes (predicted cleavage < 0.9)
  2. The number of internal cleavage sites (within epitope cleavages with a prediction larger than the predicted C-terminal cleavage)
  3. The number of new epitopes (number of processed and presented epitopes in the fusing regions spanning the epitopes)
  4. The length of the linker region inserted between epitopes.
- The optimization seeks to minimize the above four terms by use of Monte Carlo Metropolis simulations [Metropolis et al., 1953]
Therapeutic vaccines
Vaccines to treat the patients that already have a disease. Targets

- Tumors
- AIDS
- Allergies
- Autoimmune diseases
- Hepatitis B
- Tuberculosis
- Malaria
- Helicobacter pylori

Concept: Suppress/boost existing immunity or induce immune responses.

Cancer vaccines

- Break the tolerance of the immune system against tumors
- Types:
  1. Whole tumor cells, peptides derived from tumor cells in vitro, or heat shock proteins prepared from autologous tumor cells
  2. Tumor-specific antigen–defined vaccines
  3. Vaccines aiming to increase the amount of dendritic cells (DCs) that can initiate a long-lasting T cell response against tumors.
- Therapeutic cancer vaccines can induce antitumor immune responses in humans with cancer
- Antigenic variation is a major problem that therapeutic vaccines against cancer face

Allergy vaccines

- Increasing occurrence of allergies in industrialized countries
- The traditional approach is to vaccinate with small doses of purified allergen
- Example of switching a “wrong” immune response to a less harmful one.
Vaccines Against Autoimmune Diseases

- Multiple sclerosis
  - T cells specific for myelin basic protein (MBP) can cause inflammation of the central nervous system.
  - The vaccine uses copolymer 1 (cop 1), a protein that highly resembles MBP. Cop 1 competes with MBP in binding to MHC class II molecules, but it is not effective in inducing a T cell response.
  - On the contrary, Cop 1 can induce a suppressor T cell response specific for MBP, and this response helps diminish the symptoms of multiple sclerosis.
- A vaccine based on the same mechanisms is developed for myasthenia gravis.