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

1

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)

2

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

3

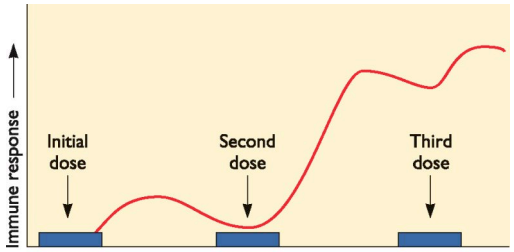
Inactivated Vaccines

- Licensed and Routine
  - Salk Polio vaccine
  - Influenza vaccine

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

4

Inactivated Vaccines



5

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

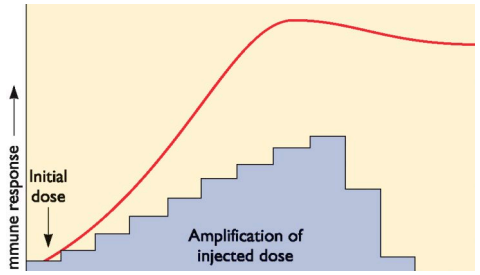
6

Attenuated Vaccines

- Licensed and Routine
  - MMR
  - Varicella
  - Rotavirus
  - (Sabin Polio vaccine)
  - (Smallpox)
- Special Risk Groups Only
  - Adenovirus
  - Yellow Fever

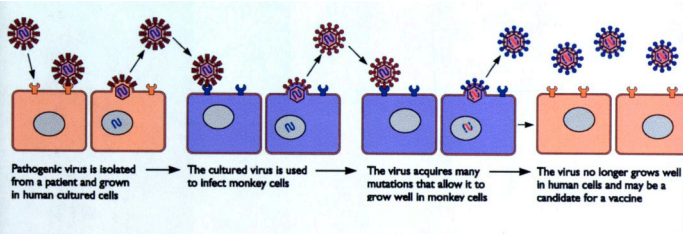
7

Attenuated Vaccines



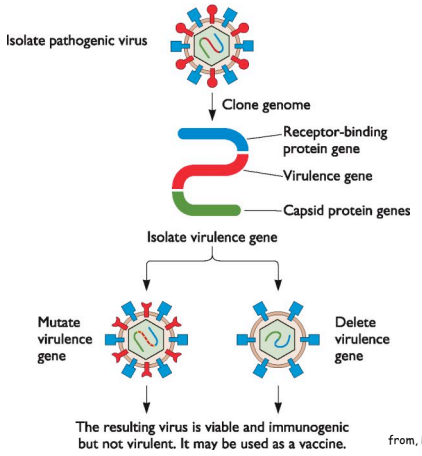
8

Classic Attenuation Process



from, Principles of Virology, 2nd edition

Genetic Attenuation Process



from, Principles of Virology, 2nd edition

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?

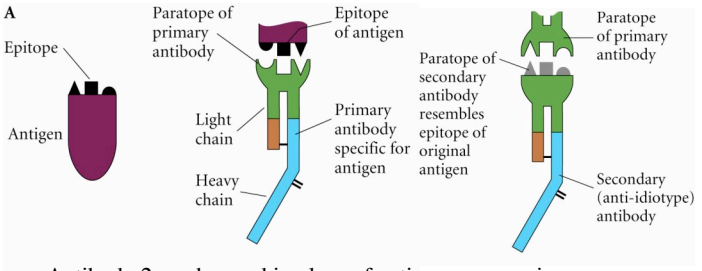
- Must choose protective antigen and appropriate delivery

- Experimental vaccines:
- Tried only in animals or in early studies in humans
  - Anti-idiotype (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

Anti-idiotype Vaccines



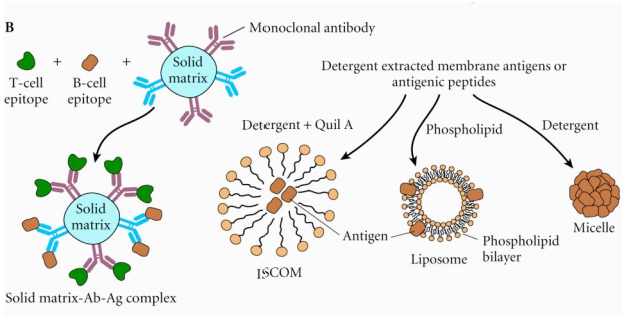
- Antibody 2 can be used in place of antigen as a vaccine
- Use one or more antibodies in the vaccine

- Mouse monoclonal Abs may induce anti-mouse response
- Human monoclonal Abs may induce autoimmune reactions

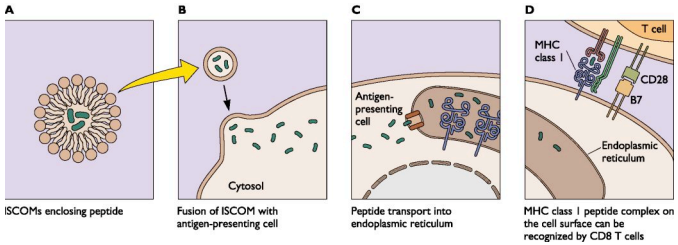
Peptide-based Vaccines

- 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



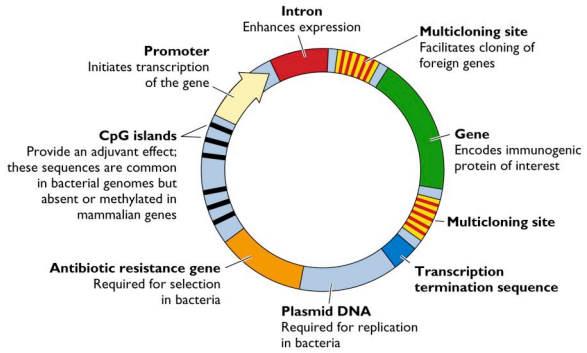
Peptide-based Vaccines Pros and Cons

- 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

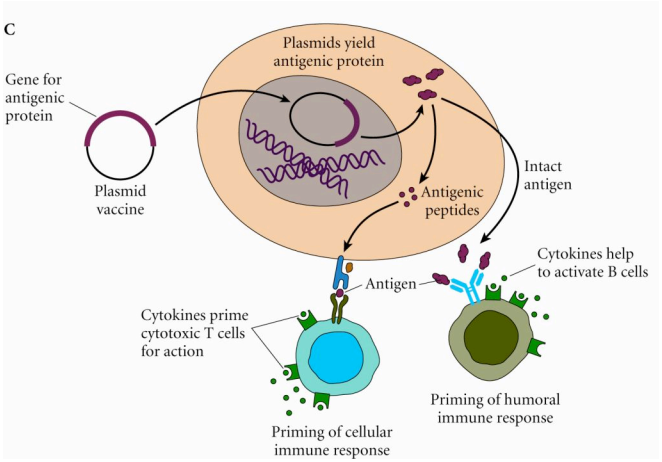
- The DNA is a recombinant bacterial plasmid with the gene for the microbial antigen is expressed by a strong promoter
- DNA is injected and taken up into cells
- Transcription and translation occurs
- Cells present these intracellular recombinant microbial antigens on MHC class 1

DNA-based Vaccines



Adapted from M. Oyaski and H. Ertl, *Sci. Med.* 7:30–39, 2000, with permission.

DNA-based Vaccines



DNA-based Vaccines

Virus	Proteins	Induction of antibody	Induction of CTL response	Protection against challenge
Bovine herpesvirus	gD	+	ND	+ (cattle)
Hepatitis B virus	Surface and core antigens	+ (chimpanzees); ND (humans)	+ (chimpanzees)	+ (chimpanzees)
Hepatitis C virus	Nucleocapsid	+	+	+ (mice)
Herpes simplex virus type 1	gD, gB	+	+	+ (mice)
HIV type 1	Env, Gag, Rev	+	+	+ (rhesus macaques)
Influenza virus	HA, M1, Np	+	+	+ (chickens, mice)
Lymphocytic choriomeningitis virus	NP	+	+	+ (mice)
Rabies virus	Glycoprotein, NP	+	+	+ (cynomolgus monkeys)
Respiratory syncytial virus	Glycoprotein	+	+	+ (mice)

[a]Data from A. Reyes-Sandoval and H. C. Ertl, *Curr. Mol. Med.* **1**:217–243, 2001, with permission. ND, not detected.

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

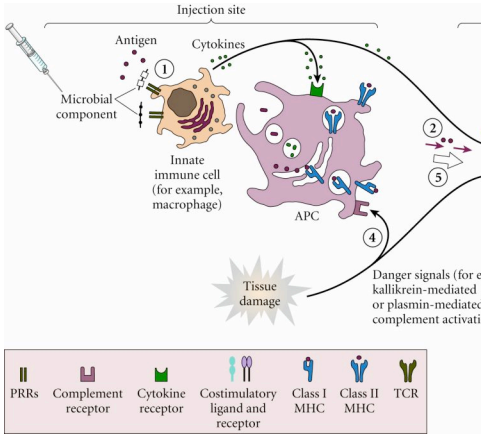
- substances that when co-introduced with antigen enhance the immunogenicity of that antigen

Table 21.6 Mechanisms of action of some adjuvants[a]

Concept of action	Examples of adjuvants
Facilitation of antigen uptake, transport, and presentation by APCs	ISCOMs, Quil A, $Al(OH)_3$, liposomes, cochleates, poly(lactic/glycolic acid)
Depot effect	Oil emulsions, $Al(OH)_3$, gels, polymer microspheres, nonionic block copolymers
Alert/activate initial responding cells	Complement, CpG-rich motifs, LPS (monophosphoryl lipid A), mycobacteria (muramyl dipeptide), yeast extracts, cholera toxin, ISCOMs?
Danger signal	Oil-emulsion surface-active agents, $Al(OH)_3$, IFNs, heat shock proteins, hypoxia, etc.
Recombinant signal 2	Cytokines, costimulatory molecules

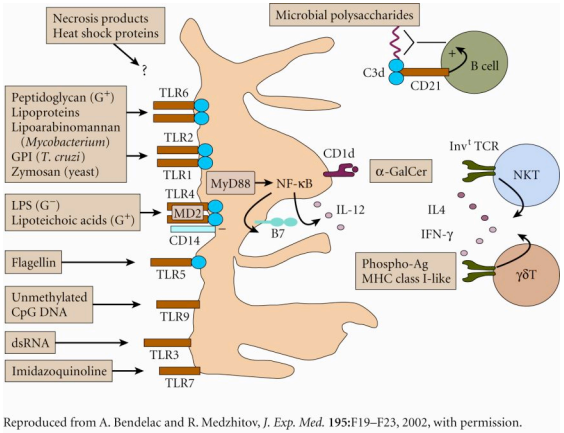
[a]Modified from V. E. Schijns, *Curr. Opin. Immunol.* **12**:456–463, 2000, with permission.
[b]PRR, pattern-recognition receptors; HSPs, heat shock proteins.

Adjuvant Mechanisms of Action



25

Pathways of Adjuvant Activation



Reproduced from A. Bendelac and R. Medzhitov, *J. Exp. Med.* **195:**F19–F23, 2002, with permission.

26

Adjuvants

Table 8.1 Type of adjuvants currently used or under investigation

Adjuvant	Mode of action[a]	Relative toxicity
Complete Freund's adjuvant	Activates TH1 cells through TLR2 and TLR4	Very high
Alum	Activates TH2 cells	Very low
Immunostimulating complexes	Activate $CD4^+$ cells Induce interferon-gamma Modulate MHC class II	Low
Non-ionic block polymers	Increase antibody responses Activate TH1 cells	Low
Monophosphoryl lipid A	Induces interferon-gamma and TNF Induces TH1 cells Inhibits TH2 cells Activates through TLR4	Moderate
Muramyl dipeptides	Induce humoral responses Augment both antibody and cellular responses when given as oil-in-water emulsion Induce IL-1 secretion Activate through TLR2	Moderate
Cytokines	Activity based on biologic specificity	Moderate

[a]TH cell, helper T cell.

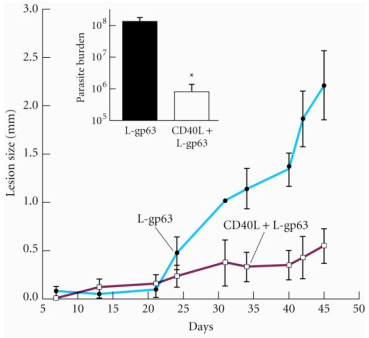
27

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

28

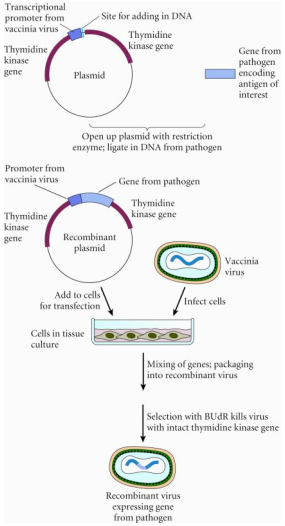
Antigen Production in Infected or Transfected Mammalian Cells



Reprinted from G. Chen et al., *Infect. Immun.* **69**:3255–3263, 2001, with permission.

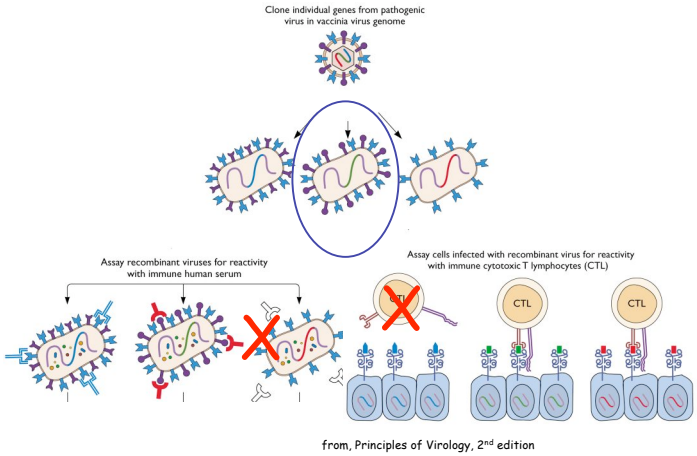
Live Recombinant Attenuated Viruses

- 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

Live Recombinant Attenuated Viruses



from, Principles of Virology, 2nd edition

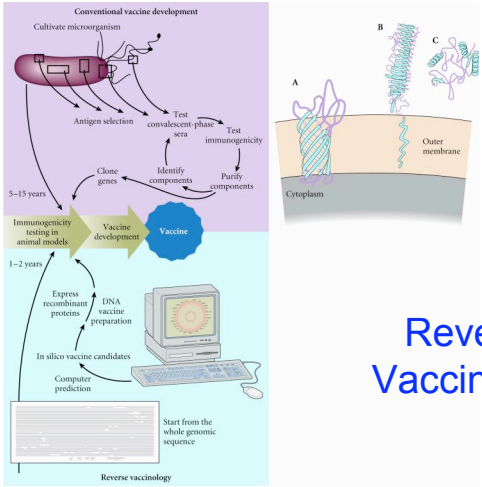
Live Recombinant Attenuated Viruses Pros and Cons

- 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

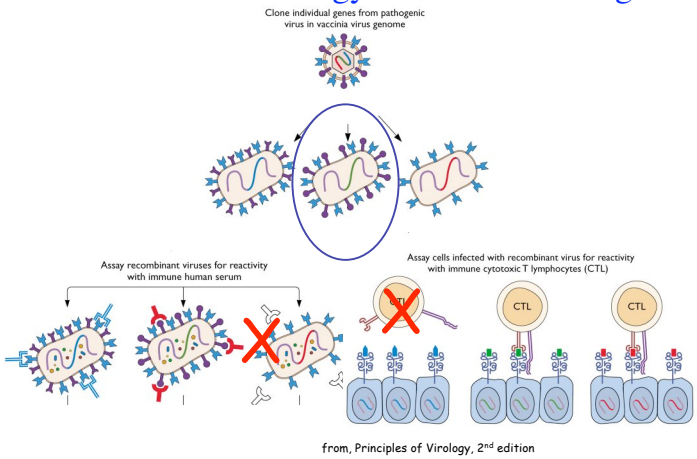
- Computer prediction of surface antigens capable of eliciting an immune response by using the genome sequence of the pathogen
- Use recombinant DNA of these identified genes to make a vaccine through DNA vaccines, transfected cells, or live, recomb vaccine
- Large number of recombinant proteins can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



Reprinted from R. Rappuoli, *Vaccine* 19:2688–2691, 2001, with permission.

Reverse Vaccinology

Reverse Vaccinology Candidate Testing



from, Principles of Virology, 2nd edition

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

37