ROLE OF PHARMACEUTICAL BIOTECHNOLOGY IN PRODUCTION OF VACCINES

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INTRODUCTION

- Vaccination is perhaps the most effective means of controlling infectious diseases.
- It has been mainly responsible for the eradication of smallpox and for the control of yellow fever, poliomyelitis and German measles in **the human population**
- Newcastle disease, and Marek's disease in **domestic animals**.
- The art of deliberate immunization against infections has been practiced for centuries but the mechanisms of protective immunity were not fully appreciated until the advent of modern immunology.

IMMUNOLOGICAL PRINCIPLES

1. As a reaction to infection, the human immune system launches a series of immunological responses with the goal of eliminating the pathogen.
2. Innate immune cells will be the first to respond and will attempt to clear the pathogen through phagocytosis and/or lysis.
3. Second line of immunity is The adaptive immune system which can generate humoral immunity and cell-mediated immunity.

ANTIBODIES

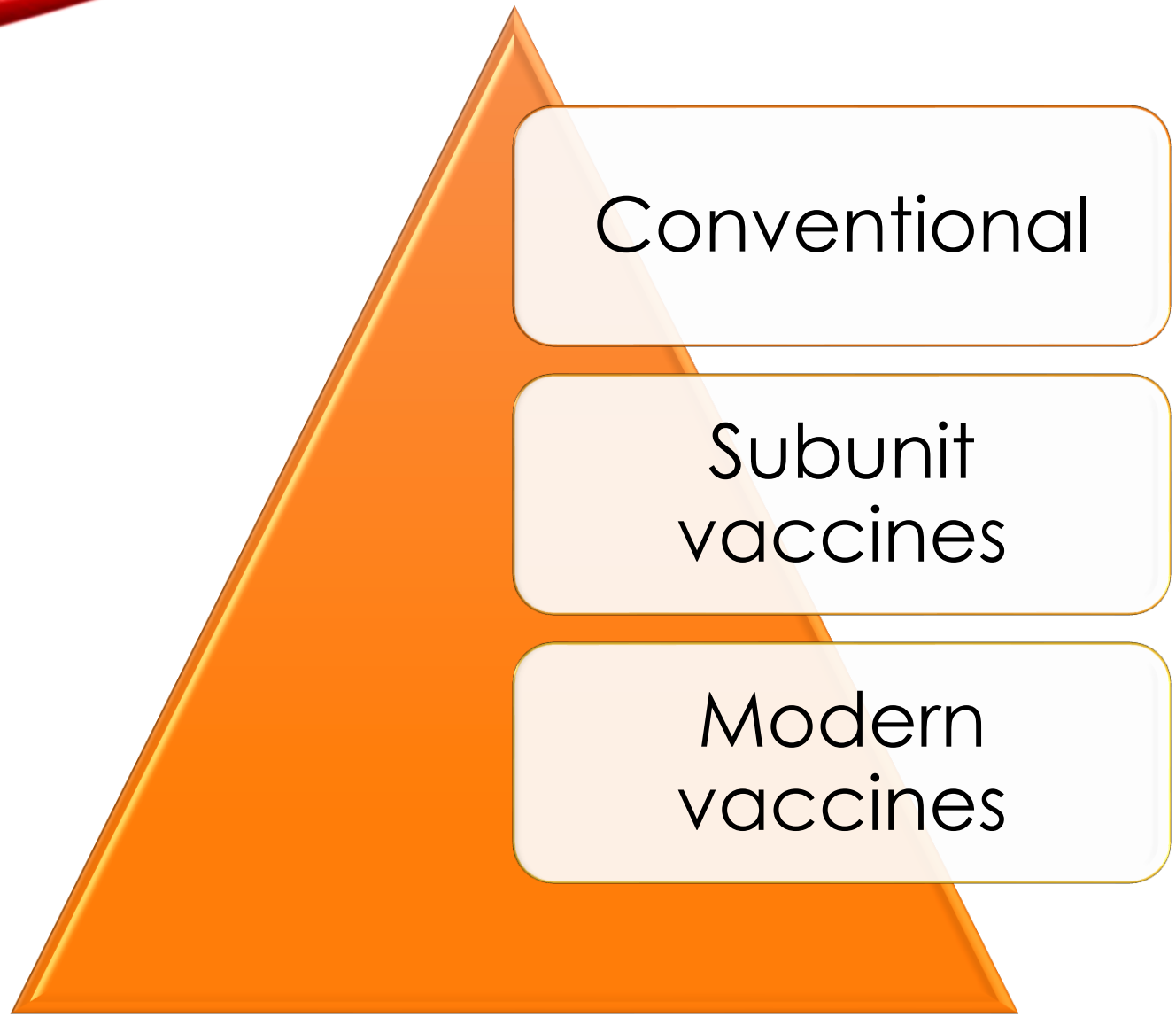
- Antibodies, produced by B-cells, are the typical representatives of humoral immunity.
- An antibody belongs to one of four different immunoglobulin classes (IgM, IgG, IgA, or IgE) .

- some of the B- and T-cells resist apoptosis and can maintain themselves for many years as memory B- and T-cells so, unlike the primary response, the response after repeated infection is very fast and usually sufficiently strong to prevent reoccurrence of the disease.
- Vaccination exploits the formation of this immunological memory by the adaptive immune system.
- **The principle of vaccination is mimicking an infection in such a way that the natural specific defense mechanism of the host against the pathogen will be activated and immunological memory is established**, but the host will remain free of the disease that normally results from a natural infection. This is effectuated by administration of antigenic components that consist of, are derived from, or are related to the pathogen.

APPLICATION OF VACCINES

- It is currently not limited to the prevention of infectious diseases.
- therapeutic vaccines are available against allergies, cancer, and Alzheimer's disease.
- Most of these vaccines are still in an experimental phase

TYPE OF VACCINES



CONVENTIONAL

live

- The earliest vaccines were live wild-type organisms. eg. viable Leishniania
- still used in small doses to induce a controlled lesion at a selected site with no boosting dose
- Can infect and cause illnesses

Attenuated

- Attenuation – to reduce in force, value, amount, or degree; weaken
- Attenuation is generally achieved by growing the pathogens in an 'unnatural' host (passage) or to grow at a temperature lower than normal (cold-adaptation)
- attenuated or killed organisms by exposure to heating or chemical treatment or living in host other than human
- **Ex** poliovirus and smallpox vaccines, Bacillus Calmette-Guerin BCG

Disadvantages of killed-virus vaccines include relatively brief immunity requiring boosting shots to maintain effectiveness, poor cell-mediated response, and occasional hypersensitivity to subsequent infection.

Attenuated live-virus vaccines have the advantage of acting more like the natural infection with regard to their effect on immunity. They multiply in the host and tend to stimulate longer-lasting antibody production, induce a good cell-mediated response, and induce antibody production and resistance at the portal of entry

Disadvantages :

of attenuated live-virus vaccines include a risk of reversion to greater virulence, severe infection in immunocompromised hosts, and limited storage and shelf life in some cases. Additionally, unrecognized adventitious agents have been found in vaccine stocks (eg, simian polyomavirus SV40, porcine circovirus).

SUBUNIT VACCINES

- Subunit vaccines contain purified antigens instead of whole organisms. Such a preparation consists of only those antigens that elicit protective immunity.
- Subunit vaccines are composed of toxoids, subcellular fragments, or surface antigens.
- Administration of whole organism, as in case of pertussis was found unfavorable immune reactions resulting in severe side effects.
- The effectiveness of subunit vaccines in increased by giving them in adjuvants.
- Adjuvants slow antigen release for a more sustained immune stimulation.

SUB UNIT VACCINES

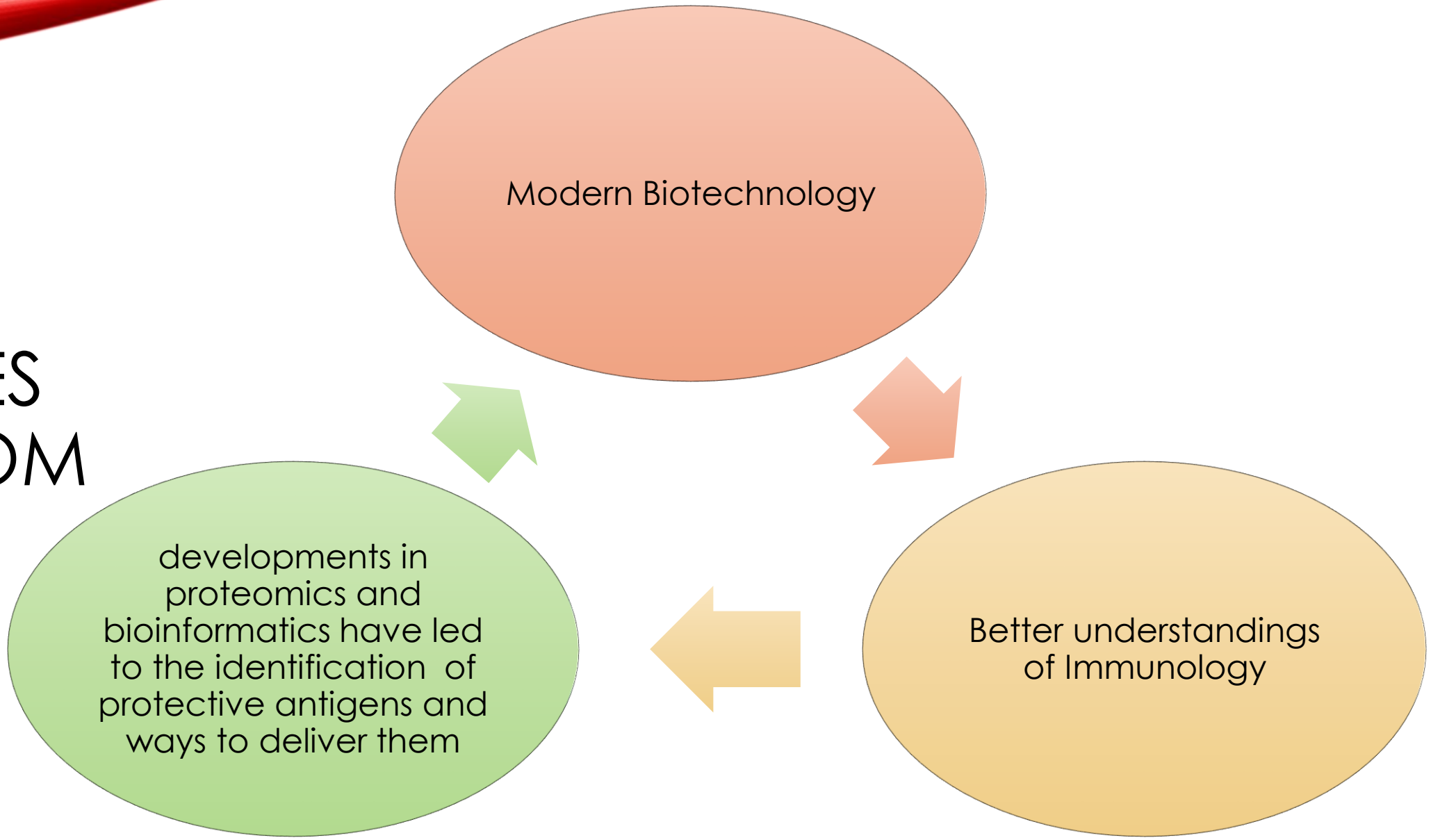
Advantages

- They can safely be given to immuno suppressed people
- They are less likely to induce side effects.

Disadvantages

- Antigens may not retain their native conformation, so that antibodies produced against the subunit may not recognize the same protein on the pathogen surface.
- Isolated protein does not stimulate the immune system as well as a whole organism vaccine

MODERN VACCINES ROSE FROM



SUBUNIT VACCINES BY RECOMBINANT DNA TECHNIQUE

- The constellation of recombinant DNA techniques for placing and maintaining new genetic materials in bacteria, yeasts or mammalian cells is generally known as gene cloning, which is now a powerful tool for synthesizing protein materials, ranging from peptide hormones and cytokines to subunit vaccines.
- In principle, the procedure involves finding the gene, insertion of the gene into a plasmid or other suitable carrier, introduction of this complex into bacteria, yeast, flowering plants or mammalian host cells and, finally, the expression and purification of the material desired

RECOMBINANT VIRAL VACCINES

- The overriding impetus for using the recombinant DNA method to produce vaccines is the lack of immunogenic materials. This is certainly the case of hepatitis B virus (HBV) vaccine.
- The yeast-derived recombinant hepatitis B virus vaccine is the first commercially available human vaccine produced by the genetic engineering technology.
- Other subunit viral vaccines include the influenza virus haemagglutinin, rabies virus glycoproteins, herpes simplex virus-1

RECOMBINANT BACTERIAL VACCINES

- The first commercially available genetically engineered vaccine is a bacterial vaccine effective against enterotoxigertic E. coli (ETEC) strains causing diarrhoeal diseases in young piglets.

PHARMACEUTICAL ASPECTS

■ PRODUCTION

- Animal cells are used for the cultivation of viruses and for the production of some subunit vaccine components and have the advantage that the vaccine components are released into the culture medium.
- However, some viruses cause cell lysis and consequently the culture medium will contain high concentrations of host cell proteins and host cell DNA, requiring extensive purification steps.
- Three stages can be discerned in the manufacture of cell-derived vaccines:
- (1) cultivation or upstream processing,
- (2) purification or downstream processing, and
- (3) formulation.

FORMULATION

- *Adjuvants: Immune Potentiators and Delivery Systems*

- The formulation of the vaccine is one of the major determinants that influence the type of immune response that is elicited, as it determines the type of co-stimulatory molecules and cytokines that are expressed by APCs.
- vaccines should be formulated in such a way that the appropriate T-cell response will be triggered.
- This can be done by presenting the antigen in its native format, as is the case for the live-attenuated vaccines, or by formulating the native antigen with adjuvants that stimulate the desired response.

- Besides immune stimulatory molecules, a vehicle to deliver antigen to antigen presenting cells and B-cells may be crucial, especially for highly purified subunit antigens.

- Immune stimulatory molecules and delivery systems are called adjuvants

ADJUVANTS

- are defined as any material that can increase or modulate the immune response against an antigen. Adjuvants can stimulate the immune system by several mechanisms:
- (1) a depot effect leading to slow antigen release and prolonged antigen presentation,
- (2) attraction and stimulation of Antigen Presenting Cells by some local tissue damage
- (3) delivery of the antigen to regional lymph nodes by improved antigen uptake
- examples
- Colloidal aluminum salts (hydroxide, phosphate) are widely used adjuvants in many classical vaccine formulations. A few other adjuvants, e.g., monophosphoryl lipid A in HPV vaccine and oil-in-water emulsions in influenza vaccines, have been introduced in marketed vaccines. Moreover, numerous adjuvants are in several stages of (pre)clinical testing or are used in veterinary vaccines.

COMBINATION VACCINES

- Since oral immunization is not possible for most available vaccines, the strategy to mix individual vaccines in order to limit the number of injections has been common practice since many decades.
- Currently, vaccines are available containing up to six nonrelated antigens: diphtheria-tetanus-pertussis-hepatitis B-polio-Haemophilus *influenzae* type b vaccine.
- Another example is MMR vaccine, alone or in combination with varicella vaccine.
- Sometimes a vaccine contains antigens from several subtypes of a particular pathogen. E.g. Pneumococcal conjugate vaccine 13 (PCV13) . This vaccine contains polysaccharides from 13 pneumococcal strains, conjugated to a carrier protein to provide T-helper cell recognition and, as a result, induce immunological memory.
- Combining vaccine components sometimes results in pharmaceutical as well as immunological problems. For instance, formaldehyde-containing components may chemically react with other components; an unstable antigen may need freeze drying, whereas other antigens should not be frozen.