Nanovaccinology

application of nanotechnology in vaccine design

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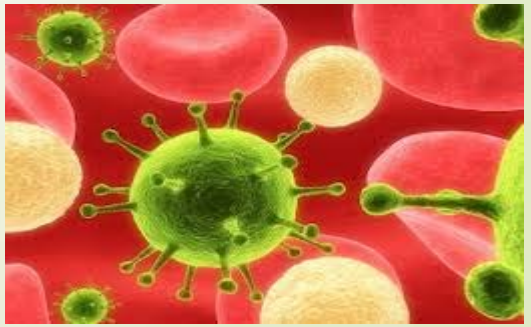
Types of vaccine

Three main types of vaccine

- live-attenuated vaccines composed of a virus or bacterium that is less pathogenic than the real pathogen
- inactivated vaccines that are heat-inactivated or chemically-inactivated particles of the pathogen
- subunit vaccines that are made from components of the pathogen.



Types of adjuvants

Adjuvants can generally be divided into two classes :

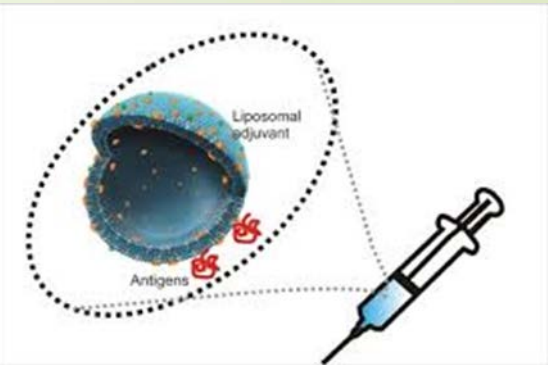
- Vehicles, such as mineral salts, emulsions, liposomes and virosomes, which present vaccine antigens to the immune system in a more efficient way and control the release and storage of antigens to increase the specific immune response.
- Immunostimulants, which affect the immune system and increase the immune responses to antigens.

Nanotechnology in vaccine

- Nanotechnology offers the opportunity to design nanoparticles varying in composition, size,shape and surface properties

- Nanoparticles because of their size **similarity to cellular components**, can enter living cells using the cellular **endocytosis** mechanism, in particular **pinocytosis**.

- The use of nanotechnology in vaccinology , in particular, has been increasing to the birth of "Nanovaccinology"



Nanoparticles in vaccine

- Delivery systems
- Immunostimulant adjuvants

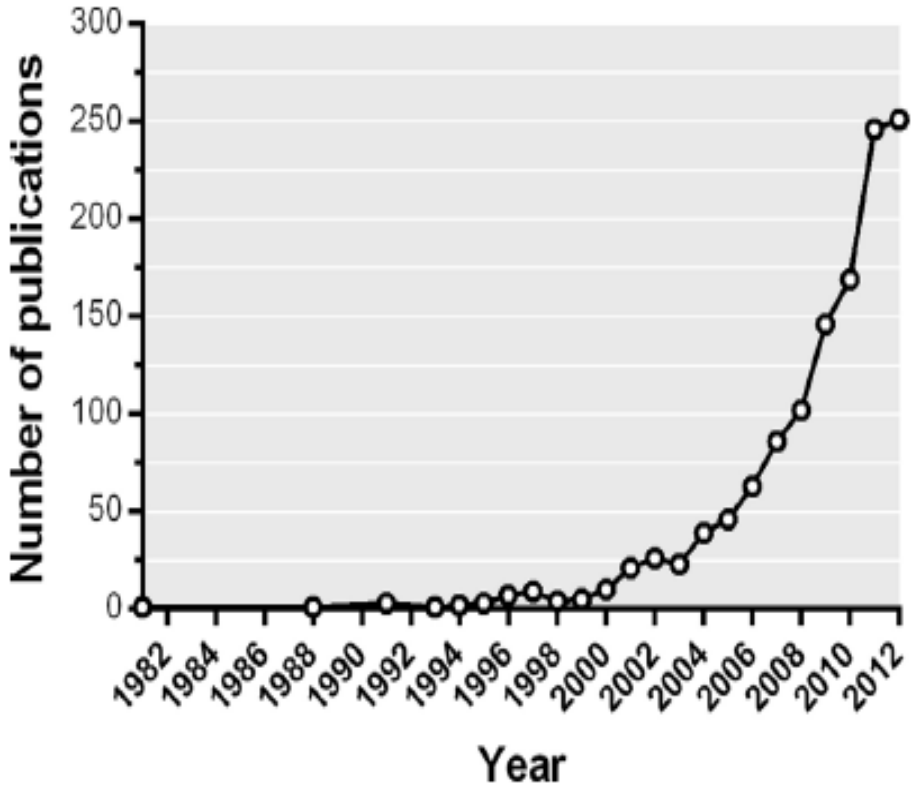


Fig. 1. Number of publications returned using the search terms "nanoparticle* and vaccin*" from Web of Science (http://apps.webofknowledge.com/; results for a search conducted on 29 July 2013).

Types of nanoparticles

- Polymeric nanoparticles
- Inorganic nanoparticles
- Liposomes
- Immunostimulating complex (ISCOM)
- Virus-like particles
- Self-assembled proteins
- Emulsions

Polymeric nanoparticles

- A great variety of synthetic polymers are used to prepare nanoparticles, such as:
- poly(d,l-lactide-co-glycolide) (PLG)
- poly(d,l-lactic-coglycolic acid)(PLGA)
- poly(g-glutamic acid) (g-PGA)
- poly(ethylene glycol) (PEG)
- polystyrene

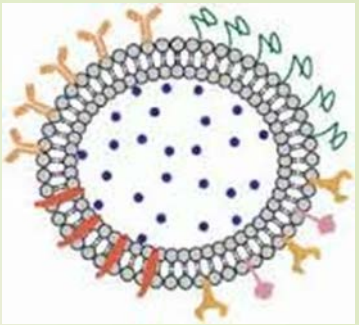
Natural polymers

- pullulan
- Alginate
- inulin, a potent adjuvant: nanoparticle adjuvants derived from inulin, such as AdvaxTM
- chitosan

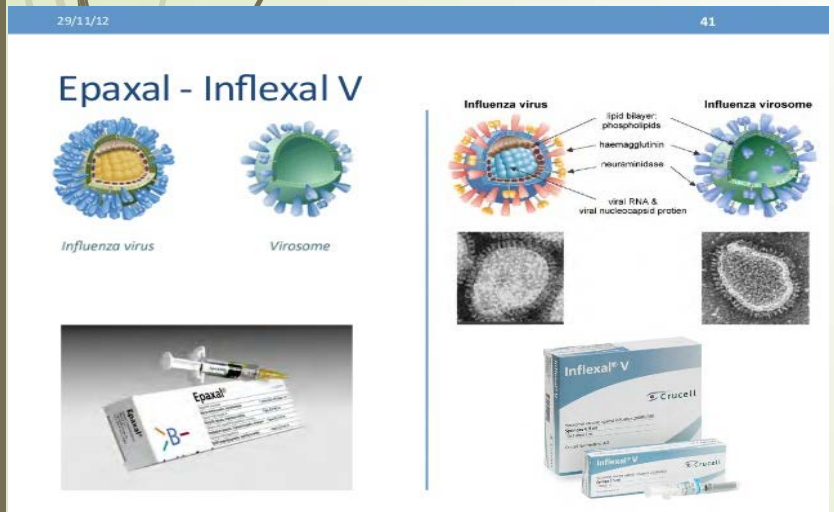
Inorganic nanoparticles

- Mostly nonbiodegradable, controllable synthesis
- ✓ Gold nanoparticles: easily fabricated into different shapes (spherical, rod, cubic, etc.), size range 2-150nm
- ✓ Carbon nanoparticles: drug and vaccine delivery, nanotubes(0.8–2 nmwith a length of 100–1000 nm) and mesoporous spheres (500 nm), good biocompatibility
- ✓ Silica
- ✓ Calcium phosphate nanoparticles

Liposomes



- Liposomes are formed by biodegradable and nontoxic phospholipids.
- Liposomes can encapsulate antigen within the core for delivery
- liposome-polycation-DNA(LPD)
- Inflexal® V and Epaxal®



Immunostimulating complex (ISCOM)

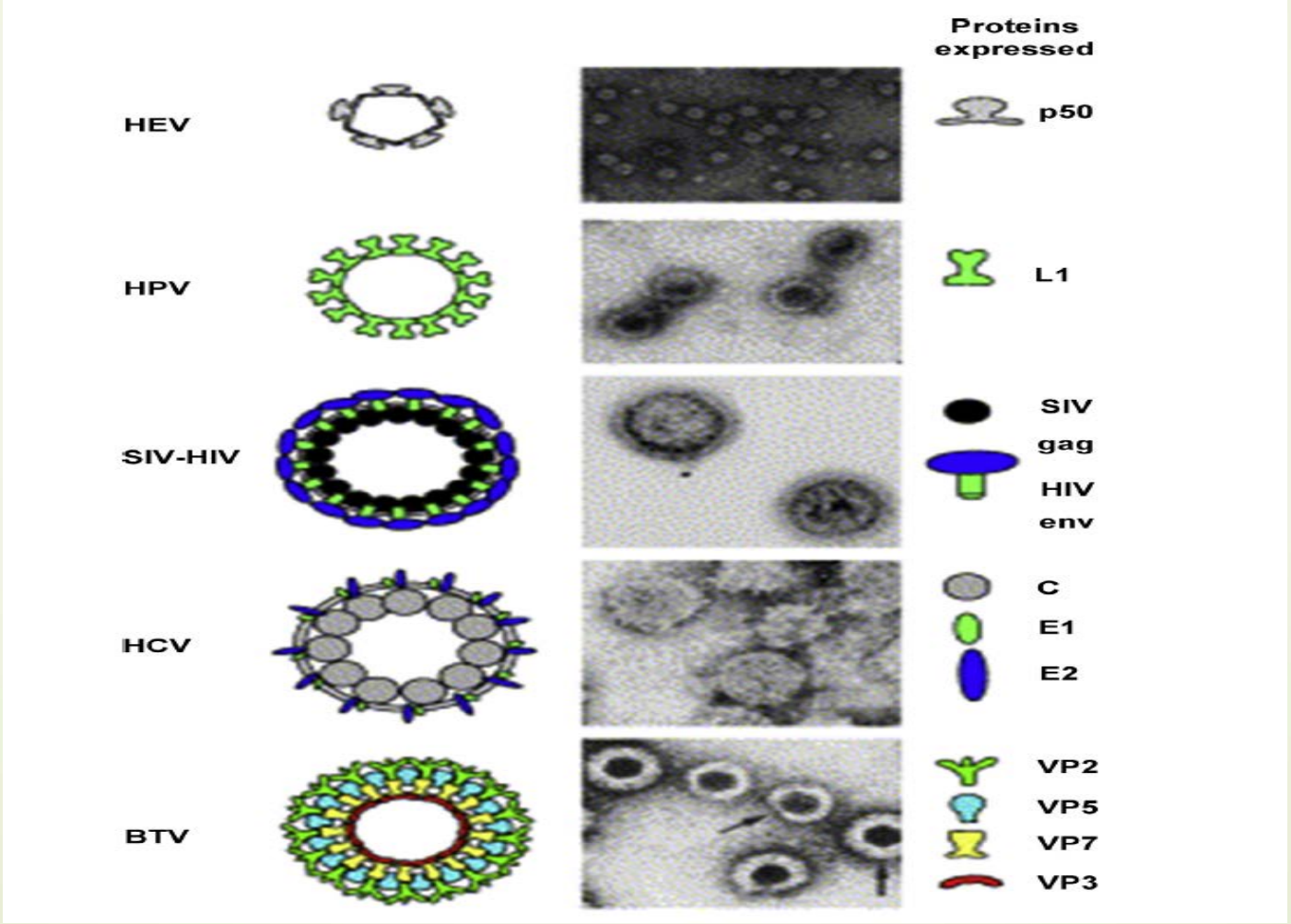
- ISCOMs are cage like particles about 40 nm large in size, made of the saponin adjuvant Quil A, cholesterol, phospholipids, and protein antigen .

Virus-like particles

- Virus-like particles (VLP) are self-assembling nanoparticles, lacking infectious nucleic acid, formed by self-assembly of biocompatible capsid proteins

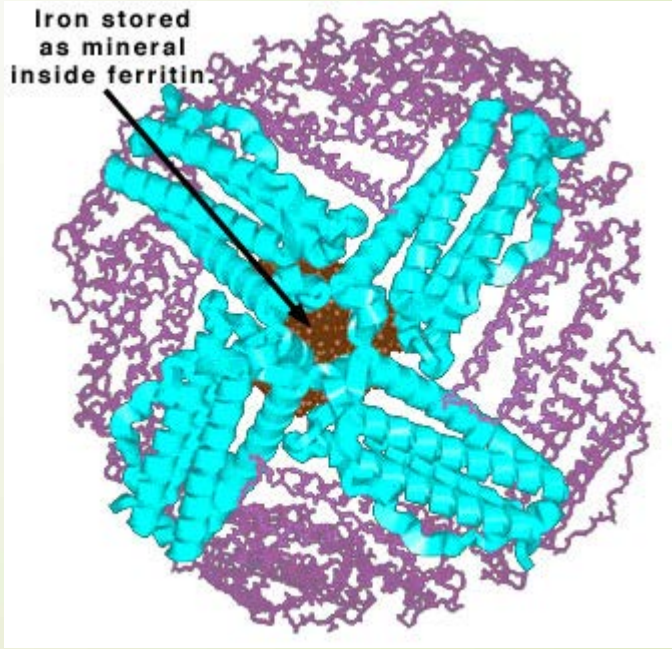
- VLPs are the ideal nanovaccine system as they harness the power of evolved viral structure, which is naturally optimized for interaction with the immune system, but avoid the infectious components. VLPs take the good aspects of viruses and avoid the bad. VLPs can be derived from a variety of viruses , with sizes ranging from 20 nm to 800 nm.

Structure of virus-like particles



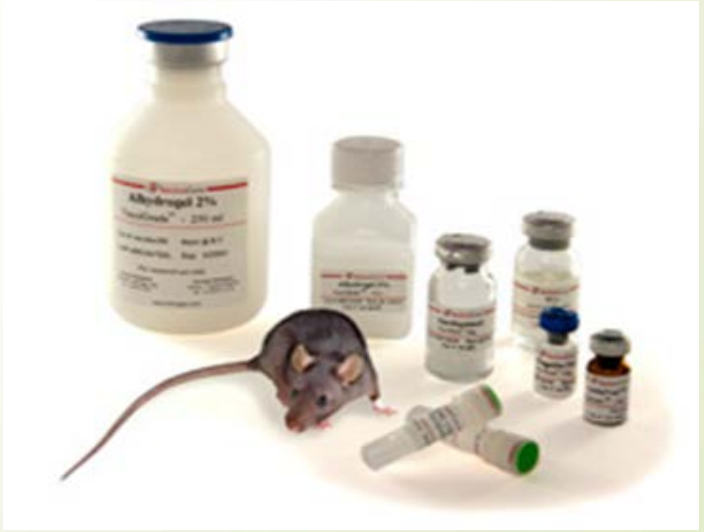
Self-assembled proteins

- Recognizing the power of the VLP approach, self-assembling systems that attempt to drive higher levels of protein quaternary structuring have emerged for the preparation of nanoparticle based vaccines.
- ✓ Ferritin is a protein that can self-assemble into nearly-spherical 10 nm structure

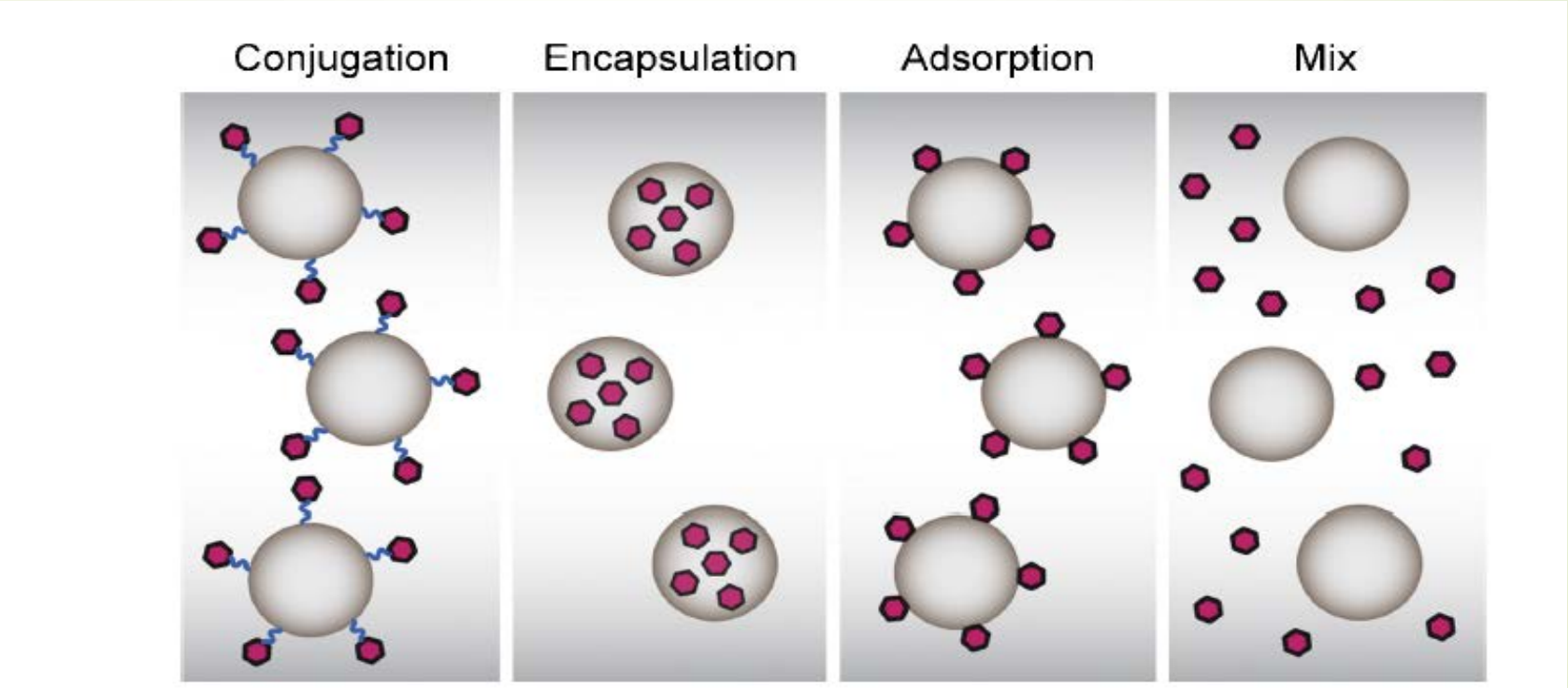


Emulsions

- Another type of nanoparticles used as adjuvants in vaccines delivery is nano-sized emulsions . These nanoparticles can exist as oil-in-water or water-in-oil forms, where the droplet size can vary from 50 nm to 600 nm . Emulsions can carry antigens inside their core for efficient vaccine delivery or can also be simply mixed with the antigen. One commonly used emulsion is MF59.
- Montanide

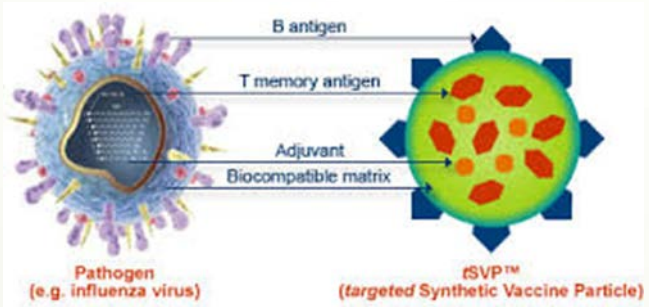


Nanoparticle interaction with antigen



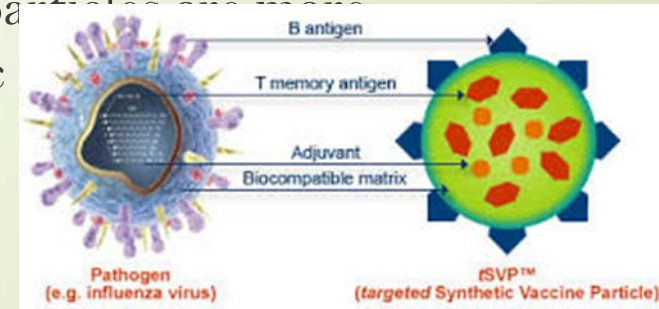
Nanoparticle interactions with APCs

- **Effect of Size:**
- Dendritic cells (DCs) and macrophages are often targeted in vaccine design.
- Size, charge and shape of nanoparticles play significant roles in antigen uptake.
- DCs preferentially uptake virus-sized particles (20–200 nm)
- Macrophages preferentially uptake larger particles (0.5–5 µm)



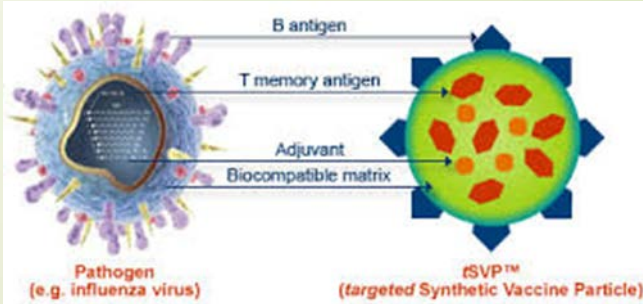
Nanoparticle interactions with APCs

- **Effect of charge:**
- In addition to particle size, surface charge also plays a significant role in the activation of immune response
- Cationic nanoparticles have been shown to induce higher APC uptake due to electrostatic interactions with anionic cell membranes.
- In vitro studies suggested that a cationic surface could significantly enhance the uptake of polystyrene particles of micron size (~1 μm) by macrophages and DCs in comparison with a neutral or negative surface , but not for the smaller nanoparticles (100 nm)
- either positively or negatively charged liposomes could act as efficient adjuvants to induce cell-mediated immune response.
- due to the electrostatic interaction with anionic cell membranes, cationic particles are more likely to induce hemolysis and platelet aggregation than neutral or anionic



Nanoparticle interactions with APCs

- Effect of shape
- Effect of hydrophobicity or hydrophilicity



Nanoparticle-biosystem interactions

- The lymph node (LN) is a target organ for vaccine delivery since cells of the immune system, in particular B and T cells, reside there.
- Ensuring delivery of antigen to LNs, by direct drainage or by migration of well-armed peripheral APCs, for optimum induction of immune response is therefore an important aspect of nanoparticle vaccine design.
- Distribution of nanoparticles to the LN is mainly affected by size . Nanoparticles with a size range of 10–100 nm can penetrate the extracellular matrix easily and travel to the LNs where they are taken up by resident DCs for activation of immune response.
- Particles of larger size (>100 nm) linger at the administration point and are subsequently scavenged by local APCs , while smaller particles (<10 nm) drain to the blood capillaries .

Nanoparticle-biosystem interactions

- In addition to targeting lymphatic organ for efficient activation of immune response, design of nanoparticle vaccines also needs to consider nanoparticle clearance from the body.
- Adverse effects may occur when nanoparticles are not degraded or excreted from the body and hence, accumulate in different organs and tissues.

Clearance

- Clearance of nanoparticles could be achieved through degradation by the immune system or by renal or biliary clearance.
- Renal clearance through kidneys can excrete nanoparticles smaller than 8 nm.
- Surface charge also plays an important role in determining renal clearance of nanoparticles. Few reports have suggested that for appropriate identically sized particles, based on surface charge, ease of renal clearance follows the order of positively-charged < neutral < negatively charged.
- This may be attributed to the presence of negatively-charged membrane

  of glomerular capillary

Clearance

- biliary clearance through liver allows excretion of nanoparticles larger than 200 nm .
- Surface charge also plays role in biliary clearance with increase in surface charges showing increased distribution of nanoparticles in the liver.
- a study reported shape dependent distribution of nanoparticles where short rod nanoparticles were predominantly found in liver, while long rods were found in spleen.

Concluding Remarks

- Nanoparticle-containing vaccines have attracted tremendous interest in recent years, and a wide variety of nanoparticles have been developed and employed as delivery vehicles or immune potentiators, allowing not only

- improvement of antigen stability
- enhancement of antigen processing and immunogenicity,
- targeted delivery , slow release of antigens
- deliver not only antigen of interest but also co-adjuvant, such as poly(I:C), CpG and MPL

Thanks for your attention