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Role of Nanomedicines in Cancer Immunotherapy

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I. INTRODUCTION

Nanomedicines play a pivotal role in cancer immunotherapy by aiming to reinforce the cancer- immunity cycle, via potentiating key steps in the immune reaction cascade, namely antigen release, antigen processing, antigen presentation and immune cell- mediated tumor killing. Combination of nanomedicines with immunotherapy can be realized via three targeting strategies, i.e. by targeting cancer cells, targeting the tumor immune microenvironment and targeting the peripheral immune system.

Nanomedicine is a new science that emerged along with the establishment of technologies such as high resolution microscopes for biotechnology applications that allow investigations of nanomaterials(less than 100 nm) at cellular levels. Among several different nanomedicine techniques, nanotechnology- based drug delivery has gained the greatest interest. Incorporation of therapeutic drugs in to nanomaterials and using these as carriers to target specific tissues avoiding systemic side effects, remains a major challenge in therapeutics. Many types of nanocarrier systems from diverse materials with distinctive physiochemical properties have been established for use in multiple diseases. Liposomal drug carrier system is the most common and explored type of nanocarrier systems.(Figure 1)

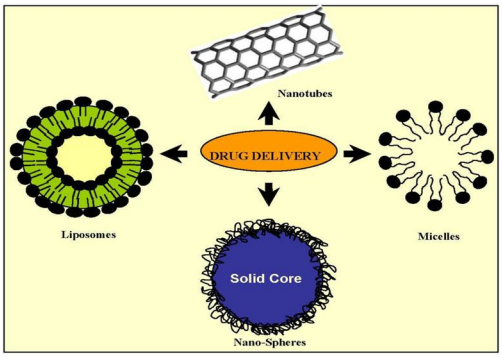

Fig. 1- Some different drug delivery systems.

Primary tumors are conventionally treated by surgery, chemotherapy and radiotherapy. However, tumor relapse and ultimate therapeutic failure remained a big challenge in the clinic. The innate and adaptive immune system can make a large contribution to the therapeutic effects of conventional cancer treatments. Circumstantial evidence in the pre- clinical studies suggest that the long - term success of cancer therapies lies in immunotherapy. Therefore, cancer immunotherapy is considered as an effective treatment technique to eliminate primary and metastatic tumors as well as to establish immunological memory. (Figure 2)

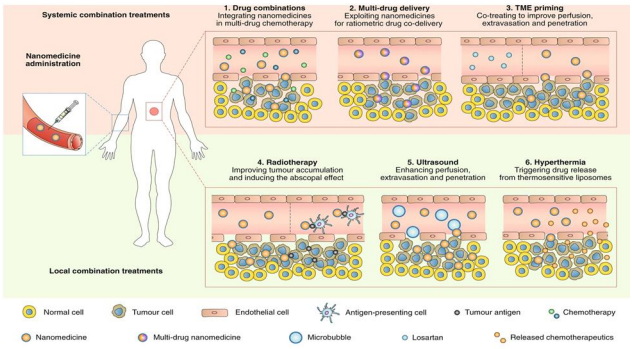

Fig.2- Smart Cancer nanomedicine- based combination therapies.Systemic combination: 1.Drug combination; 2.Multi-drug delivery; 3.Tumor microenvironment(TME) priming. Local combination: 4.Radiotherapy; 5. Ultrasound and Microbubbles; 6Hyperthermia.

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The ultimate application of nanomedicine is to reprogram or modulate the immune response by precisely targeting biological pathways. Nonomedicines can simultaneously deliver various immunological agents to the intended target site (tumor or lymph node). Rational drug selection is crucial for making cancer nanomedicines clinically and commercially successful. Nonoparticles(size in nanometer range) provide a new mode of cancer drug delivery functioning as a carrier for entry through fenestrations in tumor vascular allowing direct cell access. These particles allow exquisite modification for binding to cancer cell membranes, the microenvironment, or to cytoplasmic or nuclear receptor sites.This results in delivery of high drug concentrations to the targeted cancer cell, with reduced toxicity of normal tissue. Several such engineered drugs are in clinical practice, including liposomal doxorubicin and albumin conjugate paclitaxel. The carrier mediated paclitaxel has already shown significant efficacy in taxane resistant cancers, an approach highly relevant in prostate cancer, where taxanes are the treatment of choice. Other modifications including transferrin receptor and folate receptor targeted drug delivery molecules are in study. This new technology provides many exciting therapeutic approaches for targeted drug delivery to cancer cells with reduced injury of normal cells.

Many nano- immunotherapies target the adaptive immune system, modulating components of the innate immune system has far remained largely unexplored. The innate immune system functions as a rapid and relatively non- specific first line of defense against infections, mediated by the complement system and by cells such as phagocytes and natural killer cells. These cells contain pattern recognition receptors(PRRs), which detect pathogen- associated molecular patterns (PAMPs) and damage- associated molecular patterns(DAMPs) . PAMPs and DAMPs can induce an innate immune response and subsequently activate the adaptive immune system.

The advent of immunotherapy is a game changer in cancer therapy with monoclonal antibody and T- cell based therapeutics being the current flagships. However, small molecular inmunotherapeutics might offer advantages over biologicals in terms of complexity, tissue penetration, manufacturing cost, stability and shelf- life. However, small molecule drugs are prone to rapid systemic distribution which might induce sever off - target side effects. Nanotechnology could aid in the formulation of these drug molecules to improve their delivery to specific immune cells subsets.

A diversity of immunotherapy agents, including tumor- associated antigens, adjuvants, Cytokines and immunomodulators, have been explored for their ability to induce a cascading adaptive immune response. Nanoscale metal - organic frameworks(nMOFs) are attractive for cancer immunotherapy because they feature tunable pore size, high surface area and loading capacity, and intrinsic biodegradability.

Advanced nonomaterials, including liposomes, polymers, and silica, play a vital role in the codelivery of drugs and immunonomodulators. These nanobiomaterial- based delivery systems could effectively promote antitumor immune responses and simultaneously reduce toxic adverse effects. Furthermore, nanobiomaterials may also combine with each other or with traditional drugs via different mechanisms, thus giving rise to more accurate and efficient tumor treatments. The most well- studied nanocarriers are liposomes, dendrimers, polymer- based platforms, Superparamagnetism nanoparticulates, gold nanoshells, carbon-60 fullerenes, nanocrystal, silica and silica - based Nanoparticle. (Figure 3)

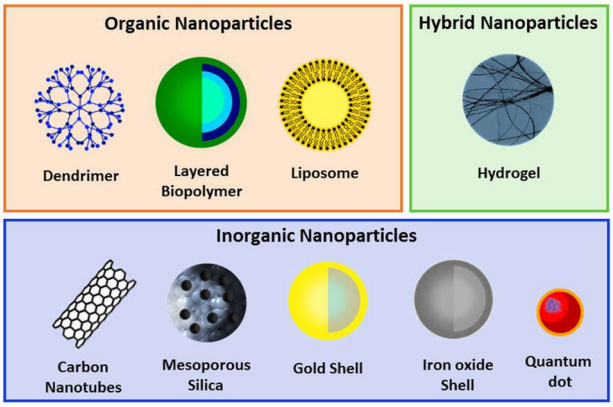

Fig. 3- Different types of Nanoparticles

To conclude, nanomedicine - based treatment strategies are well -suited to immunotherapy on the basis of nanomaterials' ability to direct immunomodulators to tumors and lymphoid organs . Hence, efforts have been made towards clinical translation of nanomedicine - based immunotherapy.

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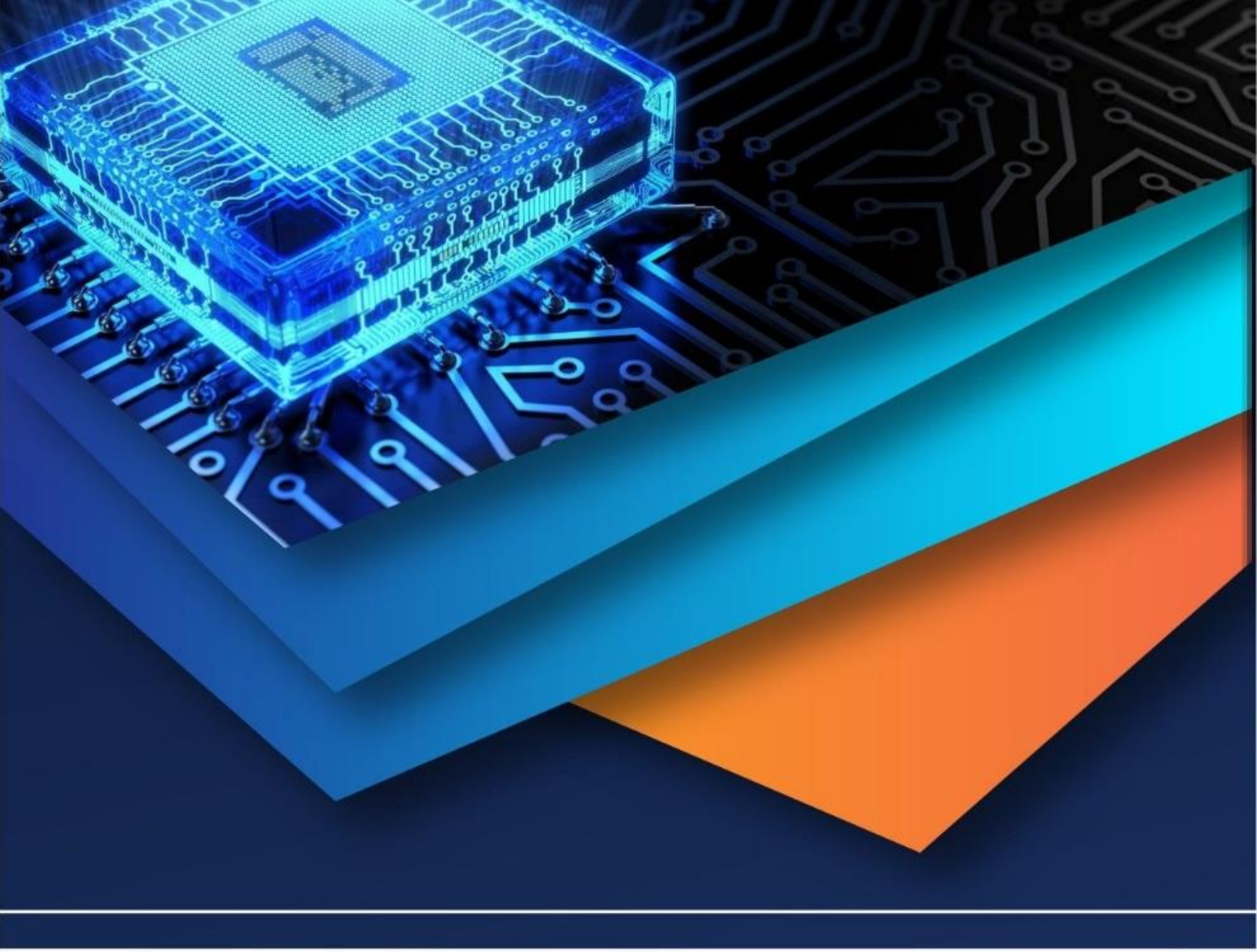

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