DIRNANO

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Nanoparticles for nucleic acid delivery

Nanotechnology has protagonized serious scientific revolutions in the past decades and has led to the era of nanovaccines. Nanoparticle (NP) vaccines are being able to overcome the drawbacks of traditional vaccines with a pronounced modulation in favor of the immune system.
Nanovaccines are based on NPs as adjuvants or carriers of biological moieties such as DNA, RNA or recombinant proteins. NPs have an overall size range between 10-1,000 nm. In NP-based vaccines, the biological moiety can be encapsulated inside the NP by chemical conjugation or can be bound to the surface, as a decoration.
These features provide the capability to incorporate the antigen and adjuvant components together in order to maximize immune stimulation. The recent lipid NP-based COVID-19 mRNA vaccine represents a milestone for NP-based nucleic acid delivery [1], [2] .

A third-generation vaccine is an emerging concept established in the early 1990s and includes DNA and RNA vaccines. Since it is easier to establish and modify the antigen, nucleic acid-based immunization technology is very adaptable and dynamic.
A successful delivery system is necessary to protect the nucleic acids from premature degradation as well as ensuring transport across cellular membranes to their subcellular site of action. A range of nanoparticle delivery systems have been developed to deliver nucleic acid therapeutics, with a major focus on protection over degradation.
The diverse array of NP-materials includes lipid, polymer, and inorganic/metallic nanoparticles [3]–[5] (Fig. 1).

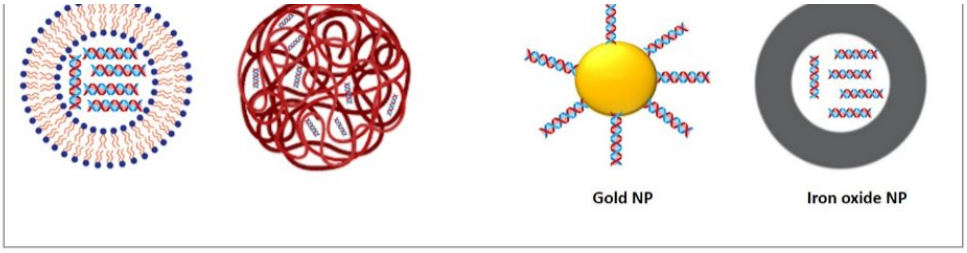

Figure 1. Schematic representation of nanoparticle designs for nucleic acid delivery. Image adapted from *M. Lim et al*[5].

Lipid nanoparticles (LNPs) have gained much attention right after the covid-19 pandemic. Lipid-based delivery systems have good biocompatibility and are usually captured by endocytosis, which aids transfection. Cationic LNPs are the most widely used LNPs. These consist of mainly synthetic cationic lipids that form a stable complex with anionic nucleic acids. Polymeric NPs are also attractive because of their stability, safety, ease of surface modification, biocompatibility and predictability. The list of components for these NPs includes polysaccharides, poly amino acids, and poly hydroxy acids that forms vesicles which can either encapsulate or exhibit the antigens.
The presence of a large number of amino, carboxyl, and hydroxyl groups in the molecular structure of polymers always make them an ideal delivery platform. Inorganic NPs add an additional benefit for vaccine distribution due to their hard structure and predictable fabrication; however, they are predominantly non-biodegradable. Usually inorganic NPs have been used as adjuvants and delivery vehicles for antigens to enhance the immune response. The main inorganic NPs are based on carbon, silica, calcium, aluminum, or gold [6]–[8] .

For the past 20 years, nucleic acid therapeutics have held great therapeutic potential, but until the COVID-19 pandemic their application was limited to a small group of genetic rare diseases. However, the great success of COVID-19 mRNA vaccines has paved the way to apply nucleic acid therapeutics to a wider array of conditions. A broad range of NP delivery systems, acting either as vaccine carriers or vaccine adjuvants, has shown clear merits due to their size similar to pathogens, enhanced antigen protection, and immune response induction.
Finally, the promise of nanovaccines goes beyond the simple induction of humoral or cell mediated immunity, reaching for the development of personalized vaccines.
Nonetheless, the NP-based vaccine delivery strategy can be a promising platform for the treatment of several infectious diseases and could be adapted for other non-infectious diseases, such as cancer [9], [10] .

Within the DIRNANO framework, I am working in Dr. Alfredo Martínez´s group (Angiogenesis group), Oncology area, CIBIR, La Rioja, Spain, to create nucleic acid vaccines against angiogenic factor in order to investigate preventive vaccines against cancer.
More specifically, I am trying to create an oral DNA vaccine based on

angiogenesis factor Pro-adrenomedullin N-terminal 20 Peptide (PAMP) to prevent tumor metastasis. In this project I am using attenuated *Salmonella typhimurium* bacteria for the oral delivery of DNA and in addition trying to develop a silica NP (ormosil) platform too for the plasmid DNA dispatch. In general group employs various NP based *in vivo* delivery systems such as gold, silica and lipid for mice vaccination of these systems as a part of their preclinical studies.

Tom Kalathil Raju,
ESR Fundación Rioja Salud

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DIRNANO NEWS

Ander Eguskiza Bilbao (ESR09) is currently in LipoCoat, Netherlands to study the antifouling properties of several polyethylene glycol and polyglycerol-based coatings and to synthesize lipid nanoparticles (LNPs) for the cytosolic delivery of STING agonists as adjuvants for nanovaccine formulations.

Foivos S. Lazaris (ESR14) just started his second secondment in LipoCoat, Netherlands. He is trying to conjugate the modified peptides, featuring unnatural amino acids, to gold nanoparticles coated with a lipid bilayer.

Rita Riberio (ESR 08) is doing her secondment in the group of Dr. Alfredo Martínez, CIBIR, Spain where she is getting acquainted with the immunization of in vivo models, hypoxic cell culture in order to mimic tumor microenvironment and techniques to study the mitochondrial metabolism.

The 3rd regular meeting of DIRNANO was held at University of Verona, Italy from the date 28/02/2023 to 03/03/20203 and ESR8 and ESR9 got awarded for the best posters.

The 4th regular network meeting is scheduled for 25/09/2023-28/09/2023 at STAB VIDA, Caparica, Portugal.

NEWS IN THE FIELD

- Global meeting on nanotechnology (GMNANO2023) is scheduled for 12-14 June 2023 at Ana Crowne Plaza, Osaka, Japan.

- 2nd Annual Conference on global nanotechnology is scheduled for 19-21 June 2023 at Material Science Institute of Madrid, Spain.

- Q. Zhou et al., recently published their study with polymeric metal-organic framework nanoparticles loaded with STING agonist showed enhanced antitumor immunity via photodynamic-immunotherapy [11].

- L. Stertman et al., has published an interesting review article about Matrix-M™ from Novavax as critical adjuvant of vaccines for 21st century [12].

- The German company BioNTech has signed a memorandum with UK government for randomized clinical trials of their personalized mRNA cancer vaccines [13].

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