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Review

Topical review on nano-vaccinology: Biochemical promises and key challenges

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ABSTRACT

Nanomaterials have wide-ranging biomedical applications in prevention, treatment and control of diseases. Nanoparticle based vaccines have proven prodigious prophylaxis of various infectious and non-infectious diseases of human and animal concern. Nano-vaccines outnumber the conventional vaccines by virtue of plasticity in physio-chemical properties and ease of administration. The efficacy of nano-based vaccines may be attributed to the improved antigen stability, minimum immuno-toxicity, sustained release, enhanced immunogenicity and the flexibility of physical features of nanoparticles. Based on these, the nano-based vaccines have potential to evoke both cellular and humoral immune responses. Targeted and highly specific immunological pathways required for solid and long lasting immunity may be achieved with specially engineered nano-vaccines. This review presents an insight into the prevention of infectious diseases (of bacterial, viral and parasitic origin) and non-infectious diseases (cancer, auto-immune diseases) using nano-vaccinology. Additionally, key challenges to the effective utilization of nano-vaccines from bench to clinical settings have been highlighted as research domains for future.

1. Introduction

'Chemistry' behind the nanoparticles and their multi-dimensional exclusive applications is quite fascinating. Nanoparticles (materials having at least one dimension of <100 nm size) have been successfully applied in many fields of biomedical science including therapeutics e.g. drug screening and targeted delivery, diagnostics, vaccine production, surgical intervention, gene delivery, theragnostic, biomarker assisted mapping, toxicity of pathogenic organisms, etc. [1–4]. The nano-carriers/adjuvants e.g. liposomes, proteasomes, emulsions, synthetic polymeric nanoparticles, nano-beads, ISCOMs, biological polymeric nanoparticles (exosome, bacteriophage) and inorganic nanomaterials have been utilized to prevent infectious and non-infectious diseases [5,6]. The inertia of surface modification and ability to effectively co-deliver the adjuvants makes nanoparticles potential candidate for commercial vaccines. Also, the nano adjuvants in vaccines protect the target antigen from degradation and enhance uptake by immune mediators of biological systems. This approach is malleable, having the ability to present the antigen in a repetitive manner leading to stable immunogenic properties.

Nano-vaccines have been widely experimented as prophylaxis of important diseases such as: bacterial (*E. coli*, *Helicobacter* sp.), viral (HIV, HPV, influenza), cancers (primary and metastatic), parasitic (malaria, toxoplasmosis, coccidiosis) and auto-immune disorders [7–9]. The concept of deploying nanovaccines from a broader perspective has been depicted in Fig. 1 schematic illustration of nano-vaccinology in a nutshell. Wide variety of nanoparticles as vaccine scaffolds, enzyme, cargo have opened a new avenue towards precision medicine. These vaccines could be replicated in disease models of multi-drug resistant pathogens, which historically have presented as a great clinical

Abbreviations: ISCOMS, immune stimulating complexes; HIV, human immune deficiency virus; HPV, human papilloma virus; MRSA, methcillin resistant *Staphylococcus aureus*; IgA, immunoglobulin A; SARS-CoV-1, severe acute respiratory syndrome Coronavirus-1; MERS, Middle-East respiratory syndrome; VLP, virus like particles; SAPN, Self-Assembling Protein Nanoparticle; COVID-19, Corona virus disease-2019; PSNP, polystyrene nanoparticles; PLGA, poly(lactic-co-glycolic acid); CNT, carbon nanotube; NMVs, nano multilamellar lipid vesicles; CAPN, calcium-phosphate nanoparticles; Chi-Alg, chitosan alginate.

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challenge. Deploying biological nano-polymers like proteins, peptides, DNA, RNA and others have improvised the immunotherapy up to 100 folds, compared to previous clinical options [10].

The efficacy of nano-assembled vaccines may be attributed to the improved an Fig. 1 tigen stability, minimum immuno-toxicity, sustained release, enhanced immunogenicity and the flexibility of physical features (e.g. Size, morphology, surface characteristics) [11]. Nano-vaccines have a huge potential of relatively easy engineering. Moreover, tailor-made personalized immune therapy is possible by harnessing the potential of nano-vaccines reveals a conceptual idea. The challenge areas of nano-vaccines are understanding of exact mechanisms for bio-distribution and possible commercialization which need to be well-investigated and consigned. The quantitation of host immune interactions on exposure to nano-based vaccine demand clinical trials for efficient commercialization. The exclusive manuscript reflects into account the novel promises, utilizations and future perspectives of nano-vaccines in human and animal diseases. Brief insights and way forward for commercialization of nano-vaccines in clilnical settings have been summarized in the entire research innovation.

2. The biochemistry of nano-vaccines

Contemporary vaccine strategies employ either killed or live attenuated antigens. Live attenuated vaccines may induce clinical disease arising from same or mutated genotypes [12]. Therefore, the level of desired immune response may not be achived. The nanoparticles having efficient surface properties, making them more suitable candidates for stimulating the immune system and eliciting better immunological response. The hydrophobicity of nanoscale materials enhances the expression and release of inflammatory mediators and cytokines. Superior adjuvancity, owing to the exceptional surface properties of nanomaterials make them stand-out the conventional vaccine adjuvants [13]. Some of nano-based adjuvants have been officially licensed for use in making commercial antiviral vaccines [14]. Moreover, increment towards dendritic-cell mediated autophagy and presentation of antigens to the immune cells lead to a solid cellular and humoral immunity against target pathogen.

First and second generation vaccines differ from nano-vaccines on the basis of low-functionalized plasmid DNA, highly labile to degrading enzymes, lacking the smart size and hydrophobic nature. All of these properties contribute to halt efficient transfection of antigens within target cells [15]. Moreover, the difficulty in administration and development of slower immunological response based on time-taking chemical interactions at cellular levels were major issues with DNA vaccines. Chitosan nanoparticles have the intrinsic ability to adhere with mucosal layers of host; this cationic feature makes them efficient cargo for antigen delivery [16]. Similarly, by virtue of ionic cross-linkages, the utilization of biopolymers could improvise endocytosis by host cells. This internalization stimulates a sustained pattern of exposure to antigen presenting cells, resulting in a stable immunological response. This response is characterized by the interaction and front-line response by many immunomodulators of the host. The liposomal vaccine carriers, due to hydrophobic interactions, can facilitate fusion within cellular membranes [17]. Also, the cationic nature further enhances cytosolic release, which is highly desirable in DNA based vaccines.

Most importantly, nanoparticle-based vaccines have been shown to stimulate longer immunological memory in the host [18]. This property, combined with the ability to elicit antigen-specific (IgA) mucosal immunity is the mainstay of popularity earned by nano-vaccines. Brief pathway opted by nano-vaccines to bring forward the cell mediated and/or humoral immunity in host are being illustrated in Fig. 3. The nucleic peptides might become very unstable within the host cells and may fail to produce desired immunological response due to proteolytic degradation inside the cells [13]. Nano-adjuvants provide a biologically compatible carrier platforms, that not only enhance antigen protection and sustained release, but also enhance immune stimulation in the host for a stable and solid immunity.The concept of deploying nanovaccines from a broader perspective has been depicted in Fig. 1.

Use of natural biomolecules such as albumin, chitosan, mannose, peptides, enzymes, chemical immunomodulators (Interleukins, cytokines) or immunoglobulins as nano-carriers for vaccines have shown long span, more stable and ubiquitous peripheral tissue response in cancer immune therapy [10]. Nano-vaccines have brought a revolution in the science of small by evading degrading cellular pathways and efficient absorption up to blood vessels [15]. Based on admirable performance explored in pre-clinical and clinical trials, liposomal and VLPs based nano-vaccines, there are more than 10 commercial vaccines in human practice or clinical trials. Classical examples to VLP-based commercial vaccines include the porcine-circo virus vaccine, human cervical cancer and anti-hepatitis B nano-vaccines and multi-epitope anti-malarial and anti-hepatitis B vaccines [19,20]. The desired level of epitope density and co-stimulation is a very unique and high precision characteristic of nano-vaccines. Additionally, revamping the ability of nanomaterials to selectively enhance one of desirable, antigen specific immune responses in order to achieve optimal immunity holds huge potential in future engineered vaccines. As a case study, it is imperative to commend the most effective yet rapidly developed COVID-19 vaccine which is based on gold nanomaterials [21–23]. The plasmonic stabilization and functionalization has made the vaccine perform fairly well in pre-clinical as well as clinical trials and safety evaluations.

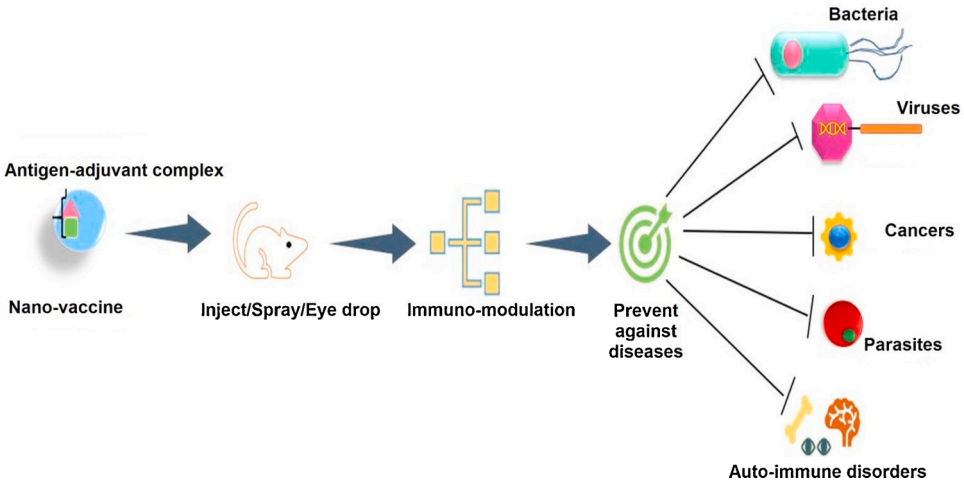

Fig. 1. A schematic illustration of nano-vaccinology in a nutshell.

3. Nano-vaccines against pathogens

The world is dealing with ever rising population of super bug pathogens, the multi-drug resistant bacteria, rapidly mutating viruses, anthelmintic resistant parasites and secondary cancers. Most recently, COVID-19 pandemic has moved the major stakeholders to come up with very practical and promising candidates for prevention and therapeutic management of the virus [24]. The first-ever, highly progressive anti-Covid-19 vaccine is also based on nanomaterials [21]. Overview of most recent developments in nano-vaccinology during the current decade have been given in Table 1.

Owing to the non-judicious use of anti-microbials, bacterial strains have undergone certain mutations/ modifications that have enabled them to degrade and render the previously used anti-microbials, totally ineffective. In this scenario, there is an emergent desire to come up with practical solutions to the resistant populations. Moreover, the nanoparticles have been successfully trialed for effective wound management, healing and infection prevention of primary or secondary nature [25]. The clinical presentation and associated secondary systemic diseases present a great deal of challenge, ending up in the form of high morbidities or even higher death rate of the patients [26]. 'Nanotechnology' has marked a ground breaking success in novel therapeutics, prophylaxis and management options against bacteria, viruses, parasites and cancers. Major types of nano-adjuvants/ nano-carriers/ nano-scaffolds employed for Vaccinology have been illustrated in Fig. 2.

3.1. Nano-vaccines against bacteria

Nano-vaccinology has also been trialed to control many human and animal diseases of bacterial origin, to improvise quality of living in both. To this end, *Escherichia coli* (*E. coli*.) is one of the most widely utilized model organism for different nano-vaccines. Bacteria causing drop in production and performance of farm animals have also been counteracted by employing nano-vaccines. Also, the vaccine mediated protection against MRSA has been made possible using nano-toxoid of polymeric nature [26]. Toxins from bacteria have also been utilized to produce nano-vaccines at lab scale. This development in conventional Vaccinology has opened enormous avenues for safer, least toxigenic, more immunogenic alternative for control of super bug pathogens. Also, the concept of nano-vaccines endorses the One Health-One Welfare, looking after the well-being of humans, animals and the environment at a shared interface. Examples of nano-vaccines against clinically important bacteria have been developed against *E.coli, Salmonella, Helicobacter, Staphylococcus, Pseudomonas*, *Clostridium*, *Mycobacterium*, etc. [6,27–30]. None of nano-vaccination has made its way to the clinical applications against bacterial diseases, however, by upscaling the lab studies, it is possible to commercialize toxoids against bacteria for human administration. Brief pathway opted by nano-vaccines to bring cell mediated and humoral immunity in host are being illustrated in Fig. 2.

3.2. Nano-vaccinology against virology

Viral diseases have historically caused and still posing a great threat to the integrity of entire ecosystems. Limitation of availability, high cost of production and promise in emerging viral strains are major challenges to anti-viral drug production. However, vaccines have shown to almost counter these areas of concern. Heterosubtypic immune protection in influenza strains (H1N1, H5N1) is a much-needed approach for rapidly mutating viruses [31,32]. Highly significant pathogen of humans, including HBV, HPV, HIV, DENV-E have been prevented using precisely engineered nano-vaccines, that have shown to offer up to 95–100 % effective immune protection [33]. Anti-AIDS nano-vaccines may be utlilized at clilnical settings to prevent the disease and associated complications at endemic regions of the world. The viral moieties in HIV are better functionalized and presented in a sustained manner. The nano-adjuvants to AIDS vaccines have shown a stable, least toxigenic and a long-lived immunological response, based on specific immunologlobulin activation.

'Poliovirus' is one of the most significant endemic pathogens of many developing countries. To this end, Marsian and co-workers have proposed a plant-mediated nano-vaccine, by utilizing virus like particles [34]. A complementary approach has shown reasonable immune protection against dengue virus challenge [35]. Other viral diseases that have been shown to be prevented by nano-vaccines include avian influenza (H3N2), respiratory syncytial viruses, parainfluenza virus, Rift Valley Fever Virus and most importantly, the corona viruses (MERS, SARS) [16,36].

The rampant promise of nano-vaccines against a wider range of virus subtypes indicates high potential against viruses having aerosol route of transmission. Examples of pre-clinical design and evaluation of nano-vaccines have also been found to be successful against other coronaviruses of humans in SARS-CoV-1 and MERS. This could be a way forward for effective prevention of emerging and re-emerging human diseases, for instance SARS, MERS, CoVID-19 and influenza.

3.3. Nano-vaccines against parasites

Drug resistance and slower development of modern anti-parasitic drugs are the major concerns to widespread neglected tropical diseases. Parasitic diseases of prime concern like-wise: leishmaniasis, malaria, toxoplasmosis, anaplasmosis, schistosomiasis, and coccidiosis have been treated and prevented using several forms of nanoparticles [33,37]. To date, there is no commercially available nano-vaccine against any parasite. The benefit of nanoparticles-assembled vaccines has shown highly desirable, Th1-mediated immunological protection against leishmaniasis. Recently, epitope-based nano-vaccine, using Self-Assembling Protein Nanoparticle approach (SAPN) has been successfully developed against toxoplasma sp. Similarly, malaria (*Anaplasma sp*.) nano-vaccines have undergone huge development and several promising vaccine antigens have offered protective immunity in laboratory attempts [38,39]. This approach could be applied to parasitic vectors (mosquito, tick, flies) of human, animal and zoonotic diseases. There is a need to further channelize and utilize the potential of nano-vaccine induced mucosal immunity for development of anti-parasitic vaccines.

3.4. Nano-vaccines against cancer

'Cancer' is the second leading cause of deaths worldwide, claiming almost 10 million lives each and every year. Chances of survival are meagre, and quality of life is compromised in case of secondary cancers. To this end, 'Nanotechnology' has provided alternative coverage to anti-cancer therapy and prevention [2,5,40]. Conventional cancer vaccines have a moderate immune coverage due to limited antigen presentation at draining lymph nodes and quicker degradation [41]. Cancers of various organs and systems, including nervous, respiratory, reproductive, digestive, brain, endocrine and urinary systems could be prevented by use of nano-vaccines [8,10,42]. Also, the cancers of hereditary seat and secondary nature can be prevented by adopt nano-vaccines. Tumor cells have a heterogeneous collection of antigens, known as 'neo-antigens'. They have lower immune protection if delivered solely. Bio-conjugation with nanoparticles has exhibited improvised immune response, offering protection against recurrence of tumors [10]. High precision and tailor-made, personalized nano immune protection in cancer highlights the most superior application of nano-vaccines. A similar model for immune protection could be opted for auto-immune diseases in humans.

4. Challenges and future prospects in nano-vaccines

Engineering the surfaces of nanoparticles by chemical means may alter their potential bio-compatibilities [43]. The chemical

Table 1
Concise report of some advancement in nano-vaccines (current decade data).

Target pathogen/ disease	Type of nanoparticle	Properties	Type of Immunity	Reference
Cancer	Polystyrene (PSNPs)	PSNP size = 40−50nm Peptide antigen conjugated vaccine	Cell-mediated	[8]
COVID-19 (SARS CoV-2/ Pandemic corona virus, 2019)	Liposomes	Diameter = 135−158 nm (conjugate) Sub-unit vaccine	Humoral	[50]
SARS CoV-1 (Severe Acute Respiratory Syndrome)	Gold nanoparticles	AuNP diameter = 40−100 nm Nano-adjuvant vaccine	Antigen specific	[51]
Influenza and circo viruses	Virus-like Particles (VLPs)	Self-assembling, Bivalent vaccine	Cellular and humoral response	[9]
Escherichia coli	Silver (Plasmonic NP)	Size = 15nm AuNP Vaccine scaffold	Humoral immunity	[30]
Malaria	Virus-like Particles (VLPs)	VLP size = 22nm Anti-sporozoite vaccine	Cellular and humoral response	[12]
Coronaviruses	Protein	Diameter ~25nm SARS and MERS protein	Neutralizing antibody response	[36]
Cancer	Biopolymeric (Albumin NP)	Self assembling, Halted primary or metastatic tumors	Antigen specific immune therapy	[10]
Avian influenza	PLGA, Chitosan and mannan coated PLGA	Size = 719, 819 nm	Antigen specific mucosal immunity	[52]
Mycobacterium tuberclosis	Chitosan (Bio-polymer)	Radius = 300−400 nm Mannosylated chitosan based DNA vaccine	Antigen specific and T cell mediated	[53]
Anaplasma marginale	Nano-vesicles	VirB9−1 antigen with silica nano adjuvant	Antibody and Cell mediated	[33]
Helicobacter pylori	PLGA	Size ~200 nm	Cell mediated	[28]
Schistosomiasis	Dendrimers	Diameter = 50−100 nm DNA, nano-delivered vaccine	Cellular and humoral	[37]
Cancer	Micelle	Diameter = 171 ± 22 nm Bi-adjuvant neo-antigen nano vaccine (banNV)	Antigen specific immune therapy	[5]
Salmonella	Chitosan (Bio-polymer)	Sub-unit, orally administered vaccine with membrane and flagellin antigens	Cell mediated and humoral immunity	[6]
Respiratory Syncytial virus	Virus-like particle (VLP)	Bi-valent Single shot vaccine	Cell-mediated	[54]
Mycobacterium paratuberculosis	Polyanhydride NP	Diameter = 200 nm PAN coated Lysate and Cf	Antigen specific, Cell mediated	[55]
E. coli	Polymeric (PLGA-MPLA)	Biomimetic, MPLA modified, antigen loaded nano vaccine	Cell mediated	[27]
Coronavirus	Protein	MERS-CoV vaccine	Antigen specific and Th-cell mediated	[56]
Toxoplasmosis	Self-Assembling Polypeptide nanoparticle (SAPN)	Diameter = 38nm Uniform, multi-epitope	Cell-mediated	[38]
Trypanosoma cruzi	Nano-vector	TcG2, TcG4 mediated Immune therapy	Cell mediated	[57]
Rhabdovirus	Carbon nanotube (CNT)	Single walled nano tubes, bioconjugated with mannosylated antigen	Cell mediated	[58]
Brucella melitensis	PLGA	Diameter = 126 nm OPS (antigen)-PLGA conjugated vaccine	Antigen specific	[59]
Listeria monocytogenes	PLGA	Sub-unit vaccine	Humoral	[60]
Shiga toxin by *E.coli*	Nano multilamellar lipid vesicles (NMVs)	NMV diameter = 142.2 ± 28.63	Hummoral	[61]
Leishmaniasis	Virus-like Particle (VLP)	Polyvalent, carbohydrate conjugate vaccine	Antigen specific	[62]
Streptococcus	Chitosan	Peptide vaccine	Antigen specific and mucosal	[63]
Rift Valley Fever Virus	Chitosan (Bio-polymer)	Size = 130−140nm Inactivated, nano-adjuvant vaccine	Cell mediated (Better than alum-based vaccine)	[16]
Methicillin resistant *Staphylococcus aureus* (MRSA)	Polymeric	Size = 115nm Nano-toxoid	Humoral	[26]
Influenza and cancer	Virus-like Particles (VLPs)	Chimeric, protozoan protein decorated on VLPs vaccine	Humoral and Cell mediated	[64]
Influenza virus	3M2e-rHF	Self-assembling, intra-nasal vaccine	Cell- mediated (Homo and hetero subtypic)	[32]
Hepatitis-B virus	Ferritin	Dual target, therapeutic vaccine	Cell-mediated and potential of humoral immunity	[65]
Influenza A virus	Virus-like proteins (VLP)	Multi-valent, Self-adjuvant modular vaccine	Antigen and site specific immune response	[66]
Cancer (HER2+)	Viral nanoparticles (Plant-based)	CPMV size = 30nm Bio-compatible adjuvant vaccine and therapeutic	Specific (anti-HER2) Immune response	[42]
Leishmania major	Liposomal vesicles	Vesicle diameter = 100 nm	Cell mediated	[39]
Brucella melitensis and *Brucella abortus*	Calcium-phosphate (CaPN)	CaPN size = 90nm Cross-protective nanovaccine	Cell mediated and humoral	[67]
Bacillus anthracis	Chitosan alginate (Chi-Alg)	Mean size of Chi-Alg = 500nm	Antigen specific, mucosal immunity	[68]
AIDS- Humman Immune Deficiency Virus	Liposome	Liposome vesicle size = 150 nm	Cell mediated	[69]
Hepatitis B Virus (HBV)	Virus-Like Particles (VLPs)	Au functionalized TLR-9 agonist Size of HBV-VLP ~34nm	Humoral and Cell mediated	[70]
Cancer	AuNP	Size ~ 200 nm Non-covalent based on β-Cyclodextrin, vaccine and therapeutic potential	Humoral	[71]

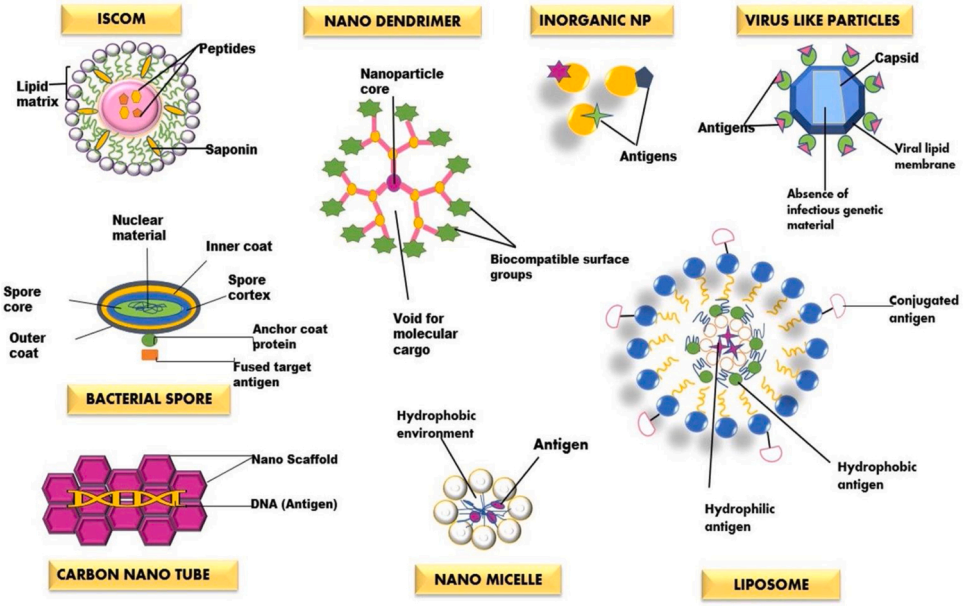

Fig. 2. Brief pathway opted by nano-vaccines to bring cell mediated and humoral immunity in host are being illustrated in Fig. 2.

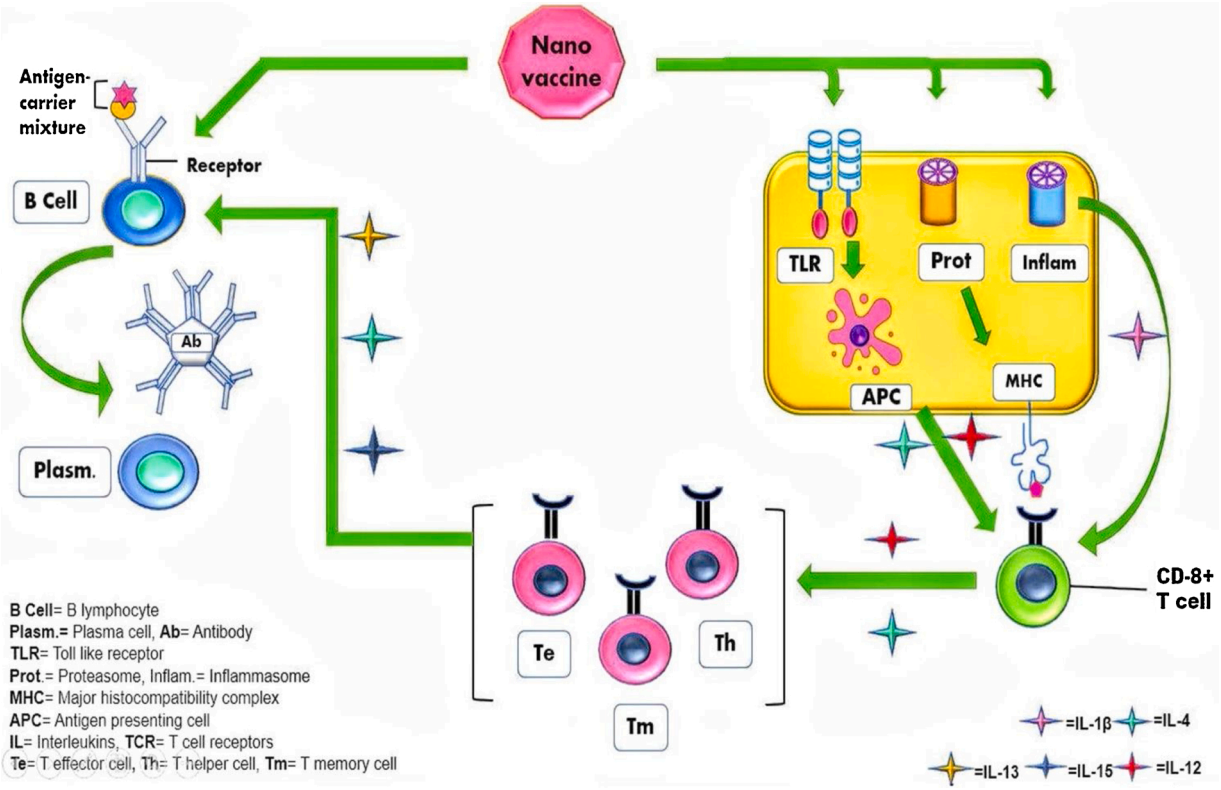

Fig. 3. Possible morphology of nano adjuvants/cargo/scaffolds embedding target antigens.
Line 138-139: Nanotechnology has marked a ground breaking success in therapeutics, prophylaxis and management options against bacteria, viruses, parasites and cancers. Major types of nano-adjuvants/ nano-carriers/ nano-scaffolds employed for vaccinology have been illustrated in Fig. 3

transformations therefore, indicate the necessity of developing the assays/tests indicative of owning target set of characteristics, before functionalization with candidate antigens/proteins. Similarly, the uniformity of nanomaterials and the reproducibility of experiments yielding nano-vaccines needs to be enhanced. This applies as a significant quality standard for biogenic nanomaterials, where scaling-up uniformly is a concern.

VLPs have shown promising performance, regarding their easy engineering, exceptionally malleable size and surface properties and potential immunogenic properties. However, there is a concern of associated ability to rapidly mutate the proteins of viral origin, being utilized for their synthesis [44]. Similar concerns may arise in the application of other nano-carriers or adjuvants adopted in the vaccine core antigen potentiation. Closely relevant animal models may be

devised to carry out the pre-clinical evaluation of such nano-vaccines [45]. Biologically mediated nanomaterials have been proven as effective carriers of chemotherapeutic and chemoprophylactic agents.

Proven non-pathogenic viral vectors for protective immune coverage and sustained immunological memory may be further investigated for probability of efficient commercialization [46,47]. The exact biochemical interactions and the active constitutents of nano-vaccines making them a good choice need further exploration within biological models. Thorough studies upto molecular pathways are warranted to understand the dynamics of actual mechanism behind protective immunological response due to nano-vaccines. Moreover, to harness the collaborative potential of computational modelling and simulation, its highly indicated to analyze and declare most promising nano-adjuvants or peptides, due to their in-silico biological structures and functions analyses. It is imperative to look up and further rationalize the potential aspects of nanomaterials, for instance the facile synthesis, requirement of lower doses yet alleviation of repetitive booster injections, easy routes of administration, etc. of nano-vaccines over conventional vaccines [48, 49].

There is need to materialize the concept of nano-immunology against auto-immune diseases of idiopathic origin. For this purpose, the investigation and communication of biochemical and molecular pathways making nano-vaccines promising is imperative. The ease of administration and efficient immunogenesis has made nano-vaccines applicable at aquatic eco-systems. Biological distribution of nanoparticles and uptake by excretory systems within the host need further explanation and safety evaluation. Also, the commercialization of biological adjuvant-based nano-vaccines needs greater reproducibility and scaling-up future production.

5. Conclusions

'Nano-vaccinology' is the science of nanoscale particles, possessing huge potential. The laboratory as well as the clinical scale promise of nano-vaccines can push the boundaries towards an eco-friendly, more immunogenic, sustained and stabilized releasing novel approach against infectious and non-infectious diseases. Integrity, in terms of desirable surface properties during manufacturing and storage of nano-vaccines in field conditions are concerned to be addressed in commercial nano-vaccine production. The nano-vaccines have opened an entrance to boundless hopes in efficiently preventing pathogenic, cancerous and non-infectious diseases in immune-tolerant individuals. More research focus in collaboration with commercial industries can lead to rapid commercialization of nano-vaccines.

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Research involving human participation and/or animals

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Informed consent

None.

Ethical approval

This article does not contain any studies with animals or humans performed by any of the authors.

Declaration of Competing Interest

There is no conflict of interest amongst the author for publishing this exclusive review.

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Appendix A. Supplementary data

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References

[1] Y.F. Sayed, H.A. El-Banna, H.Y. Elzorba, A.M. Galal, Application of some nanoparticles in the field of veterinary medicine, Int. J. Vet. Sci. Med. 7 (2019) 78–93, https://doi.org/10.1080/23144599.2019.1691379.

[2] A.A. Aljabali, H.A. Bakshi, F.L. Hakkim, Y. Haggag, M.K. Al-Batanyeh, M. Al Zoubi, B. Al-Trad, M.M. Nasef, S. Satija, M. Mehta, K. Pabreja, V. Mishra, M. Khan, S. Abobaker, M.I. Azzouz, H. Dureja, M.R. Pabari, A.K. Dardouri, P. Kesharwani, G. Gupta, D. Shukla, P. Prasher, N.B. Charbe, P. Negi, D.N. Kapoor, D. K. Chellappan, M.W. da Silva, P. Thompson, K. Dua, P. McCarron, M.M, Tambuwala Albumin Nano-Encapsulation of Piceatannol Enhances Its Anticancer Potential in Colon Cancer Via Downregulation of Nuclear p65 and HIF-1α Cancers, 12, 2020, https://doi.org/10.3390/cancers12010113.

[3] A.A. Oun, S. Shankar, J.W. Rhim, Multifunctional nanocellulose/metal and metal oxide nanoparticle hybrid nanomaterials, Crit. Rev. Food Sci. Nutr. 60 (2020) 435–460, https://doi.org/10.1080/10408398.2018.1536966.

[4] A.A. Yaqoob, H. Ahmad, T. Parveen, A. Ahmad, M. Oves, I.M.I. Ismail, H.A. Qari, K. Umar, M.N.M. Ibrahim, Recent advances in metal decorated nanomaterials and their various biological applications: a review, Front. Chem. 8 (2020), https://doi.org/10.3389/fchem.2020.00341.

[5] Q. Ni, F. Zhang, Y. Liu, Z. Wang, G. Yu, B. Liang, G. Niu, T. Su, G. Zhu, G. Lu, L. Zhang, X. Chen, A bi-adjuvant nanovaccine that potentiates immunogenicity of neoantigen for combination immunotherapy of colorectal cancer, Sci. Adv. 6 (2020), https://doi.org/10.1126/sciadv.aaw6071.

[6] S. Renu, A.D. Markazi, S. Dhakal, Y.S. Lakshmanappa, R. Shanmugasundaram, R. K. Selvaraj, G.J. Renukaradhya, Oral deliverable mucoadhesive chitosan-salmonella subunit nanovaccine for layer chickens, Int. J. Nanomed. Nanosurg. 15 (2020) 761–777, https://doi.org/10.2147/IJN.S238445.

[7] K.A. Collins, R. Snaith, M.G. Cottingham, S.C. Gilbert, A.V.S. Hill, Enhancing protective immunity to malaria with a highly immunogenic virus-like particle vaccine, Sci. Rep. 7 (2017), https://doi.org/10.1038/srep46621.

[8] S.D. Xiang, K.L. Wilson, A. Goubier, A. Heyerick, M. Plebanski, Design of peptide-based nanovaccines targeting leading antigens from gynecological cancers to induce HLA-A2.1 restricted CD8+ t cell responses, Front. Immunol. 9 (2018), https://doi.org/10.3389/fimmu.2018.02968.

[9] P. Ding, Q. Jin, X. Chen, S. Yang, J. Guo, G. Xing, R. Deng, A. Wang, G. Zhang, Nanovaccine confers dual protection against influenza A virus and porcine circovirus type 2, Int. J. Nanomed. Nanosurg. 14 (2019) 7533–7548, https://doi.org/10.2147/IJN.S218057.

[10] G. Zhu, G.M. Lynn, O. Jacobson, K. Chen, Y. Liu, H. Zhang, Y. Ma, F. Zhang, R. Tian, Q. Ni, S. Cheng, Z. Wang, N. Lu, B.C. Yung, Z. Wang, L. Lang, X. Fu, A. Jin, I.D. Weiss, H. Vishwasrao, G. Niu, H. Shroff, D.M. Klinman, R.A. Seder, X. Chen, Albumin/vaccine nanocomplexes that assemble *in vivo* for combination cancer immunotherapy, Nat. Commun. 8 (2017), https://doi.org/10.1038/s41467-017-02191-y.

[11] J. Jeevanandam, M.K. Danquah, Nanosensors for better diagnosis of health, in: Kaushik Pal, Fernando Gomes (Eds.), Micro and Nano Technologies, Nanofabrication for Smart Nanosensor Applications, Elsevier, 2020, pp. 187–228. ISBN 9780128207024.

[12] M.D. Shin, S. Shukla, Y.H. Chung, V. Beiss, S.K. Chan, O.A. Ortega-Rivera, D. M. Wirth, A. Chen, M. Sack, J.K. Pokorski, N.F. Steinmetz, COVID-19 vaccine development and a potential nanomaterial path forward, Nat. Nanotechnol. 15 (2020) 646–655, https://doi.org/10.1038/s41565-020-0737-y.

[13] G. Chauhan, M.J. Madou, S. Kalra, V. Chopra, D. Ghosh, S.O. Martinez-Chapa, Nanotechnology for COVID-19: therapeutics and vaccine research, ACS Nano 14 (2020) 7760–7782, https://doi.org/10.1021/acsnano.0c04006.

[14] A.L. Cunningham, H. Lal, M. Kovac, R. Chlibek, S.-J. Hwang, J. Díez-Domingo, O. Godeaux, M.J. Levin, J.E. McElhaney, J. Puig-Barberà, V.A. Carline, T. Vesikari, D. Watanabe, T. Zahaf, A. Ahonen, E. Athan, J.F. Barba-Gomez, L. Campora, F. de Looze, H.J. Downey, W. Ghesquiere, I. Gorfinkel, T. Korhonen, E. Leung, S. A. McNeil, L. Oostvogels, L. Rombo, J. Smetana, L. Weckx, W. Yeo, T.C. Heineman, Efficacy of the herpes zoster subunit vaccine in adults 70 years of age or older, N. Engl. J. Med. 375 (2016) 1019–1032, https://doi.org/10.1056/NEJMoa1603800.

[15] A. Tejeda-Mansir, A. García-Rendón, P. Guerrero-Germá, Plasmid-DNA lipid and polymeric nanovaccines: a new strategic in vaccines development, Biotechnol. Genet. Eng. 35 (2019) 46–68, https://doi.org/10.1080/02648725.2018.1560552.

[16] A.F. El-Sissi, F.H. Mohamed, N.M. Danial, A.Q. Gaballah, K.A. Ali, Chitosan and chitosan nanoparticles as adjuvant in local Rift Valley Fever inactivated vaccine, 3 Biotech 10 (2020), https://doi.org/10.1007/s13205-020-2076-y.

[17] D.S. Watson, A.N. Endsley, L. Huang, Design Considerations for Liposomal Vaccines: Influence of Formulation Parameters on Antibody and Cell-Mediated Immune Responses to Liposome Associated Antigens Vaccine, 30, 2012, pp. 2256–2272, https://doi.org/10.1016/j.vaccine.2012.01.070.

[18] S.L. Demento, A.L. Siefert, A. Bandyopadhyay, F.A. Sharp, T.M. Fahmy, Pathogen-associated molecular patterns on biomaterials: a paradigm for engineering new vaccines, Trends Biotechnol. 29 (2011) 294–306, https://doi.org/10.1016/j.tibtech.2011.02.004.

[19] P. Vandoolaeghe, L. Schuerman, The RTS,S/AS01 malaria vaccine in children 5 to 17 months of age at first vaccination, Expert Rev. Vaccines 15 (2016) 1481–1493, https://doi.org/10.1080/14760584.2016.1236689.

[20] B.V. Syomin, Y.V. Ilyin, Virus-like particles as an instrument of vaccine production, Mol. Biol. 53 (2019) 323–334, https://doi.org/10.1134/S0026893319030154.

[21] N. Lurie, M. Saville, R. Hatchett, J. Halton, Developing Covid-19 vaccines at pandemic speed, New Engl. J. Med. 382 (2020) 1969–1973, https://doi.org/10.1056/NEJMp2005630.

[22] F. Amanat, F. Krammer, SARS-CoV-2 vaccines: status, Rep. Immunity 52 (2020) 583–589, https://doi.org/10.1016/j.immuni.2020.03.007.

[23] T. Thanh Le, Z. Andreadakis, A. Kumar, R. Gómez Román, S. Tollefsen, M. Saville, S. Mayhew, The COVID-19 vaccine development landscape, Nat. Rev. Drug Discov. 19 (2020) 305–306, https://doi.org/10.1038/d41573-020-00073-5.

[24] H. Amawi, G.I.A. Deiab, A.A.A. Aljabali, K. Dua, M.M. Tambuwala, COVID-19 pandemic: an overview of epidemiology, pathogenesis, diagnostics and potential vaccines and therapeutics, Ther. Deliv. 11 (2020) 245–268, https://doi.org/10.4155/tde-2020-0035.

[25] D.H. Abdelkader, M.M. Tambuwala, C.A. Mitchell, M.A. Osman, S.A. El-Gizawy, A. M. Faheem, M. El-Tanani, P.A. McCarron, Enhanced cutaneous wound healing in rats following topical delivery of insulin-loaded nanoparticles embedded in poly (vinyl alcohol)-borate hydrogels, Drug Deliv. Transl. Res. 8 (2018) 1053–1065, https://doi.org/10.1007/s13346-018-0554-0.

[26] F. Wang, R.H. Fang, B.T. Luk, C.J. Hu, S. Thamphiwatana, D. Dehaini, P. Angsantikul, A.V. Kroll, Z. Pang, W. Gao, W. Lu, L. Zhang, Nanoparticle-based antivirulence vaccine for the management of methicillin-resistant *Staphylococcus aureus* skin infection, Adv. Funct. Mater. 26 (2016) 1628–1635, https://doi.org/10.1002/adfm.201505231.

[27] A.L. Siefert, M.J. Caplan, T.M. Fahmy, Artificial bacterial biomimetic nanoparticles synergize pathogen-associated molecular patterns for vaccine efficacy, Biomaterials 97 (2016) 85–96, https://doi.org/10.1016/j.biomaterials.2016.03.039.

[28] Z. Tan, W. Liu, H. Liu, C. Li, Y. Zhang, X. Meng, T. Tang, T. Xi, Y. Xing, Oral *Helicobacter pylori* vaccine-encapsulated acid-resistant HP55/PLGA nanoparticles promote immune protection, Eur. J. Pharm. Biopharm. 111 (2017) 33–43, https://doi.org/10.1016/j.ejpb.2016.11.007.

[29] M. Wu, H. Zhao, M. Li, Y. Yue, S. Xiong, W. Xu, Intranasal vaccination with mannosylated chitosan formulated DNA vaccine enables robust IgA and cellular response induction in the lungs of mice and improves protection against pulmonary mycobacterial challenge, Front. Cell. Infect. Microbiol. 7 (2017), https://doi.org/10.3389/fcimb.2017.00445.

[30] J.I. Sanchez-Villamil, D. Tapia, A.G. Torres, Development of a gold nanoparticle vaccine against enterohemorrhagic *Escherichia coli* O157:H7, mBio 10 (2019), https://doi.org/10.1128/mBio.01869-19.

[31] H. Wei, Z. Chen, Z.A. Elson, Z. Li, M. Abraham, S. Phan, S. Kristhnamurthy, P.B. J. McCray, S. Andrews, S. Stice, K. Sakamoto, C. Jones, S.M. Tompkins, B. He, Developing a platform system for gene delivery: amplifying virus-like particles (AVLP) as an influenza vaccine, NPJ Vaccines 2 (2017), https://doi.org/10.1038/s41541-017-0031-7.

[32] M. Qi, X. Sun, X. Zhang, W. Li, Z. Zhang, Z. Cui, Intranasal Nanovaccine Confers Homo- and Hetero-Subtypic Influenza Protection Small, 14, 2018, https://doi.org/10.1002/smll.201703207.

[33] B. Zhang, A. Cavallaro, K. Mody, J. Zhang, J. Deringer, W. Brown, T.J. Mahony, C. Yu, N. Mitter, Nanoparticle-based delivery of *Anaplasma marginale* membrane proteins; VirB9-1 and VirB10 produced in the *Pichia pastoris* expression system, Nanomaterilas 6 (2016), https://doi.org/10.3390/nano6110201.

[34] J. Marsian, H. Fox, M.W. Bahar, A. Kotecha, E.E. Fry, D.I. Stuart, A.J. Macadam, D. J. Rowlands, G.P. Lomonossoff, Plant-made polio type 3 stabilized VLPs-a candidate synthetic polio vaccine, Nat. Commun. 8 (2017), https://doi.org/10.1038/s41467-017-00090-w.

[35] M.Y. Kim, C. Van Dolleweerd, A. Copland, M.J. Paul, S. Hofmann, G.R. Webster, E. Julik, I. Ceballos-Olvera, J. Reyes-Del Valle, M.S. Yang, Y.S. Jang, R. Reljic, J. K. Ma, Molecular engineering and plant expression of an immunoglobulin heavy chain scaffold for delivery of a dengue vaccine candidate, Plant Biotechnol. J. 15 (2017) 1590–1601, https://doi.org/10.1111/pbi.12741.

[36] C.M. Coleman, Y.V. Liu, H. Mu, J.K. Taylor, M. Massare, D.C. Flyer, G.E. Smith, M. B. Frieman, Purified coronavirus spike protein nanoparticles induce coronavirus neutralizing antibodies in mice, Vaccine 32 (2014) 3169–3174, https://doi.org/0.1016/j.vaccine.2014.04.016.

[37] X. Wang, Y. Dai, S. Zhao, J. Tang, H. Li, Y. Xing, G. Qu, X. Li, J. Dai, Y. Zhu, X. Zhang PAMAM-Lys, a novel vaccine delivery vector, enhances the protective effects of the SjC23 DNA vaccine against *Schistosoma japonicum* infection, PLoS One 9 (2014), https://doi.org/10.1371/journal.pone.0086578.

[38] K. El Bissati, Y. Zhou, S.M. Paulillo, S.K. Raman, C.P. Karch, C.W. Roberts, D. E. Lanar, S. Reed, C. Fox, D. Carter, J. Alexander, A. Sette, J. Sidney, H. Lorenzi, I. J. Begeman, P. Burkhard, R. McLeod, Protein nanovaccine confers robust immunity against toxoplasma, NPJ Vaccines 2 (2017), https://doi.org/10.1038/s41541-017-0024-6.

[39] H. Firouzman, A. Badiee, A. Khamesipour, Induction of protection against leishmaniasis in susceptible BALB/c mice using simple DOTAP cationic nanoliposomes containing soluble *Leishmania* antigen (SLA), Acta Trop. 128 (2013) 528–535, https://doi.org/10.1016/j.actatropica.2013.07.021.

[40] Q. Zhao, S. Li, H. Yu, N. Xia, Y. Modis, Virus-like particle-based human vaccines: quality assessment based on structural and functional properties, Trends Biotechnol. 31 (2013) 654–663, https://doi.org/10.1016/j.tibtech.2013.09.002.

[41] M.N. Khan, Y.A. Haggag, M.E. Lane, P.A. McCarron, M.M. Tambuwala, Polymeric nano-encapsulation of curcumin enhances its anti-cancer activity in breast (MDA-MB231) and Lung (A549) Cancer cells through reduction in expression of HIF-1α and nuclear p65 (Rel A), Curr. Drug Deliv. 15 (2018) 286–295, https://doi.org/10.2174/1567201814666171019104002.

[42] S. Shukla, M. Jandzinski, C. Wang, X. Gong, K.W. Bonk, R.A. Keri, N.F. Steinmetz, A viral nanoparticle cancer vaccine delays tumor progression and prolongs survival in a HER2+ tumor mouse model, Adv. Therap. 2 (2019), https://doi.org/10.1002/adtp.201800139.

[43] O. Janson, S. Gururaj, S. Pujari-Palmer, M. Karlsson Ott, M. Strømme, H. Engqvist, K. Welch, Titanium surface modification to enhance antibacterial and bioactive properties while retaining biocompatibility, Mater. Sci. Eng. C Mater. 96 (2019) 272–279, https://doi.org/10.1016/j.msec.2018.11.021.

[44] J. Jeevanandam, K. Pal, M.K. Danquah, Virus-like nanoparticles as a novel delivery tool in gene therapy, Biochimie 157 (2019) 38–47, https://doi.org/10.1016/j.biochi.2018.11.001.

[45] A. Page, F. Fusil, F.L. Cosset, Towards physiologically and tightly regulated vectored antibody, Therapies Cancers 12 (2020), https://doi.org/10.3390/cancers12040962.

[46] J.M. Brady, D. Baltimore, A.B. Balazs, Antibody gene transfer with adeno-associated viral vectors as a method for HIV prevention, Immunol. Rev. 275 (2017) 324–333, https://doi.org/10.1111/imr.12478.

[47] M.R. Gardner, Promise and progress of an HIV-1 Cure by adeno-associated virus vector delivery of anti-HIV-1 biologics, Front. Cell. Infect. Microbiol. 10 (2020), https://doi.org/10.3389/fcimb.2020.00176.

[48] S.I. Asiya, K. Pal, S. Kralj, G.S. El-Sayyad, F.G. de Souza, T. Narayanan, Sustainable preparation of gold nanoparticles via green chemistry approach for biogenic applications, Mater. Today Chem. 17 (2020), https://doi.org/10.1016/j.mtchem.2020.100327.

[49] P. Bhardwaj, E. Bhatia, S. Sharma, N. Ahamad, R. Banerjee, Advancements in prophylactic and therapeutic nanovaccines, Acta Biomater. 108 (2020) 1–21, https://doi.org/10.1016/j.actbio.2020.03.020.

[50] L. Liu, L. Zhijia, C. Haolin, L. Hong, G. Qiang, C. Feng, G. Gao, Y. Chen, A translatable subunit nanovaccine for COVID-19 ChemRxiv, Preprint (2020), https://doi.org/10.26434/chemrxiv.12301157.v1.

[51] H. Sekimukai, N. Iwata-Yoshikawa, S. Fukushi, H. Tani, M. Kataoka, T. Suzuki, H. Hasegawa, K. Niikura, K. Arai, N. Nagata, Gold nanoparticle-adjuvanted S protein induces a strong antigen-specific IgG response against severe acute respiratory syndrome-related coronavirus infection, but fails to induce protective antibodies and limit eosinophilic infiltration in lungs, Microbiol. Immunol. 64 (2020) 33–51, https://doi.org/10.1111/1348-0421.12754.

[52] T.N. Alkie, A. Yitbarek, K. Taha-Abdelaziz, J. Astill, S. Sharif, Characterization of immunogenicity of avian influenza antigens encapsulated in PLGA nanoparticles following mucosal and subcutaneous delivery in chickens, PLoS One 13 (2018), https://doi.org/10.1371/journal.pone.0206324.

[53] W. Gao, R.H. Fang, S. Thamphiwatana, B.T. Luk, J. Li, P. Angsantikul, Q. Zhang, C. M. Hu, L. Zhang, Modulating antibacterial immunity via bacterial membrane-coated nanoparticles, Nano Lett. 15 (2015) 1403–1409, https://doi.org/10.1021/nl504798g.

[54] M.C. Huertas-Díaz, S. Phan, A. Elson, I. Nuñez, H. Wei, K. Sakamoto, B. He, Parainfluenza virus 5 (PIV5) amplifying virus-like particles expressing respiratory syncytial virus (RSV) antigens protect mice against RSV infection, Vaccine 37 (2019) 2925–2934, https://doi.org/10.1016/j.vaccine.2019.04.042.

[55] A. Thukral, K. Ross, C. Hansen, Y. Phanse, B. Narasimhan, H. Steinberg, A. M. Talaat, A single dose polyanhydride-based nanovaccine against paratuberculosis infection, NPJ Vaccines 5 (2020), https://doi.org/10.1038/s41541-020-0164-y.

[56] H.-J. Park, E.-Y. Lee, S.Y. Jung, H.L. Ko, S.-M. Lee, J.-H. Nam, Spike nanoparticle and recombinant adenovirus 5 vaccines induce specific antibodies against the Middle East respiratory syndrome coronavirus (MERS-CoV), J. Immunol. 198 (2017) http://doi.org/198/1_Supplement/225.5.

[57] N. Lokugamage, S. Choudhuri, C. Davies, I.H. Chowdhury, N.J. Garg, Antigen-based nano-immunotherapy controls parasite persistence, inflammatory and oxidative stress, and cardiac fibrosis, the hallmarks of chronic chagas cardiomyopathy, in a mouse model of *Trypanosoma cruzi* infection, Vaccines-Basel 8 (2020), https://doi.org/10.3390/vaccines8010096.

[58] C. Zhang, G. Wang, B. Zhu, Application of antigen presenting cell-targeted nanovaccine delivery system in rhabdovirus disease prophylactics using fish as a model organism, J. Nanobiotechnol. 18 (2020), https://doi.org/10.1186/s12951-020-0584-x.

[59] M. Maleki, M. Salouti, M.S. Ardestani, A. Talebzadeh, Preparation of a nanovaccine against *Brucella melitensis* M16 based on PLGA nanoparticles and oligopolysaccharide antigen, Artif. Cells Nanomed. Biotechnol. 47 (2019) 4248–4256, https://doi.org/10.1080/21691401.2019.1687490.

[60] S.L. Demento, W. Cui, J.M. Criscione, E. Stern, J. Tulipan, S.M. Kaech, T.M. Fahmy, Role of sustained antigen release from nanoparticle vaccines in shaping the T cell memory phenotype, Biomaterials 33 (2012) 4957–4964, https://doi.org/10.1016/j.biomaterials.2012.03.041.

[61] M.J. Rodrigues-Jesus, W.L. Fotoran, R.M. Cardoso, K. Araki, G. Wunderlich, L. Ferreira, Nano-multilamellar lipid vesicles (NMVs) enhance protective antibody responses against Shiga toxin (Stx2a) produced by enterohemorrhagic *Escherichia coli* strains (EHEC), Braz. J. Microbiol. 50 (2019) 67–77, https://doi.org/10.1007/s42770-018-0035-0.

[62] A. Moura, L. Santos, C. Brito, E. Valencia, C. Junqueira, A. Filho, M. Sant'Anna, N. F. Gontij, D.C. Bartholomeu, R.T. Fujiwara, R.T. Gazzinelli, C.S. McKay, C. A. Sanhueza, M.G. Finn, A.F. Marques, Virus-like particle display of the α-Gal carbohydrate for vaccination against *leishmania* infection, ACS Cent. Sci. 3 (2017) 1026–1031, https://doi.org/10.1021/acscentsci.7b00311.

[63] R.J. Nevagi, Z.G. Khalil, W.M. Hussein, J. Powell, M.R. Batzloff, R.J. Capon, M. F. Good, M. Skwarczynski, I. Toth, Polyglutamic acid-trimethyl chitosan-based intranasal peptide nano-vaccine induces potent immune responses against group A streptococcus, Acta Biomater. 80 (2018) 278–287, https://doi.org/10.1016/j.actbio.2018.09.037.

[64] M.C. Serradell, L.L. Rupil, R.A. Martino, C.G. Prucca, P.G. Carranza, A. Saura, E. A. Fernández, P.R. Gargantini, A.H. Tenaglia, J.P. Petiti, R.R. Tonelli, N. Reinoso-Vizcaino, J. Echenique, L. Berod, E. Piaggio, B. Bellier, T. Sparwasser, D. Klatzmann, H.D. Luján, Efficient oral vaccination by bioengineering virus-like particles with protozoan surface proteins, Nat. Commun. 10 (2019), https://doi.org/10.1038/s41467-018-08265-9.

[65] W. Wang, X. Zhou, Y. Bian, S. Wang, Q. Chai, Z. Guo, Z. Wang, P. Zhu, H. Peng, X. Yan, W. Li, F. Yang-Xin, M. Zhu, Dual-targeting nanoparticle vaccine elicits a therapeutic antibody response against chronic hepatitis B, Nat. Nanotechnol. 15 (2020) 406–416, https://doi.org/10.1038/s41565-020-0648-y.

[66] J. Sharma, K. Shepardson, L.L. Johns, J. Wellham, J. Avera, B. Schwarz, A. Rynda-Apple, T. Douglas, A self-adjuvanted, modular, antigenic VLP for rapid response to influenza virus variability, ACS Appl. Mater. Interfaces 12 (2020) 18211–18224, https://doi.org/10.1021/acsami.9b21776.

[67] Z. Sadeghi, M. Fasihi-Ramandi, S. Bouzari, Nanoparticle-based vaccines for brucellosis: calcium phosphate nanoparticles-adsorbed antigens induce cross protective response in mice, Int. J. Nanomed. 15 (2020) 3877–3886, https://doi.org/10.2147/IJN.S249942.

[68] D. Bento, H.F. Staats, T. Gonçalves, O. Borges, Development of a novel adjuvanted nasal vaccine: C48/80 associated with chitosan nanoparticles as a path to enhance mucosal immunity, Eur. J. Pharm. Biopharm. 93 (2015) 149–164, https://doi.org/10.1016/j.ejpb.2015.03.024.

[69] M.C. Hanson, W. Abraham, M.P. Crespo, S.H. Chen, H. Liu, G.L. Szeto, M. Kim, E. L. Reinherz, D.J. Irvine, Liposomal vaccines incorporating molecular adjuvants and intrastructural T-cell help promote the immunogenicity of HIV membrane-proximal external region peptides, Vaccine 33 (2015) 861–868, https://doi.org/10.1016/j.vaccine.2014.12.045.

[70] Y. Wang, Y. Wang, N. Kang, Y. Liu, W. Shan, S. Bi, L. Ren, G. Zhuang, Construction and immunological evaluation of CpG-Au@HBc virus-like nanoparticles as a potential vaccine nanoscale, Res. Lett. 11 (2016), https://doi.org/10.1186/s11671-016-1554-y.

[71] L. Zeng, Z. Liao, W. Li, Q. Yuan, P. Wu, Z. Gu, Z. Liu, G. Liao, Non-covalent glycosylated gold nanoparticles/peptides nanovaccine as potential cancer vaccines, Chin. Chem. Lett. 31 (2019) 1162–1164, https://doi.org/10.1016/j.cclet.2019.10.015.