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The other side of nano-medicines and nano-vaccines

Tuan Anh Nguyen

[1]Institute for Tropical Technology, Vietnam Academy of Science and Technology, Hanoi, Vietnam.

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***Corresponding author:** Tuan Anh Nguyen, Institute for Tropical Technology, Vietnam Academy of Science and Technology, Hanoi, Vietnam. Email: ntanh@itt.vast.vn

1. Nano-toxicity and Nano-ecotoxicology

Nano-materials can be used widely or not, depending mainly on their toxicity [1]. Market consumption of nanomaterials is accelerating. Freedonia Group expected demand for nanomaterials to grow to $100 billion by 2025. However, the uses of nanomaterials in commercial products nowadays increase at a higher speed than the development of research and regulations to prevent their potential toxicity in the manufacture/application/disposal.

In general, their potential toxic effects might be contributed not only by the type of base materials, but also by their size/ ligands/surface (chemical) modifications. Regarding the size effect, some studies reported that nanoparticles (<100 nm) might be more toxic than microparticles (>2 µm). These small nanoparticles (<100 nm) were considerably smaller than many cells in the body. Once getting in the body, some kinds of nanoparticles may have the ability to translocate to other organs, depending on their chemical reactivity/surface characteristics/ chemical affinity on body proteins. In addition, cells growing in tissue culture could pick up most nanoparticles. In case of gold, bulk gold has been considered to be “safe” and chemically inert. It was reported that nanogolds (> 5 nm) can be chemically inert like the bulk. However, nanogolds less than 2 nm had chemical reactivity that was different than both organogold complexes and larger nanogolds. Besides, at certain doses, the cationic nanogolds (2 nm) found to be toxic, but these negatively charged nanogolds do not exhibit toxicity (became not toxic) at the same concentration.

For bacteria, nanoparticles could attack/kill the bacteria through various processes, such as i) production of reactive oxygen species (ROS); ii) electrostatic interaction with cell membrance; iii) ion releases; and iv) internalization [1].

For human, studies on inhaled nanoparticles from air pollution (PM10/PM2.5; combustion/diesel exhaust) indicated that these ultrafine particles/nanoparticles are associated with a wide variety of effects including pulmonary inflammation, immune adjuvant effects [2] and systemic effects including blood coagulation and cardiovascular effects [3]. Besides, when nanoparticles enter systemic circulation they immediately interact with blood cells/proteins/endothelial cells, and components of the coagulation system (platelets/plasma coagulation factors) [4]. These nanoparticles could induce undesirable alterations in the balanced function of these components, then may cause severe and even life-threatening toxicities. Therefore, there are increasing concerns about nanoparticle-induced coagulopathies (i.e., coagulation disorders caused by perturbation of the blood coagulation system), such as the prognosis of cardiovascular diseases due to the induction of

thrombotic complications [5–8]. Other toxic risks are the disseminated intravascular coagulation (DIC), consumptive coagulopathy, and deep vein thrombosis (DVT) [9].

2. Nano-medicine

As low-dose and multiple drugs, nano-medicines might have many advantages over the conventional medicines, such as improved efficacy, bioavailability, dose–response, targeting ability, and personalization [10].

The aims for drugs-loaded nanocontainers/nanocapsules are either enhanced delivery to, or uptake by, target cells and/or a reduction in the toxicity of the free drug to non-target organs. The smart nanocontainers are typically related with the smart releasing property for their embedded drugs. These smart releases could be obtained by using the smart coatings as their outer nanoshells. In this regard, the embedded drugs could be released from nanocontainers by external or internal stimuli, which referred to the chemical/physical/biochemical changes within or surrounding of the nanocontainer [11]. Various types of nanomaterials have been used to fabricate these nanocontainers, such as polymers, lipids, metals... Natural and biodegrable nanomaterials are usually preferred over synthetic nanomaterials [12]. As reported, current nano-medicines used the phenylboronic acid-installed polymeric micelles, matrix metalloproteinase 2-sensitive poly(ethylene glycol)-drug conjugate, multifunctional DNA nanoflowers, single vehicular delivery of small interfering RNA (siRNA), nanoparticle-mediated codelivery of siRNA and prodrug, lipopeptide nanoparticles for siRNA delivery, ferrous iron-dependent drug delivery, polyprodrug amphiphiles, transepithelial transport of Fc-targeted nanoparticles, mutant KRAS target, monovalent molecular shuttle, near-infrared-actuated devices, transferrin receptor trafficking, remote loading of preencapsulated drugs, ATP-mediated liposomal drug delivery, nanoparticle-based combination chemotherapy delivery system, nucleic acid nanoparticle conjugates, ultrasound-triggered disruption of cross-linked hydrogels, refilling drug delivery depots through the blood, siRNA payloads to target KRAS-mutant cancer, delivery of antibody mimics into mammalian cells, biologically “smart” hydrogel, combination of liposomes containing bio-enhancers, and tetraether lipids [12].

The main problem in the use of drug-loaded nanoparticles is the entrapment of nanomaterials/nanoparticles in the mononuclear phagocytic system as present in the liver and spleen [13, 14]. For liposomes with sizes >100 nm the clearance rate by the mononuclear phagocytic system increased with increasing size, while for sizes < 100 nm, their charge was more important [15, 16].

In addition, nanoparticles have been used for drug delivery to the brain. Nanoparticles (nano-medicines) could get access to the brain by two different pathways: i) transsynaptic transport after inhalation through the olfactory epithelium, and ii) uptake through the blood-brain barrier (BBB) [17]. As report, the brain is a challenging organ for drug delivery, due to the BBB- as the best gatekeeper in the body toward exogenous substances [18]. Passage of the BBB was suggested to be possible by the toxicity of nanoparticles (size of 200 nm) on cerebral endothelial cells [19], but not possible for similar nanoparticles in larger size (~ 300 nm) [20]. Thus, healthy BBB contains defense mechanisms protecting it from blood borne nanoparticle exposure.

3. Nano-vaccine

As low-dose and multiple vaccines, nano-vaccines might have many advantages over the conventional vaccines. For Covid-19 pandemic, several types of pre-clinical and approved nano-vaccinces have been developed, with the average size of nanoparticles is about 60–100 nm [21].

3.1. mRNA-based Covid-19 vaccine

Since the mRNA is unstable and very fragile/sensitive, mRNA vaccines must be carefully preserved at very low temperatures [22].

-The Pfizer–BioNTech Covid-19 is an mRNA-based Covid-19 vaccine developed by the German biotechnology company BioNTech (mRNA producer) and for its development collaborated with American company Pfizer (medicines and vaccines producer). The vaccine is given by intramuscular injection. It is composed of nucleoside-modified mRNA (modRNA) encoding a mutated form of the full-length spike protein of SARS-CoV-2, which is encapsulated in lipid nanoparticles. The standard dose of Pfizer is 30 micrograms[22].

-Moderna vaccine is mRNA vaccine composed of nucleoside-modified mRNA (modRNA) encoding a spike protein of SARS-CoV-2, which is encapsulated in lipid nanoparticles. Each dose of Moderna contains 100 micrograms of a vaccine [22].

-CVnCoV (CureVac) is mRNA vaccine is developed in Germany (phase 3) with a lipid nanoparticle-encapsulated mRNA vaccine that encodes full-length, pre-fusion stabilised SARS-CoV-2 spike protein (each dose contains12 micrograms of vaccine) [23].

-Novavax vaccine (NVX-CoV2373) is developed by Novavax and the Coalition for Epidemic Preparedness Innovations. CoV2373 has been described as both a protein subunit vaccine and a virus-like particle vaccine through the producers call it a "recombinant nanoparticle vaccine". The vaccine is produced by creating an engineered baculovirus containing a gene for a modified SARS-CoV-2 spike protein. In phase 1 of the clinical trial, two dose levels of 5 micrograms and 25 micrograms have been evaluated [22].

- ARCoV (Walvax) is mRNA vaccine is developed inMexico (phase 1) with lipid nanoparticle formulation that contains the full spike protein plus CpG7909 to trigger immune response[24]

3.2. Other RNA-based vaccines

-COVAC1 is self-amplifying RNA vaccine developed in Imperial College (UK, phase 1-2) using cationic liposome formulation containing the spike protein sequence [25].

- HDT-301 (HDT Bio) is repRNA vaccine developed in Brasil (phase 1) with lipid inorganic nanoparticle (LION) emulsion containing the viral spike protein sequence [26].

- HGC019 (Gennova-HDT) is RNA vaccine developed in India (phase 1-2) with lipid inorganic nanoparticle (LION) emulsion containing the full spike protein plus CpG7909 to trigger immune response [27].

-Arct-021 (LUNAR-COV19) by Duke NUS Med School (Singapore) is a self-transcribing and replicating RNA (STARR)-based vaccine (Phase 1-2) with lipid nanoparticle formulation for delivery the spike protein sequence. Single-dose vaccines (2 micrograms or 10 micrograms) have been evaluated [28].

3.3. COVID-19 vaccination and neurological effects

It was reported in the literature [29] that conventional (intramuscular) vaccines mostly remain near the site of injection (the arm muscle) and local lymph nodes. However, in case of nano-vaccines, as nanoparticles they could enter the systemic circulation/cardiovascular system, then travel to heart/brain/lung and other organs.

The main effects of nanoparticles/nanomaterials have been found in the lungs and others inflammation/tissue damage/fibrosis/tumour generation. The cardiovascular system may also be affected [30].

Nanoparticles (nanomaterials) are not harmless. They have their own nano-toxicity [1]. Similarity, mRNA is also not fully safe but spike proteins are pathogen.

The most frequent neurological side effects of SARS-CoV-2 vaccines are headache, Guillain-Barre syndrome (GBS), venous sinus thrombosis (VST), and transverse myelitis [31, 32]. Patone et al. [33] reported an increased risk of hemorrhagic stroke with Pfizer vaccine. Classen [34] signaled the connection between COVID-19 RNA-based vaccines and the risk of prion disease.

Chaurasia et al. [35] reported the cognitive deficits and memory impairments after COVID-19 vaccination (AstraZeneca vaccine).

In addition, Guillain-Barre syndrome (GBS) following Pfizer COVID-19 vaccine has been reported [36, 37].

3.4. COVID vaccination and blood clots

From 8 to 28 days after a first dose of the AstraZeneca vaccine, researchers identified an increased risk of rare blood clotting events and low platelet counts. In the same time period after a first dose of the Pfizer-BioNTech vaccine, the study found the risk of blood clots and strokes caused by restricted blood flow to the brain (ischaemic stroke) increased [38].

Chui et al. [39] reported that among 5,526,547 doses of Pfizer and 3,146,741 doses of CoronaVac vaccines were administered, there were 334 and 402 thromboembolic events, and 57 and 49 hemorrhagic stroke cases occurred within 28 days after Pfizer and CoronaVac vaccinations, respectively. The authors also found thrombosis or hemorrhage in the brain or leg were reported with Pfizer-BioNTech vaccine. Other case reports of thrombosis or hemorrhage in the brain or leg were also reported with Pfizer-BioNTech vaccine [40-42].

Recently, we proposed the use of artificial bloods for severe Covid-19 patients [43].

3.5. COVID vaccination and Myocarditis/Pericarditis

Myocarditis is inflammation of the heart muscle, whereas pericarditis is inflammation of the outer lining of the heart. Myocarditis and pericarditis have been reported especially in adolescents and young adult males within several days after mRNA COVID-19 vaccination (Pfizer-BioNTech or Moderna) [44, 45]. In June 2021, the U.S. Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices reported a likely link between mRNA COVID-19 vaccination and myocarditis, particularly in people younger than 39 [46]. In addition, the evidence grows stronger for Covid vaccine link to heart issue [47].

References

1. Nanotoxicity: Prevention, fundamentals and antibacterial applications of nanomaterials, Editors: Susai Rajendran, Anita Mukherjee, Tuan Anh Nguyen, Chandraiah Godugu, Ritesh K Shukla, March 2020, Elsevier, USA ISBN: 978-0-12-819943-5
2. Granum B, Lovik M. The effect of particles on allergic immune responses. Toxicol Sci. 2002;65:7–17
3. Oberdörster G, Oberdörster E, Oberdörster J. Nanotoxicology: An emerging discipline evolving from studies of ultrafine particles. Environ Health Perspect. 2005;113:823–39.
4. Ilinskaya AN, Dobrovolskaia MA. Nanoparticles and the blood coagulation system. Part II: safety concerns. Nanomedicine (Lond). 2013 Jun;8(6):969-81.
5. Brook RD, Rajagopalan S, Pope CA, 3rd, et al. Particulate matter air pollution and cardiovascular disease: an update to the scientific statement from the American Heart Association. Circulation. 2010;121(21):2331–2378.
6. Rückerl R, Ibald-Mulli A, Koenig W, et al. Air pollution and markers of inflammation and coagulation in patients with coronary heart disease. Am J Respir Crit Care Med. 2006;173(4):432–441.
7. Baccarelli A, Martinelli I, Zanobetti A, et al. Exposure to particulate air pollution and risk of deep vein thrombosis. Arch Intern Med. 2008;168(9):920–927.
8. Utell MJ, Frampton MW, Zareba W, Devlin RB, Cascio WE. Cardiovascular effects associated with air pollution: potential mechanisms and methods of testing. Inhal Toxicol. 2002;14(12):1231–1247.
9. Furie B, Furie BC. Mechanisms of thrombus formation. N Engl J Med. 2008;359(9):938–949

10. Ventola CL. The nanomedicine revolution: part 1: emerging concepts. Pharmacy and Therapeutics 2012 Sep;37(9):512-25.
11. Tuan Anh Nguyen, Aymen Amine Assadi (2018) Smart Nanocontainers: Preparation, Loading/Release Processes and Applications. Kenk Nanotec Nanosci 4: S1-1-6
12. Odiba, Arome, Ukegbu, Chimere, Anunobi, Oluchukwu, Chukwunonyelum, Ike and Esemonu, Juliet. "Making drugs safer: improving drug delivery and reducing the side effect of drugs on the human biochemical system" Nanotechnology Reviews, vol. 5, no. 2, 2016, pp. 183-194
13. Demoy M, Gibaud S, Andreux JP, et al. Splenic trapping of nanoparticles: complementary approaches for in situ studies. Pharm Res. 1997;14:463–8.
14. Moghimi SM, Hunter AC, Murray JC. Long-circulating and target specific nanoparticles: theory and practice. Pharmacol Rev. 2001;53:283–318
15. Senior J, Crawley JCW, Fisher D, et al. Influence of surface hydrophobicity of liposomes on their interaction with plasma protein and clearance from the circulation: studies with poly(ethylene glycol)-coated vesicles. Biochim Biophys Acta. 1985;1062:77–82.
16. Senior J, Gregoriadis G. Is half-life of circulating small unilamellar liposomes determined by changes in their permeability? FEBS Lett. 1982;145:109–14. [PubMed]
17. De Jong WH, Borm PJ. Drug delivery and nanoparticles:applications and hazards. Int J Nanomedicine. 2008;3(2):133-49.
18. Pardridge WM. Blood-brain barrier delivery. Drug Discovery Today. 2007;12:54–61.
19. Olivier JC, Fenart L, Chauvet R, et al. Indirect evidence that drug brain targeting using polysorbate 80-coated polybutylcyanoacrylate nanoparticles is related to toxicity. Pharm Res. 1999;16:1836–42.
20. Kreuter J, Ramge P, Petrov V, et al. Direct evidence that polysorbate-80-coated poly(butylcyanoacrylate) nanoparticles deliver drugs of the CNS via specific mechanisms requiring prior binding of drug to the nanoparticles. Pharm Res. 2003;20:409–16
21. Linde Schoenmaker, Dominik Witzigmann, Jayesh A. Kulkarni, Rein Verbeke, Gideon Kersten, Wim Jiskoot, Daan J.A. Crommelin, mRNA-lipid nanoparticle COVID-19 vaccines: Structure and stability, International Journal of Pharmaceutics,Volume 601, 2021,120586,
22. Tuan Anh Nguyen, Ram K. Gupta (2021) The other side of Covid-19 vaccines: Is correct vaccine still under investigation?, Kenk Nanotec Nanosci 7:14-31
23. Rauch S, Roth N, Schwendt K, Fotin-Mleczek M, Mueller SO, Petsch B. mRNA-based SARS-CoV-2 vaccine candidate CVnCoV induces high levels of virus-neutralising antibodies and mediates protection in rodents. NPJ Vaccines. 2021;6(1):57.
24. Zhang NN, Li XF, Deng YQ, Zhao H, Huang YJ, Yang G, Huang WJ, Gao P, Zhou C, Zhang RR, Guo Y, Sun SH, Fan H, Zu SL, Chen Q, He Q, Cao TS, Huang XY, Qiu HY, Nie JH, Jiang Y, Yan HY, Ye Q, Zhong X, Xue XL, Zha ZY, Zhou D, Yang X, Wang YC, Ying B, Qin CF. A Thermostable mRNA Vaccine against COVID-19. Cell. 2020;182(5):1271-1283.e16
25. McKay PF, Hu K, Blakney AK, Samnuan K, Brown JC, Penn R, Zhou J, Bouton CR, Rogers P, Polra K, Lin PJC, Barbosa C, Tam YK, Barclay WS, Shattock RJ. Self-amplifying RNA SARS-CoV-2 lipid nanoparticle vaccine candidate induces high neutralizing antibody titers in mice. Nat Commun. 2020;11(1):3523.
26. Erasmus JH, Khandhar AP, O'Connor MA, Walls AC, Hemann EA, Murapa P, Archer J, Leventhal S, Fuller JT, Lewis TB, Draves KE, Randall S, Guerriero KA, Duthie MS, Carter D, Reed SG, Hawman DW, Feldmann H, Gale M Jr, Veesler D, Berglund P, Fuller

DH. An Alphavirus-derived replicon RNA vaccine induces SARS-CoV-2 neutralizing antibody and T cell responses in mice and nonhuman primates. Sci Transl Med. 2020;12(555):eabc9396.

27. Kaur H, Kaur M, Bhattacharyya A, Prajapat M, Thota P, Sarma P, Kumar S, Kaur G, Sharma S, Prakash A, Saifuddin PK, Medhi B. Indian contribution toward biomedical research and development in COVID-19: A systematic review. Indian J Pharmacol. 2021;53(1):63-72.
28. De Alwis R, Gan ES, Chen S, Leong YS, Tan HC, Zhang SL, Yau C, Low JGH, Kalimuddin S, Matsuda D, Allen EC, Hartman P, Park KJ, Alayyoubi M, Bhaskaran H, Dukanovic A, Bao Y, Clemente B, Vega J, Roberts S, Gonzalez JA, Sablad M, Yelin R, Taylor W, Tachikawa K, Parker S, Karmali P, Davis J, Sullivan BM, Sullivan SM, Hughes SG, Chivukula P, Ooi EE. A single dose of self-transcribing and replicating RNA-based SARS-CoV-2 vaccine produces protective adaptive immunity in mice. Mol Ther. 2021;29(6):1970-1983.
29. Sebastian Ols, Lifei Yang, Elizabeth A. Thompson, Pradeepa Pushparaj, Karen Tran, Frank Liang, Ang Lin, Bengt Eriksson, Gunilla B. Karlsson Hedestam, Richard T. Wyatt, Karin Loré, Route of Vaccine Administration Alters Antigen Trafficking but Not Innate or Adaptive Immunity, Cell Reports, Volume 30, Issue 12, 2020, Pages 3964-3971.e7.
30. Managing nanomaterials in the workplace.
31. Finsterer J. Neurological side effects of SARS-CoV-2 vaccinations. Acta Neurol Scand. 2022 Jan;145(1):5-9.
32. Sriwastava S, Sharma K, Khalid SH, Bhansali S, Shrestha AK, Elkhooly M, Srivastava S, Khan E, Jaiswal S, Wen S. COVID-19 Vaccination and Neurological Manifestations: A Review of Case Reports and Case Series. Brain Sci. 2022 Mar 18;12(3):407.
33. Patone, M., Handunnetthi, L., Saatci, D. et al. Neurological complications after first dose of COVID-19 vaccines and SARS-CoV-2 infection. Nat Med 27, 2144–2153 (2021)
34. J Bart Classen, COVID-19 RNA based vaccines and the risk of prion disease
35. Microbiol Infect Dis 5 (1), 1-3, 2021
36. Bipin Chaurasia, Vishal Chavda, Bingwei Lu, Kanwaljeet Garg, Nicola Montemurro, Cognitive deficits and memory impairments after COVID-19 (Covishield) vaccination, Brain, Behavior, & Immunity - Health, Volume 22, 2022, 100463
37. Waheed S., Bayas A., Hindi F., Rizvi Z., Espinosa P.S. Neurological complications of COVID-19: Guillain-Barre syndrome following Pfizer COVID-19 vaccine. Cureus. 2021;13:2–5 June Young Chun et al. Guillain-Barré syndrome after vaccination against COVID-19, The Lancet Neurology, Vol. 21, issue 2, p.117-119, 2022
38. Covid - not vaccination - presents biggest blood clot risk, large study finds, 2021,
39. Celine Sze Ling Chui et al., Thromboembolic events and hemorrhagic stroke after mRNA (BNT162b2) and inactivated (CoronaVac) covid-19 vaccination: A self-controlled case series study, The Lancet - eClinicalMedicine, Vol. 50, 101504, 2022
40. Zakaria Z Sapiai NA Ghani ARI. Cerebral venous sinus thrombosis 2 weeks after the first dose of mRNA SARS-CoV-2 vaccine. Acta Neurochir. 2021; : 1-4
41. Shimazawa R Ikeda M. Potential adverse events in Japanese women who received tozinameran (BNT162b2, Pfizer-BioNTech). J Pharma Policy Pract. 2021; 14: 46
42. Carli G Nichele I Ruggeri M Barra S Tosetto A. Deep vein thrombosis (DVT) occurring shortly after the second dose of mRNA SARS-CoV-2 vaccine. Intern Emerg Med. 2021; 16: 803-804

43. Nanotechnology for hematology, blood transfusion and artificial blood. Editors: Adil Denizli, Tuan Anh Nguyen, Mariappan Rajan, Mohammad Feroz Alam, Khaliqur Rahman, March 2021, Elsevier, USA. ISBN: 9780128239711
44. Myocarditis
45. Tori Rodriguez, Rare Cases of Myocarditis in Adolescents, Young Adults After COVID-19 Vaccination, 2021.
46. Dongngan T. Truong, Audrey Dionne, Juan Carlos Muniz, Kimberly E. McHugh, Michael A. Portman, Linda M. Lambert, Deepika Thacker, Matthew D. Elias, Jennifer S. Li, et al., Clinically Suspected Myocarditis Temporally Related to COVID Vaccination in Adolescents and Young Adults: Suspected Myocarditis After COVID-19 Vaccination, Circulation. 2022;145:345–356
47. Evidence grows stronger for Covid vaccine link to heart issue, CDC says.