COVID-19 and the Vaccine Scenario via Nanotechnology

Abstract

Background:

Nanotechnology provides multiple solutions for fighting the viruses, both inside and outside the host cell, and multiple nanotechnology-based platforms have already been fruitful in the preclinical studies countering numerous viral pathogens of humans like humans papillomavirus, respiratory viruses, herpes simplex virus, and HIV.

Methodology:

An extensive literature review on nanotechnology's role in the current framework of the vaccine development of SARS-CoV-2.

Conclusion:

There is ongoing research on targeting the cytokine storm in the COVID-19 pneumonia as it is the main concern. Many bioactive compounds have been known to control multiple respiratory viruses through nanoencapsulation, such as Curcumin. Many other research types are being done on the formulation of nanomaterials that can help detect and reduce the SARS-CoV-2.

1. Introduction:

The development process for anti-viral therapies normally requires a number of years before the remedies can be made available on a wider scale as there are many regulatory steps required to establish the efficacy and safety of the drugs and vaccines. Furthermore, the highly explicit viral targets may change as the SARS-CoV-2 continues to transform and undergo mutations that will result in medication resistance, as has been previously observed in the attempt to treat other infections of viral nature. The past decade was filled with the increasing interest in the novel and broad-spectrum anti-viral compounds that might have a lesser disposition towards the resistance and which can be applied against a broader class of multiple viruses, including their newer variants and strains. More importantly, such treatments can be prescribed until further more sophisticated and targeted vaccines, and drugs are accessible for every new and emerging virus (Weiss et al., 2020).

Nanotechnology provides multiple solutions for fighting the viruses, both inside and outside the host cell, and multiple nanotechnology-based platforms have already been fruitful in the preclinical studies countering numerous viral pathogens of humans like humans papillomavirus, respiratory viruses, herpes simplex virus, and HIV. The nanotechnology-based methods must be leveraged for helping in fighting against the COVID-19 infection as well as any pandemic of the future in multiple ways, with the inclusion of:

- Novel drugs and vaccines, in which the nanomaterials would be leveraged for the straight delivery of the broad-spectrum anti-virals and for supporting the targeted lung therapies.
- Tests that are rapid, highly specific, and sensitive for the detection of infection or the detection of immunity (serological tests)

- Face masks filter that is superfine or blood-filtering
- Viral adhesion resistant novel surfaces or the surface coating and ones that can help in the inactivation of the virus
- Contact tracing tools improvement (Weiss et al., 2020).

The main obstacles faced in the delivery of the drug to the upper respiratory tract are the lower blood flow, foreign objects filtration, smaller surface area, and the mucus layer (trapping of the substances inhaled). The larger surface area and the lower respiratory tract's ciliated cells might be the perfect area for the delivery as it is directly connected to the systemic circulation through the pulmonary circulation presenting a few challenges such as the branched nature of the alveolar macrophages and the pulmonary surfactants (like proteins, mucins, and phospholipids) decrease the efficiency of delivery. Nevertheless, the lower tract delivery must overcome the cough clearance and mucociliary mechanisms. To address these specific barriers, the implementation of multiple nanotechnology-based approaches can be achieved due to their distinguishing features (Bhavana et al., 2020).

Multiple studies reported that the aerodynamic size ranging from 1-5 µm of the microparticles (MP) would be able to deposit in the lower region airways by escaping through the mucociliary clearance. This aerodynamic range of size is chiefly used in the multiple inhalation products that are available commercially. Interferon-α-2, Ribavirin, Laninamivir, and Zanamivir are presently available anti-viral inhaled agents against the human respiratory viruses like influenza A and B, adenovirus, RSV, parainfluenza, rhinovirus, and coronavirus (Bhavana et al., 2020).

Nanotechnology has huge potential in helping in the development of drug delivery for COVID-19 because of a wider range of advantages like;

- Morphology and smaller size of the nanoparticles enabling the delivery of the drug to the in-accessible site physiologically and elimination of the immune response by the reticular endothelial cells
- The larger surface-to-volume ratio of the nanoparticles increases the drug loading
- The ability to cross the negatively charged membranes because of the surface charge modification of the nanoparticles
- Possession of the intrinsic virucidal activity by the nanoparticles like gold and silver nanoparticles (Bhavana et al., 2020).

2. Methodology:

This research article's chosen methodology is the qualitative investigation of the current literature on the topic. The present literature on the subject provides a comprehensive understanding of the topic's potential limitations, allowing the researcher to consider overcoming them to appraise their research efficiently.

The search engines used for the research are PubMed and Google Scholar, using relevant keywords to look for relevant research on the topic. The researches selected for reviewing were critically analysed to formulate relevant findings with the most appropriate and useful information on the topic.

2.1. Criterion for Inclusion and Exclusion

The research's inclusion criteria are based on factors relevant to the topic of the research. The factors relevant to the research can be notes like the following;

- Complete relevance to the topic, like discussing nanotechnology's role in the vaccine development framework of COVID-19.
- Studies that highlight the role of nanotechnology in vaccine development of SARS-CoV-2.
- Empirical researches utilizing multiple approaches for the production of authentic results.
- Literature reviews, doctoral dissertations, and reports which contain rigorous research.

The research's exclusion criteria encompass research that does not address the issue regarding the current framework of vaccine development via nanotechnology of COVID-19.

3. Literature Review:

Both the viruses and nanoparticles attain the operation on a similar size scale; that is why the nanoparticles carry the ability for entering into the cells and enabling the antigens' expression from the nucleic acids delivered (DNA vaccines and mRNA), and the directly targeted immune cells for antigens delivery (subunit vaccines). Multiple technologies for the vaccine have employed the benefits directly by the encapsulation of the genomic material or the peptide/protein antigens in the nanoparticles like the lipid nanoparticles (LNPs) or for the other viruses like Ads. BioNTech/Pfizer and the Moderna work on the encapsulation of the mRNA vaccines inside the LNPs whereas, the University of Oxford/Astrazeneca and CanSino work on the incorporation of the sequences of antigen-encoding inside the Ads carried DNA (Folegatti et al., 2020; Jackson et al., 2020; Mulligan et al., 2020; Zhu et al., 2020). Novavax achieves decoration of the recombinant S proteins of the SARS-CoV-2 onto the proprietary virus-like particles (VLP) nanoparticles developed by them (Chung et al., 2020).

The selection of a nanocarrier that will bypass the potential drug candidate's conventional limitations is of importance, like the comparatively safer conjugates of the antibody-drug of auristatin that are highly toxic have approval in the treatment of the haematological cancers. The chief limitation for the use of these conjugates is the comparatively lower tolerability of the payloads of drugs. To solve this problem, the development of polymeric nanoparticles was achieved with a higher auristatin payload for the efficient achievement and suppression of tumour safely (Qi et al., 2017). Similarly, the formulation of the nanoparticles that are poly (ethylene glycol)-poly(lactide)-based loaded with the Aurora B kinase inhibitor have revealed increased efficiency and the toxicity reduction in comparison with the free form producing the unendurable side effects in the second phase of the clinical trials (Ashton et al., 2016). An eminent limitation of the drug candidates that are nucleic acid (such as RNAi) is the systemic circulation instability and the delivery requirement on an intracellular level (Davis et al., 2010; Draz et al. siRNA carried by the Lipid nanoparticles (LNPs) are one of the examples for the platform of nanotechnology (Onpattro) used for the prevention of the degradation systematically along with the liver-targeting benefits (Adams et al., 2018). The mesoporous silica nanoparticles that are lipid-coated that are used for the delivery of a highly hydrophilic and the unstable anti-viral molecule ML336 (the chemical inhibitors for the Venezuelan equine encephalitis virus), showing the improved circulation time and the biocompatibility of the ML336 in-vivo (Chauhan et al., 2020; LaBauve et al., 2018).

It is known that the ability of modification of the encapsulated drug's pharmacokinetic parameters is shown by the nanocarriers and the decrease in the concentration of the drug that is required for the biological activity because of the controlled or sustainable release (Abo-zeid et al., 2018). Additionally, the target ligands application on the nanocarriers' surface for molecular components

recognition of the interested organ/tissue is quite a promising approach for boosting anti-viral effects (Sofias et al., 2018). (Leuschner et al., 2011) performed a study on bringing direction in the nanotechnology usage for controlling the cytokine storm. The Cytokine storm is the most common complication clinically of the COVID-19, consisting of the intensified production of the pro-inflammatory cytokines, leading to multiple organ dysfunction and rapid deterioration (Sun et al. A small interfering RNA (siRNA) was produced via the encapsulation in the lipidic nature nanoparticles that are explicitly for the silencing of chemokine receptor CCR2, on which the inflammatory monocytes are dependant on for finding the inflammation areas. The suitable degradation of the CCR2 messenger RNA in the monocytes evade its growth in the inflammatory sites, solving the uncontrolled monocytes recruitment in the inflammatory process, with promising results in the mice trial. Some commercial medicines available, like C_1 esterase inhibitor and tocilizumab, have already been known to show positive results in the cytokine storm control; nevertheless, these drugs are quite expensive, and the production is not quite scalable easily. For reducing the cost of treatment and streamlining the production, it was suggested by (Testori, 2020) that the plasmids use as engineered vectors for the production of interleukin (IL)-10 within the cells for the containment of the inflammatory process. The nanoparticles composed of PLGA (Zeng et al., 2019), PLA-PEG (Duncan et al., 2019), polyethyleneimine (PEI) (Khalvati et al., 2017), PEG-PCL (Gao et al., 2014), and so one have been studied successfully in regard with the delivery of interleukins systematically as an immunotherapy for multiple diseases types. These studies' findings could be supportive in the efficient nanoparticle development therapies for the cytokine storm in the COVID-19 patients.

The use of Squalene was achieved by (Dormont et al., 2020), having an endogenous lipid for the preparation of anti-inflammatory drugs α-tocopherol (Vit. E) and adenosine loaded nanoparticles

for the targeted actions in acute inflammation regions. Treatment of mice with the squalene nanoparticles in a state of acute hyper inflammation and cytokine storm. The pro-inflammatory cytokines levels were reduced, and the IL-10 levels increment was observed by the results of the study, leading to uncontrolled inflammation mitigation. Additionally, it was observed that adenosine encapsulation increased the half-life, consequently increasing the effects therapeutically in comparison with the drugs that were non-encapsulated. Because of the adenosine's targeted delivery to the inflammation loci, in combination with the decreased reactive oxygen species (ROS) ability at the site of inflammation, the formulation that is nano-based holds promising results as an uncontrolled inflammation treatment that is due to coronavirus. Curcumin has also been known to show anti-viral activity in relation to multiple viral infections, including influenza, chikungunya virus, hepatitis, Zika virus, and other viruses that are sexually transmitted. Recently, the chitosan nanoparticles loaded with Curcumin were synthesized by (Loutfy et al., 2020) against the hepatitis C virus genotype 4a. The Chitosan nanoparticles achieved 100% inhibition of the viral infection and the replication in the human hepatoblastoma cells (Huh7). The Curcumin contained nanoparticles' anti-viral activity was because of the fluidity disturbance of the virion membrane; however, no changes in the integrity of virion were observed. The nanoparticles achieved inhibition of both the entry of the virus inside the hepatoblastoma cell and the replication. Curcumin is just a single example in the variety of natural compounds that can potentially use controlling the viral infections, with the inclusion of COVID-19. That is why the nano-based formulation usage has indicated huge potential in controlling the viral infections. Both the efficiency enhancement can be achieved by the nanoparticles and the toxicity reduction (Singh et al., 2017). The use of nanotechnology has also been applied in enhancing the anti-viral drugs' efficiency by overcoming the lower bioavailability. The nanomaterials development, like the

nanogels, can capture the virus particles that are viable or the viral RNA/proteins, which are also promising developments having the potential to fight against the SARS-CoV-2 (Dey et al., 2018; Hendricks et al., 2013). The key goal for the nano-based anti-viral therapies future research will be the nano-based formulations development that are able to successfully target the specific sites of the viral infection (such as the respiratory system in the COVID-19 case), reduction in the toxicity of the drug in other tissues, and the potential to have some intrinsic anti-viral activity of their own (Campos et al., 2020).

The designing of the appropriate nanomaterials for the inhibition of the SARS-CoV-2 on the basis of the SARS-CoV-2 lifecycle, and inspired by the previous studies, the following possibilities were put forward by (Tang et al., 2021); (1) designing of the DNA/RNA modified origami nanostructures for the inhibition of the host cells attachment; (2) nanomaterials modified via the multivalent ligands or the HSPG-mimicking nanomaterials for the utilization for inhibiting the process of infusion; (3) the external biocompatible nanomaterials that are Zn-based may also help in the inhibition of the RNA polymerase via the release of zinc ion; (4) the membrane-targeting nanomaterials might be able to induce the oxidation of lipids for the prohibition of viral fusion through the generation of O_2; and (5) the potential destruction of the virus through the viral membrane-targeted photothermal nanomaterials (like gold) via local hypothermia' since heat has been used for the inactivation of virus for many years. Additionally, the nanomaterials having the anti-viral capabilities as mentioned can also be embedded in the personal protective equipment (PPEs) for the production of anti-viral PPEs, for instance, with the combination of mass production and eco-friendly methods that are available for the synthesis of materials that are nano-fibrous with the mentioned anti-viral properties as the PPE components.

3.1. Potential of Introduction of Nanomaterial in Relieving Symptoms of Pneumonia:

Pneumonia is the main symptom of the infection of COVID-19, and it urgently requires nanotechnology incorporation. With the use of nanomaterials for the delivery of drugs that are anti-inflammatory, introduction of the anti-oxidant nanomaterials, provision of the methods for inhalation, the fabrication of the nanomaterials that are platelet-derived actively targeting the sites of inflammation, and the offering of the capability for the controlled release of drug, to the utilization of oxygen-generation nanomaterials, these strategies will provide not only appropriate solutions but also induce future researches. Such as, the platelet-derived nanomaterials have the potential to be introduced for the encapsulation of [5-(p-fluorophenyl)-2-ureido] thiophene-3-carboxamide (TPCA-1) for targeting the site of pneumonia and calming the cytokine storm. Furthermore, the anti-oxidant nanomaterials like cerium dioxide nanoparticles can be utilized for the elimination of reactive oxygen species (ROS) at the site of inflammation (Figure 1). Further technologies can also be used symbiotically with nanotechnology to facilitate and promote applications in the treatment of COVID-19. Such as, artificial intelligence, that has been discovered in-depth for the diagnosis of COVID-19, and the drugs identification that have the potential to be repurposed for the treatment of COVID-19, can also be considered for helping in the isolation of or finding of the appropriate vaccines-loaded nanomaterials, the nanomaterials providing pneumonia relief, and the therapeutic nanomaterials (Tang et al., 2021).

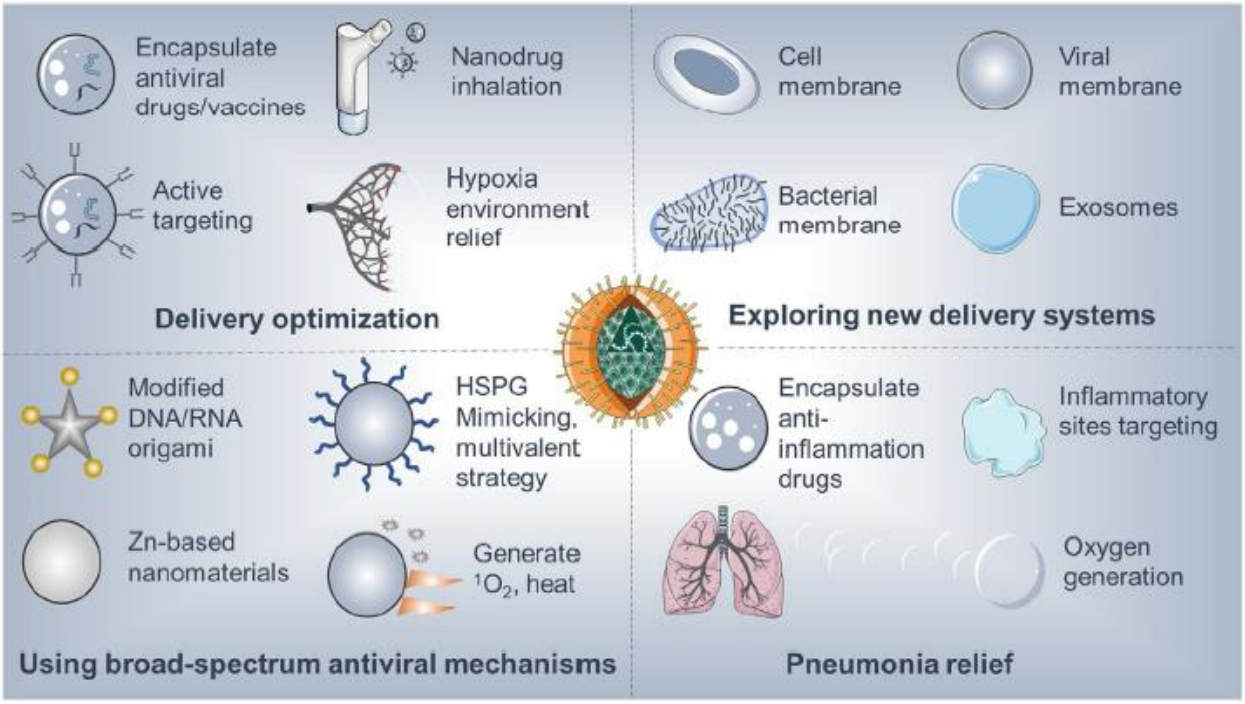

Figure 1: Outlooks from nanotechnology against SARS-CoV-2. (Tang et al., 2021)

4. Conclusion:

The present study aimed to discuss the role of nanotechnology in the vaccine development framework of the SARS-CoV-2. Multiple pieces of literature were reviewed concerning the research area; many studies are looking into the role of nanomaterials in the development of vaccines due to their size and higher absorption rate. There is ongoing research on targeting the cytokine storm in the COVID-19 pneumonia as it is the main concern. Many bioactive compounds have been known to control multiple respiratory viruses through nanoencapsulation, such as Curcumin. Many other kinds of research are being done on the formulation of nanomaterials that can help detect and reduce the SARS-CoV-2.

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5. References:

Abo-zeid, Y., Urbanowicz, R. A., Thomson, B. J., Irving, W. L., Tarr, A. W., & Garnett, M. C. (2018). Enhanced nanoparticle uptake into virus infected cells: Could nanoparticles be useful in anti-viral therapy? *International Journal of Pharmaceutics*, *547*(1–2), 572–581.

Adams, D., Gonzalez-Duarte, A., O'Riordan, W. D., Yang, C.-C., Ueda, M., Kristen, A. V., Tournev, I., Schmidt, H. H., Coelho, T., Berk, J. L., Lin, K.-P., Vita, G., Attarian, S., Planté-Bordeneuve, V., Mezei, M. M., Campistol, J. M., Buades, J., Brannagan, T. H., Kim, B. J., … Suhr, O. B. (2018). Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis. *New England Journal of Medicine*, *379*(1), 11–21. https://doi.org/10.1056/NEJMoa1716153

Ashton, S., Song, Y. H., Nolan, J., Cadogan, E., Murray, J., Odedra, R., Foster, J., Hall, P. A., Low, S., Taylor, P., Ellston, R., Polanska, U. M., Wilson, J., Howes, C., Smith, A., Goodwin, R. J. A., Swales, J. G., Strittmatter, N., Takáts, Z., … Barry, S. T. (2016). Aurora kinase inhibitor nanoparticles target tumors with favorable therapeutic index in vivo. *Science Translational Medicine*, *8*(325), 325ra17-325ra17. https://doi.org/10.1126/scitranslmed.aad2355

Bhavana, V., Thakor, P., Singh, S. B., & Mehra, N. K. (2020). COVID-19: Pathophysiology, treatment options, nanotechnology approaches, and research agenda to combating the SARS-CoV2 pandemic. *Life Sciences*, *261*, 118336. https://doi.org/10.1016/j.lfs.2020.118336

Campos, E. V. R., Pereira, A. E. S., de Oliveira, J. L., Carvalho, L. B., Guilger-Casagrande, M.,

de Lima, R., & Fraceto, L. F. (2020). How can nanotechnology help to combat COVID-19? Opportunities and urgent need. *Journal of Nanobiotechnology, 18*(1), 125. https://doi.org/10.1186/s12951-020-00685-4

Chauhan, G., Madou, M. J., Kalra, S., Chopra, V., Ghosh, D., & Martinez-Chapa, S. O. (2020). Nanotechnology for COVID-19: Therapeutics and Vaccine Research. *ACS Nano, 14*(7), 7760–7782. https://doi.org/10.1021/acsnano.0c04006

Chung, Y. H., Beiss, V., Fiering, S. N., & Steinmetz, N. F. (2020). COVID-19 Vaccine Frontrunners and Their Nanotechnology Design. *ACS Nano*, *14*(10), 12522–12537. https://doi.org/10.1021/acsnano.0c07197

Davis, M. E., Zuckerman, J. E., Choi, C. H. J., Seligson, D., Tolcher, A., Alabi, C. A., Yen, Y., Heidel, J. D., & Ribas, A. (2010). Evidence of RNAi in humans from systemically administered siRNA via targeted nanoparticles. *Nature*, *464*(7291), 1067–1070. https://doi.org/10.1038/nature08956

Dey, P., Bergmann, T., Cuellar-Camacho, J. L., Ehrmann, S., Chowdhury, M. S., Zhang, M., Dahmani, I., Haag, R., & Azab, W. (2018). Multivalent flexible nanogels exhibit broad-spectrum anti-viral activity by blocking virus entry. *ACS Nano, 12*(7), 6429–6442.

Dormont, F., Brusini, R., Cailleau, C., Reynaud, F., Peramo, A., Gendron, A., Mougin, J., Gaudin, F., Varna, M., & Couvreur, P. (2020). Squalene-based multidrug nanoparticles for improved mitigation of uncontrolled inflammation in rodents. *Science Advances*, *6*(23), eaaz5466.

Draz, M. S., Fang, B. A., Zhang, P., Hu, Z., Gu, S., Weng, K. C., Gray, J. W., & Chen, F. F. (2014). Nanoparticle-Mediated Systemic Delivery of siRNA for Treatment of Cancers and

Viral Infections. *Theranostics*, *4*(9), 872–892. https://doi.org/10.7150/thno.9404

Duncan, S. A., Dixit, S., Sahu, R., Martin, D., Baganizi, D. R., Nyairo, E., Villinger, F., Singh, S. R., & Dennis, V. A. (2019). prolonged release and functionality of interleukin-10 encapsulated within PLA-PEG nanoparticles. *Nanomaterials*, *9*(8), 1074.

Folegatti, P. M., Ewer, K. J., Aley, P. K., Angus, B., Becker, S., Belij-Rammerstorfer, S., Bellamy, D., Bibi, S., Bittaye, M., Clutterbuck, E. A., Dold, C., Faust, S. N., Finn, A., Flaxman, A. L., Hallis, B., Heath, P., Jenkin, D., Lazarus, R., Makinson, R., … Yau, Y. (2020). Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. *The Lancet*, *396*(10249), 467–478. https://doi.org/10.1016/S0140-6736(20)31604-4

Gao, H., Xiong, Y., Zhang, S., Yang, Z., Cao, S., & Jiang, X. (2014). RGD and interleukin-13 peptide functionalized nanoparticles for enhanced glioblastoma cells and neovasculature dual targeting delivery and elevated tumor penetration. *Molecular Pharmaceutics*, *11*(3), 1042–1052.

Hendricks, G. L., Weirich, K. L., Viswanathan, K., Li, J., Shriver, Z. H., Ashour, J., Ploegh, H. L., Kurt-Jones, E. A., Fygenson, D. K., & Finberg, R. W. (2013). Sialylneolacto-N-tetraose c (LSTc)-bearing liposomal decoys capture influenza A virus. *Journal of Biological Chemistry*, *288*(12), 8061–8073.

Jackson, L. A., Anderson, E. J., Rouphael, N. G., Roberts, P. C., Makhene, M., Coler, R. N., McCullough, M. P., Chappell, J. D., Denison, M. R., Stevens, L. J., Pruijssers, A. J., McDermott, A., Flach, B., Doria-Rose, N. A., Corbett, K. S., Morabito, K. M., O'Dell, S., Schmidt, S. D., Swanson, P. A., … Beigel, J. H. (2020). An mRNA Vaccine against SARS-

CoV-2 — Preliminary Report. *New England Journal of Medicine*, *383*(20), 1920–1931. https://doi.org/10.1056/NEJMoa2022483

Khalvati, B., Sheikhsaran, F., Sharifzadeh, S., Kalantari, T., Behzad Behbahani, A., Jamshidzadeh, A., & Dehshahri, A. (2017). Delivery of plasmid encoding interleukin-12 gene into hepatocytes by conjugated polyethylenimine-based nanoparticles. *Artificial Cells, Nanomedicine, and Biotechnology*, *45*(5), 1036–1044.

Ku, S. H., Jo, S. D., Lee, Y. K., Kim, K., & Kim, S. H. (2016). Chemical and structural modifications of RNAi therapeutics. *Advanced Drug Delivery Reviews*, *104*, 16–28. https://doi.org/10.1016/j.addr.2015.10.015

LaBauve, A. E., Rinker, T. E., Noureddine, A., Serda, R. E., Howe, J. Y., Sherman, M. B., Rasley, A., Brinker, C. J., Sasaki, D. Y., & Negrete, O. A. (2018). Lipid-Coated Mesoporous Silica Nanoparticles for the Delivery of the ML336 Antiviral to Inhibit Encephalitic Alphavirus Infection. *Scientific Reports*, *8*(1), 13990. https://doi.org/10.1038/s41598-018-32033-w

Leuschner, F., Dutta, P., Gorbatov, R., Novobrantseva, T. I., Donahoe, J. S., Courties, G., Lee, K. M., Kim, J. I., Markmann, J. F., & Marinelli, B. (2011). Therapeutic siRNA silencing in inflammatory monocytes in mice. *Nature Biotechnology*, *29*(11), 1005–1010.

Loutfy, S. A., Elberry, M. H., Farroh, K. Y., Mohamed, H. T., Mohamed, A. A., Mohamed, E. B., Faraag, A. H. I., & Mousa, S. A. (2020). Anti-viral Activity of Chitosan Nanoparticles Encapsulating Curcumin Against Hepatitis C Virus Genotype 4a in Human Hepatoma Cell Lines. *International Journal of Nanomedicine*, *15*, 2699.

Mulligan, M. J., Lyke, K. E., Kitchin, N., Absalon, J., Gurtman, A., Lockhart, S. P., Neuzil, K.,

Raabe, V., Bailey, R., & Swanson, K. A. (2020). *Phase 1/2 Study to Describe the Safety and Immunogenicity of a COVID-19 RNA Vaccine Candidate (BNT162b1) in Adults 18 to 55 Years of Age: Interim Report. medRxiv. 20202020.06. 30.20142570*.

Qi, R., Wang, Y., Bruno, P. M., Xiao, H., Yu, Y., Li, T., Lauffer, S., Wei, W., Chen, Q., Kang, X., Song, H., Yang, X., Huang, X., Detappe, A., Matulonis, U., Pepin, D., Hemann, M. T., Birrer, M. J., & Ghoroghchian, P. P. (2017). Nanoparticle conjugates of a highly potent toxin enhance safety and circumvent platinum resistance in ovarian cancer. *Nature Communications*, *8*(1), 2166. https://doi.org/10.1038/s41467-017-02390-7

Singh, L., Kruger, H. G., Maguire, G. E. M., Govender, T., & Parboosing, R. (2017). The role of nanotechnology in the treatment of viral infections. *Therapeutic Advances in Infectious Disease*, *4*(4), 105–131.

Sofias, A. M., Andreassen, T., & Hak, S. (2018). Nanoparticle ligand-decoration procedures affect in vivo interactions with immune cells. *Molecular Pharmaceutics*, *15*(12), 5754–5761.

Sun, X., Wang, T., Cai, D., Hu, Z., Liao, H., Zhi, L., Wei, H., Zhang, Z., Qiu, Y., & Wang, J. (2020). Cytokine storm intervention in the early stages of COVID-19 pneumonia. *Cytokine & Growth Factor Reviews*.

Tang, Z., Zhang, X., Shu, Y., Guo, M., Zhang, H., & Tao, W. (2021). Insights from nanotechnology in COVID-19 treatment. *Nano Today*, *36*, 101019. https://doi.org/10.1016/j.nantod.2020.101019

Testori, A. (2020). The “perfect cytokine storm” of covID-19. *Mayo Clinic Proceedings*.

Weiss, C., Carriere, M., Fusco, L., Capua, I., Regla-Nava, J. A., Pasquali, M., Scott, J. A., Vitale, F., Unal, M. A., Mattevi, C., Bedognetti, D., Merkoçi, A., Tasciotti, E., Yilmazer, A., Gogotsi, Y., Stellacci, F., & Delogu, L. G. (2020). Toward Nanotechnology-Enabled Approaches against the COVID-19 Pandemic. *ACS Nano*, *14*(6), 6383–6406. https://doi.org/10.1021/acsnano.0c03697

Ye, Q., Wang, B., & Mao, J. (2020). The pathogenesis and treatment of the Cytokine Storm'in COVID-19. *Journal of Infection*, *80*(6), 607–613.

Zeng, L., Ma, W., Shi, L., Chen, X., Wu, R., Zhang, Y., Chen, H., & Chen, H. (2019). Poly (lactic-co-glycolic acid) nanoparticle-mediated interleukin-12 delivery for the treatment of diabetic retinopathy. *International Journal of Nanomedicine*, *14*, 6357.

Zhu, F.-C., Guan, X.-H., Li, Y.-H., Huang, J.-Y., Jiang, T., Hou, L.-H., Li, J.-X., Yang, B.-F., Wang, L., Wang, W.-J., Wu, S.-P., Wang, Z., Wu, X.-H., Xu, J.-J., Zhang, Z., Jia, S.-Y., Wang, B.-S., Hu, Y., Liu, J.-J., … Chen, W. (2020). Immunogenicity and safety of a recombinant adenovirus type-5-vectored COVID-19 vaccine in healthy adults aged 18 years or older: a randomised, double-blind, placebo-controlled, phase 2 trial. *The Lancet*, *396*(10249), 479–488. https://doi.org/10.1016/S0140-6736(20)31605-6