Journal of Scientific and Innovative Research 2018; 7(2): 55-59
Available online at: www.jsirjournal.com

Research Article

ISSN 2320-4818
JSIR 2018; 7(2): 55-59

Received: 26-06-2018
Accepted: 14-07-2018

Rishikesh Kumar
Biomedical and Nanomedicine Department, Rajendra Memorial Research Institute of Medical Sciences (RMRIMS), Patna, India

Ganesh C Sahoo
Biomedical and Nanomedicine Department, RMRIMS, Patna, India

Bhawna
Biomedical and Nanomedicine Department, RMRIMS, Patna, India

Aparna Ramachandran
Biomedical and Nanomedicine Department, RMRIMS, Patna, India

Md. Yousuf Ansari
Division of Virology, National Institute of Cholera and Enteric Diseases, Kolkata, India

Krishna Pandey
Clinical Medicine Department, RMRIMS, Agamkuan, Patna, India

VNR Das
Clinical Medicine Department, RMRIMS, Agamkuan, Patna, India

RK Topno
Clinical Medicine Department, RMRIMS, Agamkuan, Patna, India

Major Madhukar
Department of Microbiology, All India Institute of Medical Science (AIIMS), Patna, India

Pradeep Das
Molecular Biology Department, Rajendra Memorial Research Institute of Medical Sciences (ICMR), Patna, India

Correspondence:
Rishikesh Kumar
Biomedical and Nanomedicine Department, Rajendra Memorial Research Institute of Medical Sciences (RMRIMS), Agamkuan, Patna, India
Email: virgo.rishii@gmail.com

Nanotechnology: A promising approach of antiviral treatments against chikungunya virus (CHIKV)

Rishikesh Kumar, Ganesh C Sahoo, Bhawna, Aparna Ramachandran, Md. Yousuf Ansari, Krishna Pandey, VNR Das, RK Topno, Major Madhukar, Pradeep Das*

Abstract

Following its emergence in Africa, spread to the Indian Ocean islands in 2006, and occurrences in regions of the world where it hadn't been reported in the past, Chikungunya has become an emerging public health concern in many countries. The past outbreaks of the chikungunya virus (CHIKV) have caused widespread morbidity and mortality. No specific antiviral remedy against chikungunya is presently available and therapy only involves treating its symptoms and may involve side-effects. For instance, non-steroidal anti-inflammatory drugs (NSAIDs) can be used to treat chikungunya-related arthritis, but can cause extremely adverse effects such as haemorrhage, especially when co-infected with dengue. Hence, there is an urgent need to devise novel strategies to combat this disease. Nanotechnology is an emerging discipline that has the ability to transform the diagnosis and treatment of viruses and other microbial pathogens. A vast number of promising antiviral treatments involving nanotechnology are currently under investigation. In this review, we provide a brief overview of this disease over the years and the current treatments available to alleviate the symptoms of chikungunya. We then summarize prospective treatments integrating the ever-expanding field of nanotechnology that have proven to be successful against other viruses such as HIV, Influenza virus and HSV, with the objective of showing that these can potentially be developed as anti-CHIKV therapy.

Keywords: Chikungunya virus, CHIKV, Nanotechnology.

INTRODUCTION

Chikungunya virus (CHIKV) is an arthropod-borne virus that is transmitted to humans by the *Aedes* mosquitoes [1]. It is an alphavirus of the Togaviridae family [2]. This virus was first isolated in 1952 during an outbreak of febrile illness in Makonde, a province in southern Tanzania [2]. Since it was reported in 1952, this virus has resulted in millions of infections in different parts of the world such as Asia, the Indian Ocean islands, Africa, Europe, and America [4]. Chikungunya can cause an abrupt onset of joint pains, fever, and erythematous skin manifestations such as a morbilliform rash, scattered hyperpigmentation, especially on the face, and aphthous-like ulcers [5]. The term "chikungunya", literally meaning "that which bends up", originates from Bantu language of the Makonde ethnic group and points to the curved stature of the patient due to the incapacitating joint pain [6]. Acute symptoms of chikungunya typically disappear in one or two weeks, but polyarthralgia is recurrent in 30–40% of the patients and may continue to afflict the individual for years [7].

Over the past 50 years, a number of re-emergences of CHIKV have been documented, mainly in Asia and Africa, with intermissions of 2–20 years [8]. CHIKV emerged in Kenya in 2004 and spread eastward to the Comoro Islands by January 2005 [9]. In 2005–2006, the outbreak spread to other islands in the Indian Ocean, such as La Réunion, Mauritius and the Seychelles [10]. The virus infected about one-third of La Réunion's population, resulting in more than 266,000 cases with over 200 associated deaths [11]. The epidemic also spread to India. By the end of 2006, it was approximated that more than 1.5 million cases have been reported in 7 countries, with about 1.25 million of the suspected cases originating in India alone [12] CHIKV was also identified in Europe, believed to have been transported by infected travellers from regions afflicted with chikungunya [13]. The first epidemic outbreak in the north-east of Italy was reported between July and September 2007, with more than 200 human infections [14]. This outbreak exhibited, for the first time, the potential of CHIKV to move to ecological niches it hasn't been observed in before, such as Europe and regions of the Western Hemisphere [15]. In 2013, CHIKV was reported in the Caribbean, marking its first documented autochthonous appearance in the Americas, from where it

continued to spread [16]. In Brazil, the first reported case of autochthonous CHIKV was in September 2014, in Amapá, followed by an outbreak in Feira de Santana [4]. Chikungunya continues to be reported across different parts of the world. In these outbreaks, it was seen women were usually affected more than men, and adults (over 30 years of age) were more susceptible than children [10]. Recently, In India, outbreak of chikungunya has been reported in Guntur, Andhra Pradesh in September-October 2013 [17]. In 2010, Delhi witnessed an outbreak of CHIKV, after which only sporadic cases were reported. However, in August 2016, another massive outbreak occurred in New Delhi and the National Capital Region, (NCR) [18]. Three genotypes of CHIKV have been identified till date: West African, East/Central/South African (ECSA), and Asian [19]. In India, CHIKV was first seen in West Bengal in 1963, with the epidemic lasting for 2 years, and was of the Asian genotype [5]. In the following decades, only scattered cases at irregular intervals were reported [20]. The re-emergence of CHIKV in 2006 was of the ECSA genotype [21]. The Indian Ocean lineage (IOL) virus, which originated from the ECSA genotype, is responsible for the re-emergence of chikungunya that occurred in India and the Indian Ocean islands in 2005-2006 [22]. In December 2013, through the Caribbean, Asian genotype of CHIKV was introduced to the Americas. In the outbreak in Brazil in 2014, two genotypes were reported: Asian genotype was found in Amapá and ECSA genotype was seen in Feira de Santana City [23].
In humans, CHIKV is transmitted largely by *Aedes aegypti*, mosquitoes of the genus *Aedes*. *Aedes albopictus* was discovered to be the second-largest transmitter of CHIKV as observed in case of the IOL virus that circulated during the Indian Ocean islands outbreak. Due to a mutation associated with the substitution of an amino acid in the enveloped glycoprotein (E1–A226V) the virus adapts better to this vector, increasing its ability to spread the virus [24].

In spite of the large number of human infections caused by CHIKV annually, no vaccine or treatment against the virus is currently available. The infection remains unfamiliar to a significant fraction of the population as well as health professionals. Clinical management of the disease is complicated and often requires laboratory tests for its diagnosis and confirmation, which is not available on a large scale. Hence, there is a need to devise novel strategies to diagnosis CHIKV with ease and to combat this virus.

Current Treatment

Currently, no specific antiviral therapy is available for the treatment of chikungunya. Combating of the disease involves treatment of symptoms. In majority of the patients, the acute symptoms resolve within a week or two [1]. Treatment of CHIKV arthritis includes use of analgesics such as paracetamol, opioids and non-steroidal anti-inflammatory drugs (NSAIDs). Arthritis can be treated with NSAIDs, but they possess risks such as haemorrhage and renal insufficiency associated with severe forms of Chikungunya. Also, care should be taken in areas where overlap of dengue virus and CHIKV occurs, as NSAIDs can cause thrombocytopenia and hemorrhagic symptoms like gastrointestinal bleeding in a patient co-infected with dengue [25]. Symptoms of chikungunya fever have been shown to be reduced, in the short-term, by systemic corticosteroids [26] but they can be associated with augmented risks and complications in the acute phase [25]. The use of chloroquine phosphate to treat CHIKV arthritis has demonstrated mixed results [27]. If the pain has a neuropathic component, it can be treated with antidepressants or antiepileptic drugs [28].

No specific antiviral drugs against CHIKV are available in the market. Several drugs have been tested against CHIKV, in-vitro, to give positive results. One such drug is Ribavirin, but limited information about its efficiency is available [29]. Other examples include arbidol, chloroquine, favipiravir, and furin inhibitors. However, most of these compounds have modest activity and their in-vivo efficacy has not yet been assessed [30]. Recently, a small molecule, Pep I, which has already been successfully used against HIV and HCV, was repurposed against CHIKV and showed high antiviral activity in-vitro. The molecule was found to bind to nsP2 protease of the virus and prevent its replication [31].

No vaccines against CHIKV are currently available. Options like viral-like particles, recombinant antigens, chimeric alphaviruses, electroporated DNA, and virus attenuated by large-scale codon re-encoding, are being looked into but no commercial vaccine exists as of now [29].

Nanotechnology-based Applications against CHIKV

Nanotechnology is the application of particles with dimension(s) that in the nanometer scale [32]. Nanoparticles (NPs) offer an array of advantages for use in antiviral therapy. The small size of NPs can allow drug delivery into anatomically inaccessible sites [33]. Their large surface area to volume ratios facilitates accommodation of large drug payloads [34]. As their surface charge can be modified, NPs can cross negatively charged cellular membranes [35]. NPs have been seen to exhibit biomimetic properties [36], which can give rise to intrinsic virucidal activity against a range of viruses, such as that observed in silver NPs against a broad range of viruses such as HIV, HBV, HSV, among others [37]. Encapsulation of drug in NPs [35], modifications with polymers such as PEG [34] or formation of stable structures with NPs [38], can decrease the amount of drug required by enhancing stability and bioavailability (Figure 2). NPs can also be engineered with moieties that would target certain cell or tissue types to increase specificity to the target [39].

Nanoencapsulation of drugs offers multiple benefits such as improved efficacy and bioavailability and controlled release of the therapeutic agent [40]. For example, in a study, encapsulation of silibinin, a potential anti-HCV agent, by leptosomes increased its absorption into the cell as well as pharmacological effect when compared to the free molecule alone [41]. PLGA NPs loaded with Nelfinavir, an anti-HIV drug, exhibited increased solubility and oral bioavailability as well as sustained release of the drug in in-vivo studies in rabbits [42]. Acyclovir, an anti HSV-drug, when loaded in chitosan nanospheres, displayed antiviral activity higher than that seen in free acyclovir against HSV-1 and the HSV-2 strains and no cytotoxicity in-vitro [43].

Functionalization of NPs can make them excellent vehicles of drug delivery and greatly enhances their activity. NPs can be modified with a number of substances, including antibodies for targeted drug delivery or the drug itself for enhanced activity. Oseltamivir-modified silver NPs have been demonstrated to greatly decrease H1N1 infection by inhibiting the activities of hemagglutinin (HA) and neuraminidase (NA), prevention of DNA fragmentation, chromatin condensation, and caspase-3 activity in vitro [44]. In an in vitro study against HIV, glucose-coated gold NPs were functionalized with NRTI drugs abacavir (ABC) and lamivudine (3TC) to give an ester bond that can be cleaved under acidic conditions to render the hydroxyl group for chain termination. Based on this scheme, more complex GNPs with carrying various antiviral inhibitors simultaneously can be designed [45]. Chitosan NPs modified with transferrin and bradykinin B2 antibodies have been developed for the targeted delivery of siRNA across the BBB, into astrocytes to inhibit HIV replication [46]. Selenium NPs have been shown to possess low toxicity and excellent antiviral activity. Functionalization of selenium NPs with Oseltamivir against H1N1 influenza virus showed high antiviral properties as well as constraint on drug resistance [47]. Modification of selenium NPs with amantadine, another anti H1N1 influenza agent, also gave similar results [48].

NPs can be employed for the delivery of nucleic acids to inhibit the replication of the virus. An example of the use of nucleic acid would be STP909 (by Sirnaomics), a nano-based potential drug integrating siRNA for the treatment of HPV16 and HPV18 genotypes of HPV. In vitro studies demonstrated duplex formation with the mRNA from the E7 genes in HPV16 as well as HPV18, and in vivo studies in rabbits also showed the antiviral activity of these NPs due to knock-down of the E7 gene by them [49]. STP702 (from Sirnaomics) is another polymer-based drug system which incorporates siRNA targeting the conserved regions of influenza for antiviral activity against a range of influenza viruses [50]. Anti-herpetic siRNA-loaded NPs also gave positive results in mice due to the knock-down of nectin [51]. An instance of the use of DNA would be titanium dioxide NPs functionalized with DNA fragments and

produced by using a polylysine linker as effective inhibitors of influenza A virus, in-vitro. These nanocomposites targeted the non-coding 3′region of influenza A virus and could enter the cells without transfection agents [52]. siRNA encapsulated in lipid NPs have been shown to target the Makona strain of Ebola virus in vivo in rhesus monkeys [53]. Dual-antibody-modified chitosan NPs when used to transport siRNA across the blood-brain barrier (BBB) target HIV-infected brain astrocytes and inhibit replication of the virus [46].

The novel technology of capture of the virus can be extended to the treatment of chikungunya. 'Nanotrap' particles are thermoresponsive hydrogels capable of capturing antigens by coupling of bait to the particles by affinity. Live infectious virus, viral proteins and viral RNA can be captured by these Nanotrap particles [54]. Sialylneolacto-N-tetraose c (LSTc) bearing decoy liposomes have been used to capture influenza A viruses, inhibiting the infection of cells in-vitro [55]. It has been demonstrated that graphene oxide (GO) nanomaterial can effectively capture viruses and destroy their surface proteins, consequently extracting their viral nucleic acid in an aqueous environment due to the superficial bioreduction of GO [56]. Modification of GO to give sulfonated magnetic NPs functionalized with reduced graphene oxide (SMRGO) was shown to capture and photothermally kill HSV-1. This system consisted of graphene sheets anchored uniformly with spherical magnetic NPs of different sizes [57].

NPs are also being developed as potential vaccines. Immense research is going into the development of NPs to provide immunity against viral infection. NPs offer a range of advantages over conventional vaccines. They can overcome disadvantages of traditional vaccines such as *in vivo* instability, weak immunogenicity, potential toxicity and the need for multiple administrations [58]. NPs can be used as carriers and for presentation of biomolecules on the NP [59]. Polymer NPs and liposomes, among others, can be used to encapsulate antigens. The antigen will be released on the decomposition of the nanoparticle inside the cell or in vivo [60]. When the NP is functionalized with the antigen, antigen will be taken in by the cell along with the NP and released inside the cell [60]. In a study, chitosan NPs were used to encapsulate and deliver HA-split influenza virus product, producing greater immunogenicity than HA-split influenza virus alone in mouse models [61]. In another study, inactivated swine flu influenza virus antigens encapsulated in PLGA NPs showed enhanced immune activity in pig models [62]. Gold nanorods modified with fusion protein (F), protective antigen of the Respiratory Syncytial Virus (RSV), produced positive results when tested in-vivo [63]. Double-layered protein NPs, produced by desolvation of tetrameric M2e, a highly conserved protein in human influenza A viruses, into protein NP cores followed by coating these cores by cross-linking headless HAs, have been shown to hold great potential as a universal influenza vaccine. These NPs resembled virion surface antigen display and size, making them highly immunogenic to generate immune protection against influenza A viruses [64].

Virus-like particles (VLPs) are non-infectious, non-replicating nanoscale structures that assemble identical to native virion, consisting of viral proteins but no viral genetic material. Their ability to act as carriers for antigens, drugs and genetic material, potential to modify these VLPs and their immunogenecity makes them a prospective system for a number of applications [65]. An example of their use for drug delivery would be the design of pH-responsive virus-like NPs with increased tumour-targeting ligands for tumour-specific delivery of doxorubicin and polyacrylic acid in a controlled manner [66]. Studies are also being conducted to develop these particles into a potential vaccine. For instance, HIV-1 VLPs made up of a viral capsid protein with native Env trimers on the surface, which could induce immune responses against HIV hold immense promise as a vaccine [67]. VLPs built from the HBV tandem core platform that present conserved antigens of influenza that mostly remain unchanged with time confer immunity against influenza-related illnesses in mouse models [68].

CONCLUSION

Since no specific antiviral therapy or vaccine is currently available against chikungunya, nanotechnology can potentially be applied to combat CHIKV. The use of nanotechnology against a variety of other viruses has already been demonstrated in-vitro as well in some in-vivo models. These techniques can potentially be extrapolated against CHIKV. Some of these techniques were outlined here. Although the use of nanotechnology against viruses such as HIV, Influenza viruses, HSV and Hepatitis viruses has been studied widely, the potential application of NPs against CHIKV is unexplored. NPs possess a multitude of advantages over other conventional methods of therapy and these advantages can be exploited to provide a prospective therapy or vaccine against Chikungunya. Chikungunya has spread across the world and new cases continue to be reported worldwide every year. Hence, there is an immediate need to devise a therapeutic approach against CHIKV.

REFERENCES

1. Da Cunha, R. V., & Trinta, K. S. (2017). Chikungunya virus: clinical aspects and treatment - A Review. Memórias Do Instituto Oswaldo Cruz, 112(8), 523–531. http://doi.org/10.1590/0074-02760170044
2. Strauss JH, Strauss EG. 1994. The alphaviruses: gene expression, replication, and evolution. Microbiol. Rev. 58:491–562
3. Mohan, A., Kiran, D., Manohar, I. C., & Kumar, D. P. (2010). EPIDEMIOLOGY, CLINICAL MANIFESTATIONS, AND DIAGNOSIS OF CHIKUNGUNYA FEVER: LESSONS LEARNED FROM THE RE-EMERGING EPIDEMIC. Indian Journal of Dermatology, 55(1), 54–63. http://doi.org/10.4103/0019-5154.60355
4. Faria, N. R., Lourenço, J., de Cerqueira, E. M., de Lima, M. M., Pybus, O., & Alcantara, L. C. J. (2016). Epidemiology of chikungunya virus in Bahia, Brazil, 2014-2015. PLoS currents, 8.
5. Handler, M. Z., Handler, N. S., Stephany, M. P., Handler, G. A., & Schwartz, R. A. (2017). Chikungunya fever: an emerging viral infection threatening North America and Europe. International journal of dermatology, 56(2).
6. Taubitz, W., Cramer, J. P., Kapaun, A., Pfeffer, M., Drosten, C., Dobler, G., ... & Löscher, T. (2007). Chikungunya fever in travelers: clinical presentation and course. Clinical Infectious Diseases, 45(1), e1-e4.
7. Schwartz, O., & Albert, M. L. (2010). Biology and pathogenesis of chikungunya virus. Nature Reviews Microbiology, 8(7), 491.
8. Powers, A. M., & Logue, C. H. (2007). Changing patterns of chikungunya virus: re-emergence of a zoonotic arbovirus. Journal of General Virology, 88(9), 2363-2377.
9. Presti, A. L., Ciccozzi, M., Cella, E., Lai, A., Simonetti, F. R., Galli, M., ... & Rezza, G. (2012). Origin, evolution, and phylogeography of recent epidemic CHIKV strains. Infection, Genetics and Evolution, 12(2), 392-398.
10. Pialoux, G., Gaüzère, B. A., Jauréguiberry, S., & Strobel, M. (2007). Chikungunya, an epidemic arbovirosis. The Lancet infectious diseases, 7(5), 319-327.
11. Renault, P., Solet, J. L., Sissoko, D., Balleydier, E., Larrieu, S., Filleul, L., ... & Ilef, D. (2007). A major epidemic of chikungunya virus infection on Reunion Island, France, 2005–2006. The American journal of tropical medicine and hygiene, 77(4), 727-731.
12. World Health Organization. (2006). OUTBREAK NEWS: Chikungunya, India= LE POINT SUR LES ÉPIDÉMIES: Chikungunya, Inde. Wkly Epidemiol Rec, 81(43), 409-410.
13. Pfeffer, M., Löscher, T., & Eurosurveillance editorial team. (2006). Cases of chikungunya imported into Europe. Weekly releases (1997–2007), 11(11), 2922.
14. Rezza, G., Nicoletti, L., Angelini, R., Romi, R., Finarelli, A. C., Panning, M., ... & Silvi, G. (2007). Infection with chikungunya virus in Italy: an outbreak in a temperate region. The Lancet, 370(9602), 1840-1846.
15. Staples, J. E., Breiman, R. F., & Powers, A. M. (2009). Chikungunya fever: an epidemiological review of a re-emerging infectious disease. Clinical infectious diseases, 49(6), 942-948.
16. Leparc-Goffart I, Nougairede A, Cassadou S, Prat C, de Lamballerie X. Chikungunya in the Americas. Lancet. 2014;383(9916):514
17. Parashar, D., Amdekar, S., More, A., Patil, P., More, R., & Babu, V. R. (2015). Chikungunya fever outbreak in Guntur, Andhra Pradesh, India. The

Indian Journal of Medical Research, 142(Suppl 1), S111–S115. http://doi.org/10.4103/0971-5916.176639
18. Kaur, N., Jain, J., Kumar, A., Narang, M., Zakaria, M. K., Marcello, A., ... & Sunil, S. (2017). Chikungunya outbreak in Delhi, India, 2016: report on coinfection status and comorbid conditions in patients. New Microbes and New Infections, 20, 39-42.
19. Powers, A. M., Brault, A. C., Tesh, R. B., & Weaver, S. C. (2000). Re-emergence of Chikungunya and O'nyong-nyong viruses: evidence for distinct geographical lineages and distant evolutionary relationships. Journal of General Virology, 81(2), 471-479.
20. Mourya, D. T., Thakare, J. R., Gokhale, M. D., Powers, A. M., Hundekar, S. L., Jayakumar, P. C., ... & Padbidri, V. S. (2001). Isolation of chikungunya virus from Aedes aegypti mosquitoes collected in the town of Yawat, Pune district, Maharashtra State, India. Acta virologica, 45(5-6), 305-309.
21. Taraphdar, D., & Chatterjee, S. (2014). Molecular characterization of chikungunya virus circulating in urban and rural areas of West Bengal, India after its re-emergence in 2006. Transactions of The Royal Society of Tropical Medicine and Hygiene, 109(3), 197-202.
22. Schuffenecker, I., Iteman, I., Michault, A., Murri, S., Frangeul, L., Vaney, M. C., ... & Biscornet, L. (2006). Genome microevolution of chikungunya viruses causing the Indian Ocean outbreak. PLoS medicine, 3(7), e263.
23. Figueiredo, L. T. M. (2017). Large outbreaks of Chikungunya virus in Brazil reveal uncommon clinical features and fatalities. Revista da Sociedade Brasileira de Medicina Tropical, 50(5), 583-584.
24. Tsetsarkin, K. A., Vanlandingham, D. L., McGee, C. E., & Higgs, S. (2007). A single mutation in chikungunya virus affects vector specificity and epidemic potential. PLoS pathogens, 3(12), e201.
25. Brito, C. A. A. D., Sohsten, A. K. A. V., Leitão, C. C. D. S., Brito, R. D. C. C. M., Valadares, L. D. D. A., Fonte, C. A. M. D., ... & Brito, C. M. D. (2016). Pharmacologic management of pain in patients with Chikungunya: a guideline. Revista da Sociedade Brasileira de Medicina Tropical, 49(6), 668-679.
26. Simon F, Parola P, Grandadam M, et al. Chikungunya infection: an emerging rheumatism among travelers returned from Indian Ocean islands. Report of 47 cases. Medicine (Baltimore) 2007; 86: 123–137
27. Bettadapura, J., Herrero, L. J., Taylor, A., & Mahalingam, S. (2013). Approaches to the treatment of disease induced by chikungunya virus. The Indian Journal of Medical Research, 138(5), 762–765.
28. Galán-Huerta, K. A., Rivas-Estilla, A. M., Fernández-Salas, I., Farfan-Ale, J. A., & Ramos-Jiménez, J. (2015). Chikungunya virus: A general overview. Medicina universitaria, 17(68), 175-183.
29. Thiberville, S. D., Moyen, N., Dupuis-Maguiraga, L., Nougairede, A., Gould, E. A., Roques, P., & de Lamballerie, X. (2013). Chikungunya fever: epidemiology, clinical syndrome, pathogenesis and therapy. Antiviral research, 99(3), 345-370.
30. Abdelnabi, R., Neyts, J., & Delang, L. (2016). Antiviral strategies against chikungunya virus. Chikungunya Virus: Methods and Protocols, 243-253.
31. Singh, H., Mudgal, R., Narwal, M., Kaur, R., Singh, V. A., Malik, A., ... & Tomar, S. (2018). Chikungunya virus inhibition by peptidomimetic inhibitors targeting virus-specific cysteine protea
32. Allhoff, F., Lin, P., & Moore, D. (2009). What is nanotechnology and why does it matter?: from science to ethics. John Wiley & Sons. Pg 4.
33. Mahajan, S. D., Aalinkeel, R., Law, W.-C., Reynolds, J. L., Nair, B. B., Sykes, D. E., … Schwartz, S. A. (2012). Anti-HIV-1 nanotherapeutics: promises and challenges for the future. International Journal of Nanomedicine, 7, 5301–5314. http://doi.org/10.2147/IJN.S25871
34. McNeil, S. E. (2011). Unique benefits of nanotechnology to drug delivery and diagnostics. In Characterization of Nanoparticles Intended for Drug Delivery (pp. 3-8). Humana Press.
35. Petros, R. A., & DeSimone, J. M. (2010). Strategies in the design of nanoparticles for therapeutic applications. Nature reviews Drug discovery, 9(8), 615.
36. Gagliardi, M. (2017). Biomimetic and bioinspired nanoparticles for targeted drug delivery. Therapeutic delivery, 8(5), 289-299.
37. Galdiero, S., Falanga, A., Vitiello, M., Cantisani, M., Marra, V., & Galdiero, M. (2011). Silver nanoparticles as potential antiviral agents. Molecules, 16(10), 8894-8918.
38. Goldberg, M., Langer, R., & Jia, X. (2007). Nanostructured materials for applications in drug delivery and tissue engineering. Journal of Biomaterials Science, Polymer Edition, 18(3), 241-268.
39. Muthu, M. S., & Singh, S. (2009). Targeted nanomedicines: effective treatment modalities for cancer, AIDS and brain disorders.
40. Kumari, A., Singla, R., Guliani, A., & Yadav, S. K. (2014). Nanoencapsulation for drug delivery. EXCLI Journal, 13, 265–286.
41. Ripoli, M., Angelico, R., Sacco, P., Ceglie, A., & Mangia, A. (2016). Phytoliposome-based silibinin delivery system as a promising strategy to prevent hepatitis C virus infection. Journal of biomedical nanotechnology, 12(4), 770-780.
42. Venkatesh, D. N., Baskaran, M., Karri, V. V. S. R., Mannemala, S. S., Radhakrishna, K., & Goti, S. (2015). Fabrication and in vivo evaluation of Nelfinavir loaded PLGA nanoparticles for enhancing oral bioavailability and therapeutic effect. Saudi Pharmaceutical Journal, 23(6), 667-674.
43. Donalisio, M., Leone, F., Civra, A., Spagnolo, R., Ozer, O., Lembo, D., & Cavalli, R. (2018). Acyclovir-Loaded Chitosan Nanospheres from Nano-Emulsion Templating for the Topical Treatment of Herpesviruses Infections. Pharmaceutics, 10(2), 46.
44. Li, Y., Lin, Z., Zhao, M., Xu, T., Wang, C., Hua, L.,& Zhu, B. (2016). Silver nanoparticle based codelivery of oseltamivir to inhibit the activity of the H1N1 influenza virus through ROS-mediated signaling pathways. ACS applied materials & interfaces, 8(37), 24385-24393.
45. Chiodo, F., Marradi, M., Calvo, J., Yuste, E., & Penadés, S. (2014). Glycosystems in nanotechnology: Gold glyconanoparticles as carrier for anti-HIV prodrugs. Beilstein Journal of Organic Chemistry, 10, 1339–1346. http://doi.org/10.3762/bjoc.10.136
46. Gu, J., Al-Bayati, K., & Ho, E. A. (2017). Development of antibody-modified chitosan nanoparticles for the targeted delivery of siRNA across the blood-brain barrier as a strategy for inhibiting HIV replication in astrocytes. Drug delivery and translational research, 7(4), 497-506.
47. Li, Y., Lin, Z., Guo, M., Xia, Y., Zhao, M., Wang, C.,Zhu, B. (2017). Inhibitory activity of selenium nanoparticles functionalized with oseltamivir on H1N1 influenza virus. International Journal of Nanomedicine, 12, 5733–5743. http://doi.org/10.2147/IJN.S140939
48. Li, Yinghua et al. "Inhibition of H1N1 Influenza Virus-Induced Apoptosis by Functionalized Selenium Nanoparticles with Amantadine through ROS-Mediated AKT Signaling Pathways." International Journal of Nanomedicine 13 (2018): 2005–2016. PMC. Web. 17 May 2018.
49. 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. http://doi.org/10.1177/2049936117713593
50. Barik, S. (2012). New treatments for influenza. BMC medicine, 10(1), 104.
51. Steinbach, J. M., Weller, C. E., Booth, C. J., & Saltzman, W. M. (2012). Polymer nanoparticles encapsulating siRNA for treatment of HSV-2 genital infection. Journal of controlled release, 162(1), 102-110.
52. Levina, A. S., Repkova, M. N., Mazurkova, N. A., & Zarytova, V. F. (2016). Nanoparticle-mediated nonviral DNA delivery for effective inhibition of influenza A viruses in cells. IEEE Transactions on Nanotechnology, 15(2), 248-254.
53. Thi, E. P., Mire, C. E., Lee, A. C., Geisbert, J. B., Zhou, J. Z., Agans, K. N., ... & MacLachlan, I. (2015). Lipid nanoparticle siRNA treatment of Ebola-virus-Makona-infected nonhuman primates. Nature, 521(7552), 362.
54. Shafagati, N., Patanarut, A., Luchini, A., Lundberg, L., Bailey, C., Petricoin III, E., ... & Kehn Hall, K. (2014). The use of Nanotrap particles for biodefense and emerging infectious disease diagnostics. Pathogens and disease, 71(2), 164-176.
55. Hendricks, G. L., Weirich, K. L., Viswanathan, K., Li, J., Shriver, Z. H., Ashour, J., ... & Comolli, J. C. (2013). Sialylneolacto-N-tetraose c (LSTc)-bearing liposomal decoys capture influenza A virus. Journal of Biological Chemistry, 288(12), 8061-8073.
56. Song, Z., Wang, X., Zhu, G., Nian, Q., Zhou, H., Yang, D., ... & Tang, R. (2015). Virus Capture and Destruction by Label-Free Graphene Oxide for Detection and Disinfection Applications. small, 11(9-10), 1171-1176.
57. Deokar, A. R., Nagvenkar, A. P., Kalt, I., Shani, L., Yeshurun, Y., Gedanken, A., & Sarid, R. (2017). Graphene-Based "Hot Plate" for the Capture and Destruction of the Herpes Simplex Virus Type 1. Bioconjugate chemistry, 28(4), 1115-1122.
58. Kim, M. G., Park, J. Y., Shon, Y., Kim, G., Shim, G., & Oh, Y. K. (2014). Nanotechnology and vaccine development. asian journal of pharmaceutical sciences, 9(5), 227-235.

59. Sokolova, V., Westendorf, A. M., Buer, J., Überla, K., & Epple, M. (2015). The potential of nanoparticles for the immunization against viral infections. Journal of Materials Chemistry B, 3(24), 4767-4779.
60. Zhao, L., Seth, A., Wibowo, N., Zhao, C. X., Mitter, N., Yu, C., & Middelberg, A. P. (2014). Nanoparticle vaccines. Vaccine, 32(3), 327-337.
61. Sawaengsak, C., Mori, Y., Yamanishi, K., Mitrevej, A., & Sinchaipanid, N. (2014). Chitosan nanoparticle encapsulated hemagglutinin-split influenza virus mucosal vaccine. AAPS PharmSciTech, 15(2), 317-325.
62. Dhakal, S., Hiremath, J., Bondra, K., Lakshmanappa, Y. S., Shyu, D. L., Ouyang, K., ... & Krakowka, S. (2017). Biodegradable nanoparticle delivery of inactivated swine influenza virus vaccine provides heterologous cell-mediated immune response in pigs. Journal of Controlled Release, 247, 194-205.
63. Stone, J. W., Thornburg, N. J., Blum, D. L., Kuhn, S. J., Wright, D. W., & Crowe Jr, J. E. (2013). Gold nanorod vaccine for respiratory syncytial virus. Nanotechnology, 24(29), 295102.
64. Deng, L., Mohan, T., Chang, T. Z., Gonzalez, G. X., Wang, Y., Kwon, Y. M., ... & Wang, B. Z. (2018). Double-layered protein nanoparticles induce broad protection against divergent influenza A viruses. Nature Communications, 9(1), 359
65. D Hill, B., Zak, A., Khera, E., & Wen, F. (2018). Engineering Virus-like Particles for Antigen and Drug Delivery. Current Protein and Peptide Science, 19(1), 112-127.
66. Biabanikhankahdani, R., Alitheen, N. B. M., Ho, K. L., & Tan, W. S. (2016). pH-responsive virus-like nanoparticles with enhanced tumour-targeting ligands for cancer drug delivery. Scientific reports, 6, 37891.
67. Zhao, C., Ao, Z., & Yao, X. (2016). Current Advances in Virus-Like Particles as a Vaccination Approach against HIV Infection. Vaccines, 4(1), 2. http://doi.org/10.3390/vaccines4010002
68. Ramirez, A., Morris, S., Maucourant, S., D'Ascanio, I., Crescente, V., Lu, I. N., ... & Rosenberg, W. (2018). A virus-like particle vaccine candidate for influenza A virus based on multiple conserved antigens presented on hepatitis B tandem core particles. Vaccine.